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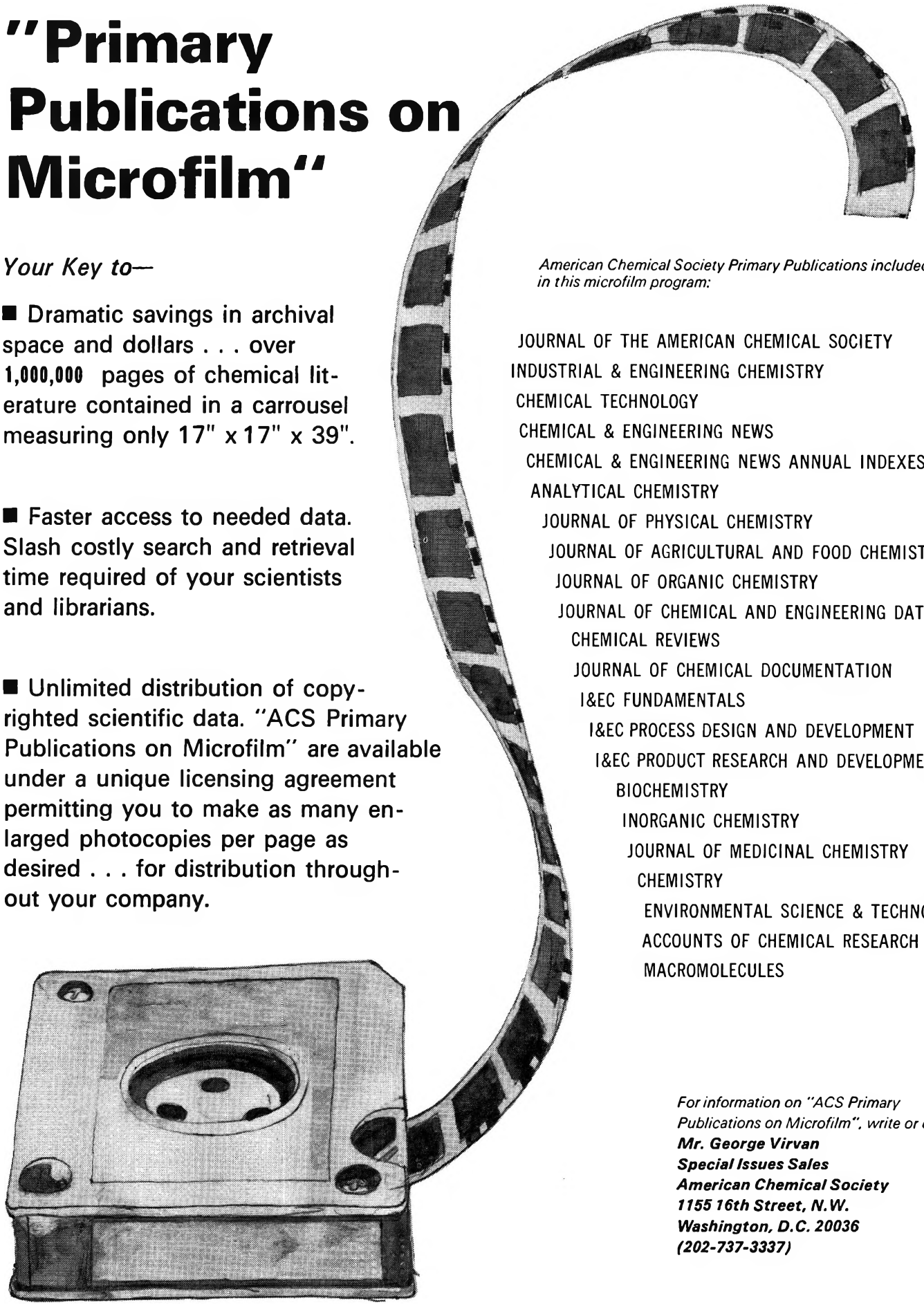

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THE JOURNAL OF Organic Chemistry®

VOLUME 36, NUMBER 23

NOVEMBER 19, 1971

Carboxysilanes and -germanes. II.[1,2] Synthesis and Spectral Properties of Triorganosilane- and Triorganogermanecarboxylic Acid

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Received January 6, 1971

Procedures for the synthesis of carboxysilanes and -germanes of the type $Me_nPh_{3-n}MCO_2H$, where M = Si and Ge and n = 0–3, and $(XC_6H_4)_3GeCO_2H$, where X = *m*-CH_3, *p*-CH_3, *m*-OCH_3, *p*-OCH_3, *m*-F, *p*-F, and *p*-CF_3, by carbonation of the corresponding triorganosilyl- and triorganogermyllithium reagents are given. The spectral properties, uv, ir, and pmr, of a number of these acids and their carbon analogs are listed and discussed. The uv spectra of Me_3MCO_2H and $Me_3MCO_2^-$, n → π* transition, are interpreted in terms of inductive release by the metalloid and π (π* → d) bonding between the functional group and the metalloid.

In this and the following paper,[3] further studies are reported on the chemical and physical properties of triorganosilane- and triorganogermanecarboxylic acids. These studies were undertaken in order to obtain a better understanding of the bonding in and the properties of the structural unit, $\equiv MCO_2-$, where M = Si or Ge, which is novel in that the carboxyl group is bonded directly to the metalloid through carbon.

The chemical and physical properties of the carboxysilanes and -germanes and their derivatives differ markedly from their carbon analogs.[1-10] The differences in properties can be accounted for in terms of the inductive effect of the metalloid, the ability of the metalloid to form additional bonds, and π (π → d) bonding between the metalloid and the carboxy group.[11] In this paper, the spectral properties of carboxysilanes and -germanes are reported and interpreted in terms of inductive effects and π bonding between the carboxyl group and the vacant d orbitals of the metalloid, particularly in reference to the excited state. General methods for the preparation of carboxysilanes and -germanes are also discussed.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are corrected. The spectra were obtained on the following instruments: ir, Beckman IR-8 and IR-20 spectrophotometers; uv, Cary 14 spectrophotometer; nmr, Varian A-60 spectrometer. The elemental analyses were performed by Alfred Bernhardt Microanalytical Laboratory, West Germany.

Preparation of the Triorganosilane- and Triorganogermanecarboxylic Acids.—Detailed descriptions of the synthetic procedures used are given below by citing typical examples. The yields, melting points, and analyses for the acids, intermediates, and by-products are given in Tables I and II.[12,13] For acids not included in Table I, *cf.* ref 1 and 2c.

A. Procedure 1.—Small pieces of lithium wire, 1.7 g (0.24 g-atom), were added to HMPA (80 ml), and the mixture was stirred until a permanent blue-black color was observed.[14] Trimethylbromogermane, bp 112–114° (lit.[15] bp 113.5°), 12.0 g (60 mmol), dissolved in HMPA (20 ml), was added to the above solution over a period of 2.5 hr. During the addition, the flask was cooled in an ice–water bath. After stirring for 3 hr, the reaction mixture remained colorless; therefore, the reaction was initiated by adding an aliquot of a solution prepared from lithium (0.5 g) and HMPA (20 ml). After stirring for 10 min, the reaction mixture was a light greenish brown. After stirring for 7 hr, the dark greenish-brown solution was filtered through glass wool and carbonated by pouring onto powdered Dry Ice. The Dry Ice slurry was poured directly into a 5% hydrochloric acid solution (150 ml). The aqueous solution was extracted several times with ether (750 ml) and the combined ethereal solution was dried (EtOH). Removal of the solvent under reduced pressure gave the crude trimethylgermanecarboxylic acid (1.7 g,

(1) For preliminary reports on this work, *cf.* (a) O. W. Steward, J. E. Dziedzic, and J. O. Frohliger, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, INOR 118; (b) O. W. Steward, J. E. Dziedzic, and J. S. Johnson, Abstracts, Fourth International Conference on Organometallic Chemistry, Bristol, England, July 1969, D18; (c) O. W. Steward and J. E. Dziedzic, *J. Organometal. Chem.*, **16**, P5 (1969).

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(14) A dry nitrogen atmosphere was maintained over all reactions involving lithium and organosilyl- and organogermyllithium reagents.

(15) V. F. Mironov and A. L. Kravchenko, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1026 (1965); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 988 (1965).

TABLE I

PREPARATIONS OF R_3MCO_2H[a]

R_3M	Registry no.	Procedure	% yield[b]	Mp, °C[c]	% C Calcd	% C Found	% H Calcd	% H Found
Me_3Si	31593-12-1	2	42	38–40	40.64	40.74	8.53	8.67
Me_3Ge[d]	22776-20-1	1	17	36–37.5	29.52	29.69	6.20	6.19
$PhMe_2Ge$	31593-16-5	5	47	49–50.5	48.08	48.18	5.38	5.41
Ph_2MeGe[e]	31593-18-7	4	54	131.5–133 dec	58.60	58.49	4.93	4.88
$(p\text{-}MeC_6H_4)_3Ge$	2887-10-7	3	84	168–170 dec[f]	67.75	67.71	5.68	5.68
$(m\text{-}MeC_6H_4)_3Ge$	31593-21-2	3[g]	43	161–163 dec	67.75	67.63	5.68	5.65
$(p\text{-}MeOC_6H_4)_3Ge$	31593-22-3	5	35	132–134 dec	60.19	60.12	5.02	5.20
$(m\text{-}MeOC_6H_4)_3Ge$	31593-23-4	6	38	126.5–128 dec	60.19	60.16	5.02	4.93
$(p\text{-}FC_6H_4)_3Ge$	31593-24-5	5	17	153–155 dec	56.64	56.60	3.25	3.20
$(m\text{-}FC_6H_4)_3Ge$	31593-25-6	6[g]	13	180–183 dec	56.64	56.64	3.25	3.24
$(p\text{-}CF_3C_6H_4)_3Ge$	31593-26-7	5	14	163–165 dec	47.79	47.77	2.37	2.47

[a] For acids not in this table, *cf.* ref 1 and 2c. [b] Crude acid. [c] Corrected. [d] Reference 2c. [e] Nmr (CCl_4) 0.91 (s, 3, CH_3Ge), *ca.* 7.40 (10, C_6H_5Ge), 11.60 (s, 1, CO_2H). [f] Lit.[12] mp 141–143 dec. [g] Intermediate not isolated.

TABLE II

INTERMEDIATES AND BY-PRODUCTS

Compd	Registry no.	Procedure	% yield[a]	Mp or bp (mm), °C	% C Calcd	% C Found	% H Calcd	% H Found
$[(p\text{-}MeC_6H_4)_3Ge]_2$		3	30	345–347[b]				
$[(p\text{-}MeOC_6H_4)_3Ge]_2$	31593-81-4	3	40	371–373	64.01	64.04	5.37	5.40
$[(m\text{-}MeOC_6H_4)_3Ge]_2$	31593-82-5	3	36	189–191	64.01	63.84	5.37	5.45
$(p\text{-}MeOC_6H_4)_2$		5		172–173[c]				
$(p\text{-}CF_3C_6H_4)_2$	581-80-6	5		91–92	57.93	58.07	2.78	2.93
$(p\text{-}CF_3C_6H_4)_4Ge$	31593-84-7	5	14	173–174	51.50	51.63	2.47	2.58
$(m\text{-}CF_3C_6H_4)_2GeH_2$	31593-85-8	5	34	93–94 (0.6)[d]	46.09	46.07	2.76	2.83
$(m\text{-}CF_3C_6H_4)_3GeOH$[e]	31593-86-9	5	27	142–143	48.05	47.94	2.49	2.38
$(m\text{-}CH_3OC_6H_4)_3GeH$[f]	2816-29-7	6	91	83.5–85	63.84	63.71	5.61	5.62
$(C_6H_5)_2GeMe_2$	7301-42-0	4	45	80–81.5 (0.15)[g]	65.50	65.46	6.27	6.20

[a] Crude yield. [b] Lit.[12] mp 345°. [c] Lit.[13] mp 171–172°. [d] Bp; $n^{25}D$ 1.4873; ir (neat), GeH, 2092 cm^{-1}. [e] From decarbonylation of crude $(m\text{-}CF_3C_6H_4)_3GeCO_2H$. [f] Ir (Nujol), GeH, 2041 cm^{-1}. [g] Bp; $n^{25}D$ 1.5711; nmr (CCl_4) 0.53 (s, 3, CH_3Ge), *ca.* 7.30 (5, C_6H_5Ge).

11 mmol). Five successive crystallizations from pentane at −78° gave a sample of high purity.

B. **Procedure 2.**—Small pieces of lithium wire (12.5 g, 0.36 g-atom) were added to bis(trimethylsilyl)mercury[16] (17.1 g, 43 mmol) dissolved in THF (150 ml). After stirring for 6 hr, the black solution was filtered through glass wool, carbonated, and extracted as described in procedure 1. Removal of the ether under reduced pressure gave crude trimethylsilanecarboxylic acid (4.2 g, 23 mmol). Five successive crystallizations from pentane at −78° gave a sample of high purity.

C. **Procedure 3.**—A THF solution (450 ml) of *p*-tolylmagnesium bromide (0.20 mol) was added over a period of 2 hr to germanium tetrachloride (12.5 g, 58 mmol) dissolved in THF (250 ml). Small pieces of lithium wire (2.5 g, 0.36 g-atom) were added and the mixture was stirred for 10 hr. The mixture was filtered through glass wool, poured onto powdered Dry Ice, and acidified with a 5% hydrochloric acid solution (300 ml). The insoluble white solid, crude hexa-*p*-tolyldigermane, 6.0 g (8.7 mmol, 30%), mp 350–360°, was separated by filtration. A sample was purified by sublimation. The remaining organic material was extracted with ether (500 ml), and the combined ethereal solution was extracted with two 100-ml portions of a 5% sodium hydroxide solution. After acidification and ether extraction (300 ml), the ethereal layer yielded crude *p*-toluic acid (2.8 g) on evaporation. A sample was purified by sublimation, mp 179–180.5° (lit.[17] mp 180°). Hexa-*p*-tolyldigermane (5.0 g, 7.2 mmol) and small pieces of lithium wire (0.69 g, 0.10 g-atom) were added to a mixture of THF (100 ml) and HMPA (30 ml). After the solution was stirred for 21 hr, the dark green solution was filtered through glass wool and poured onto powdered Dry Ice. The Dry Ice slurry was acidified with 5% hydrochloric acid (300 ml) and extracted several times with ether (300 ml). The combined ethereal solution was extracted with two 50-ml portions of 5% sodium hydroxide, and the combined aqueous solution was acidified and extracted with ether (400 ml). After drying (EtOH), removal of the ether under reduced pressure gave crude tri-*p*-tolylgermanecarboxylic acid (4.8 g, 12.2 mmol), mp 145–155° dec. Several successive crystallizations from ethanol gave a sample of high purity.

D. **Procedure 4.**—An ethereal solution (75 ml) of phenyllithium (0.12 mol) was added over a period of 40 min to dimethyldichlorogermane (10.0 g, Alfa Inorganics, Inc.) dissolved in THF (250 ml). (After this experiment was completed, it was found that the dimethyldichlorogermane employed was a mixture of 19 mol % methyltrichlorogermane and 81 mol % dimethyldichlorogermane by nmr analysis.) After the addition of phenyllithium was completed, small pieces of lithium wire (2.8 g, 0.405 g-atom) were added and the mixture was stirred for 11 hr. The reaction mixture was carbonated and the crude acid extracted as described for procedure 3. Crystallization of the syrupy material from a pentane solution (−15°) gave crude diphenylmethylgermanecarboxylic acid (2.0 g, 7.0 mmol), mp 110–120°, a 54% yield based on the methyltrichlorogermane added. Several successive crystallizations from pentane–ether gave a sample of high purity. Evaporation of the ethereal layer remaining after basic extraction gave a syrupy residue. Fractional distillation under reduced pressure gave crude biphenyl (0.40 g), mp 65–68°, and diphenyldimethylgermane (6.0 g, 23.5 mmol), bp 75–85° (0.15 mm), a 45% yield based on the dimethyldichlorogermane added. Sublimation yielded a sample of high purity of biphenyl, mp 67–68° (lit.[18] mp 68.5°). Fractional distillation under reduced pressure of crude diphenyldimethylgermane gave a sample of high purity.

E. **Procedure 5.**—A THF solution (450 ml) of *p*-anisylmagnesium bromide (0.21 mol) was added over a period of 3 hr to germanium tetrachloride (12.0 g, 56 mmol) dissolved in THF (250 ml). After the addition was completed, lithium aluminum hydride (1.3 g, 34 mmol) dissolved in ether was added, and the mixture was stirred for 18 hr. After the excess lithium aluminum hydride was decomposed with absolute ethanol, the reaction mixture was poured onto a mixture of cracked ice and dilute hydrochloric acid. The organic material was extracted with ether (500 ml) and, after drying (EtOH), the solvent was removed under reduced pressure. Distillation under reduced pressure

(16) C. Eaborn, R. A. Jackson, and R. W. Walsingham, *J. Chem. Soc. C*, 2188 (1967).

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(18) H. Gilman and E. A. Zuech, *J. Org. Chem.*, **26**, 3035 (1961).

of the remaining material gave crude, *p,p'*-bianisole (1.2 g), mp 165–178°. A sample of high purity was obtained by sublimation. An ir spectrum (neat) of the syrupy residue remaining after removal of the *p,p'*-bianisole showed a strong Ge–H absorption band (2045 cm^{-1}), indicative of tri-*p*-anisylgermane. The syrupy residue was dissolved in THF (120 ml) and HMPA (60 ml), and small pieces of lithium wire (4.4 g, 0.63 g-atom) were added. After the solution was allowed to stir for 12 hr, the reaction mixture was carbonated and the crude acid extracted as described for procedure 3. Crystallization of the syrupy material from benzene–hexane (0–5°) gave crude tri-*p*-anisylgermanecarboxylic acid, (8.7 g, 19.8 mmol), mp 115–125° dec. Several successive crystallizations from benzene–hexane gave a sample of high purity.

F. **Procedure 6.**—A THF solution (450 ml) of *m*-anisylmagnesium bromide (0.21 mol) was added over a period of 3.5 hr to germanium tetrachloride (12.5 g, 58 mmol), dissolved in THF (250 ml). After the addition was completed, lithium aluminum hydride (1.8 g, 47 mmol) was added, and the procedure described for procedure 5 was followed. On removal of the solvent under reduced pressure, crude tri-*m*-anisylgermane (20.9 g, 53 mmol), mp 78–84°, was obtained. Two successive crystallizations from ethanol–benzene gave a sample of high purity. *n*-Butyllithium (10 ml, 1.6 *M* in hexane) was added over a period of 10 min to tri-*m*-anisylgermane (5.0 g (0.125 mol) dissolved in ether (30 ml). After the solution had been stirred for 10 min, the yellow-orange solution was carbonated and the crude acid extracted as described for procedure 3. Crude tri-*m*-anisylgermanecarboxylic acid (3.2 g, 4.8 mmol), mp 124–128°, gave a sample of high purity, after several successive crystallizations from benzene–petroleum ether (bp 30–60°).

Results and Discussion

Synthesis.—To date, the only known method of preparing triorganosilane- and triorganogermanecarboxylic acids is by carbonation of triorganosilyl- and triorganogermyl–alkali metal derivatives[19,20] and triarylgermylmagnesium compounds.[20]

In this paper the syntheses of Me_3SiCO_2H and Me_3GeCO_2H,[2c] by the carbonation of Me_3SiLi[21] and Me_3GeLi,[22] respectively, are reported. The alkylarylgermanecarboxylic acids, $Me_2PhGeCO_2H$ and $MePh_2GeCO_2H$, were synthesized by carbonation of the corresponding germyllithium derivatives.

A series of triarylgermanecarboxylic acids with substituent groups on the aromatic rings in the meta and para positions were synthesized for spectral studies and pK_a determinations. Previously, only the *p*-tolyl derivative had been reported.[23] The triarylgermyllithium reagents, which were carbonated to yield the carboxylic acids, were synthesized as indicated in eq 1–3. Method 1 was employed to prepare the *p*-CH_3

$$[(XC_6H_4)_3Ge]_2 \xrightarrow[THF\text{-}HMPA]{Li} 2(XC_6H_4)_3GeLi \quad (1)$$

$$(XC_6H_4)_3GeH \xrightarrow[THF\text{-}HMPA]{Li} (XC_6H_4)_3GeLi \quad (2)$$

$$(XC_6H_4)_3GeH \xrightarrow[Et_2O]{n\text{-}BuLi} (XC_6H_4)_3GeLi \quad (3)$$

derivative; method 2, the *m*-CH_3, *p*-CH_3O, *p*-F, and *p*-CF_3 derivatives; and method 3, the *m*-CH_3O and *m*-F derivatives. In most cases, methods 1 and 2 were modified from the cited procedures[20] by adding hexamethylphosphoramide (HMPA) to the reaction mixture. Addition of HMPA to the reaction decreases the initiation time for germyllithium formation by partially dissolving the lithium metal[24] and generally enhances the yield of the carboxylic acid. Method 2 was found to be the most versatile of the methods employed and thus was used most frequently for the synthesis of the carboxylic acids. Method 1 would seem to be a good approach to synthesizing all of the triarylgermanecarboxylic acids, but difficulties were encountered in preparing the starting materials, $(XC_6H_4)_6Ge_2$. In two cases, hexa-*p*-anisyldigermane and hexa-*m*-anisyldigermane, cleavage of the Ge–Ge bond was not successful.

The stability of triorganosilane- and triorganogermanecarboxylic acids toward base-catalyzed decarbonylation has been discussed in several papers. Whereas Ph_3GeCO_2H and Et_3GeCO_2H are reported to be stable toward dilute alkali,[4,8,22] $Me_nPh_{3-n}SiCO_2H$, n = 0–2, are reported to undergo decarbonylation.[4,7] In connection with the studies reported in this and the following paper, we have observed that both silane- and germanecarboxylic acid undergo base-catalyzed decarbonylation, the silanecarboxylic acids decomposing more rapidly than the analogous germanecarboxylic acids and the rate of decarbonylation being facilitated by electron-withdrawing groups.

Both Me_3SiCO_2H and Me_3GeCO_2H are quite stable toward base, and the corresponding anions can be prepared in 76 wt % ethanol–water. The triarylgermanecarboxylic acids with electron-withdrawing substituent groups on the aromatic ring decarbonylate when the base, sodium 4-nitrophenoxide, is added to solutions of the acids in dimethyl sulfoxide. The triorganosilanecarboxylic acids decarbonylate on dissolving in dimethyl sulfoxide.

All of the arylgermanecarboxylic acids prepared were isolated from an ethereal solution of the reaction mixture by extraction with 5% aqueous sodium hydroxide. However, attempts to isolate $(m\text{-}CF_3C_6H_4)_3GeCO_2H$ by this method were not successful. The acid decomposed on extraction at 0° as was evident from the disappearance of the carbonyl stretching band (1667 cm^{-1}) which is characteristic of the germanecarboxylic acids (*cf.* ir section).

Ultraviolet Spectra.—The electronic spectral properties of triorganosilane- and triorganogermanecarboxylic acids and their conjugate base forms differ markedly from their carbon analogs. The spectra of the acids, R_3MCO_2H, and anions, $R_3MCO_2^-$, show an absorption band in the ultraviolet region, λ_{max}^{EtOH} 246–254 nm (ϵ <870), while aliphatic carboxylic acids absorb at a shorter wavelength, λ_{max}^{EtOH} 205–213 nm (ϵ <150) and aliphatic carboxylate ions show no absorption maximum above 200 nm;[25,26] *cf.* Figure 1. For the compounds studied to date, the absorption maximum of the silicon derivatives occurs at a slightly longer wavelength than for the corresponding germa-

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(26) J. P. Philips, "Spectra-Structural Correlations," Academic Press, New York, N. Y., 1964, pp 80–84.

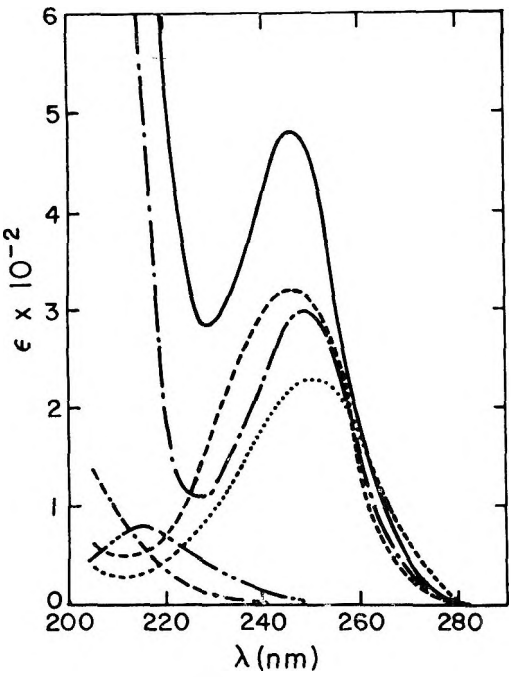

Figure 1.—The ultraviolet spectra of Me_3MCO_2H and $M_3MCO_2^-Na^+$ in absolute ethanol: acid, M = Ge (----), Si (· · · · ·), C (-·-·-·); anion, M = Ge (——), Si (·-·-·), C (- - - - -).

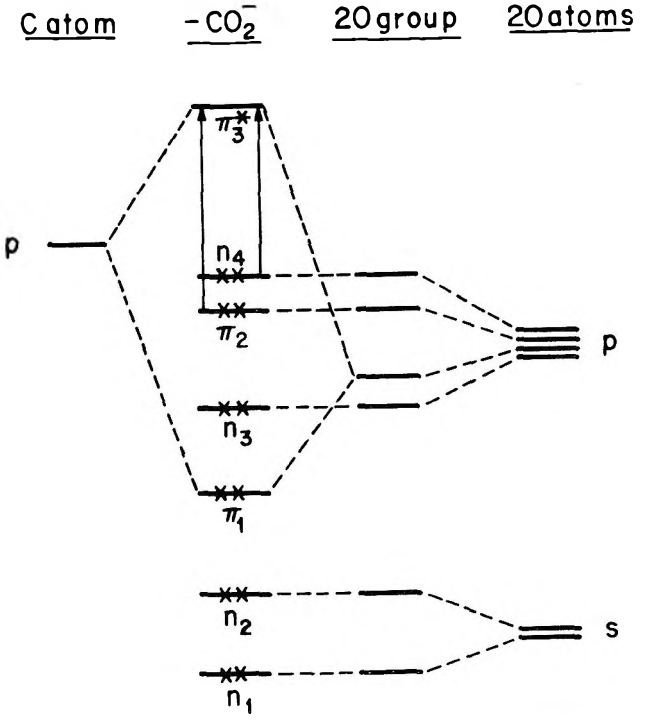

Figure 2.—A qualitative MO diagram for the $-CO_2^-$ ion.

nium derivatives (2–6 nm), while the extinction coefficient of the germanium derivatives is larger. The ultraviolet spectral data for the acids and anions are given in Table III along with some recently reported

TABLE III
ULTRAVIOLET SPECTRA DATA FOR R_3MCO_2R' AND $R_3MCO_2^-$

Compd	n → π* transition: λmax, nm (ε)	eV	Solvent
Me_3CCO_2H[a]	205 (117)	6.05	C_6H_{12}
	213 (71)	5.82	EtOH
$Me_3CCO_2^-$[a]	<205		EtOH
Me_3SiCO_2H	243 (299)	5.10	C_6H_{12}
	249 (228)	4.98	EtOH
$Me_3SiCO_2^-$	248 (305)	5.00	EtOH
Me_3GeCO_2H[a]	241 (413)	5.14	C_6H_{12}
	246 (325)	5.04	EtOH
$Me_3GeCO_2^-$[a]	246 (480)	5.04	EtOH
$Me_2PhSiCO_2H$	~254 (<790)	4.94	EtOH
$Me_2PhGeCO_2H$	~248 (<870)	5.00	EtOH
$H_3GeCO_2^-$[b]	239 (<500)	5.19	H_2O
Me_3CCO_2Me[c]	212 (100)	5.85	C_6H_{12}
Me_3SiCO_2Me[c]	245 (330), 250 (330)	5.06, 4.96	C_6H_{12}
	245 (320)	4.96	95% EtOH

[a] Reference 2c. The values previously reported for the germanium acid and anion have been revised since the acid used for the spectral data contained small amounts of decarbonylation products. [b] Reference 9. [c] Reference 10.

data on the corresponding methyl esters. The assignment of these bands as n → π* transition is based on their low intensity and on the bathochromic shift of the absorption maximum as the solvent is made more polar (cyclohexane to ethanol, $\Delta\lambda_{max}$ 5–6 nm), which is consistent with the data on aliphatic carboxylic acids.[27]

For triorganosilane- and triorganogermanecarboxylic acids with substituent phenyl groups, the n → π* transition of the carboxyl group is masked by the phenyl π → π* transition with peaks in the region 247–272 nm. In all cases the molar extinction coefficients of the peaks in this region of the spectra are larger for the phenyl substituted silane- and germanecarboxylic acids than for their carbon analogs. The absorption maximum and molar extinction coefficient for the n → π* transition of $PhMe_2MCO_2H$ were estimated from the difference in the spectra of the acids and the corresponding compounds, $PhMMe_3$;[29] *cf.* Table III.

The relative positions of the energy levels for the n and π orbitals of the carboxylate ion, which is isoelectric with the nitro group,[28] are given in the qualitative molecular orbital diagram (Figure 2). The lowest energy transition is expected to be a forbidden transition, n → π*; a higher energy allowed transition, π → π*, is also expected. These electronic transitions are not observed above 200 nm for aliphatic carboxylate ions.[25,26] A similar ordering of transitions is expected for the carboxyl group when the change in electron repulsion on electronic excitation is considered.[30] In this case, the forbidden n → π* transition is observed, *ca.* 205–213 nm, just within the range of conventional spectrophotometric instruments.

The nature of the atom bonded to the carboxyl group or carboxylate ion through carbon will change the energy requirements for the electronic transitions. Substituting a metalloid, silicon or germanium, for carbon can significantly influence the energy of the n and π levels by inductive (+*I*) and π (π → d) bonding effects. The unfilled d orbitals on silicon (3d) and germanium (4d) can interact with the π system of the carboxyl group or carboxylate ion to lower the energy, of the π

(27) The solvent shift is in the opposite direction for carbonyl derivatives which are not associated due to hydrogen bonding; see ref 25, 28.

(28) H. H. Jaffé and M. Orehin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962, Chapter 9.

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levels, particularly the π^* level because of better matching of energy, while the greater electropositive nature of the metalloid than carbon would be expected to raise the energy of the n and π levels; *cf.* Figure 3.

The effect of metalloid substitution on the spectra of ketones, a simpler chromophore, has been reported.[31-33] The energy of the n → π^* transition of acylsilanes and -germanes is lower than for aliphatic ketones by about 1.0 eV resulting in absorption in the visible region.[34,35] Recent experimental measurements indicate that roughly one-fourth of the bathochromic shift of the n → π^* transition of acylsilanes is due to π (π → d) bonding with the remainder resulting from the inductive effect of silicon relative to carbon.[33]

Calculations based on ionization potentials[36] and electronic transition energies, n → π^*, of aliphatic carboxylic acids indicate that the n level is ~0.8 eV lower and the π^* level is ~0.8 eV higher than the corresponding levels in aliphatic ketones. MO calculations indicate that the d orbitals of silicon and germanium are higher in energy than the π^* level of aliphatic ketones.[37] Thus, there is a better matching of energy between the metalloid nd orbital and the π^* orbital of the silane- and germanecarboxylic acids than for the acylsilanes and -germanes, indicating that π (π^* → d) bonding should be more important in the former and thus result in a larger bathochromic shift of the n → π^* transition. However, smaller spectral shifts are observed for the silane- and germanecarboxylic acids, $\Delta\lambda_{max}^{EtOH}$ ~35 nm. Since the energy of the n → π^* transition is the result of two energy states, the smaller shift for the carboxysilanes and -germanes could be the result of a much lower sensitivity of the n levels of the carboxyl chromophore to the inductive effect of the metalloid. There is no reason to expect that the inductive effect on the n levels of the carboxyl group would be the same as on the n level of the ketone group.

The π^* level of the carboxylate ion should be higher in energy than in the conjugate acid form due to greater electron delocalization in the ion. Thus, larger spectral shifts would be expected for $Me_3MCO_2^-$ than for the conjugate acid form due to better matching between the carboxylate ion π^* level and the metalloid nd level. The observed shift, $\Delta\lambda_{max}^{EtOH}$ >42 nm, is indeed larger; the λ_{max}^{EtOH} for $Me_3CCO_2^-$ occurs below 205 nm. The larger extinction coefficient for $Me_3MCO_2^-$ than for the conjugate acid form, ratio of anion to acid form equals ~1.4, is indicative of greater d-orbital participation in the anion form.

Infrared Spectra.—Two of the most interesting features of the infrared spectra of the triorganosilane- and triorganogermanecarboxylic acids are the positions of the >C=O stretching frequency and the ≡MCO_2H stretching frequency. The carbonyl stretching absorption maximum for the acids, R_3MCO_2H (CCl_4 solution), is observed between 1645 and 1663 cm^{-1}, while this absorption occurs between 1693 and 1707 cm^{-1} for the carbon analogs. The positions of the absorption maximum for the acids in the solid state, KBr pellet, generally fall at lower energy. The shift of the carbonyl stretching absorption of the acids, R_3MCO_2H, from their carbon analogs, $\Delta\nu$ 28–53 cm^{-1}, is a good criterion for the structural unit, ≡MCO_2H.[2c] For the series of triarylgermanecarboxylic acids with substituent groups on the aromatic rings, the position of the carbonyl stretching band parallels the inductive properties of the substituent group.

The stretching absorption for the ≡MCO_2H bond for the acids studied occurs between 572 and 600 cm^{-1} for R_3SiCO_2H and between 563 and 580 cm^{-1} for R_3GeCO_2H. The ≡MCH_3 stretching absorption occurs at a shorter wavelength: $Me_nPh_{3-n}MCO_2H$, where n = 1–3; M = Si, ν 624–707 cm^{-1}; M = Ge, ν 584–607 cm^{-1}. The infrared spectral data are given in Tables IV and V.

Proton Magnetic Resonance Spectra.—The pmr spectra of the acids Me_3MCO_2H, where M = C, Si, and Ge, were determined in CCl_4; *cf.* Table VI. Each spectrum consists of two singlet resonance lines, ≡MCH_3* and ≡MCO_2H*. The chemical shifts of the methyl proton are consistent with closely related C, Si, and Ge compounds.[11] The chemical shifts of the acidic proton are in accord with the electronegativities of the group IVb elements, C > Si ≈ Ge.

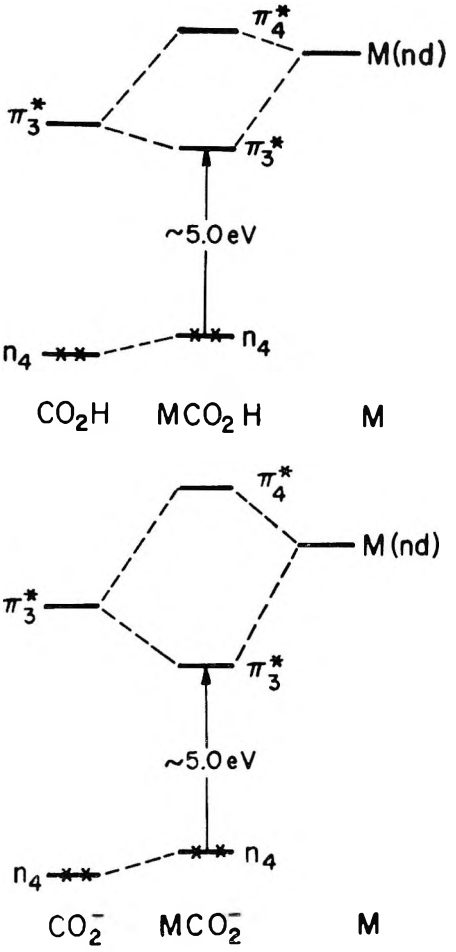

Figure 3.—Qualitative MO diagrams showing the effect of a metalloid and its d orbitals on the energy levels of the carboxyl group and the carboxylate ion.

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(33) H. Bock, H. Alt, and H. Seidl, *J. Amer. Chem. Soc.*, **91**, 355 (1969).
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(35) F. Agolini, S. Klemenko, J. G. Csizmadia, and K. Yates, *Spectrochem. Acta, Part A*, **24**, 169 (1968).
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(37) Based on ionization potentials as a reference, the relative order is reported to be Si (3d), −1.6 to −2.6 eV; Ge (4d), −1.2 to −2.8 eV; $R_2C{=}O$ (π^*), −5.1 eV.[10,35]

TABLE IV
INFRARED SPECTRAL DATA FOR $(CH_3)_n(C_6H_5)_{3-n}MCO_2H$

Compd	ν, C=O, cm⁻¹ CCl₄	ν, C=O, cm⁻¹ KBr	ν, MCO_2H, cm⁻¹ (CCl_4)	ν, MCH_3, cm⁻¹ (CCl_4)
Me_3CCO_2H	1693	1686		
Me_2PhCCO_2H	1693	1670		
$MePh_2CCO_2H$	1696	1675		
Ph_3CCO_2H	1706	1670		
Me_3SiCO_2H	1654	1646	572	707, 624
$Me_2PhSiCO_2H$	1645	1636	588	649, 631 sh
$MePh_2SiCO_2H$	1647	1636	593	661
Ph_3SiCO_2H	1654	1633	600	
Me_3GeCO_2H	1648	1650	563 sh	614, 575
$Me_2PhGeCO_2H$	1646	1640	566 sh	607, 584
$MePh_2GeCO_2H$	1654	1647	570	595
Ph_3GeCO_2H	1663	1642	575	

TABLE V
INFRARED SPECTRAL DATA FOR $(XC_6H_4)_3GeCO_2H$

X	ν, C=O, cm⁻¹ CCl_4	ν, C=O, cm⁻¹ KBr	ν, MCO_2H, cm⁻¹ (CCl_4)
H	1663	1642	575
p-CH_3	1652	1647	563
m-CH_3	1654	1642	575
p-CH_3O	1655	1654	573
m-CH_3O	1659	1645	580
p-F	1656	1650	573
m-F	1662	1650	580
p-CF_3	1663	1661	572
n-CF_3	1667[a]		

[a] Not isolated.

TABLE VI
PROTON MAGNETIC RESONANCE DATA FOR $(CH_3)_3MCO_2H$

M	δ, ppm[a] CH_3	δ, ppm[a] OH[b]	Peak area ratio
C	1.22	12.53	1:8
Si	0.26	12.01	1:8.6
Ge	0.46	11.96	1:9.2

[a] Spectra determined in CCl_4, 22–35 w/v %, using TMS as an internal standard at 60 MHz. [b] Position slightly affected by concentration.

Both the position of the carbonyl stretching frequency and the chemical shift of the acidic proton of the acids, Me_3MCO_2H, in relation to their carbon analog suggest that there is little π ($\pi \rightarrow$ d) bonding in the ground state of the acid form and the observed order is mainly the result of the inductive properties of the group IVb elements.

Registry No.—$Me_3SiCO_2^-$, 31593-89-2; $Me_2PhSiCO_2H$, 17878-13-6; $MePh_2SiCO_2H$, 18414-58-9; Ph_3SiCO_2H, 18670-88-7; Ph_3GeCO_2H, 22718-99-6.

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Carboxysilanes and -germanes. III.[1,2] Ionization Constants of Triorganosilane- and Triorganogermanecarboxylic Acids in Ethanol–Water and Dimethyl Sulfoxide Media

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Ionization constants of the following carboxylic acids have been determined by a spectrophotometric method: $Me_nPh_{3-n}MCO_2H$, where M = C, Si and Ge, n = 0–3, in ethanol–water media and where M = C and Ge, in dimethyl sulfoxide; $(XC_6H_4)_3GeCO_2H$, where X = H, *p*-Me, *m*-Me, *p*-OMe, *m*-OMe, *p*-F, *m*-F, and *p*-CF_3, in ethanol–water media and X = H, *p*-Me, *m*-Me, *p*-OMe, in dimethyl sulfoxide. The relative order of acidity, $R_3SiCO_2H \approx R_3GeCO_2H > R_3CCO_2H$, is explained in terms of π ($\pi \rightarrow$ d) bonding between the π orbitals of the CO_2^- group and the vacant nd orbitals of the metalloid with steric hindrance to anion solvation playing a smaller role. The transmission of substituent effects through the phenyl group and germanium also are discussed.

In a previous paper,[3] we reported the ionization constants of a number of acids of the type, R_3MCO_2H, where R = Me and/or Ph and M = C, Si, and Ge, in ethanol–water media. Since the triorganosilanecarboxylic acids are susceptible to base-catalyzed decarbonylation,[4] a new potentiometric method was developed for the determination of the ionization constants in acidic media.[5] In all cases studied, the silane- and germanecarboxylic acids were found to be more acidic than their carbon analogs. It was suggested that the observed order of acidity is the result of stabilization of the silane- and germanecarboxylate ions relative to their carbon analog by π ($\pi \rightarrow$ d) bonding between the CO_2^- group and the metalloid which overcomes the inductive effect ($+I$) of the metalloid. Also it was suggested that π ($\pi \rightarrow$ d) bonding becomes an important factor in anion stability since there is a full negative charge on which to operate; *i.e.*, in the anion form there is a demand for charge delocalization by π ($\pi \rightarrow$ d) bonding.

In this study we have determined the ionization con-

(1) For preliminary reports on this work, *cf.* O. W. Steward, J. E. Dziedzic, J. S. Johnson, and J. O. Frohliger, Abstracts, Fourth International Conference on Organometallic Chemistry, Bristol, England, July 1969, D18; O. W. Steward, J. E. Dziedzic, and J. O. Frohliger, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, INOR 118.

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TABLE I

pK_a VALUES OF R_3MCO_2H IN 45% ETHANOL–WATER AT 25°

Acid	Registry no.	No. of determinations	pK_a Found (σ)[a]	pK_a Lit.[b] (σ)[a]
$MeCO_2H$	64-19-7	11	5.61 (0.01)	5.64 (0.06)
Me_3CCO_2H	75-98-9	23	6.41 (0.08)	
Me_3SiCO_2H	31593-12-1	48	6.60 (0.04)	
Me_3GeCO_2H	22776-20-1	24	6.20 (0.03)	
Me_2PhCCO_2H	826-55-1	11	6.05 (0.01)	6.00 (0.03)
$Me_2PhSiCO_2H$	17878-13-6	16	<6.06[c]	5.96 (0.10)
$Me_2PhGeCO_2H$	31593-16-5	22	6.00 (0.02)	
$MePh_2CCO_2H$	5558-66-7	11	5.81 (0.01)	5.77 (0.04)
$MePh_2SiCO_2H$	18414-58-9	11	<6.0[c]	5.66 (0.05)
$MePh_2GeCO_2H$	31593-18-7	33	5.69 (0.01)	

[a] Standard deviation. [b] Reference 3. [c] Base-catalyzed decomposition of the acid.

TABLE II

pK_a VALUES OF R_3MCO_2H IN 76% ETHANOL–WATER AT 25°

Acid	No. of determinations	pK_a Found (σ)[a]	pK_a Lit.[b] (σ)[a]
$MeCO_2H$	12	6.57 (0.02)	6.78 (0.02)
Me_3CCO_2H	19	7.96 (0.05)	
Me_3SiCO_2H	24	7.74 (0.02)	
Me_3GeCO_2H	20	7.43 (0.03)	
Me_2PhCCO_2H	6	7.45 (0.04)	7.45 (0.02)
$Me_2PhSiCO_2H$	12	7.28 (0.05)	
$Me_2PhGeCO_2H$	22	7.33 (0.04)	
$MePh_2CCO_2H$	12	7.15 (0.09)	7.20 (0.03)
$MePh_2SiCO_2H$	10	7.04 (0.05)	7.03 (0.09)
$MePh_2GeCO_2H$	35	7.04 (0.12)	
Ph_3CCO_2H	10	6.78 (0.02)	6.70 (0.03)
Ph_3SiCO_2H	9	6.10 (0.10)	6.23 (0.04)
Ph_3GeCO_2H	11	6.27 (0.03)	6.32 (0.02)

[a] Standard deviation. [b] Reference 3.

TABLE III

pK_a VALUES OF R_3MCO_2H IN DIMETHYL SULFOXIDE AT 25°

Acid	No. of determinations	pK_a (σ)[a]
$MeCO_2H$	10	11.41 (0.02)[b]
Me_3CCO_2H	13	12.39 (0.12)
Me_3GeCO_2H	18	11.13 (0.07)
Me_2PhCCO_2H	16	11.10 (0.05)
$Me_2PhGeCO_2H$	18	10.20 (0.06)
$MePh_2CCO_2H$	24	10.00 (0.04)
$MePh_2GeCO_2H$	12	9.39 (0.08)
Ph_3CCO_2H	21	9.29 (0.07)
Ph_3GeCO_2H	6	8.43 (0.06)

[a] Standard deviation. [b] Lit. pK_a = 11.4 [I. M. Kolthoff and T. B. Reddy, *Inorg. Chem.*, **1**, 189 (1962)]; pK_a = 11.6 [C. D. Ritchie and R. E. Uschold, *J. Amer. Chem. Soc.*, **89**, 1721 (1967)].

stants for the complete series of acids, $Me_nPh_{3-n}MCO_2H$, where M = C, Si, and Ge and n = 0–3, in ethanol–water and, where M = C and Ge, in dimethyl sulfoxide by a spectrophotometric technique.[6] This study also has been extended to a series of triarylgermanecarboxylic acids with substituent groups on the aromatic rings. These data allow us to elaborate on the importance of the role of π ($\pi \rightarrow$ d) bonding in stabilizing the conjugate base forms of the silane- and germanecarboxylic acids.

Experimental Section

The solvents, dimethyl sulfoxide (Fisher Certified Reagent Grade) and 95% ethanol (Commercial Solvents Corp.) were purified and the 45 and 76%[7] ethanol–water solutions were prepared as described previously.[6] The synthesis and properties of the triorganosilane- and triorganogermanecarboxylic acids used in this study are reported in previous papers in this series.[2,3] The ionization constants of the carboxylic acids were determined in 45 and 76% ethanol–water and dimethyl sulfoxide at 25 ± 0.1° by a simplified spectrophotometric procedure described elsewhere.[6] A Cary Model 14 spectrophotometer was employed for absorptivity measurements, and calculations were carried out on a Control Data G-20 computer.

Results

The ionization constants, in terms of pK_a values, of the acids, R_3MCO_2H, in 45 and 76% ethanol–water and dimethyl sulfoxide are given in Tables I–IV. The pK_a values of the triphenyl derivatives were not determined in 45% ethanol–water because of their low solubility. In some cases, as specified in the tables, base-catalyzed decarbonylation of the acids prevented the determination of the ionization constants.

The ionization constants of the acids determined by both the potentiometric and spectrophotometric[6] methods in most all cases agree within the experimental error. The spectrophotometric method is favored because of its simplicity and its adaptability to both protic and aprotic solvent systems. One disadvantage of the spectrophotometric method is that it may not be applicable if the carboxylic acids are extremely sensitive to base-catalyzed decarbonylation in the solvent employed.

Discussion

While ultraviolet spectral studies of triorganosilane- and triorganogermanecarboxylic acids and their conjugate base forms indicate that π ($\pi \rightarrow$ d) bonding occurs between the metalloid and the carboxyl group, particularly in reference to the excited state, infrared and proton magnetic resonance studies suggest there is little π ($\pi \rightarrow$ d) bonding in the ground state of the acid form.[2] A study of the ionization constants of the carboxylic acids, R_3MCO_2H, gives results related to the ground state and allows one to compare the relative stabilities of the acid and conjugate base forms.

Inductive, resonance, and steric effects can influence the ionization equilibrium of the carboxylic acids. These effects would be expected to exert their main influence on the equilibrium by changing the stability of the carboxylate ion where there is a full negative charge

(6) J. O. Frohliger, J. E. Dziedzic, and O. W. Steward, *Anal. Chem.*, **42**, 1189 (1970).

(7) Throughout this paper, per cent (%) will represent percentage by weight.

TABLE IV

pK_a VALUES OF $(XC_6H_4)_3GeCO_2H$ AT 25°

X	Registry no.	No. of determinations	pK_a, 76% EtOH–H_2O	No. of determinations	pK_a, DMSO
H	22718-99-6	11	6.27 (0.03)[a]	6	8.43 (0.06)[a]
p-Me	2887-10-7	15	7.34 (0.04)	13	9.59 (0.04)
m-Me	31593-21-2	10	6.79 (0.02)	27	8.93 (0.09)
p-OMe	31593-22-3	23	7.17 (0.04)	36	9.13 (0.03)
m-OMe	31593-23-4	10	6.48 (0.01)		<8.3[b]
p-F	31593-24-5	12	6.02 (0.08)		<8.3[b]
m-F	31593-25-6	13	5.69 (0.01)		
p-CF_3	31593-26-7	23	4.85 (0.05)		

[a] Standard deviation. [b] Base-catalyzed decomposition of the acid.

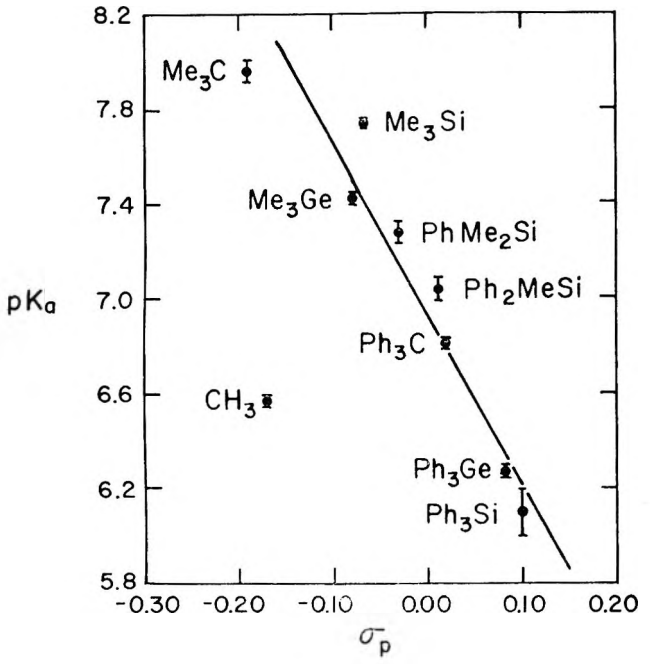

Figure 1.—Plot of the pK_a of R_3MCO_2H, 76% ethanol–water, *vs.* the σ_p value for the R_3M group: slope, −6.70; $\bar{r}$, 0.947; $\bar{s}$, 0.20.

on which to operate.[8,9] Inductive, resonance, and steric effects will contribute to both the enthalpy and entropy of ionization since the stability of the carboxylate ion is a function of electronic and solvation effects which are not separable. In the above acids, the most important steric effect probably arises from exclusion of solvent molecules from the vicinity of the carboxylate ion.[10]

The order of acidity of the carbon, silicon, and germanium analogs of the acids, R_3MCO_2H, in the various solvent systems follow: 45% ethanol–water, Si ≈ Ge ≳ C; 76% ethanol–water, Si ≈ Ge > C; dimethyl sulfoxide, Ge > C. In only one case is a reversal of the above order observed; in 45% ethanol–water, Me_3SiCO_2H is a slightly weaker acid than Me_3CCO_2H. Also, it has been reported that GeH_3CO_2H is more acidic than CH_3CO_2H in aqueous solution.[11]

Based on inductive effects alone, the order of acidity of a series of the acids would be C > Si ≈ Ge.[12] From the proximity of the group IVb atoms to the carboxyl group in the acids, R_3MCO_2H, large differences in acidity would be expected due to the differences in the electronegativities of carbon and silicon or germanium.[13] However, the differences in the ionization constants of the carbon, silicon, and germanium acids are quite small and the relative acidity is not in accord with the inductive order.

In order to explain the observed order of acidity, the steric effect or resonance effect ($-R$) must overcome the inductive effect ($+I$) of the metalloid. Based on the covalent radii of C, Si, and Ge,[14] steric inhibition of anion solvation would lead to the following order of acidity for the acids, Ge ≳ Si > C. π ($\pi \rightarrow$ d) bonding between the carboxylate ion and the metalloid would lead to the following order of acidity, Si ≳ Ge > C, and was proposed in a previous paper to explain the observed order of the series, Ph_3MCO_2H.[3] The following discussion of the experimental data is presented to differentiate between the two alternatives.

The relative order of the pK_a values of the acids, R_3MCO_2H, and the substituted benzoic acids, *p*-$R_3MC_6H_4CO_2H$,[15] are similar. Linear-free-energy correlations are observed between the σ_p values for the R_3M groups and the pK_a values of the acids, R_3MCO_2H, in 76% ethanol–water and dimethyl sulfoxide media; *cf.* Figures 1 and 2. The σ_p values used in the correlations are the values obtained from the ionization constants and reactions of *p*-$R_3MC_6H_4CO_2H$.[16]

The above correlations indicate that the interaction between the group IVb element and the functional group in the carboxylic acids, R_3MCO_2H and *p*-$R_3MC_6H_4CO_2H$, and/or the corresponding conjugate base forms are of the same type. Steric effects arising from exclusion of solvent molecules from the vicinity of the carboxylate ion must be constant or of relatively minor importance for the acids, R_3MCO_2H, in the light of the above correlations. Only the σ_p values which

(8) K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, pp 280–288.

(9) C. D. Ritchie and R. E. Uschold, *J. Amer. Chem. Soc.*, **90**, 2821 (1968).

(10) G. S. Hammond in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, 1956, pp 426–428.

(11) P. M. Kuznesof and W. L. Jolly, *Inorg. Chem.*, **7**, 2574 (1968).

(12) R. W. Bott, C. Eaborn, and T. W. Swaddle, *J. Organometal. Chem.*, **5**, 233 (1966).

(13) E. A. V. Ebsworth in "Organometallic Compounds of the Group IV Elements," Vol. I, Part I, A. G. MacDiarmid, Ed., Marcel Dekker, New York, N. Y., 1968, pp 1–104.

(14) r_C = 0.77, r_{Si} = 1.15, r_{Ge} = 1.21 Å: V. Schomaker and D. P. Stevenson, *J. Amer. Chem. Soc.*, **63**, 37 (1941).

(15) J. Chatt and A. A. Williams, *J. Chem. Soc.*, 4403 (1954); 688 (1956).

(16) The σ_p values were calculated from the data of Chatt and Williams,[15] using the correlations reported by Jaffé,[17] or were taken from the work of Benkeser, *et al.*:[18] Me_3C, −0.19; Me_3Si, −0.07; Me_3Ge, −0.08; Me_2PhSi, −0.03; $MePh_2Si$, +0.01; Ph_3C, +0.02; Ph_3Si, +0.10; Ph_3Ge, +0.08.

(17) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(18) R. A. Benkeser, C. E. DeBoer, R. E. Robinson, and D. M. Sauve, *J. Amer. Chem. Soc.*, **78**, 682 (1956); R. A. Benkeser and R. B. Gosnell, *J. Org. Chem.*, **22**, 327 (1957).

provide for a $+I$ effect and a $-R$ effect, transmitted to the point of attachment of the carboxyl group,[19] give satisfactory correlations.

Steric effects are important in determining the acidity of carboxylic acids as illustrated by the large deviation of the point for acetic acid from the regression line for the solvent 76% ethanol–water. Smaller deviations from the regression line also can be accounted for in terms of steric effects, *e.g.*, the pK_a of Me_3SiCO_2H is greater than Me_3GeCO_2H in 76% ethanol–water. In dimethyl sulfoxide, a dipolar aprotic solvent, steric effects appear to be less important as the point for acetic acid falls much closer to the regression line.

Acid–base equilibria are very sensitive to solvation effects. The largest effect for acids of similar structure is proposed to arise from differences in anion solvation.[2c] Thus, changes in pK_a values on changing solvent systems should reflect steric hindrance to anion solvation due to differences in the basicity and molecular size of the solvent molecules. In Table V, the

TABLE V

SOLVENT EFFECTS ON THE pK_a VALUES OF R_3MCO_2H

Acid	ΔpK_a, 45% EtOH–H_2O to 76% EtOH–H_2O	ΔpK_a, 76% EtOH–H_2O to DMSO
$MeCO_2H$	0.96	4.84
Me_3CCO_2H	1.55	4.43
Me_3SiCO_2H	1.14	
Me_3GeCO_2H	1.22	3.71
Me_2PhCCO_2H	1.40	3.65
$Me_2PhSiCO_2H$	1.38	
$Me_2PhGeCO_2H$	1.33	2.87
$MePh_2CCO_2H$	1.34	2.85
$MePh_2SiCO_2H$	1.38	
$MePh_2GeCO_2H$	1.35	2.34
Ph_3CCO_2H		2.51
Ph_3GeCO_2H		2.16

changes in the pK_a values, ΔpK_a, of the acids, R_3MCO_2H, on changing the solvent from 45 to 76% ethanol–water and from 76% ethanol–water to dimethyl sulfoxide are listed.

The changes in the ionization constants of the acids, $Me_nPh_{3-n}MCO_2H$, where n = 1, 2, on changing the solvent from 45 to 76% ethanol–water are relatively constant, ΔpK_a = 1.33–1.40, indicating that steric effects on anion solvation are about the same for these acids. Acetic acid which has quite different steric requirements for anion solvation shows a much smaller change in pK_a. For the acids, Me_3MCO_2H, which show the largest deviations from the linear-free-energy relationship, 76% ethanol–water, greater differences in the pK_a values are observed indicating some differences in the steric requirements for solvation.

The change in the ionization constants of the acids, R_3MCO_2H, where M = C and Ge, on changing the solvent from the protic solvent, 76% ethanol–water, to the aprotic solvent, dimethyl sulfoxide, vary over a considerable range, ΔpK_a = 2.16–4.43. Since dimethyl sulfoxide is a better solvent than ethanol–water for large anions,[20] much smaller changes in ΔpK_a are observed for Ph_3MCO_2H. However, the differences in

(19) C. Eaborn, "Organosilicon Compounds," Butterworths, London, 1960, pp 98–103.

(20) B. W. Clare, D. Cook, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *J. Amer. Chem. Soc.*, **88**, 1911 (1966).

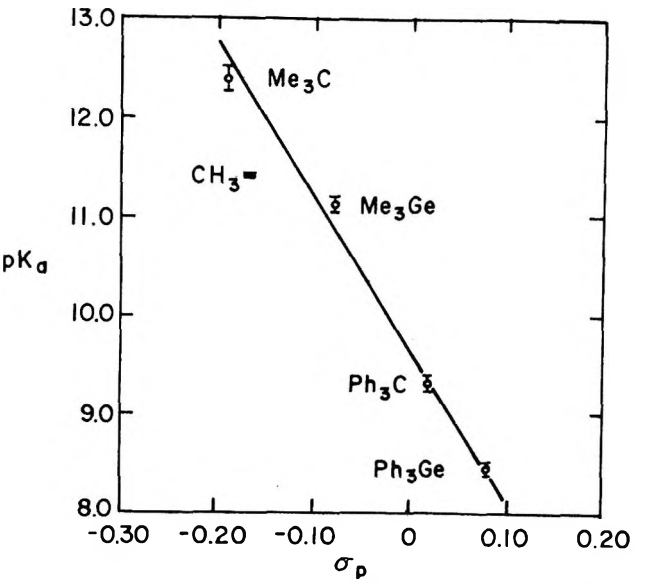

Figure 2.—Plot of the pK_a of R_3MCO_2H, dimethyl sulfoxide, *vs.* the σ_p value for the R_3M group: slope, −15.0; $\bar{r}$, 0.993; $\bar{s}$, 0.19.

the ΔpK_a values for the carbon and germanium derivatives with the same organic groups are quite small, ΔpK_a (C) − ΔpK_a (Ge) ≈ 0.6. The smaller change in pK_a for the acids, R_3GeCO_2H, could result from less steric hindrance to anion solvation. However, a greater demand for anion stabilization by π ($\pi \rightarrow$ d) bonding in the solvent dimethyl sulfoxide, a poorer ionizing solvent for carboxylic acids, could account for the smaller change.

The ionization constant of H_3GeCO_2H has been measured in aqueous solution.[11] This acid was found to be a stronger acid than acetic acid by 1.2 pK_a units. While steric hindrance to anion solvation must be reduced considerably from the alkyl derivatives, the observed order of acidity is maintained.

From the above correlations and the overall consistency of the relative order of acidity for the acids, R_3MCO_2H, in the solvent systems employed, the proposal that π ($\pi \rightarrow$ d) bonding between the metalloid and the CO_2^- group overcomes the inductive influence of the metalloid seems most reasonable. The π ($\pi \rightarrow$ d) bonding interaction is probably important only in the conjugate base forms of the acids where there is a demand for stabilization of the full negative charge.[3] Steric inhibition to anion solvation undoubtedly causes some variations in the observed order but remains fairly constant for the series studied.

Recently, Wilson, Zuckerman, *et al.*,[21] have reported the pK_a, ΔH, and $\Delta S°$ values for a series of substituted benzoic acids including *m*- and *p*-$Me_3MC_6H_4CO_2H$, where M = C and Si. In this paper, they suggest that the greater acidity of the silicon derivatives can be accounted for in terms of anion–solvation effects resulting from the larger size and more strongly hydrophobic nature of the trimethylsilyl group as compared to the *tert*-butyl group and conclude that a π ($\pi \rightarrow$ d) bonding explanation is not necessary. However, they fail to consider the effect of internal contributions, *i.e.*, inductive and π ($\pi \rightarrow$ d) bonding effects, on anion solvation. Contributions from these effects will appear in both ΔH

(21) J. M. Wilson, A. G. Briggs, J. E. Sawbridge, P. Tickle, and J. J. Zuckerman, *J. Chem. Soc. A*, 1024 (1970).

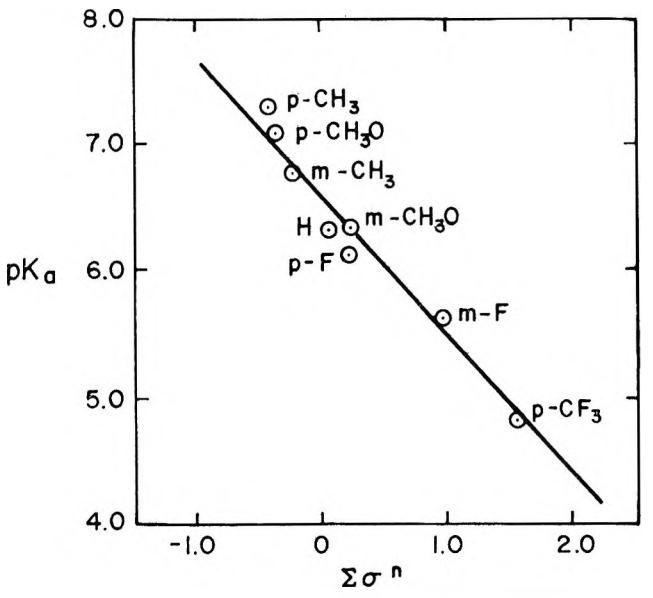

Figure 3.—Plot of the pK_a of $(XC_6H_4)_3GeCO_2H$, 76% ethanol–water, *vs.* the σ^n values for X: slope, −0.97; $\bar{r}$, 0.956.

and ΔS° of ionization. While the values of ΔS° of ionization for *m*-$Me_3MC_6H_4CO_2H$, where M = C and Si, are about the same, ΔS° is higher for *p*-$Me_3SiC_6H_4CO_2H$ than *p*-$Me_3CC_6H_4CO_2H$. π ($\pi \rightarrow$ d) bonding could account for the higher entropy of ionization of the *p*-Me_3Si derivative by reducing the anion solvation requirements through anion stabilization. The higher ΔH of ionization for the *p*-Me_3Si derivative, then, partially compensates for the reduced demand for solvation.

The relative hydrogen-bonding acidity of the acids, *m*- and *p*-$Me_3MC_6H_4CO_2H$, where M = C and Si, in carbon tetrachloride and pyridine media, determined by pmr, have been reported by Zuckerman and Fenton:[22] *m*- and *p*-*tert*-butyl > *m*- and *p*-trimethylsilyl. The same order of chemical shifts is observed for the acidic proton of the acids, Me_3MCO_2H, in carbon tetrachloride.[2] Since pmr chemical shifts for a rapidly exchanging proton indicate the average environment of the proton and little anion formation is expected in the above media, in line with the above proposal, the inductive order rather than the π ($\pi \rightarrow$ d) bonding order is expected and observed.

Transmission of Substituent Effects.—The ability of various groups, Z, to transmit substituent effects to the reaction site, Y, for several series of substituted benzene derivatives, ArZY, which differ only in the nature of Z, has been determined semiquantitatively by comparing the reaction constants, ρ, of these derivatives with the reaction constant, ρ^0, for a series of derivatives, ArY. The value for the transmission of substituent effects through phenyl, Z = $-C_6H_4-$, has been reported: $\rho/\rho^0 = 0.30 \pm 0.04$.[17] More specifically, for the base-catalyzed saponification of *p*-$ArC_6H_4CO_2Et$ and $ArCO_2Et$ in 88% ethanol–water at 30°, $\rho/\rho^0 = 0.25$.

Since a linear-free-energy relationship is observed between the pK_a values of the acids, R_3MCO_2H, and the substituent constants for the groups, R_3M, the value for the transmission of substituent effects through the phenyl group can be evaluated by comparing the reaction constant for this series with the reaction constant for the ionization of a series of substituted benzoic acids, $XC_6H_4CO_2H$. In 76% ethanol–water at 25°, $\rho^0/\rho = 0.26$,[23] in dimethyl sulfoxide at 25°, $\rho^0/\rho = 0.18$.[9]

The value for the transmission of substituent effects through the phenyl group calculated for the ethanol–water system shows good agreement with the literature value; however, in dimethyl sulfoxide a much lower value is obtained. The effect of solvent on transmission of inductive and resonance effects through phenyl has not been extensively investigated and the literature value is based on data for protic solvents only. Different steric effects in the series R_3MCO_2H and $XC_6H_4CO_2H$ would be expected to have some influence on the ρ values.

In order to compare the effectiveness of a metalloid to carbon for the transmission of inductive and resonance effects of substituent groups on the aromatic ring to the carboxyl group, the reaction constant for the ionization of a series of triarylgermanecarboxylic acids, $(XC_6H_4)_3GeCO_2H$, where X = H, *p*-Me, *m*-Me, *p*-OMe, *m*-OMe, *p*-F, *m*-F, and *p*-CF_3, were determined in 76% ethanol–water at 25°. The Hammett plot using σ^n values[24] is shown in Figure 3.[25] Synthetic difficulties prevented the extention of the plot to compounds with more strongly electron-withdrawing substituent groups.[2] The reaction constant for the series, $(XC_6H_4)_3GeCO_2H$, $\rho = 0.97$, is of the same magnitude as calculated for the series, $XC_6H_4CH_2CO_2H$, in 76% ethanol–water, $\rho = 0.87$, from previously published data.[17] Thus, the effectiveness of Ge and CH_2 for the transmission of substituent effects to the carboxyl group are quite similar.

Registry No.—Ph_3CCO_2H, 595-91-5; ethanol, 64-17-5; water, 7732-18-5; dimethyl sulfoxide, 67-68-5.

Acknowledgments.—The authors gratefully acknowledge the financial support of the Dow Corning Corp., Midland, Mich., and a grant from the National Science Foundation for the Cary Model 14 spectrophotometer. One of us (J. E. D.) is grateful to NASA for a traineeship, 1967–1969.

(22) D. E. Fenton and J. J. Zuckerman, *Inorg. Chem.*, **7**, 1323 (1968).

(23) The value for ρ^0 in 76 wt % ethanol–water, 1.77, was obtained by interpolation from the data of ref 17.

(24) P. R. Wells, *Chem. Rev.*, **63**, 171 (1963).

(25) A linear relationship of pK_a in dimethyl sulfoxide at 25° *vs.* σ^n values for $(XC_6H_4)_3GeCO_2H$, where X = H, *p*-Me, *m*-Me, *p*-OMe, *p*-F, also is observed: slope = −2.15, $\bar{r}$ = 0.96.

Reduction of δ-Lactones and Hindered Esters with Diborane[1]

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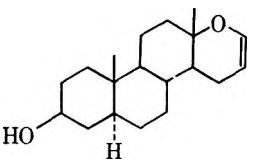
Reduction of certain esters and acetals to ethers (**5** to **6**, **9** to **10**, and **9** to **11**) with diborane–tetrahydrofuran has been studied in detail. The experimental results were also interpreted in terms of possible mechanistic pathways for ester → ether, ester → hemiacetal, and acetal → ether reduction reactions using boron hydride reagents.

The reduction of a variety of esters to ethers has been investigated employing lithium aluminum hydride or sodium borohydride and a large excess of boron trifluoride.[3] The reducing agent in such reactions was presumed to be diborane with excess Lewis acid serving to form a necessary oxonium ion.[3a,4] While this interpretation may still be generally valid, we would like to report a few examples of such reactions where employment of a large excess of boron trifluoride etherate is not necessary. Also, the scope and possible mechanism of the reduction of esters with borane reagents was examined.

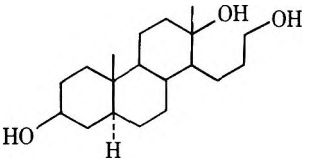
Results

Although reduction of lactone **1** (Chart I) with sodium borohydride–boron trifluoride etherate was found in the present study to give 44% ether **2a** and 42% glycol **3**, the analogous reaction of lactone **4** has been shown to give only the corresponding glycol in nearly quantitative yield.[5] This example serves to further illustrate the effect of alkyl substituents in the vicinity of the ester group upon the course of reaction.[6] Reduction of lactone **1** with diborane–tetrahydrofuran–boron trifluoride etherate gave a lower yield of ether **2a** (21%) and a higher yield of glycol **3** (52%)[7] and suggested that the borohydride anion might be participating in the reduction reaction. Utility of the Lewis acid, boron trifluoride, was emphasized by the 70% yield of glycol **3** arising from reduction of lactone **1** with diborane–tetrahydrofuran;[8] only a trace of ether **2a** could be detected. While esters such as ethyl caproate upon reduction with diborane–tetrahydrofuran were reported to provide good yields of the corresponding alcohols,[9] sterically hindered ester **5** upon reduction with excess (3 mol equiv) diborane–tetrahydrofuran provided 70–90% yields of ether **6a**.[10] We believe that this is the first unequivocal example of the reduction of an ester to an ether by diborane–tetrahydrofuran *alone*[11] and emphasizes again that substituents near the ester group favor ether formation.

Versatility of borane reduction involving conformationally stable δ-lactones is amply illustrated by the following reactions. Reduction of δ-lactones **7** and **9** with sodium borohydride–boron trifluoride gave tetrahydropyrans **8a** (75%) and **10a** (44%). Under identical conditions hemiacetal **8b** and methyl acetal **10b** reacted with sodium borohydride–boron trifluoride to yield the same tetrahydropyrans, **8a** (44%) and **10a** (47%), respectively. The acetal reduction reactions demonstrate that sodium borohydride–boron trifluoride can reduce such functional groups to ethers. Methyl acetal **10b** was used instead of hemiacetal **10c** because of more favorable solubility behavior. Treatment of lactone **1** and ester **5** with sodium borodeuteride–boron trifluoride gave ethers **2b** (41%) and **6b** (70%), respectively, thus illustrating a method for labeling the α position of certain β-substituted ethers. Reaction of δ-lactones **7** and **9** with approximately 1 mol equiv of diborane–tetrahydrofuran for a short period yielded the corresponding hemiacetals, **8b** (82%) and **10c** (95%).[12] Prolonged treatment of δ-lactone **9** with 1 mol equiv of diborane–tetrahydrofuran gave (52%) dihydropyran **11** or with approximately 3 mol equiv of diborane–tetrahydrofuran, tetrahydropyran **10a** (55%).[13] The new route to dihydropyrans represented by transformation **9** → **11** may result from elimination of the dialkoxyborine precursor of hemiacetal **10c**. The product olefin **11** might



11



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(1) (a) Steroids and Related Natural Products. 64. For part 63, refer to G. R. Pettit and T. R. Kasturi, *J. Med. Chem.*, **13**, 1244 (1970). (b) For a preliminary report pertaining to part of this study, see G. R. Pettit and J. R. Dias, *Chem. Commun.*, 901 (1970). (c) This investigation was supported by Public Health Service Research Grants CA-10115-02 and CA-11451-01 from the National Cancer Institute and is based in part on the Ph.D. dissertation of J. R. Dias, Arizona State University, 1970.

(2) NIH Predoctoral Fellow, 1968–1970.

(3) (a) G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, **26**, 4557 (1961); (b) G. R. Pettit and W. J. Evers, *Can. J. Chem.*, **44**, 1097 (1966).

(4) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 48, 49.

(5) G. R. Pettit, B. Green, T. R. Kasturi, and U. R. Ghatak, *Tetrahedron*, **18**, 953 (1962).

(6) See G. R. Pettit and D. M. Piatak, *J. Org. Chem.*, **27**, 2127 (1962), for other examples.

(7) In prior experiments we also observed that the diborane–tetrahydrofuran–boron trifluoride reagent leads to lower yields of ether than with lithium aluminum hydride–boron trifluoride.[3a]

(8) Previously it was shown that optimum yields of ether were obtained when boron trifluoride etherate was present in a large excess;[6] *cf.* K. M. Biswas and A. H. Jackson, *J. Chem. Soc. C*, 1667 (1970).

(9) H. C. Brown and W. Korytnyk, *J. Amer. Chem. Soc.*, **82**, 3866 (1960).

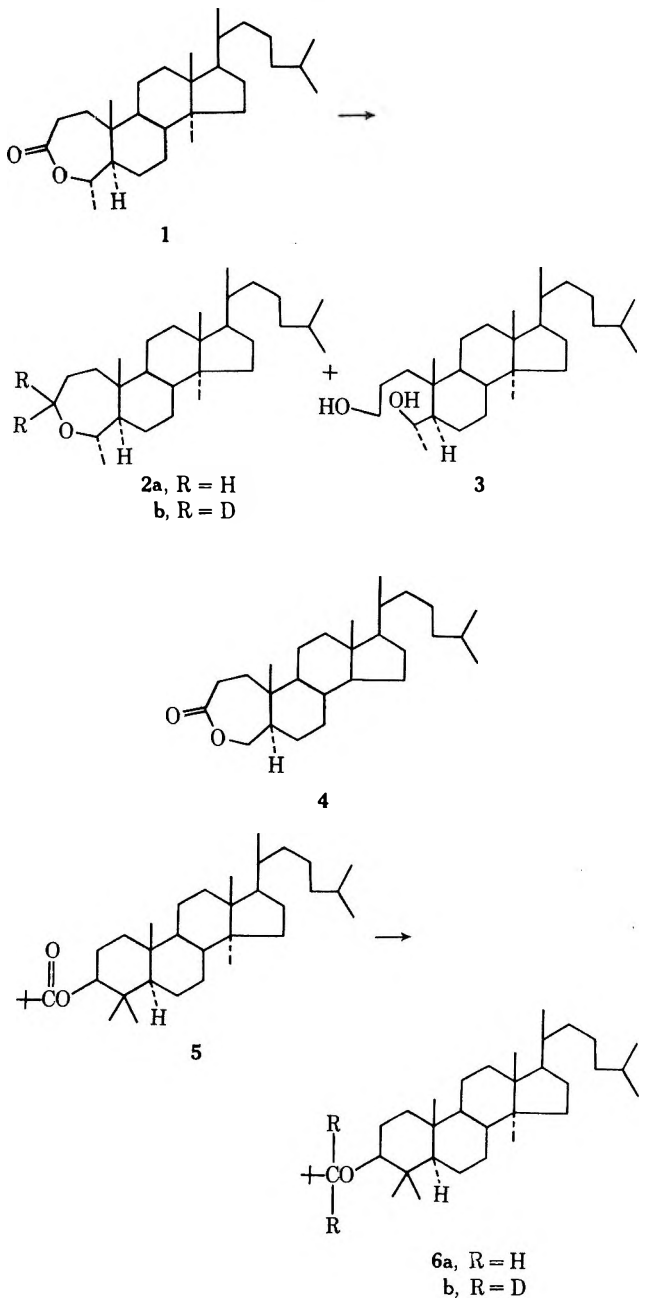
(10) Neopentyl ether **6a** would be difficult to prepare in good yield by the usual Williamson ether synthesis.

(11) Propyl ethers have been detected in the reaction of diborane–tetrahydrofuran with propionyl derivatives of alginic acid: J. H. Manning and J. W. Green, *J. Chem. Soc. C*, 2357 (1967). The reduction of amides to amines with diborane–tetrahydrofuran is formally analogous to these reactions. See W. V. Curran and R. B. Angier, *J. Org. Chem.*, **31**, 3867 (1966), for pertinent examples.

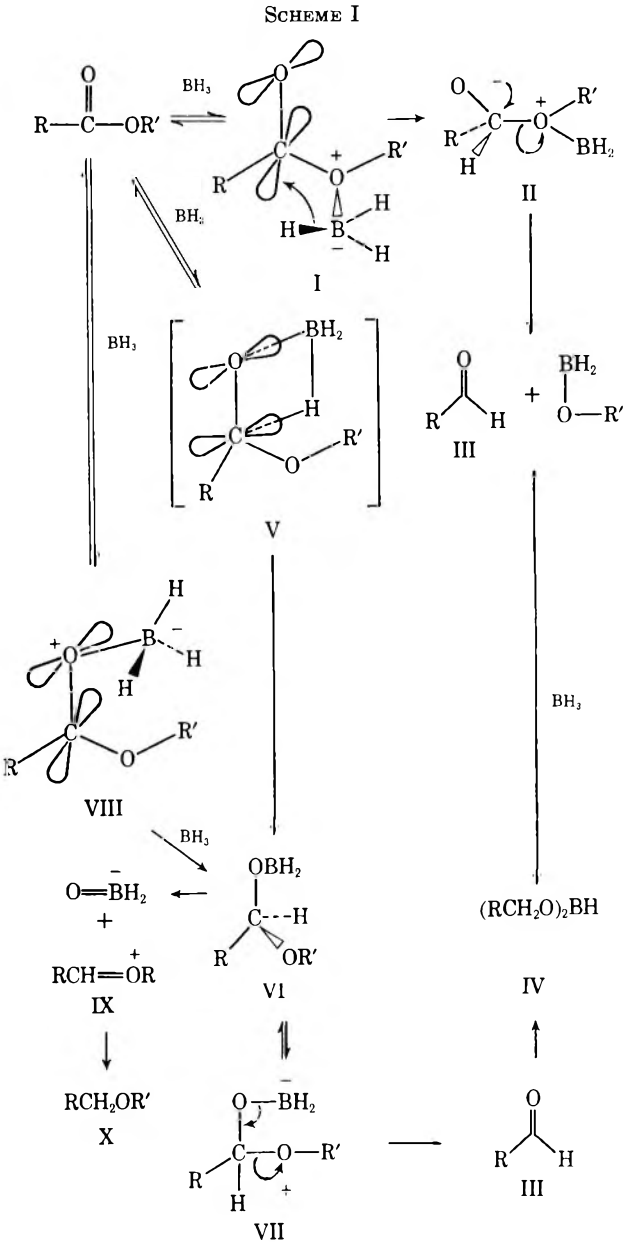
(12) G. R. Pettit, J. C. Knight, and W. J. Evers, *Can. J. Chem.*, **44**, 807 (1966).

(13) Reaction of coumarin with diborane–tetrahydrofuran has been reported to give a tetrahydropyran: B. S. Kirkiacharian and D. Raulais, *C. R. Acad. Sci.*, **269c**, 464 (1969); W. C. Still and D. J. Goldsmith, *J. Org. Chem.*, **35**, 2282 (1970).

CHART I



SCHEME I



then undergo hydroboration to **10a** with excess diborane–tetrahydrofuran.[14,15]

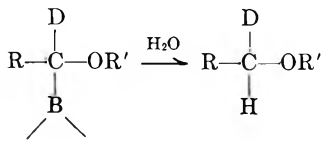
Discussion

Scheme I, an elaboration of one previously given,[15] presents some possible reaction pathways in the reduction of esters with borane. This scheme is quite general in that ethers (X) and products corresponding to intermediates IV (*cf.* alcohol **3**), VI (*cf.* hemiacetals **8b**, **10c**), and IX (*cf.* dihydropyran **11**) have all been isolated by just varying conditions or substrates. Reduction of acetals **8b** and **10b** to tetrahydropyrans **8a** and **10a**, respectively, supports the possibility that VI is an immediate precursor of IX or X. Isolation of deuterated eth-

(14) Alternatively, an oxygen-stabilized carbonium ion intermediate (*cf.* IX) may be reduced.

(15) In early work it was shown that diborane reduction of ketones and aldehydes (*e.g.*, acetaldehyde) involved only two of the three hydrogens of borane: H. C. Brown, H. I. Schlesinger, and A. B. Burg., *J. Amer. Chem. Soc.*, **61**, 673 (1939). The electronegativity requirements of two oxygens attached to borane must contribute to inertness of the third hydrogen, since all three hydrogens are consumed in the reaction of diborane with olefins (*e.g.*, propene).

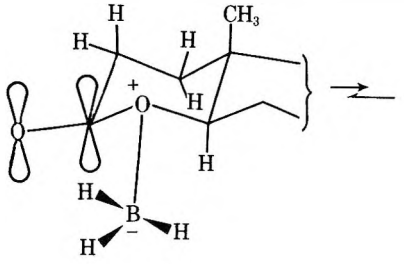
ers **2b** and **6b** is consistent with the proposed mechanistic modes presented in Scheme I and excludes the possibility expressed in eq 1. Isolation of cyclic hemiacetals



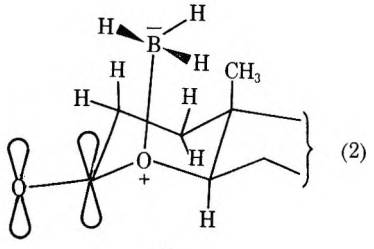
(1)

8b and **10c** demonstrates that for these systems the conversion of VI to IX is the rate-determining step. Possible F strain due to substituents in the vicinity of the ester function would inhibit formation of intermediates I or VII and thus favor ether formation (VI to X) by thwarting alcohol production.

The conversion of fused δ-lactones to alcohols can be made less favorable by inhibiting transformation I to II and/or VI to VII. Facile intramolecular hydride transfer in I can only occur when the O–B–H bonds lie in the same plane as the p orbital of the carbonyl carbon. Thus the axial-like conformer ii of eq 2 is the one which



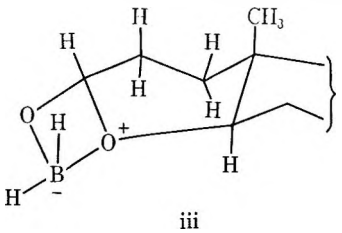
i



(2)

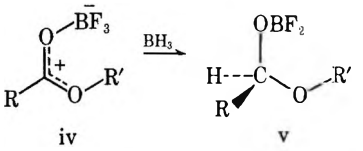
ii

is favorably disposed for intramolecular hydride transfer but is less populated than the equatorial-like conformer i due to 1,3-diaxial interaction of the O–BH_3 group with the 19-methyl and the C-2 hydrogen. The conversion of VI to VII would be retarded in δ-lactones in comparison to acyclic esters because of involvement of the strained bicyclic system iii in which the lactone ring would exist in a half-chair conformation.



iii

In the above discussion, no distinction between the two possible paths (I → II → III or VI → VII → III) by which alcohols are formed was intended. However, to explain how the Lewis acid enhances ether formation one is forced to favor the I → II → III path, *i.e.*, alcohols are formed *via* coordination of borane with alkoxy oxygen; this is a conclusion reached previously.[15] If one assumes that VI → VII → III is mainly inoperative, then boron trifluoride coordination with the carbonyl oxygen would increase production of v (*cf.* VI),[3a,16] whereas coordination with the alkoxy oxygen would be uneventful. Here iv would have a more intense charge and be more prominent than VIII. To explain why a



iv v (3)

mixture of sodium borohydride–boron trifluoride gives a higher yield of ether than a mixture of diborane–tetrahydrofuran–boron trifluoride, one is again led to favor the I → II → III path since a higher immediate concentration of BH_3 in the latter system would result in a higher population if I and not greatly influence the fate of intermediate VI. In this respect, the more nucleophilic borohydride anion would increase the rate of reaction proceeding through VIII → VI → X.[17]

Conclusion

The preceding experimental observations can be rationalized if we presume that the reaction paths proceeding through V and VII are mainly inoperative and alcohols are formed by initial coordination of borane to the alkoxy oxygen; factors disturbing this coordination slow alcohol production and permit alternative reaction paths to become more important. This mechanism eliminates the necessity of postulating a fluoroborohydride intermediate[16] with selective reducing properties. The latter proposal was excluded by the first example of ether formation from a hindered ester using only diborane–tetrahydrofuran. Also, there is no reason to believe that in the reactions utilizing sodium borohydride–boron trifluoride etherate, in a mixture of tetrahydrofuran–diglyme, that all the borohydride anion is instantaneously converted to diborane.[18] Instead, in the reactions where sodium borohydride and diglyme were added last, the conversion of sodium borohydride to diborane is probably slow enough to allow some participation by the borohydride anion.

Experimental Section

The diborane–tetrahydrofuran solution (approximately 1.0 *M* in borane), sodium borohydride (98%), and sodium borodeuteride were obtained from the Metal Hydrides Division of Ventron, Beverly, Mass. Boron trifluoride etherate (7.9 mmol/ml), practical grade obtained from J. T. Baker Chemical Co., was redistilled, bp 123–125° (729 Torr). Tetrahydrofuran was distilled from lithium aluminum hydride and stored over molecular sieves (4A). Diglyme was also stored over molecular sieves (4A). The reactions with sodium borohydride and diborane–tetrahydrofuran were performed with exclusion of moisture, and solvents were concentrated under reduced pressure on a rotating evaporator.

Alumina (Merck acid washed and basic) and silica gel (E. Merck, A. G. Darmstadt, Germany, 0.2–0.5 mm) were used for column chromatography. Silica gel HF_{254} (E. Merck) was used

(16) Refer to R. Koster, *Angew. Chem.*, **73**, 66 (1961).

(17) In this connection, it should be noted that, under usual reaction conditions, carboxylic acid esters are not reduced by sodium borohydride.

(18) Commercial sodium borohydride used with a poor solvent, such as ether, results in a slow reaction with boron trifluoride giving a low yield of diborane: H. C. Brown and P. A. Tierney, *J. Amer. Chem. Soc.*, **80**, 1552 (1958). In the present study diglyme, a generally inferior solvent for steroids, was mixed with tetrahydrofuran, a poor solvent for sodium borohydride.

for preparative thin layer while silica gel HF_{254} spread on microscope slides was used for thin layer chromatograms (tlc). The chromatograms were usually developed with benzene–ethyl acetate (5:1) and observed after using iodine vapor or by charring with 2% ceric sulfate in 2 *N* sulfuric acid. The preparative thin layer plates were viewed under ultraviolet light.

Elemental microanalyses were performed by the laboratory of Dr. A. Bernhardt, 5251 Elbach uber Engelskirchen, West Germany. All samples submitted for analysis exhibited a single spot on a tlc. Melting points were determined on a Kofler melting point apparatus. All spectra were recorded by the author or Miss K. Reimer as follows: infrared, recorded on Beckman IR-12 in potassium bromide or chloroform solution; pmr, recorded on a Varian A-60 (60 MHz) in deuteriochloroform (TMS internal standard). The mass spectra were determined using an Atlas CH-4B (low resolution) or Atlas SM-1B (high resolution) by Dr. P. Brown, E. Bebee, and R. Scott.

3-Oxo-4-oxa-4aα,14α-dimethyl-*A*-homo-5α-cholestane (1).—Reaction of 3-oxo-5α-lanostane with *m*-chloroperbenzoic acid in the presence of sulfuric acid yielded 29% of lactone 1:[19] mp 185.5–186.2° (needles from ethyl acetate); ν_{max} (0.1 *M* in chloroform) 1730 cm^{-1}; pmr δ 4.50 (m, 1 p, 4β-H), 2.58 (m, 2 p, C-2), 1.25 (d, J = 6.5 Hz, 4α-CH_3), 0.98 (s, 19-CH_3), 0.92 (peak), 0.80 (peak); RD in chloroform (c 1.75 g/100 ml) $[\alpha]_{650}$ +12°, $[\alpha]_{589}$ +15°, $[\alpha]_{500}$ +24°, $[\alpha]_{400}$ +42°, $[\alpha]_{300}$ +92°, $[\alpha]_{264}$ +114° (peak), $[\alpha]_{250}$ +71°, and $[\alpha]_{240}$ 0.0°; mass spectrum M^+ 430 (100%).

Anal. Calcd for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found: C, 80.68; H, 11.83.

4-Oxa-4aα,14α-dimethyl-*A*-homo-5α-cholestane (2a). Method A.—Sodium borohydride (90 mg, 2.3 mmol) was added to δ-lactone 1 (215 mg, 0.5 mmol) in tetrahydrofuran (3 ml, 24 mmol)–boron trifluoride etherate (2 ml). After evolution of gas subsided, diglyme (2 ml) was added to the heterogeneous mixture, which was allowed to stand for 0.5 hr and then heating at reflux for 1.5 hr. The cooled mixture was treated with saturated sodium carbonate and water (5 ml). The ethereal phase was separated and the aqueous portion was extracted with ether (five 10-ml portions). The combined ether extract was concentrated and chromatographed (preparative thin layer) on silica gel using benzene as mobile phase. Elution of the higher R_f band with ether yielded 91 mg (44%) of ether 2a as white plates: mp 69–70°; ν_{max} (KBr) 2940, 1450, 1360, and 1145 cm^{-1}; pmr δ 3.59 (m, 3 p, C-3 and C-4a), 1.22 (s), 1.10 (s), and 0.80 (s); mass spectrum 261 (100%), M^+ − 15 (30%), and M^+ 416 (33%).

Anal. Calcd for $C_{29}H_{52}O$ (416.7): C, 83.58; H, 12.58. Found: C, 83.68; H, 12.63.

Elution of the lower R_f band with ether containing 10% methanol yielded 93 mg (42%) of glycol **3** as colorless needles: mp 154.5–156.0°; ν_{max} (KBr) 3370, 2940, 1450, 1370, and 1060 cm^{-1}; pmr δ 4.05 (m, 1 p, C-4a), 3.61 (m, 2 p, C-3), 2.70 (s, 2 p, removed by D_2O), 1.18 (s), 1.10 (s), 0.93 (s, 6 p), 0.83 (s), and 0.76 (s); mass spectrum 263 (100%), M^+ − 18 (15%), M^+ − 15 (4%), M^+ − 2 (432, 0.1%).

Anal. Calcd for $C_{29}H_{54}O_2$ (434.7): C, 80.12; H, 12.52. Found: C, 80.00; H, 12.16.

Method B.—In method B reaction conditions identical with those summarized in method A were used except that diborane–tetrahydrofuran (2.4 ml) was substituted for sodium borohydride–tetrahydrofuran. The yield of ether 2a was 44 mg (21%) and of glycol **3** was 113 mg (52%).

3,4-Dihydroxy-4(*S*),14α-dimethyl-3,4-seco-5α-cholestane (3). Method A.—Diborane–tetrahydrofuran (3 ml or 6 ml) was added to a solution of lactone 1 (0.43 g) in tetrahydrofuran (6 ml). After the reaction mixture was allowed to stand for 16 hr or 0.5 hr, respectively, ice–water (16 ml) was added. The white solid was collected (0.33 g) and recrystallized from ethyl acetate to afford 0.27 g of glistening needles, mp 155.8–156.8°; the spectrum of alcohol **3** was identical with that already described in the preceding experiment.

Method B.—Lithium aluminum hydride (55 mg) was added to a solution of lactone 1 (43 mg) in tetrahydrofuran (5 ml). After standing at room temperature for approximately 1 week, the gray gelatinous mass was treated with ice–water (5 ml). The solid was collected, washed with diluted hydrochloric acid, and recrystallized from ethyl acetate. Glistening needles (25 mg), mp 156–157°, were obtained having identical tlc and spectra with that product obtained by method A.

Lanostanyl Neopentyl Ether (6a).—A 2.40-g specimen of 3β-pivaloxy-5α-lanostane (5) was made in quantitative yield from the reaction of 3β-hydroxy-5α-lanostane with pivaloyl chloride in tetrahydrofuran–pyridine: mp 186–188° (colorless needles from ethyl acetate); ν_{max} 1720 (sharp) and 1160 cm^{-1}; pmr δ 4.47 (hump, 1 p, C-3 axial hydrogen), and 1.23 (s, 9 p, pivalate methyls).

Anal. Calcd for $C_{35}H_{62}O_2$: C, 81.65; H, 12.14. Found: C, 81.70; H, 11.90.

A closed vessel containing a solution composed of ester **5** (0.69 g, 1.33 mmol), tetrahydrofuran (3.6 ml), and diborane–tetrahydrofuran (5.0 ml) was allowed to stand at room temperature for 3 days. Methanol (40 ml) was added and solvent was evaporated. Preparative thin layer chromatography using ligroin (bp 60–90°) as mobile phase and elution of the lower zone with ether gave 53 mg (9%) of 3β-hydroxy-5α-lanostane. Elution of the upper zone with ether yielded 0.53 g (79%) of ether **6a**: mp 183.0–184.0 (needles); ν_{max} (0.1 *M* in chloroform) 2960, 1470 (med), 1370, and 11.08 cm^{-1} (str); pmr δ 3.25 (d, 1 p, J = 8 Hz), 2.84 (d, 1 p, J = 8 Hz), 2.62 (hump, 1 p, 3α-H), 0.83 (large peak), and 0.78 (peak); mass spectrum 373 (100%) and M^+ 500 (2.5%).

Anal. Calcd for $C_{35}H_{64}O$ (500): C, 83.93; H, 12.88. Found: C, 84.22; H, 13.00.

4-Oxa-14α-methyl-5β-cholestane (8a). Method A. From Lactone 7.—A mixture of δ-lactone 7[20] (0.20 g, 0.5 mmol), tetrahydrofuran (2 ml), boron trifluoride etherate (2 ml, 16 mmol), and sodium borohydride (90 mg, 2.3 mmol) was allowed to stand until evolution of gas subsided. Diglyme (2 ml) was added and the mixture was allowed to stand at room temperature for 30 min. The mixture was heated at reflux for 2 hr, cooled, and treated with water (3 ml) followed by saturated sodium carbonate. Ether (12 ml) was added and the ethereal layer was washed with water (20 ml) and saturated sodium chloride (20 ml). Solvent was removed, and the residue was separated by preparative thin layer chromatography (benzene mobile phase and elution of uppermost zone with ether) to give 0.15 g (75%) of an oil which crystallized as needles upon storage under reduced pressure: mp 53–59°; ν_{max} (neat) 2960, 1460, 1370, 1090, and 1020 cm^{-1}; pmr δ 4.04 (crude doublet, J = 12 Hz, 1 p, 3α-H), 3.50 (doublet, J = 12 Hz, 1 p, 3β-H), 3.10 (peak, 1 p, 5β-H), 0.93 (s, C-19), 0.88 (s), 0.83 (s) and 0.80 (s); mass spectrum M^+ 388.3717 (100%; Beynon calculated mass 388.3705).

Anal. Calcd for $C_{27}H_{48}O$: C, 83.43; H, 12.45. Found: C, 83.22; H, 12.02.

Method B. From Acetal 8b.—A solution of lactone **7** (0.40 g, 1.0 mmol), tetrahydrofuran (2 ml), and diborane–tetrahydrofuran solution (1.4 ml) was allowed to stand at room temperature for 30 min. The reaction mixture was treated with methanol (10 ml) and concentrated to dryness. A solution of the residue in ethyl acetate–chloroform was filtered (Filter aid) and the solvent was removed to yield 0.40 g of hemiacetal **8b** as a colorless solid: mp 124–134°; ν_{max} (KBr) 3450, 2960, 1460, 1370, 1010, and 930 cm^{-1}; pmr δ 5.36 (peak, 0.5 p, equatorial 3α-H), 4.57 (hump, 0.5 p, axial 3β-H), 3.30 (peak, 1 p, 5β-H), 0.83 (m, 18 p, methyl); mass spectrum 371 (100%), M^+ − 15 (86%), and M^+ 404 (9%).

Anal. Calcd for $C_{27}H_{48}O_2$ (404.7): C, 80.14; H, 11.96. Found: C, 79.99; H, 11.88.

A solution of hemiacetal **8b** (0.12 g) in methanol (15 ml) containing 1 drop of concentrated hydrobromic acid was allowed to stand at room temperature for 2 days. The reaction mixture was concentrated, and the residue was purified by preparative thin layer chromatography using benzene–petroleum ether (bp 30–60°) (5:1) as mobile phase. Elution (ether) of the upper zone yielded 58 mg of the epimeric methyl acetals as an oil: ν_{max} (neat) 2960, 1460, 1370, 1120, 1060, and 1010 cm^{-1}; pmr δ 4.74 (peak, 0.7 p, equatorial 3α-H), 4.30 (hump, 0.3 p, axial 3β-H), 3.58 (peak, 1 p, 5β-H), 3.47 (s, 0.9 p, 3α-methoxy), 3.35 (s, 2.1 p, 3β-methoxy), and 0.83 (m, 18 p).

A mixture of hemiacetal **8b** (0.23 g), tetrahydrofuran (2.5 ml), boron trifluoride etherate (2 ml), and sodium borohydride (90 mg) was allowed to stand at room temperature for 20 min. Diglyme (2 ml) was added and 30 min later the mixture was heated at reflux for 1.5 hr and cooled. After adding water, saturated sodium carbonate, and ether (30 ml in three aliquots)

(19) J. S. E. Holker, W. R. Jones, and P. J. Ramm, *J. Chem. Soc. C*, 357 (1969).

(20) G. R. Pettit and J. R. Dias, *Can. J. Chem.*, **47**, 1091 (1969).

the ethereal extract was washed with water and saturated sodium chloride solution. The ether was removed and the yellow oil was separated by preparative thin layer chromatography using benzene as mobile phase. Elution of the upper zone with ether yielded 0.10 g (44%) of oil which solidified during several days storage in a vacuum desiccator. The needles, mp 53–60°, obtained were identical[21] with a specimen of ether **8a**.

3β-Hydroxy-17a-oxa-*D*-homo-5α-androstane (10a).[3a] **Method A. From Lactone 9.**—Sodium borohydride (0.28 g, 7 mmol) was added to a mixture of lactone **9** (0.47 g, 1.5 mmol), tetrahydrofuran (5 ml), and boron trifluoride etherate (6 ml, 48 mmol). After generation of gas terminated and 0.5 hr elapsed, diglyme (5 ml) was slowly (to prevent frothing) added. After standing at room temperature for 28 hr methanol (10 ml) was added and solvent was concentrated to 5 ml. Water (50 ml) was added to the suspension, and the brown solid was collected. Preparative thin layer chromatography (with 45:45:10 benzene–ethyl acetate–methanol) and elution of the upper zone with ether gave 0.20 g (44%) of ether **10a** as a granular white solid: mp 182.5–185.0°; ν_{max} (KBr) 3450 (sharp), 2960, 1440, 1380, and 1080 cm^{-1}; pmr δ 3.67 (m, 3 p, 3α proton and C-17), 2.22 (s, 1 p, removed by D_2O), 1.15 (s, 3 p, C-19), and 0.76 (s, 3 p, C-18); mass spectrum M$^+$ 292 (8%).

Method B. From Acetal 10b.—A solution of hemiacetal **10c**[22] (0.56 g) contaminated with glycol **12** in absolute methanol (25 ml) containing 1 drop of concentrated hydrobromic acid was allowed to stand for 48 hr. The reaction mixture was concentrated, and the residue was purified by preparative thin layer chromatography with benzene–ethyl acetate–methanol (45:45:10). Upon elution (ether) of the upper zone 0.38 g of the epimeric methyl acetals **10b** was obtained as colorless needles: mp 115–125° (clearing at 190–200°); ν_{max} (KBr) 3500 (med), 2960, 1450, 1380, 1130, and 1070 cm^{-1}; pmr δ 4.68 (peak, 0.7 p, equatorial 17α-H), 3.59 (hump, 1.3 p, axial 3α-H and 17β-H), 3.45 (s, 2 p, 17α-methoxy), 3.38 (s, 1 p, 17β-methoxy), 1.15 (s, 3 p, C-19), and 0.78 (s, 3 p, C-18); mass spectrum 215 (100%), 234 (57%), M$^+$ − 32 (56%, loss of methanol), M$^+$ − 15 (3%), M$^+$ 322 (0.1%).

Anal. Calcd for $C_{20}H_{34}O_3$ (322.5): C, 74.49; H, 1063. Found: C, 74.37; H, 10.69.

Elution (ether) of the lower zone gave 0.10 g of glycol **12** as prisms: mp 224–226° (from ethyl acetate–methanol); ν_{max} (KBr) 3350 (broad and strong), 2960, 1440, 1370, 1340, 1150, 1080, 1040, and 940 cm^{-1}; pmr (DMSO-d_6) δ 3.59 (m, 6 p, partially removed by D_2O), 0.97 (s, 3 p, C-19), and 0.71 (3, 3 p, C-18); mass spectrum 221 (100%), M$^+$ − 33 (58%), M$^+$ − 18 (28%), M$^+$ − 15 (39%), M$^+$ 310 (33%).

Anal. Calcd for $C_{19}H_{34}O_3$ (310.5): C, 73.50; H, 11.04. Found: C, 73.62; H, 10.58.

Sodium borohydride (0.28 g, 7 mmol) was added to a solution of 3-methyl acetal **10b** (0.50 g, 1.5 mmol) in tetrahydrofuran (5 ml)–boron trifluoride etherate (6 ml, 48 mmol). After 0.5 hr diglyme (5 ml) was added and the solution was allowed to stand at room temperature for 32 hr. Methanol (10 ml) and then water (20 ml) were added and the white solid was collected. Preparative thin layer chromatography (45:45:10 benzene–ethyl acetate–methanol) and ether elution of the uppermost zone gave 0.21 g (47%) of ether **10a**, mp 182.0–183.5° (platelets from ethyl acetate).[21]

3β,17-Dihydroxy-17a-oxa-*D*-homo-5α-androstane (10c).[22]—Diborane–tetrahydrofuran (4.3 ml, approximately 1 mol equiv) was allowed to react with lactone **9** (1.23 g) in tetrahydrofuran (5 ml) for 0.5 hr at room temperature. To the clear gel was added methanol. Evaporation of solvent gave 1.23 g of a mixture corresponding to hemiacetal **10c** containing some glycol **12** (estimated to be 18% as evidenced by a less mobile spot on tlc). This colorless, crystalline material gave mp 159–194°; ν_{max} (KBr) 3400 (str and broad), 2930, 1440, 1370, 1120, 1070, 1030, and 950 cm^{-1}; pmr ($CDCl_3$–DMSO-d_6) δ 5.00 (peak, 1.5 p, equatorial 17α-H), 3.59 (hump, 1.5 p, axial 3α-H and 17β-H), 1.15 (s, 3 p, C-19), and 0.77 (s, 3 p, C-18).

3,3-Dideuterio-4-oxa-4aα,14α-dimethyl-*A*-homo-5α-cholestane (2b).—The experiment described above for obtaining ether **2a** was repeated using sodium borodeuteride instead of sodium borohydride. Separation by preparative thin layer chromatography using benzene–ethyl acetate (20:1) as mobile phase and ether for final elution led to 86 mg (41%) of ether **2b** as colorless plates: mp 69.8–70.8°; ν_{max} (KBr) 2940, 2090 (vw C–D stretch), 1450 (med), 1360 (med), and 1160 (med); pmr 212 (m, 1 p, C-4a), 73 (s), 66 (s), 56 (s), and 49 Hz (s); mass spectrum 235 (100%), M$^+$ − 15 (29%), M$^+$ 418 (33%). Elution of the lower band yielded 73 mg of glycol as needles: mp 156.9–157.8°; ν_{max} (KBr) 3380 (broad), 2940, 2080 (vw C–D stret), 1450 (med), 1360 (med), 1070 (w), and 1050 cm^{-1} (w); pmr δ 4.05 (m, 1 p, C-4a), 2.48 (s, 2 p, OH), 1.18 (s), 1.08 (s), 0.93 (s), and 0.83 (broad s); M$^+$ − 2 434.

1,1-Dideuterioneopentyl Lanostanyl Ether (6b).—Sodium borodeuteride (0.18 g, 4.6 mmol) was added to a chilled suspension of ester **5** (0.50 g, 1.0 mmol) in tetrahydrofuran (2 ml)–boron trifluoride etherate (4 ml, 36 mmol). Diglyme (4 ml) and more tetrahydrofuran (2 ml) were added. After heating at reflux for 2 days, the reaction mixture was treated with saturated sodium bicarbonate (20 ml) and extracted with ether (two 30-ml portions). The ethereal extract was concentrated and the solid residue was chromatographed using silica gel (50 g of 0.2–0.5 mm). Elution with ligroin (200 ml, bp 60–90°) gave 0.34 g (70%) of ether **6b** as colorless needles: mp 178–182°; ν_{max} (0.1 *M* in chloroform) 2960, 2160 (vw C–D stretch), 2060 (vw C–D stretch), 1470 (med), 1370, and 1126 cm^{-1} (str); pmr δ 2.62 (hump, 1 p, 3α-H), 0.92 (large peak), and 0.78 (peak); mass spectrum 373 (100%), M$^+$ 502 (3%).

Further elution with benzene yielded 0.15 g (29%) of recovered starting ester **5**.

3β-Hydroxy-17a-oxa-*D*-homo-5α-androst-16-ene (11). Diborane–tetrahydrofuran (2.5 ml) was added to a solution of lactone **9** (735 mg, 2.4 mmol) in tetrahydrofuran (4.2 ml). When the vitreous gel became fluid (2 to 4 days), methanol (20 ml) was added and the solvent was concentrated. The residue was purified by preparative thin layer chromatography using ligroin (bp 60–110°)–ethyl acetate (5:7) as mobile phase. Ether elution of the second uppermost zone yielded 60 mg (8%) of saturated ether **10a**. Elution of the uppermost zone gave 0.36 g (52%) of vinyl ether **11** as a glassy substance, mp 98–102° (pure by tlc and pmr). Recrystallization from aqueous acetone yielded colorless needles: mp 144–147°; ν_{max} (KBr) 3400, 2940, 1635 (med vinyl ether C = C stretch), 1440, 1370, 1210, 1080, 1050, and 870 cm^{-1}; pmr δ 6.24 (d, 1 p, J = 6 Hz, C-17), 4.65 (crude t, 1 p, C-16), 3.60 (hump, 1 p, 3α-H), 1.13 (s, 3 p, C-19), and 0.78 (s, 3 p, C-18); mass spectrum 215 (100%), M$^+$ 290 (72%).

Anal. Calcd for $C_{19}H_{30}O_2$ (290.5): C, 78.57; H, 10.41. Found: C, 78.67; H, 10.36.

3β-Hydroxy-17a-oxa-*D*-homo-5α-androstane (10a) from Reaction of Diborane–Tetrahydrofuran with 3β-Hydroxy-17-oxo-17a-oxa-5α-androstane (9).—A tetrahydrofuran solution (2.1 ml) of lactone **9** (0.52 g, 1.7 mmol) was treated with diborane–tetrahydrofuran (1.8 ml) at room temperature for 0.5 hr. The clear gel was broken and more diborane–tetrahydrofuran (3.6 ml) was added. When the reaction mixture became fluid (2 to 4 days) methanol was added (20 ml) and the solvent was concentrated. Preparative thin layer chromatography of the colorless oily residue using ligroin (bp 60–100°)–ethyl acetate (5:7) as mobile phase yielded 0.28 g (55%) of ether **10c**[20] from the uppermost band (ether elution), mp 183.5–185.0° (prisms from ligroin–ethyl acetate).

Registry No.—**1**, 31656-58-3; **2a**, 31705-57-4; **2b**, 31705-58-5; **3**, 31659-48-0; **5**, 31659-49-1; **6a**, 28414-91-7; **6b**, 31659-51-5; **8a**, 21857-93-2; **8b**, 31659-53-7; **8b** (α-methyl acetal), 31659-54-8; **8b** (β-methyl acetal), 31656-59-4; **10a**, 6947-41-7; **10b**, 31659-56-0; **10c**, 31659-57-1; **11**, 28414-87-1; **12**, 31705-59-6; diborane, 19287-45-7.

(21) The mutual identity of both specimens was confirmed by mixture melting point determination, comparison of infrared and pmr spectra, and tlc behavior.

(22) G. R. Pettit, T. R. Kasturi, B. Green, and J. C. Knight, *J. Org. Chem.*, **26**, 4773 (1961).

Synthesis of 2-Dialkylamino-6- and -7-hydroxy-5,8-dioxoquinolines[1a]

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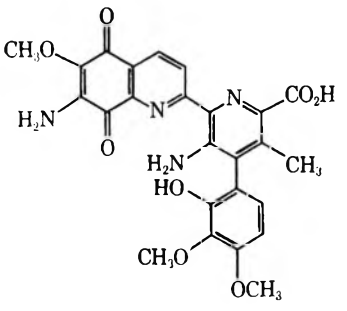
A synthetic route to 2-substituted 6- and -7-hydroxy-5,8-dioxoquinolines has been evaluated. Reaction of 5,7-dinitro-8-hydroxycarbostyril (4) with phosphorus oxychloride followed by reaction with piperidine or morpholine gave the 2-substituted 5,7-dinitro-8-quinolinols 5d and 5e. Catalytic hydrogenation, oxidation, and acid hydrolysis gave the corresponding 7-hydroxy-5,8-dioxoquinolines 9a and 9b. A similar sequence was used to proceed from 5-hydroxy-6,8-dinitrocarbostyril (12) *via* 2-chloro-6,8-dinitro-5-quinolinol (13a) and 2-piperidino-6,8-dinitro-5-quinolinol (13b) to 2-piperidino-6-hydroxy-5,8-dioxoquinoline (14a).

The potential importance of the antibiotic and antitumor agent streptonigrin (1) suggested an extension of our earlier study of the 6- and 7-hydroxy-5,8-dioxocarbostyrils[2] to preparation of 2-aminoquinolinequinones. Introduction of a secondary amine appeared relatively easy and could be expected to improve the solubility of such quinones. Even more desirable[3] would be elaboration of two isomeric quinolinequinones bearing 6-methoxy-7-amino or 6-amino-7-methoxy groups, but this objective, as noted in the sequel, was not realized.

In an extension of earlier work,[2] quinone 2 was readily brominated to give bromoquinone 3. All attempts to



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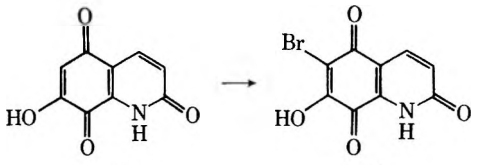
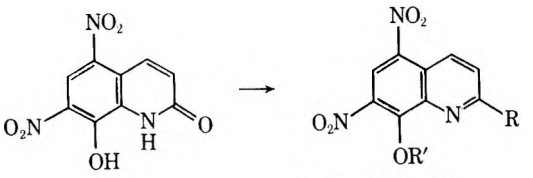


2 3

displace the bromo group with amines or azide ion were unsuccessful.[4] Attempts to form a methoxyquinone using either diazomethane or the Fischer esterification method were similarly unsuccessful with either quinone 2 or 3. Also, once the quinone was elaborated, transformations at the 2 position became more difficult. Thus, modification of the 2 position at an earlier stage of the synthesis was undertaken.

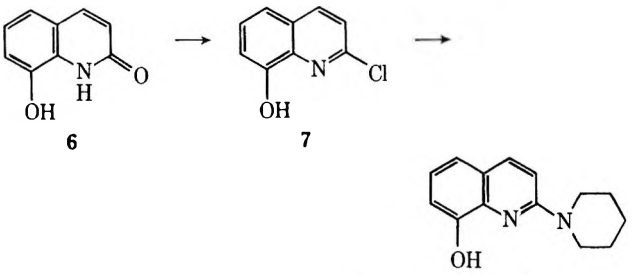
To provide a reactive group at the 2 position, 5,7-dinitro-8-hydroxycarbostyril (4) was treated with phosphorus oxychloride to afford the dinitrophenol 5a. Reaction of phenol 5a or the ammonium salt 5b with excess piperidine under mild conditions led to the piperidine salt 5c. After prolonged heating, amine 5d was



4

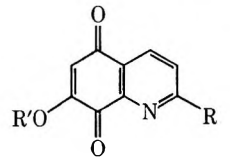
5a, R = Cl; R′ = H
b, R = Cl; R′ = NH_4^+
c, R = Cl; R′ = piperidinium
d, R = piperidino; R′ = H
e, R = morpholino; R′ = H

was obtained. An alternate synthesis of amine 5d was needed[5] to confirm the structure. Thus, 8-hydroxycarbostyril (6) was heated with phosphorus oxychloride to yield 2-chloro-8-quinolinol (7). Nitration led to quinoline 5b, while heating 7 with piperidine (→8) followed by nitration led to amine 5d. This route to amine 5d proved less convenient experimentally.



6 7 8

5d
5e



9a, R = piperidino; R′ = H
b, R = morpholin; R′ = H
c, R = piperidino; R′ = CH_3
d, R = morpholino; R′ = CH_3

Conversion of quinoline 5d to quinone 9a required considerable experimentation. Although we had isolated several amine derivatives of the nitro group precursor in the case of 7-hydroxy-5,8-dioxocarbostyril (2),[2] the corresponding intermediate from reduction of

(1) (a) This study received support from the U. S. Medical R and D Command under Contract DA-49-143-MD-3010 and National Science Foundation Grant GB-4939. The present manuscript is Contribution No. 930 from the Army Research Program on Malaria. (b) National Science Foundation Predoctoral Fellow, 1965–1968.

(2) G. R. Pettit, W. C. Fleming, and K. D. Paull, *J. Org. Chem.*, **33**, 1089 (1968).

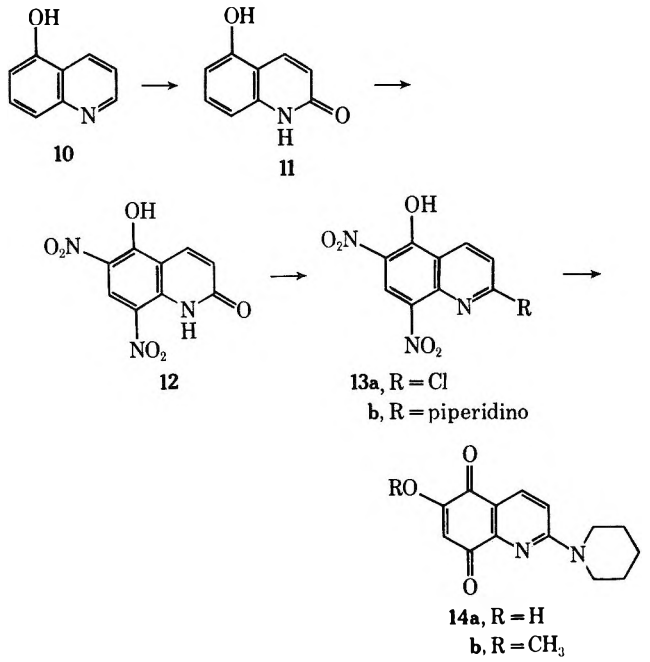
(3) For comments on the possible importance of the aminoquinone structure, see K. V. Rao, K. Bieman, and R. B. Woodward, *J. Amer. Chem. Soc.*, **85**, 2532 (1963).

(4) For an excellent example of the use of bromination to further substitute quinones, see T. K. Liao, W. H. Nyberg, and C. C. Cheng, *Angew. Chem., Int. Ed. Engl.*, **6**, 82 (1967).

(5) The conversion of 6,8-dinitro-5-quinolinol to 5-chloro-6,8-dinitroquinoline by phosphorus oxychloride–phosphorus pentachloride mixtures has been reported: G. M. Bennett and J. F. Grove, *J. Chem. Soc.*, 378 (1945).

nitroquinoline **5d** could not be isolated.[6] Instead, the overall conversion was more readily effected without isolation of intermediates. After catalytic reduction of dinitroquinoline **5d** in dilute acid, the solution was made basic. Oxygen was passed into the solution and a green color formed. Acidification yielded a purple solution which, upon continuous extraction with chloroform, led to a red extract containing quinone **9a**. Heat provided by the refluxing chloroform proved adequate to effect hydrolysis of the aminoquinone intermediate.[7] When morpholine was used in place of piperidine, the sequence proceeded as expected to give 2-(*N*-morpholino)-7-hydroxy-5,8-dioxoquinoline (**9b**).

Quinones **9a** and **9b** were readily methylated to provide ethers **9c** and **9d** using methanol and a trace of sulfuric acid.[8] Unfortunately, attempts to usefully brominate quinones **9a–d** were unsuccessful. Meanwhile, the general reaction sequence used to convert 8-quinolinol to 2-piperidino-7-methoxy-5,8-dioxoquinoline (**9c**) was applied to 5-quinolinol. With one exception, the synthesis proceeded essentially as expected to yield 2-piperidino-6-methoxy-5,8-dioxoquinoline (**14b**). We were unable to form the *N*-oxide of 5-quinolinol as required for a three-step conversion *via* rearrangement in acetic anhydride and hydrolysis to yield 5-hydroxycarbostyril (**11**). Fortunately, fusion of 5-quinolinol with potassium hydroxide gave excellent yields of carbostyril **11**.[9] In contrast to the much milder conditions required to obtain **4**, nitration of 5-hydroxyearbostyril required a mixture of nitric and sulfuric acids to obtain dinitroquinoline **12**.[10] Reaction with phosphorus oxychloride followed by prolonged heating with piperidine gave dinitroquinoline **13b**. After reduction of the nitro groups, conversion of amine **13b** to quinone **14a** required an oxidation step under acidic conditions. Under basic conditions a precipitate formed which apparently resisted oxidation. Oxidation and hydrolysis in hot dilute sulfuric acid gave quinone **14a**. Treatment of the hydroxyquinone **14a** with methanol and a trace of sulfuric acid gave methoxyquinone **14b**. The synthesis developed for obtaining 2-aminoquinolinequinones **9** and **14** appears to present a generally useful route to such substances. When an effective method becomes available for preparation of the corresponding 6- and 7-amine derivatives a more important assessment of streptonigrin structure–activity relationships will be possible. In keeping with this prospect none of the compounds described here and so far tested proved to be active in either antimalarial or antitumor screening.[11]



Experimental Section

Solvent extracts of aqueous solutions were dried over anhydrous sodium sulfate. All analytical samples exhibited a single spot on a thin layer chromatogram. Melting points were observed employing a Kofler melting point apparatus. Infrared (in potassium bromide using a Beckman IR-12 instrument), and proton magnetic resonance (Varian Associates, A-60 spectrometer, trifluoroacetic acid as solvent except where noted) measurements were performed by Miss K. Reimer. Chemical shifts (δ) are in parts per million relative to tetramethylsilane as external standard. Elemental microanalyses were provided by Dr. A. Bernhardt, Mikroanalytisches Laboratorium, 5251 Elbach über Engelskirchen, West Germany.

6-Bromo-7-hydroxy-5,8-dioxocarbostyril (3).—A sample of 7-hydroxy-5,8-dioxocarbostyril (0.25 g) was suspended in methanol (30 ml), and bromine (1.0 ml) was added slowly to the well-stirred solution. The solid rapidly dissolved. After stirring for 2 hr solvent was removed *in vacuo* leaving a red oil. Ethyl acetate (50 ml) was added, and the solvent was again evaporated. The dark solid which remained was dissolved in hot ethyl acetate–methanol and diluted (after filtration) with Skellysolve B until a cloudiness appeared. On cooling a red solid separated (0.19 g, 56%) which decomposed with partial melting above 270°. Another recrystallization by the above procedure gave an analytical sample as a red powder decomposing above 270°: ν_{max} 1685, 1656, 1630, 1602, 1424, 1360, 1297, 1196, 1052, and 697 cm^{-1}; pmr δ 6.70 (d, 1 H, J = 9 Hz) and 8.00 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_9H_4BrNO_4$: C, 40.04; H, 1.48; Br, 29.59; N, 5.18. Found: C, 39.92, 39.98; H, 1.74, 1.86; Br, 29.73; N, 5.26.

2-Chloro-5,7-dinitro-8-hydroxyquinoline Ammonium Salt (5b). Method A.—A mixture of 5,7-dinitro-8-hydroxycarbostyril (1.0 g, **6a**) and phosphorus oxychloride (10 ml) was heated (steam bath) for 2 hr. The solution was poured carefully onto ice (100 g) and concentrated ammonium hydroxide (50 ml) and the solid which formed was collected, yield 1.0 g (88%) of yellow powder melting at 230–237°. Two sublimations gave a pure specimen melting at 233–236°: ν_{max} 1590, 1565, 1518, 1396, 1320, 1270, and 755 cm^{-1}; pmr δ 5.50 (t, 3 H, J = 55 cps), 6.85 (d, 1 H, J = 9 Hz), 8.13 (s, 1 H), and 8.25 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_9H_7ClN_4O_5$: C, 37.71; H, 2.46; Cl, 12.37; N, 19.55. Found: C, 37.82; H, 2.25; Cl, 12.65; N, 19.68.

Method B.—A finely powdered sample of 2-chloro-8-hydroxyquinoline (0.2 g) was suspended in water (25 ml)–concentrated nitric acid (25 ml). The quinoline dissolved; a yellow precipitate formed and then dissolved. The solution was heated on a steam bath for 10 min, cooled, and made basic with concentrated ammonium hydroxide. A greenish yellow solid separated, which was collected and recrystallized from methanol–water to give a yellow powder melting at 240–245°. Sublimation gave a yellow powder melting at 233–236°. The infrared spectrum was identical with that of salt **5b** prepared by method A.

2-Chloro-5,7-dinitro-8-hydroxyquinoline (5a).—A sample of 2-chloro-5,7-dinitro-8-hydroxyquinoline ammonium salt (1.0 g) was recrystallized from ethanol–water containing 6 *N* hydrochloric acid (5 ml). On cooling, 0.84 g (89%) of yellow solid melting at 140–145° separated. Three recrystallizations from

(6) An exception was the isolation of 2-chloro-5,7-diacetamido-8-quinolinol after reductive acetylation of **5a**. No method could be found to convert **5a** to a quinone.

(7) Y. T. Pratt and N. L. Drake, *J. Amer. Chem. Soc.*, **79**, 5024 (1957).

(8) Y. T. Pratt and N. L. Drake, *ibid.*, **77**, 37 (1955).

(9) E. Lellman, *Ber.*, **20**, 2172 (1887).

(10) For an alternate synthesis of **12**, see J. N. Ashley, W. H. Perkins, and R. Robinson, *J. Chem. Soc.*, 382 (1930).

(11) Screening was performed under auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, and the U. S. Medical R and D Command.

ethanol–water gave the analytical sample as a yellow powder melting at 143–145°: ν_{max} 1588, 1526, 1413, 1360, 1322, 1260, 1100, 961, and 746 cm^{-1}; pmr δ 6.85 (d, 1 H, J = 9 Hz), 8.13 (s, 1 H), and 8.25 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_9H_4ClN_3O_5$: C, 40.09; H, 1.50; Cl, 13.15; N, 15.59. Found: C, 40.14; H, 1.65; Cl, 13.07; N, 15.42.

2-Chloro-5,7-dinitro-8-hydroxyquinoline Piperidinium Salt (5c).—A mixture of 5,7-dinitro-8-hydroxycarbostyril (6a, 0.5 g) and phosphorus oxychloride (10 ml) was heated (steam bath) for 1 hr. Excess phosphorus oxychloride was removed *in vacuo*, and piperidine (5 ml) in tetrahydrofuran (25 ml) was cautiously added, followed by water (100 ml). Cooling led to 0.5 g (81%) of yellow crystals melting at 205–210°. Three recrystallizations from ethanol–water gave an analytical sample as tiny yellow needles melting at 211–213°: ν_{max} 1612, 1579, 1504, 1400, 1306, and 1274 cm^{-1}; pmr δ 1.30–1.55 (broad m, 4 H), 7.55 (d, 1 H, J = 9 Hz), 8.90 (s, 1 H), and 8.95 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{14}H_{15}ClN_4O_5$: C, 47.40; H, 4.26; Cl, 9.99; N, 15.79. Found: C, 47.75; H, 4.13; Cl, 9.83; N, 15.82, 15.72.

2-(*N*-Piperidino)-5,7-dinitro-8-hydroxyquinoline (5d). Method A.—A mixture of 5,7-dinitro-8-hydroxycarbostyril (1.0 g) and phosphorus oxychloride (10 ml) was heated at steam bath temperature for 1 hr. Excess phosphorus oxychloride was removed *in vacuo*. Tetrahydrofuran (20 ml) and piperidine (30 ml) in water (100 ml) were added. The solution was heated at reflux for 36 hr, tetrahydrofuran was distilled, and the mixture was acidified with concentrated hydrochloric acid. After cooling, the crude product (melting at 260–265°) separated and one recrystallization from tetrahydrofuran–water gave 1.03 g (81%) of yellow needles melting at 263–265°. Three recrystallizations from the same solvent afforded an analytical sample: yellow needles; mp 263–265°; ν_{max} 3215, 2960, 1650, 1610, 1528, 1330, 1273, 1242, 1174, and 751 cm^{-1}; pmr δ 0.95–1.25 (broad m, 6 H), 2.95–3.30 (broad m, 4 H), 6.95 (d, 1 H, J = 10 Hz), 7.75 (s, 1 H), and 7.88 (d, 1 H, J = 10 Hz).

Anal. Calcd for $C_{14}H_{14}N_4O_5$: C, 52.83; H, 4.43; N, 17.60. Found: C, 52.91; H, 4.52; N, 17.30.

Method B.—A sample of 2-piperidino-8-hydroxyquinoline (0.2 g) was suspended in water (25 ml). Concentrated nitric acid (25 ml) was added slowly and the resulting solution was allowed to stand for 15 min. After concentrated ammonium hydroxide was added, the precipitate which formed was collected and recrystallized twice from tetrahydrofuran–water to give a yellow powder melting at 260–265°. The product was identical by infrared spectral comparison with quinoline 5d prepared by method A.

2-Chloro-8-hydroxyquinoline (7).—A mixture of 8-hydroxycarbostyril (2.0 g) and phosphorus oxychloride (10 ml) was heated on a steam bath for 1 hr. The resulting solution was poured slowly onto ice (100 g) and concentrated ammonium hydroxide (50 ml). A white solid formed and was removed by filtration. The solid melted at 270–280° and proved nearly insoluble in a variety of organic solvents, but dissolved readily in concentrated hydrochloric acid (100 ml). After heating for 1 hr at steam-bath temperature, the acid solution was cooled and made basic with concentrated ammonium hydroxide. A white precipitate formed and was collected, yield 1.44 g (67%) of solid melting at 80–83°. Three recrystallizations from methanol–water gave a pure sample of colorless needles melting at 82–83° (lit.[12,13] mp 63–64°): ν_{max} 1575, 1502, 1464, 1374, 1365, 1318, 1241, 1206, 1123, 1085, 832, 750, and 718 cm^{-1}; pmr δ 6.30–6.75 (broad m, 3 H), 6.80 (d, 1 H, J = 9 Hz),[14] and 7.80 (d, 1 H, J = 9 Hz).

Anal. Calcd for C_9H_6ClNO: C, 60.19; H, 3.34; Cl, 19.77; N, 7.80. Found: C, 60.33; H, 3.43; Cl, 19.77; N, 8.00.

2-(*N*-Piperidino)-8-hydroxyquinoline (8).—A solution composed of 2-chloro-8-hydroxyquinoline (0.5 g), piperidine (10 ml), and dioxane (100 ml) was heated at reflux for 48 hr. Although thin layer chromatography (chloroform mobile phase) indicated only starting material, colorless crystals were observed separating from solution. Most of the solvent was evaporated *in vacuo* and water (100 ml) was added. The resulting solution was extracted with chloroform (two 50-ml portions) and the extract was washed with 6 *N* hydrochloric acid (two 30-ml portions). The acid solution was treated with Norit-A, filtered, and made basic with concentrated ammonium hydroxide and, on cooling, an oil slowly separated. The aqueous solution was carefully decanted and the oil was crystallized from methanol–water to give an oily, dark solid. A second recrystallization gave 0.29 g (46%) of tan crystals melting at 68–70°. Two more recrystallizations from methanol–water gave an analytical sample as clear plates melting at 71–73°: ν_{max} 3350, 2940, 2860, 1640, 1615, 1575, 1523, 1482, 1450, 1422, 1336, 1282, 1260, 1242, 1131, 828, 749, 742, and 572 cm^{-1}; pmr δ 1.30–1.60 (m, 6 H), 3.30–3.60 (m, 4 H), 6.82 (partially obscured d, 1 H, J = 9 Hz), 6.95 (narrow m, 3 H), and 7.83 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.50; H, 7.19; N, 12.24.

2-(*N*-Morpholino)-5,7-dinitro-8-hydroxyquinoline (5e).—A mixture of 5,7-dinitro-8-hydroxycarbostyril (1.0 g) and phosphorus oxychloride (10 ml) was heated (steam bath) for 1 hr. Excess phosphorus oxychloride was removed *in vacuo*. The residue was diluted with dioxane (50 ml) and cooled, and a solution of morpholine (20 ml) in water (100 ml) was added. The solution was heated at reflux for 36 hr, cooled, and acidified with concentrated hydrochloric acid. The solid which separated was collected, yield 1.13 g (79%) of yellow powder melting at 274–277°. Three recrystallizations from tetrahydrofuran–water gave a pure sample as tiny yellow needles melting at 280–283°: ν_{max} 1610, 1577, 1523, 1436, 1360, 1310, 1270, 1110, 1013, 918, 811, and 735 cm^{-1}; pmr δ 3.70 (apparent singlet, 8 H), 7.35 (d, 1 H, J = 10 Hz), 8.65 (s, 1 H), and 8.85 (d, 1 H, J = 10 Hz).

Anal. Calcd for $C_{13}H_{12}N_4O_6$: C, 48.75; H, 3.78; N, 17.50. Found: C, 49.18; H, 3.99; N, 17.08.

2-(*N*-Piperidino)-7-methoxy-5,8-dioxoquinoline (9c).—A mixture of 2-(*N*-piperidino)-5,7-dinitro-8-hydroxyquinoline (0.3 g), water (100 ml), 6 *N* hydrochloric acid (5 ml), and 10% palladium-on-carbon catalyst (0.03 g) was stirred under a slightly positive pressure of hydrogen for 18 hr. The solution was filtered and made slightly basic with sodium bicarbonate, and oxygen was bubbled slowly through the solution for 20 min. A dark green color formed, which changed to purple on addition of concentrated sulfuric acid (10 ml). The solution was placed in an insulated continuous extraction apparatus and extracted with chloroform for 5 hr. The deep red chloroform solution was replaced with a fresh portion of chloroform, and the mixture was extracted for an additional 18 hr. Extraction of the combined chloroform extract with saturated sodium bicarbonate solution (two 40-ml portions) gave a blue-green extract. The basic extract was acidified with 6 *N* hydrochloric acid and extracted with ethyl ether (125 ml) to give a bright orange solution, which was concentrated to a red solid.[15] A solution of the latter material in ether (20 ml) was filtered, cyclohexane (20 ml) was added, and the solution was concentrated until a precipitate started to form. After cooling, the dark solid which separated was recrystallized twice from ether–hexane to give a sample suitable for spectral data, but satisfactory elemental analyses were not obtained. Such specimens decomposed above 200° without melting, and appeared to decompose slowly to a colorless powder when heated in solvents. The quinone exhibited ν_{max} 3420, 3260 (broad), 1694, 1655, 1630, 1599, 1503, 1383, and 1199 cm^{-1}; pmr δ 1.35–1.65 (broad m, 6 H), 3.35–3.65 (broad m, 4 H), 6.12 (s, 1 H), 7.20 (d, 1 H, J = 10 Hz), and 8.03 (d, 1 H, J = 10 Hz).

A sample of crude 2-(*N*-piperidino)-7-hydroxy-5,8-dioxoquinoline prepared from 0.3 g of 2-(*N*-piperidino)-5,7-dinitro-8-hydroxyquinoline was dissolved in methanol (50 ml). Concentrated sulfuric acid (3 drops) was added, and the solution was heated at reflux for 1 hr. The solution was concentrated to about 20 ml, diluted with water (180 ml), and extracted with ethyl ether (two 75-ml portions). The ether solution was washed (two 50-ml portions) with saturated sodium bicarbonate solution and concentrated to give 0.14 g (55% overall from nitro quinoline 5d) of a red powder melting at 150–170°. Two recrystallizations from ether–cyclohexane gave an analytical sample as tiny red needles melting at 178–180°: ν_{max} 2930, 1705, 1652, 1627, 1591, 1514, 1424, 1244, 1056, 972, and 825 cm^{-1}; pmr ($CDCl_3$) δ 1.55–1.85 (broad m, 6 H), 3.55–3.85 (broad m,

(12) M. Hamana and K. Funakoshi, *Yakugaku Zasshi*, **84**, 28 (1964); *Chem. Abstr.*, **61**, 3068*f* (1964).

(13) This compound is mentioned without details in U. S. Patent 2,524,725 (1950); *Chem. Abstr.*, **45**, 3272*f* (1951).

(14) The assignment must be considered tentative, since the doublet is partially obscured by the broad multiplet.

(15) The product obtained at this stage was suitable for conversion to the more stable 2-piperidino-7-methoxy-5,8-dioxoquinoline.

4 H), 3.90 (s, 3 H), 6.05 (s, 1 H), 6.85 (d, 1 H, J = 9 Hz), and 8.05 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.16, 66.27; H, 5.89, 5.92; N, 10.82.

2-(*N*-Morpholino)-7-methoxy-5,8-dioxoquinoline (9d).—A mixture of 2-(*N*-morpholino)-5,7-dinitro-8-hydroxyquinoline (0.3 g), water (50 ml), 6 *N* hydrochloric acid (5 ml), and palladium-on-carbon catalyst (0.03 g) was stirred under slightly positive pressure of hydrogen for 12 hr. The product was treated and isolated by the continuous extraction procedure summarized for obtaining quinone **9a**. The ethyl acetate (150 ml) extract was concentrated to a red powder decomposing with partial melting above 200°.[16] Two recrystallizations from tetrahydrofuran–cyclohexane gave a red powder decomposing at 200–210° with partial melting. This material did not give satisfactory elemental analyses, but spectral data were in good agreement with the assigned structure: ν_{max} 1701, 1654, 1595, 1505, 1327, 1255, 1115, and 945 cm^{-1}; pmr δ 3.70 (apparent singlet, 8 H), 6.12 (s, 1 H), 7.30 (d, 1 H, J = 10 Hz), and 8.15 (d, 1 H, J = 10 Hz).

A crude sample of 2-(*N*-morpholino)-7-hydroxy-5,8-dioxoquinoline (prepared from 0.3 g of 2-morpholino-5,7-nitro-8-hydroxyquinoline) was dissolved in methanol (50 ml) and treated with concentrated sulfuric acid (2 drops) as described for the preparation of methyl ether **9c**. In this case ethyl acetate was employed for extraction. Concentration of the ethyl acetate led to 0.14 g (54% overall from 2-morpholino-5,7-dinitro-8-hydroxyquinoline) of red powder melting at 245–255°.

Two recrystallizations from methanol–ethyl acetate–cyclohexane gave a pure sample as tiny orange needles melting at 262–264°: ν_{max} 1702, 1643, 1620, 1591, 1506, 1415, 1262, 1241, 1116, 1056, 977, and 821 cm^{-1}; pmr ($CDCl_3$) δ 3.80 (apparent singlet, 8 H), 3.90 (s, 3 H), 6.05 (s, 1 H), 6.85 (d, 1 H, J = 9 Hz), and 8.15 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.40; H, 5.21; N, 10.04.

5-Hydroxycarbostyril (11).—A mixture of 5-hydroxyquinoline (3.0 g) and potassium hydroxide (20 g) was placed in a 50-ml stainless steel beaker and heated at 300°. The frothing black mixture was heated for 3 hr, when a clear black solution was obtained. The solution was cooled and dissolved in water (150 ml), and excess concentrated hydrochloric acid was added to give 2.70 g (81%) of tan powder melting at 300–340°. Three recrystallizations from methanol–water gave an analytical sample as straw-colored needles melting at 336–341° (lit.[10] mp 320° dec): ν_{max} 1651 (broad), 1620 (broad), 1553, 1436, 1360, 1289, 1257, 1143, and 792 cm^{-1}; pmr δ 6.30–7.30 (complex multiplet, 4 H), and 8.40 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69. Found: C, 66.88; H, 4.54; N, 8.62.

5-Hydroxy-6,8-dinitrocarbostyril (12).—A sample of 5-hydroxycarbostyril (1.0 g) was dissolved in concentrated sulfuric acid (10 ml). Then concentrated nitric acid (10 ml) was added slowly with cooling (ice bath). The resulting solution was maintained at 45° for 10 min. After cooling, the solution was poured slowly onto ice (150 g), and the yellow powder which separated was collected to give 1.4 g (89%) melting at 230–270°. Three recrystallizations from methanol–water gave a pure sample as yellow needles melting at 268–271° (transition from needles to cubes with partial melting between 240 and 250°, lit.[11] mp 260°): ν_{max} 3270, 1687, 1631, 1602, 1460, 1312, 1141, 1102, 1001, and 812 cm^{-1}; pmr δ 6.75 (d, 1 H, J = 10 Hz), 8.15 (d, 1 H, J = 10 Hz), and 9.05 (s, 1 H).

Anal. Calcd for $C_9H_5N_3O_6$: C, 43.04; H, 2.01; N, 16.73. Found: C, 43.06; H, 2.41; N, 16.85.

2-(*N*-Piperidino)-6,8-dinitro-5-hydroxyquinoline (13b).—A mixture of 5-hydroxy-6,8-dinitrocarbostyril (10 ml) was heated (steam bath) with phosphorus oxychloride (10 ml) for 1 hr. The solution was poured onto ice (200 g) with constant shaking, and the yellow solid which separated was collected to give 0.42 g (78%), mp 115–120°. Three recrystallizations from acetone–water gave the chloro derivative (presumed to be **13a**)[17] as yellow needles melting at 138–140°: ν_{max} 1598, 1545 (broad), 1350, 1292, 1120, and 791 cm^{-1}; pmr (acetone) δ 7.25 (d, 1 H, J = 9 Hz), 8.30 (s, 1 H), and 8.35 (d, 1 H, J = 9 Hz).

A solution of the product (**13a**, 0.3 g) in water (100 ml)–dioxane (20 ml)–piperidine (10 ml) was heated (reflux) for 24 hr. The dark solution was cooled, acidified with concentrated hydrochloric acid, and extracted (six 50-ml portions) with ethyl acetate.[18] Evaporation of solvent left a yellow oil which soon crystallized. The solid was triturated with hot acetone (20 ml) and water (40 ml). After cooling, the yellow residue was collected to yield 0.17 g (48%) of yellow crystals melting at 215–220°. Three recrystallizations from acetone–water gave a pure sample as yellow needles melting at 223–225°: ν_{max} 1620 (broad), 1535, 1394, 1343, 1269, 1227, 1186, and 788 cm^{-1}; pmr δ 1.45–1.65 (m, 6 H), 3.43–3.75 (m, 4 H), 7.10 (d,[19] 1 H, J = 10 Hz), 8.35 (d, 1 H, J = 10 Hz), and 9.05 (s, 1 H).

Anal. Calcd for $C_{14}H_{14}N_4O_5$: C, 52.83; H, 4.43; N, 17.60. Found: C, 53.16; H, 4.25; N, 17.86.

2-(*N*-Piperidino)-6-hydroxy-5,8-dioxoquinoline (14a).—A sample of 2-(*N*-piperidino)-6,8-dinitro-5-hydroxyquinoline (0.2 g) was suspended in water (100 ml) containing 6 *N* hydrochloric acid (5 ml) and 10% palladium-on-carbon catalyst (0.02 g). After stirring under a slightly positive pressure of hydrogen for 18 hr and filtering, the solution was adjusted to pH 2.0 with sodium bicarbonate. Oxygen was bubbled through the solution for 15 min, and the solution was made basic with sodium bicarbonate, oxygenated for an additional 15 min, and acidified with concentrated sulfuric acid (10 ml). The thick green precipitate dissolved to give a very dark solution which was heated at reflux for 25 min, cooled, and partially neutralized with concentrated ammonium hydroxide. Extraction with ethyl acetate (three 75-ml portions) gave a deep red solution which was in turn extracted with 50 ml of saturated sodium bicarbonate solution. The intense red bicarbonate solution was acidified with 6 *N* hydrochloric acid and extracted with ethyl acetate (three 50-ml portions). Evaporation of the ethyl acetate left 0.11 g (68%) of red power melting at 200–205°. Two recrystallizations from tetrahydrofuran–cyclohexane gave the analytical sample as tiny dark red needles melting at 205–208°: ν_{max} 3330, 1665, 1637, 1585 (broad), 1505, 1393, 1313, 1250, 1190, 1090, 1026, 952, 801, and 765 cm^{-1}; pmr ($CDCl_3$) δ 1.55–1.85 (broad m, 6 H), 3.25–3.95 (broad m, 4 H), 6.20 (s, 1 H), 6.75 (d, 1 H, J = 9 Hz), and 8.05 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.06; H, 5.46; N, 10.84. Found: C, 65.06; H, 5.39; H, 10.70.

2-(*N*-Piperidino)-6-methoxy-5,8-dioxoquinoline (14b).—To a solution of 2-(*N*-piperidino)-6-hydroxy-5,8-dioxoquinoline (0.10 g) in methanol (50 ml) was added 1 drop of concentrated sulfuric acid. The solution was heated at reflux for 1 hr, concentrated to about 10 ml, diluted with water (100 ml), and extracted with ethyl acetate (three 50-ml portions). The organic extract was washed with saturated sodium bicarbonate solution and evaporated to yield 0.09 g (95%) of red needles melting at 205–208°. Two recrystallizations from tetrahydrofuran–cyclohexane gave a pure specimen as shiny red needles melting at 207–209°: ν_{max} 2930, 1671, 1590 (broad), 1505, 1421, 1294, 1243, 1099, 848, and 799 cm^{-1}; pmr ($CDCl_3$) δ 1.60–1.80 (broad m, 6 H), 3.70–3.95 (broad m, 4 H), 3.90 (s, 3 H), 6.10 (s, 1 H), 6.80 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 65.91; H, 5.90; N, 9.83.

Registry No.—**3,** 31568-85-1; **5a,** 31568-86-2; **5b,** 31568-87-3; **5c,** 31568-88-4; **5d,** 31568-89-5; **5e,** 31568-90-8; **7,** 31568-91-9; **8,** 31570-94-2; **9c,** 31570-95-3; **9d,** 31570-96-4; **11,** 31570-97-5; **12,** 31570-98-6; **13a,** 31570-99-7; **13b,** 31571-00-3; **14a,** 31571-01-4; **14b,** 31571-02-5.

(16) This material is suitable for conversion to 2-morpholino-7-methoxy-5,8-dioxoquinoline.

(17) Satisfactory combustion analyses were not obtained for this compound.

(18) The emulsion formed at this point may be eliminated by adding a few milliliters of tetrahydrofuran.

(19) This doublet showed considerable secondary splitting, but the doublet at δ 8.35 was quite sharp. The corresponding doublet in 2-(*N*-piperidino)-5,7-dinitro-8-hydroxyquinoline showed very faint splitting.

8-Quinolinolsulfonic Acids[1]

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The preparation of 8-quinolinol-5- and -7-sulfonic acids and their respective substitution products has been reexamined. 8-Quinolinol-7-sulfonic acid and its 5-substituted derivatives which have been reported are, in reality, 7-substituted 8-quinolinol-5-sulfonic acids. Data derived from these compounds are, consequently, also incorrect. All of the compounds in question have been prepared, and their structures were established unequivocally. The sulfonic acid group in the 7 position, as well as that in the 5 position, of 8-quinolinol is useful for blocking and unblocking those positions in synthesis.

As a result of our interest in the antifungal mechanisms of 8-quinolinol and its derivatives,[2-4] studies on methods of synthesis of these compounds have been undertaken.[5,6]

8-Quinolinol-5-sulfonic acid was first prepared by Lippmann and Fleissner,[7] and an unequivocal proof of its structure was presented by Matsumura.[8] Although 8-quinolinol-7-sulfonic acid was reported in 1906,[9] its structure was not established. That the assigned structure was correct, was questioned by Molland[10] who believed it to be the 5 isomer. Ohta and Okuda[11] also reported the preparation of 8-quinolinol-7-sulfonic acid by a modification of the earlier method.[9,12] Fujita and Goto[13] also attempted to prepare the 7-sulfonic acid by the procedure of Fritzsche.[9] With the desire to study and compare acid dissociation constants and chelate stability constants of 8-quinolinol-5- and -7-sulfonic acids with metals, Chang, *et al.*,[14] also reported the preparation of 8-quinolinol-7-sulfonic acid by a modification of the old method.[9] Srivastava and Banerji,[15] using the method of Chang, *et al.*,[14] also reported the preparation of 8-quinolinol-7-sulfonic acid.

In view of the fact that the sulfonic acid group has been found to be a convenient substituent for blocking and unblocking the 5 position of 8-quinolinol,[8,16] it was desired to examine the effectiveness of this group in the 7 position. The attempt to prepare 8-quinolinol-7-sulfonic acid by the published methods was undertaken.[9,11,14,15] In each case, a product was obtained for which the ir and nmr spectra were the same as for an authentic sample of 8-quinolinol-5-sulfonic acid. To further establish the identity of the several products, they were chlorinated and desulfonated by the method of Gershon, *et al.*,[16] and found to yield only 7-chloro-8-quinolinol, as the end material. It is apparent that in the earlier work the product of sulfonation of 8-quinolinol was not the reported 7-sulfonic acid but the 5-sulfonic acid.

The preparation of 8-quinolinol-7-sulfonic acid was achieved by sulfonation of 5-chloro-8-quinolinol, followed by removal of the chlorine by hydrogenolysis, using 10% palladium on charcoal as the catalyst. The structure for 8-quinolinol-7-sulfonic acid was established by elemental composition, as well as by the ir and nmr spectra which were consistent for the 7-sulfonic acid but different from those of 8-quinolinol-5-sulfonic acid.

In view of this finding, a review of the literature revealed a considerable number of studies which were based on what was believed to have been 8-quinolinol-7-sulfonic acid, which are incorrect.[17-25] It is further obvious that the so-called 5-substituted derivatives of what was thought to have been 8-quinolinol-7-sulfonic acid are also incorrect, as well as the data derived from these compounds.[14,15,26-29]

Since authentic 8-quinolinol-7-sulfonic acid became available, it was considered worthwhile to prepare the 5-fluoro, 5-chloro, 5-bromo, 5-nitro, and 5-amino derivatives. These reactions are summarized in Scheme I. Of the six compounds, the preparation of IIb by Riedel[30] is considered to have led to the correct product, although it was not characterized.

A further examination of the literature showed that the preparation of 7-fluoro-8-quinolinol-5-sulfonic acid from 7-amino-8-quinolinol-5-sulfonic acid by Coll and Coll[31] was found by Hollingshead[32] to lead, at best, to an impure product. The 7-fluoro derivative was pre-

(1) This work was supported in part by the U. S. Public Health Service Grant No. AI-05808.

(2) H. Gershon, R. Parmegiani, A. Weiner, and R. D'Ascoli, *Contrib. Boyce Thompson Inst.*, **23**, 219 (1966).

(3) H. Gershon, S. G. Schulman, and D. Olney, *ibid.*, **24**, 167 (1969).

(4) H. Gershon, M. W. McNeil, and Y. Hinds, *J. Med. Chem.*, **12**, 1115 (1969).

(5) H. Gershon and M. W. McNeil, *J. Hetrocycl. Chem.*, **8**, 129 (1971).

(6) H. Gershon, M. W. McNeil, and S. G. Schulman, *J. Org. Chem.*, **36**, 1616 (1971).

(7) E. Lippmann and F. Fleissner, *Sitzungsber. Akad. Wiss. Wien, Math. Naturwiss. Kl, Abt. 2B*, **98**, 761 (1889).

(8) K. Matsumura, *J. Amer. Chem. Soc.*, **49**, 810 (1927).

(9) F. Fritzsche and Co., German Patent 187,869 (1906).

(10) J. Molland, *Arch. Math. Naturvidensk*, **43**, 67 (1940), cited by J. P. Phillips, *Chem. Rev.*, **56**, 271 (1956).

(11) T. Ohta and O. Okuda, *Yokugaku Zasshi*, **71**, 784 (1951).

(12) A series of 7,8-substituted derivatives was prepared subsequently, based on the sulfonic acid. A critical examination of this work revealed that none of the structures of these compounds was established, and they could just as well have been 5,8-substituted derivatives.

(13) E. Fujita and N. Goto, *Yakugaku Zasshi*, **75**, 28 (1955); *Chem. Abstr.*, **50**, 1021 (1956). The purpose of this work was to prepare 7,8-phenylene dioxyquinoline. The reactions following the sulfonation failed to yield the desired product.

(14) T.-H. Chang, J.-T. Lin, T.-I. Chou, and S.-K. Yang, *J. Chinese Chem. Soc. (Taipei)*, **11**, 125 (1964).

(15) K. C. Srivastava and S. K. Banerji, *Chem. Age India*, **18**, 351 (1967).

(16) H. Gershon, M. W. McNeil, and A. T. Grefig, *J. Org. Chem.*, **34**, 3268 (1969).

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(18) J. Pintsch, Kommanditgesellschaft in Berlin, German Patent 160,240 (1941).

(19) Ciba, Swiss Patent 239,322 (1946).

(20) Ciba, Swiss Patent 240,364 (1946).

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(23) F. Feigl, *Mikrochem. Ver. Mikrochim. Acta*, **39**, 404 (1952).

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(25) R. R. Davies, British Patent 757,727 (1956).

(26) Chemische Fabrik, Swiss Patent 179,980 (1935).

(27) K. Balachandran and S. K. Banerji, *Chem. Age India*, **19**, 455 (1968).

(28) K. Balachandran and S. K. Banerji, *Curr. Sci.*, **38**, 563 (1969).

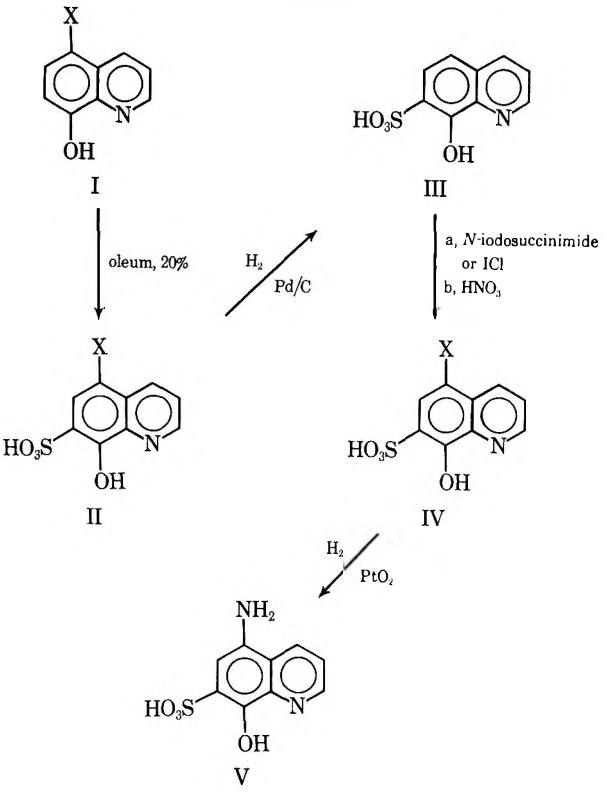
(29) K. Balachandran and S. K. Banerji, *ibid.*, **32**, 3333 (1970).

(30) J. D. Riedel, German Patent 552,920 (1932).

(31) A.-L. Coll and G. P. Coll, *Afinidad*, **28**, 163 (1951).

(32) R. G. W. Hollingshead, "Oxine and Its Derivatives," Vol. 3, Butterworths, London, 1956, pp 883, 884.

Scheme I



Ia, IIa, X = F IVa, X = I
Ib, IIb, X = Cl IVb, X = NO_2
Ic, IIc, X = Br

pared by sulfonation of 7-fluoro-8-quinolinol.[33] Since 7-amino-8-quinolinol-5-sulfonic acid, as reported by Matsumura,[8] had an incorrect elemental composition and did not agree in melting point with the corresponding product reported by Coll and Coll,[31] which was not further characterized, we obtained the compound as the hemihydrate by hydrogenation of 7-nitro-8-quinolinol-5-sulfonic acid.[5]

To complete the preparative studies of the 5-, 7-, and 5,7-sulfonic acids of 8-quinolinol, 8-quinolinol was disulfonated by a modification of the method of Claus and Posselt.[34] The isolation was simplified by crystallizing the copper(II) bischelate of the acid, followed by decomposition of the precipitate with hydrogen sulfide.

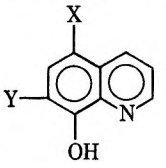
The data characterizing the new compounds are contained in Table I, and the proton chemical shifts of all the sulfonic acids are summarized in Table II. Infrared spectra for these sulfonic acids have been obtained.[35]

To determine whether the sulfonic acid group in the 7 position of 8-quinolinol can be used for both blocking and unblocking that position, 5-fluoro-, 5-chloro-, 5-bromo-, and 5-iodo-8-quinolinol-7-sulfonic acids were heated under reflux in a mixture of 15% sulfuric acid and 85% acetic acid for 24 hr, according to Gershon, *et al.*[16] 5-Fluoro-, 5-chloro-, and 5-bromo-8-quinolinols were obtained. The iodosulfonic acid yielded 8-quinolinol, as was expected, in view of the previously reported deiodination of iodonitroquinolinol.[36]

It is of interest to note that on treatment of 7-iodo-8-quinolinol-5-sulfonic acid with the sulfuric–acetic acid mixture under reflux, until the compound was just brought into solution, the products that formed were 5-iodo-8-quinolinol and 8-quinolinol. These compounds were obtained in 90% and 10% yields, respectively. The mechanism of this rearrangement is unclear.

Table I

8-Quinolinolsulfonic Acids



Compd	X	Y	Yield, %	Mp, °C[a]	Formula
III	H	SO_3H	60	274–277	$C_9H_9NO_5S$
IIa	F	SO_3H	92	351–352 dec	$C_9H_6FNO_4S$
IIb[b]	Cl	SO_3H	78	>340 dec[c]	$C_9H_6ClNO_4S$
IIc	Br	SO_3H	69	316–317 dec	$C_9H_6BrNO_4S$
IVa	I	SO_3H	89	274–275 dec	$C_9H_6INO_4S$[d]
IVb	NO_2	SO_3H	67	300 dec	$C_9H_6N_2O_6S$[e]
V	NH_2	SO_3H	78	>300 dec[c]	$C_9H_8N_2O_4S$[f]
	SO_3H	F	67	>340 dec[c]	$C_9H_6FNO_4S$
	SO_3H	NH_2	90	292–293 dec	$C_{18}H_{18}N_4O_9S_2$[g]
	SO_3H	SO_3H	85	310–315 dec	$C_9H_{11}NO_9S_2$[h]

[a] Analytical sample. Satisfactory analytical values (±0.3% for C, H, and N) were reported for all compounds (C and H only for IVb): Ed. All samples were recrystallized from 10% aqueous H_2SO_4 except 7-amino-8-quinolinol-5-sulfonic acid which was recrystallized from 1:1 aqueous DMF. [b] Compound prepared but not characterized, ref 30. [c] Indistinct decomposition point above this temperature. [d] Analysis for I satisfactory. [e] Analysis for O and S satisfactory. [f] Analysis for S satisfactory. [g] Analysis of O and S satisfactory. [h] Analysis for O satisfactory.

Experimental Section[37]

Sulfonation of 5- and 7-Halogeno-8-quinolinols.—Halogeno-8-quinolinol (0.5 mol) (F, Cl, or Br) was dissolved in 300 ml of 20% oleum. The solution was heated to 170–180° with stirring. After the solution was allowed to cool to 40–50°, it was poured onto ice. The halogeno-8-quinolinolsulfonic acid was obtained by filtration, followed by washing with Me_2CO and drying at 70° overnight.

8-Quinolinol-7-sulfonic Acid (III).—A mixture of 5-chloro-8-quinolinol-7-sulfonic acid (IIb) (55 g, 0.2 mol), 4 g of Pd/C (10%) and 200 ml of H_2O containing 50 g of H_2SO_4 was shaken under 3 atm of H_2 in a Parr hydrogenator until 0.2 mol of H_2 was taken up. The mixture was heated to 80–90°, and the catalyst was removed by filtration. The warm solution was diluted with an equal volume of H_2O and refrigerated overnight. A yield of 29.5 g (60%) of product was obtained as the monohydrate by filtration, washing (Me_2CO), and drying at 70° overnight.

5-Iodo-8-quinolinol-7-sulfonic Acid (IVa).—8-Quinolinol-7-sul-

(33) H. Gershon and M. W. McNeil, *J. Heterocycl. Chem.*, in press.

(34) A. Claus and M. Posselt, *J. Prakt. Chem.*, **41**, 32 (1890).

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

(36) H. Gershon, *J. Med. Chem.*, **11**, 1094 (1968).

(37) Methods found in the literature were used for the preparation of 7-chloro-8-quinolinol-5-sulfonic acid,[16] 7-bromo-8-quinolinol-5-sulfonic acid,[16] 7-nitro-8-quinolinol-5-sulfonic acid,[5] and 5-fluoro-8-quinolinol.[38] 8-Quinolinol-5-sulfonic acid, 7-iodo-8-quinolinol-5-sulfonic acid, 5-chloro-8-quinolinol, and 5-bromo-8-quinolinol were commercially available. Melting points were taken in a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Model 221 spectrophotometer. Gas chromatography was performed on a Varian Aerograph Model 1200 gas chromatograph with a flame ionization detector. Methods and columns were previously described.[16,39] Nmr spectra were taken with a Jeolco JMN-C-60HL spectrometer.

(38) A. F. Helin and C. A. Vanderwerf, *J. Org. Chem.*, **17**, 229 (1952).

(39) H. Gershon and M. W. McNeil, *ibid.*, **35**, 3993 (1970).

TABLE II

PROTON CHEMICAL SHIFTS FOR 8-QUINOLINOLSULFONIC ACIDS[a] (TMS INTERNAL STANDARD)

Substituent on 8-quinolinol[b]	Proton 2	3	4	5	6	7
5-SO_3H	0.80 (q, J_{23} = 5, J_{24} = 1.5)	1.75 (q, J_{32} = 5, J_{34} = 9)	0.05 (q, J_{42} = 1.5, J_{43} = 9)		1.80 (d, J_{67} = 9)	2.58 (d, J_{76} = 9)
7-F, 5-SO_3H	0.82 (q, J_{23} = 5, J_{24} = 1.5)	1.88 (q, J_{32} = 5, J_{34} = 8)	0.23 (q, J_{42} = 1.5, J_{43} = 8)		1.90 (d, J_{HF} = 11)	
7-Cl, 5-SO_3H	0.89 (q, J_{23} = 5, J_{24} = 1.5)	1.93 (q, J_{32} = 5, J_{34} = 9)	0.44 (q, J_{42} = 1.5, J_{43} = 9)		1.93 (s)	
7-Br, 5-SO_3H	0.88 (q, J_{23} = 5, J_{24} = 1.5)	2.00 (q, J_{32} = 5, J_{34} = 9)	0.46 (q, J_{42} = 1.5, J_{43} = 9)		1.80 (s)	
7-I, 5-SO_3H	0.98 (q, J_{23} = 4, J_{24} = 1.5)	2.12 (q, J_{32} = 4, J_{34} = 9)	0.59 (q, J_{42} = 1.5, J_{43} = 9)		1.66 (s)	
7-NO_2, 5-SO_3H	0.85 (q, J_{23} = 5, J_{24} = 2)	1.94 (q, J_{32} = 5, J_{34} = 9)	0.54 (q, J_{42} = 2, J_{43} = 9)		1.43 (s)	
7-NH_2, 5-SO_3H	1.13 (d, J_{23} = 6)	2.30 (q, J_{32} = 6, J_{34} = 8)	0.40 (d, J_{43} = 8)		2.00 (s)	
7-SO_3H	0.73 (s)	1.70–1.95 (unresolved multiplet)	0.85 (s)	1.95 (d, J_{56} = 10)	2.19 (d, J_{65} = 10)	
5-F, 7-SO_3H	0.78 (q, J_{23} = 5, J_{24} = 1.5)	1.86 (q, J_{32} = 5, J_{34} = 9)	0.92 (q, J_{42} = 1.5, J_{43} = 9)		2.30 (d, J_{HF} = 9)	
5-Cl, 7-SO_3H	0.75 (d, J_{23} = 6)	1.79 (d, J_{32} = 6, J_{34} = 9)	0.84 (d, J_{43} = 9)		2.02 (s)	
5-Br, 7-SO_3H	0.74 (q, J_{23} = 5, J_{24} = 1.5)	1.78 (q, J_{32} = 5, J_{34} = 9)	0.92 (q, J_{42} = 1.5, J_{43} = 9)		1.86 (s)	
5-I, 7-SO_3H	0.80 (q, J_{23} = 5, J_{24} = 1.5)	1.87 (q, J_{32} = 5, J_{34} = 9)	1.10 (q, J_{42} = 1.5, J_{43} = 9)		1.62 (s)	
5-NO_2, 7-SO_3H	0.78 (q, J_{23} = 4, J_{24} = 1.5)	1.90 (q, J_{32} = 4, J_{34} = 9)	0.61 (q, J_{42} = 1.5, J_{43} = 9)		1.20 (s)	
5-NH_2, 7-SO_3H	0.89 (d, J_{23} = 6)	2.07 (q, J_{32} = 6, J_{34} = 9)	1.00 (s)		2.63 (s)	
5,7-$(SO_3H)_2$	0.73 (q, J_{23} = 6, J_{24} = 2)	1.68 (q, J_{32} = 6, J_{34} = 9)	0.09 (q, J_{42} = 1.5, J_{43} = 9)		1.60 (s)	

[a] Spectra were taken on 3% solutions of free base in DMSO-d_6; proton chemical shifts are given in parts per million (τ), J in hertz. [b] Registry numbers are, respectively, 84-88-8, 384-31-6, 3062-36-0, 3062-37-1, 547-91-1, 15851-63-5, 15851-62-4, 3062-35-9, 31568-78-2, 3244-71-1, 3062-38-2, 3075-21-6, 31568-82-8, 31568-83-9, 31568-84-0.

fonic acid (III) (2.24 g, 0.01 mol) and *N*-iodosuccinimide (2.25 g, 0.01 mol) were slurried in a mixture of 20 ml of MeOH and 5 ml of H_2O. Stirring was continued for 2 hr, and the product was removed by filtration. After washing with H_2O and Me_2CO and drying at 70° overnight, a yield of 89% of IVa was obtained. When ICl was employed for iodination, the iodosulfonic acid was obtained in 72% yield.

5-Nitro-8-quinolinol-7-sulfonic Acid (IVb).—A solution of 12g (0.053 mol) of III in 50 ml of H_2SO_4 was cooled to 0°, and 3.2 ml (0.051 mol) of HNO_3 was added dropwise with stirring. The temperature was maintained below 10°. Agitation was continued for 5 min, after completion of addition of the acid. The mixture was poured onto ice, and the product was recovered by filtration, followed by washing with H_2O and Me_2CO. A yield of 9.5 g (67%) of IVb was obtained.

5-Amino-8-quinolinol-7-sulfonic Acid (V).—A suspension of 6 g (0.022 mol) of IVb and 25 mg of PtO_2 in 50 ml of H_2O and 25 ml of DMF was heated to 70° and hydrogenated under 5 atm of H_2 in a Parr hydrogenator until 0.066 mol of H_2 was taken up. The amino derivative which was insoluble in the solvent mixture was removed along with the catalyst by filtration. The residue was extracted twice with a boiling mixture composed of 100 ml of DMF and 25 ml of H_2O. Upon cooling, 3.5 g (78%) of product was obtained.

7-Amino-8-quinolinol-5-sulfonic Acid.—A suspension of 8.1 g (0.03 mol) of 7-nitro-8-quinolinol-5-sulfonic-acid[5] and 50 mg of PtO_2 in 100 ml of 95% MeOH was shaken in a Parr hydrogenator until 0.09 mol of H_2 was consumed. The catalyst was removed by filtration, and the solvent was flash evaporated. The yield of product was 6.8 g (90%), as the hemihydrate, mp 292–293° dec.

8-Quinolinol-5,7-disulfonic Acid.—8-Quinolinol (29 g, 0.2 mol) was heated in 100 ml of 20% oleum to 150°, after which it was cooled and poured onto ice. The solution was diluted to 2000 ml, and 125 g (0.5 mol) of solid $CuSO_4 \cdot 5H_2O$ was added. After stirring overnight, 95 g of the Cu(II) salt of the disulfonic acid was obtained by filtration, followed by washing with Me_2CO and air drying. The salt was dissolved in 1500 ml of hot H_2O and treated with H_2S until all of the Cu(II) was precipitated as Cu_2S. The sulfide was removed by filtration, and the colorless filtrate was flash evaporated to near dryness. The residue was slurried in Me_2CO to remove all color, and 43 g of product was obtained after filtration. An additional crop of 4.3 g was recovered from the Me_2CO. The total yield of product was 85%, as the dihydrate, mp 310–315° dec.

The Synthesis and Spectral Properties of Some N-Substituted Derivatives of Phenol Blue

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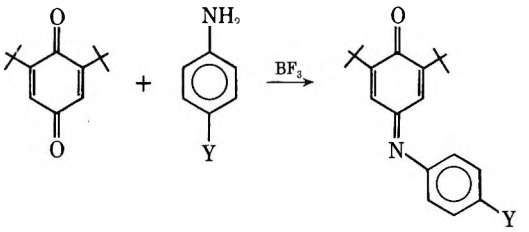
A number of 4-substituted anilines were condensed with 2,6-di-*tert*-butylbenzoquinone in the presence of BF_3 to give substituted azomethine dyes 1 in good yield. *p*-Phenylenediamine gave the corresponding dye 1, or, in the presence of sufficient quinone, a bis dye. Studies of the effects of substituents on absorption spectra were made; as Y became more electron releasing, absorption shifted bathochromically and became more intense. Maximum electron release was obtained from dyes in which Y was anionic, as in RSO_2N^- or O^-, produced by ionization of the proton on a sulfonamide or hydroxyl group in the presence of base. The neutral sulfonamide dyes gave two-banded spectra in DMSO because of partial ionization. Anomalous shifts in absorption were observed when amido dyes were methyl-substituted on nitrogen. These shifts are the result of steric hindrance between the *N*-methyl substituent and nearby ring protons, which prevents coplanarity of the amide group and the adjacent ring. Nmr studies confirmed the nonplanar conformation of the amide group relative to the aromatic ring. Studies were made of the effects of solvents on the spectra of these dyes; increasing solvent polarity produces bathochromic shifts, but hydrogen-bonding solvents produce hypsochromic shifts in cases where Y is a substituent capable of accepting a hydrogen bond.

A previous publication describes the preparation of anils by condensation of aldehydes or ketones with anilines in chloroform, using boron trifluoride as catalyst.[1] We wish to report the extension of this synthesis to the preparation of azomethine dyes by condensation of 2,6-di-*tert*-butylquinone with para-substituted anilines. Normally, quinones undergo nuclear addition *cum* redox reactions with anilines to give complex mixtures. We have found, however, that 2,6-di-*tert*-butylbenzoquinone undergoes smooth condensation with a wide variety of anilines to give the desired azomethine dyes 1. This behavior of 2,6-di-*tert*-butylbenzoquinone is consistent with several other



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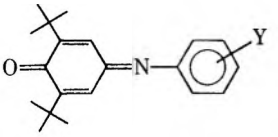
reactions in which the hindered quinone shows typical carbonyl reactivity, namely, formation of a monophenylhydrazone in high yield[2] and formation of a monoxime and 2,4-DNPH.[3]

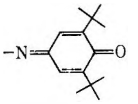
The structures and yields of the dyes prepared by this scheme are reported in Table I. We have modified the original procedure[1] by substituting tetrahydrofuran as a solvent to replace chloroform. This permits extension of the reaction to a wider variety of anilines, since insolubility of the substituted aniline in chloroform is often a limiting factor in using the procedure as originally described.

As expected, the condensation failed for benzoquinones other than 2,6-di-*tert*-butylbenzoquinone; no dyes were obtained from benzoquinone or its halogenated derivatives. With respect to choice of anilines, those containing electron-releasing substituents gave good yields of dyes; we were not able to condense *p*-nitroaniline with the hindered benzoquinone. It is notable that *p*-phenylenediamine may react at one amino group only to give a good yield of the monoazomethine dye 2. If 2 mol of benzoquinone per mole of *p*-phenylenediamine is used and the reaction is carried out for an extended period of time, a good yield of the bis dye **3** is formed. The structure of the bis dye was confirmed by its mass spectrum (parent ion peak at *m/e* 512) and its nmr spectrum. The nmr spectrum contained two intense peaks at 1.20 and 1.32 ppm corresponding to two sets of nonequivalent *tert*-butyl groups and, in the aromatic region, a single peak,

Table I

2,6-Di-*tert*-butylquinone Monoimines 1[a]



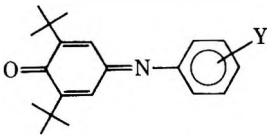
Y[b]	Mp, °C	Yield, % theory
$-NH_2$	163–165	56
$-NHCH_3$	172–172.5	62
$-N(CH_3)_2$[c]	118–120	59
$-NHSO_2Ph$	196–197	54
$-NHSO_2C_6H_4$-*p*-OCH_3	210–212	76
$-NHSO_2C_6H_4$-*p*-NO_2	213–214	77
o-$NHSO_2C_6H_4$-*p*-CH_3	164–165, resolidified 192–193	83
$-NHSO_2CH_3$	221–222	80
$-NHCOCF_3$	174.5–175.5	85
$-NHCOCH_3$	200–201	50
$-N(Me)SO_2CH_3$	141–142	82
o-$NHSO_2CH_3$ *p*-NEt_2	194.5–196	28
$-OCH_3$[c]	72–73	67
$-H$[c]	75–78	81
$-OH$	203–204	35
 (bis dye)	244–245	46

[a] Satisfactory analytical values (±0.4% for C, H, N, and, when present, s) were reported for all compounds: Ed. [b] All substituents Y are in the position para to the azomethine nitrogen atom unless otherwise noted. [c] Previously reported by A. Rieker and H. Kessler, *Tetrahedron*, **23**, 3723 (1967).

(1) M. E. Taylor and T. L. Fletcher, *J. Org. Chem.*, **26**, 940 (1960).
(2) E. Muller and K. Ley, *Chem. Ber.*, **88**, 601 (1955).
(3) S. J. Metro, *J. Amer. Chem. Soc.*, **77**, 2901 (1955).

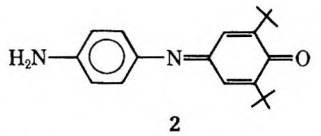
TABLE II

SPECTRAL DATA FOR AZOMETHINE DYES



No.	Y[a]	Registry no.	Cyclohexane	CCl_4	DMSO	DMSO + NaAc	DMSO + NaOMe	*m*-Creso
			A. Wavelength Data (nm)					
A	$-NH_2$	31568-56-6	504	508	569	569	658	514
B	$-NHCH_3$	31568-57-7	527	532	583	582	682	586
C	$-N(CH_3)_2$	14329-32-9	542	549	585	583	584	617
D	$-NHSO_2Ph$	31568-59-9	457	456	480	612	615	440
E	$-NHSO_2C_6H_4$-*p*-OCH_3	31568-60-2		458	480	620	622	444
F	$-NHSO_2C_6H_4$-*p*-NO_2	31568-61-3		444	475	599	603	436
G	*o*-$NHSO_2C_6H_4$-*p*-CH_3	31568-62-4	465	467	460	625	625	453
H	$-NHSO_2CH_3$	31568-63-5	458	456	480	625	628	440
I	$-NHCOCF_3$	31568-64-6	452	452	470	576	576	434
J	$-NHCOCH_3$	31615-26-6	473	472	494	494	662	455
K	$-N(Me)COCH_3$	31568-65-7	446	442	454	452	*b*	418
L	$-N(Me)SO_2Me$	31568-66-8	452	449	456	454	*b*	424
M	*o*-$NHSO_2CH_3$, *p*-NEt_2	31568-67-9	573	578	605	692	694	623
N	$-OCH_3$	17119-01-6	455	477	487	486	*b*	475
O	$-H$	14329-20-5	443	439	445	443	*b*	420
P	$-OH$	31568-70-4	465	468	496	657	657	466
			B. Intensity Data (Oscillator Strengths)					
A	$-NH_2$			0.214	0.312	0.311	0.584	0.218
B	$-NHCH_3$			0.242	0.315	0.326	0.486	0.303
C	$-N(CH_3)_2$		0.264	0.258	0.313	0.322	0.302	0.352
D	$-NHSO_2Ph$		*c*	0.111	0.154[d]	0.410	0.403	0.173
E	$-NHSO_2C_6H_4$-*p*-OCH_3			*c*	0.150[d]	0.418	0.422	0.183
F	$-NHSO_2C_6H_4$-*p*-NO_2			*c*	0.174[d]	0.399	0.412	0.220
G	*o*-$NHSO_2C_6H_4$-*p*-CH_3		0.133	0.138	0.090	0.088	0.126	0.129
H	$-NHSO_2CH_3$		*c*	*c*	0.160[d]	0.427	0.440	0.198
I	$-NHCOCF_3$		0.116	0.119	0.139	0.289	0.291	0.154
J	$-NHCOCH_3$		*c*	0.148	0.169	0.172	0.421	0.192
K	$-N(Me)COCH_3$		0.101	0.098	0.106	0.100	*b*	0.171
L	$-N(Me)SO_2Me$		0.108	0.106	0.112	0.111	*b*	0.180
M	*o*-$NHSO_2CH_3$, *p*-NEt_2		0.331	0.390	0.394	0.452	0.473	0.436
N	$-OCH_3$		0.138	0.142	0.144	0.146	*b*	0.199
O	$-H$		0.079	0.075	0.074	0.073	*b*	0.134
P	$-OH$		0.134	0.134	0.181	0.510	0.592	0.196

[a] All substituents Y are in the position para to the azomethine nitrogen atom unless otherwise noted. [b] Broad absorption at 400 nm with ill-defined maximum. [c] Insoluble at 10^{-4} *M*. [d] Double peaks present. Oscillator strength taken over both peaks.



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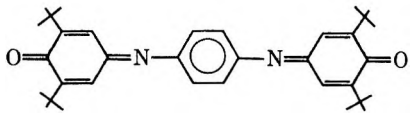

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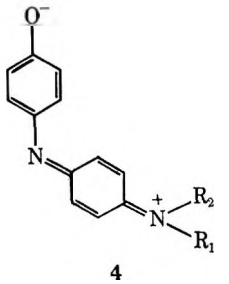
at 6.80 ppm, characteristic of the equivalent protons on the central benzenoid ring, superimposed on an AB-type pattern characteristic of the protons on the quinonoid rings.

Spectral Studies. Substituent Effects. –One of our motives in preparing the series of dyes (Table I) was to study the effects of substituents Y (1) on the visible spectra of the dyes. Results of spectral measurements are summarized in Table II, which reports the position of the absorption maxima (λ_{max}, Table II, section A) and the integrated absorption intensity (oscillator strength, Table II, section B). Spectra were obtained in several different solvents to ascertain the effects of dye structure on response of the spectra to changes in solvent polarity. Solvent effects are discussed in detail in the next section.

Introduction of an amino substituent into the benzenoid portion of dye A (Y = NH_2) has a large hyperchromic (intensity-enhancing) effect and shifts the dye absorption 70 nm toward the red (Table II, compare dyes A and O). This effect of the amino group can be understood in terms of charge transfer from the amino group to the chromophore, represented in valence bond terminology as an increased contribution of the dipolar structure 4 to the excited state, which is made possible by the amino group. In terms of molecular orbital language, the unshared electron pair on the terminal nitrogen atom becomes delocalized into



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the chromophore on excitation. Hückel calculations with reasonable parameter sets[4,5] confirm that the terminal nitrogen atom in the amino compound becomes more positive in the first excited state, assuming promotion of an electron from the highest filled molecular orbital to the lowest energy virtual orbital. Accordingly, structural factors which increase the electronegativity of the nitrogen substituent will result in hypsochromic shifts and, conversely, electron release at that atom will give bathochromic effects. The effects of substituents reported in Table II are readily rationalized by this picture; *e.g.*, introduction of electron-releasing methyl groups at the terminal amino group (Table II, compounds A and C) cause bathochromic shifts, while electron-attracting substituents such as sulfonyl (D, E, F, G, H), acetyl (J), and trifluoroacetyl (I) cause hypsochromic shifts. Likewise, replacement of the amino group by a hydroxyl group (P) causes a hypsochromic shift, presumably because of the higher electronegativity of the oxygen atom. The intensity variations follow the wavelength shifts; *i.e.*, a decrease in availability of electrons at the para substituent is accompanied by a decrease in the intensity of the absorption.

Although an *N*-methyl substituent causes a bathochromic shift when substituted on *amino* nitrogen (compare A and B, Table II), an opposite kind of shift is observed when the methyl group is substituted on *amido* nitrogen; compare compounds J and K, Table II, which show that introduction of a methyl group on the *p*-acetamido group causes a hypsochromic shift of 30 nm or more. Analogous (but smaller) effects occur with sulfonyl analogs (H and L, Table II) in carbon tetrachloride solution. These hypsochromic shifts produced by methyl substitution are also accompanied by small decreases in the intensity of the absorption. This reversal of the "normal" effect of the methyl group can be explained by steric hindrance, which prevents coplanarity of the amido group with the adjacent aromatic ring owing to interference between the *N*-methylacetamido group and the ring protons ortho to it. The possibility of such steric interference is confirmed by Courtauld models and also by observations of the nmr spectra of the methylated and unmethylated amido dyes.

The nmr spectra of the acetamido dye and of its *N*-methyl analog contain two overlapping AB-type spin-splitting patterns. One of these AB patterns corresponds to protons with chemical shifts of δ 6.70 and 6.84 ppm in the case of the *p*-acetamido compound (J, Table II) and δ 6.65 and 6.85 ppm in the case of the *N*-methylacetamido compound (K, Table II). These absorptions may be assigned to the protons on the quinonoid ring of structure 1. This assignment is supported by the relative intensities of the absorptions (two protons) and the small value of the coupling constant, $J_{AB} = 2$ cps, expected as a result of the meta orientation of the two protons. As expected, these protons are not much affected by replacement of the proton on the remote amide group with a methyl substituent.

The other AB-type pattern corresponds to protons with chemical shifts of δ 6.70 and 7.45 ppm in the case of the *p*-acetamido compound (J, Table II) and δ 6.79 and 7.14 ppm in the case of the *N*-methylacetamido compound (K, Table II). These absorptions may be assigned to the AA'BB' protons on the benzenoid ring in structure 1; this is consonant with the relative intensities (four protons) and the larger coupling constant, $J_{AB} = 9$ cps, characteristic of protons situated ortho to each other. In this case, there is a relatively large *upfield shift* of about 20 cps (0.31 ppm) in the absorption of one set of protons resulting from replacement of the proton on the amide group by a methyl substituent. This is attributable to aplanarity of the *N*-methylacetamide group and the adjacent benzene ring, which exposes ortho protons to the diamagnetic portion of the field associated with the carbonyl group.[6]

Spectral Studies. Solvent Effects.—A survey of the spectral data in Table II, section A shows that all of the dyes are more or less bathochromically shifted in DMSO *vs.* carbon tetrachloride. On the other hand, there are distinct differences in responses of the dyes to *m*-cresol as solvent; while the *N*-methylamino and *N*,*N*-dimethylamino dyes (B, C, Table II) show large *bathochromic* shifts in *m*-cresol (*vs.* CCl_4), the parent amino compound (A, Table II, section A) shows a much smaller bathochromic shift and all of its amido derivatives (D–L, Table II, section A) give *hypsochromic* shifts in *m*-cresol.

In an earlier paper,[7] a mathematical model was used to measure the spectral changes produced by hydrogen bonding for a series of dyes related to 1. In brief, the analysis depended upon fitting spectral data to an equation proposed by McRae (see ref 7) which was shown to be successful in correlating the absorption frequency ν_s of a solute in a given solvent having refractive index n and dielectric constant D, given the absence of extraneous factors such as hydrogen bonding between solvent and solute. The equation has the form (eq 1) where ν_g, A and B are parameters

$$\nu_s = \nu_g + \frac{n^2 - 1}{2n^2 + 1}A + \left(\frac{D - 1}{D + 2} - \frac{n^2 - 1}{n^2 + 2}\right)B \qquad (1)$$

evaluated by regression of observed frequencies ν_s on n and D. We showed that this equation fitted spectral data well in cases where hydrogen bonding was absent and argued that *deviations* of spectral data from this equation could be attributed to factors other than solvent polarity (measured by n and D), such as hydrogen bonding. In this way, we could separate effects of hydrogen bonding on spectra from other solvent polarity effects. In the previous work, it was concluded that the relatively small bathochromic shift shown by the amino dye (A, Table II) for the change in solvent

(4) W. F. Smith, *Tetrahedron*, **20**, 671 (1964).
(5) A. J. Wohl, *ibid.*, **24**, 6889 (1968).
(6) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," Pergamon Press, Elmsford, N. Y., 1969, p 88.
(7) J. Figueras, *J. Amer. Chem. Soc.*, **93**, 3255 (1971).

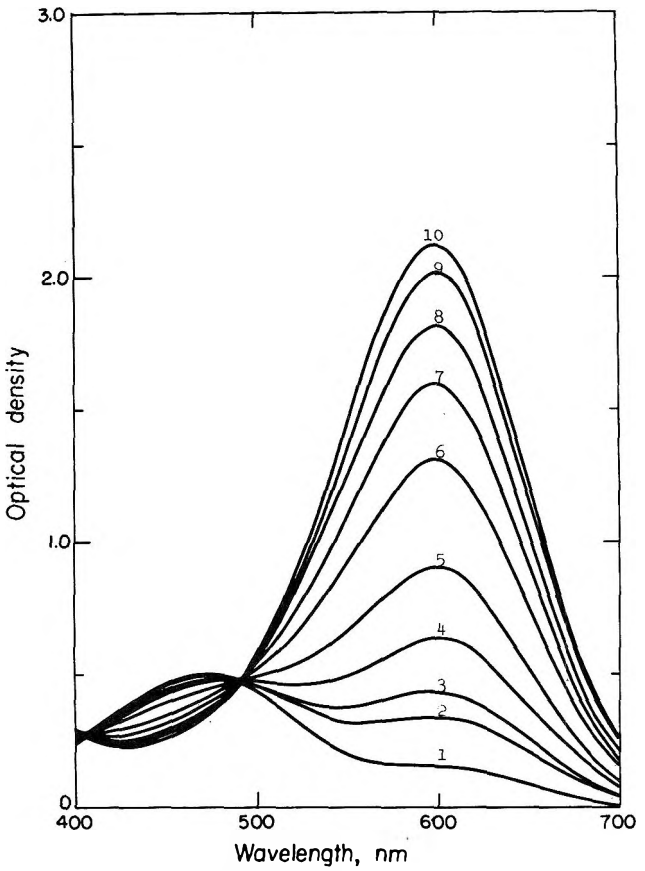
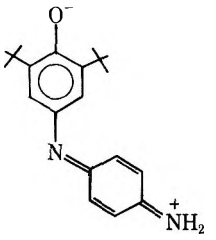


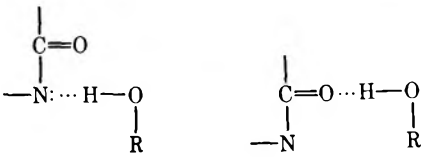
Figure 1.—Absorption spectra of *N*-[4-(4-nitrobenzenesulfonamido)phenyl]-2,6-di-*tert*-butylenenzoquinone monoimine: triethylethylamine concentrations (mol/l.), (1) 0, (2) 1×10^{-5}, (3) 2×10^{-5}, (4) 4×10^{-5}, (5) 8×10^{-5}, (6) 2×10^{-4}, (7) 4×10^{-4}, (8) 8×10^{-4}, (9) 2×10^{-3}, (10) 1×10^{-2}; dye concentration, 10^{-4} *M*; solvent, dimethyl sulfoxide.

from CCl_4 to *m*-cresol, as compared with the much larger shifts shown for the same solvent change by *N*-alkylated analogs (B and C, Table II) was the result of a hypsochromic component arising from stronger hydrogen bonding of the primary amino group of dye A with the O–H group of *m*-cresol. Hydrogen bonding at the terminal nitrogen atom is expected to shift dye absorption hypsochromically owing to increased localization of the unshared pair on nitrogen, which would destabilize the dipolar contributing structure 2. Ex-



2

tension of this argument to the amide dyes (D–L, Table II) explains the hypsochromic shift which they generally show in the more polar *m*-cresol *vs.* CCl_4 even though the "normal" effect of increasing solvent polarity appears to be bathochromic (compare spectral data in DMSO *vs.* those in CCl_4, Table II). It is not possible to discern whether bonding involves the terminal amide nitrogen as in **5**, or acyl (sulfonyl) oxygen as in **6**, although bonding at oxygen is believed to be more



5 6

likely (*vide infra*). Both kinds of interaction would be expected to give hypsochromic spectral shifts.

Quantitative estimates of deviations from the McRae eq 1 for solutions in *m*-cresol and trifluoroethanol (TFE) were made for four of the amido dyes,[8] namely, the acetamido dye, the *N*-methylacetamido dye, the sulfonamido dye, and the *N*-methylsulfonamido dye (J, K, H, L, respectively, Table II). Spectral data were obtained in 16 different solvents for each dye and were fitted to the McRae eq 1 using the computer program described in ref 7. The deviations from the McRae equation for the amide dyes in *m*-cresol and TFE are particularly large, and negative, compared with the large, positive deviation shown by the dimethylamino derivative. These deviations are obtained by subtracting the calculated transition energy (in kcal/mol) using the McRae equation from the observed transition energy. The results are summarized in Table III; data for the parent amino and methyl-

TABLE III

DEVIATIONS[a] FROM THE MCRAE EQUATION, KILOCALORIES/MOLE

Substituent Y	*m*-Cresol	TFE
$-NH_2$	−3.6	−6.7
−NHMe	1.1	−2.2
$-N(CH_3)_2$	3.6	−2.2
$-NHCOCH_3$	−4.0	−4.7
$-N(Me)COCH_3$	−3.5	−5.4
$-NHSO_2CH_3$	−2.6	−4.7
$-N(Me)SO_2CH_3$	−2.1	−5.0

[a] Deviation = $E - \hat{E}$ where E = observed transition energy and $\hat{E}$ = transition energy calculated from eq 1.

amino dyes are taken from our earlier study. As noted previously, and as exemplified in Table III, the introduction of methyl groups at the terminal amino nitrogen atom reduces in large degree the hypsochromic effect resulting from interaction of the amino group with solvent O–H groups (first three lines of Table III). This is not observed, however, with the amido dyes, where N-methylation has a relatively small effect on the magnitude of the hydrogen-bond shift, a result which suggests that the interaction of the amide group with cresol solvent or TFE involves acyl oxygen rather than nitrogen (*cf.* ref 6, above). Gramstad and Fuglevik[9] found, by means of infrared spectroscopy with mixtures of N,N-disubstituted amides and phenol, that the carbonyl oxygen atom in all of the amides that they studied participated in hydrogen bonding. It is of interest that these authors observed enthalpies of hydrogen-bond formation of 4.0–5.7 kcal/mol in carbon

(8) Listings of solvents, solvent parameters, spectral data, and results from regression analysis will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page numbers. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(9) T. Gramstad and J. Fuglevik, *Acta Chem. Scand.*, **16**, 1369 (1962).

Table IV
Effects of Structural Change on Absorption Spectra in DMSO

	Substituents, Y (para)									
	H	$NHSO_2CH_3$	$NHCOCH_3$	NH_2	NHMe	NMe_2	$^-NSO_2Me$	$^-NHCOCH_3$	^-NH	^-NMe
λ_{max}	445	480	494	569	583	585	628	662	658	682
f	0.074	0.160	0.169	0.312	0.315	0.313	0.440	0.421	0.584	0.486

tetrachloride solution, which is of the same order of magnitude as the hypsochromic spectral shifts which we have attributed to hydrogen bonding (Table III).

Substantial positive deviations from the McRae equation were obtained for spectra in DMSO and DMF. The source of these deviations is not known. Similar deviations for highly polar solvents were noted in the earlier study.[7] The deviations may not be related to hydrogen bonding, since the *N*-methyl dyes, which have no labile protons, show deviations in DMSO which are as large as those given by their parent amides.

Spectral Studies. Ionization.—In DMSO, the sulfonamido dyes D, E, F, and H (Table II, section A) give two absorption peaks: a principal band in the 480-nm region (reported in Table II, section A) and a much weaker band at ~620 nm. The long wavelength band does not appear in the spectra of the *N*-acetyl dyes, nor in those cases in which the N–H proton is replaced by methyl, nor does it appear in nonpolar media. This band is assigned to absorption of the anion resulting from ionization of the N–H proton. Addition of sodium methoxide to DMSO solutions of the sulfonamido dyes converts them completely to anions, with a large shift in the absorption peak of the dye to longer wavelengths and a large increase in absorption intensity. In fact, sodium methoxide is a sufficiently strong base in DMSO to convert all of the dyes having terminal N–H groups into their corresponding anions, as shown in the seventh columns of Table II, sections A and B. With a weaker base, sodium acetate in DMSO, only the sulfonamido dyes (D–H, Table II, section A, B) and the trifluoroacetyl dye (I, Table II, section A, B) are sufficiently acidic to be converted to anions. Analogous spectral shifts on addition of base are observed with the terminal hydroxy dye (Y = OH, dye P, Table II, section A, B). Figure 1 illustrates the changes in spectra of the 4-nitrobenzenesulfonamido dye (1, Y = $-NHSO_2C_6H_4$-*p*-NO_2) in a concentration series of triethylamine; a well-defined isosbestic point is obtained.

The anions absorb at very much longer wavelengths than do the parent dyes and with almost twice the intensity. This behavior agrees with the trend previously noted that an electron-releasing substituent on the terminal amino group causes bathochromic and hyperchromic shifts; such electron release will be greatest for anion formation at the terminal nitrogen atom. In Table IV are summarized the effects of structural change at terminal nitrogen, including anion formation. The substituents, Y, at the head of Table IV are arranged from left to right in order of increasing electron density expected at terminal nitrogen from consideration of resonance and inductive effects. Particularly striking is the large variation of nearly 240 nm in λ_{max} produced by changes in a single substituent.

Experimental Section

Dye Preparation.—2,6-Di-*tert*-butylbenzoquinone (2.20 g, 0.01 mol), an equivalent amount of the desired substituted aniline, and 6 drops of boron trifluoride etherate were dissolved in 25 ml of dry tetrahydrofuran. The mixture was heated at the boiling point for 2–3 hr. The solvent was stripped off, and the residue was taken up in chloroform and chromatographed on a 6-cm × 24-in. column packed with Florisil. The main band was eluted with chloroform and the recovered product was recrystallized from methanol–water.

In cases where the aniline hydrochloride only was available, an equivalent amount of sodium acetate or sodium methoxide was added to free the amine from its salt. The anilines were commercial materials, used without purification, or were prepared by straightforward methods. *p*-Phenylenediamine was prepared by hydrogenation of *p*-nitroaniline in THF and used directly without isolation; commercially available material gave poor results.

Spectral Measurements.—These were made at room temperature with a Hardy model spectrophotometer manufactured by the General Electric Co. Solvents were Eastman Spectro-Grade or White Label materials and were dried and stored over Linde 4A Molecular Sieves. *m*-Cresol was Practical Grade material, distilled before use. The nmr spectra were determined by means of a Varian A-60 machine.

Registry No.—3, 31662-27-8.

Acknowledgments. –Visible spectral measurements were obtained by Mr. Franc Grum of these laboratories. We wish to acknowledge valuable assistance from Dr. Thomas H. Regan in interpreting the reported nmr data.

Pyrimido[5,4-*e*]-*as*-triazines. VI. The Preparation of Some 5-Substituted 7-Aminopyrimido[5,4-*e*]-*as*-triazines[1]

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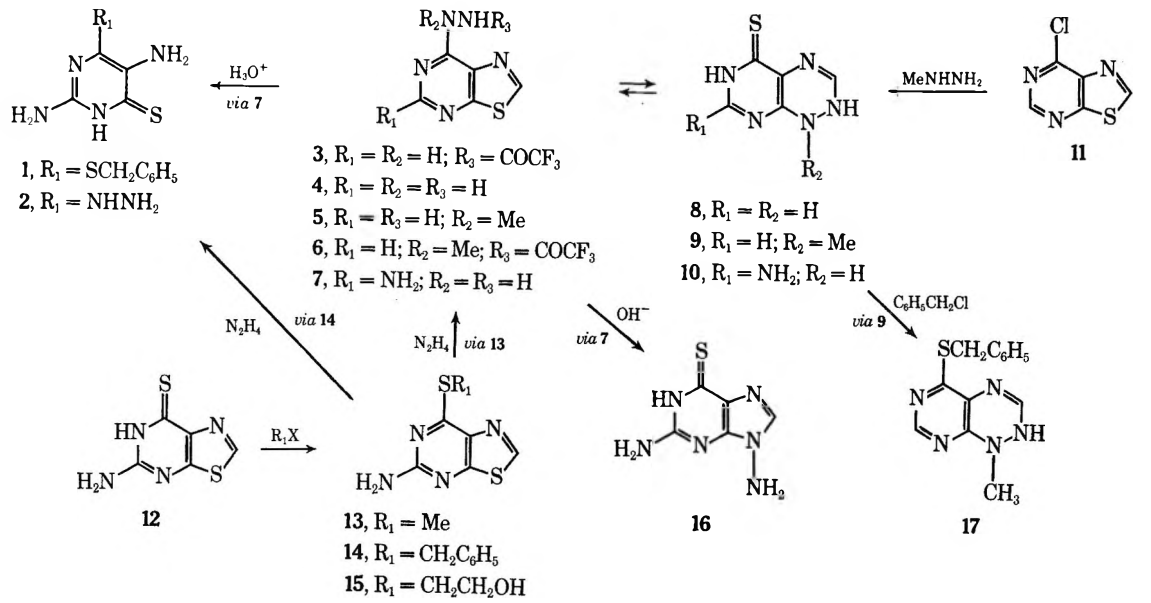
The rearrangement of one thiazolo[5,4-*d*]pyrimidine to a pyrimido[5,4-*e*]triazine and another to a 9-aminopurine is described. Reaction of methyl 6-amino-*as*-triazine-5-carboxylate (**18**) with guanidine to give 7-aminopyrimido[5,4-*e*]-*as*-triazin-5(6*H*)-one (**21**) was unsuccessful. The successful route to 7-amino compounds of this type involved the preparation and cyclization of 2,5-diamino-6-(benzylthio)-4-hydrazinopyrimidine (**30**) to give 7-amino-5-(benzylthio)pyrimido[5,4-*e*]-*as*-triazine (**31**). Nucleophilic displacement of the 5-(benzylthio) group of **31** gave the corresponding 1,2-dihydro-5(6*H*)-thione (**10**), 5(6*H*)-one (**21**), and 5-amino (**32**) derivatives. Air oxidation of **10** appeared to give mainly the corresponding hetreoaromatic 5(6*H*)-thione (**33**).

Part A

This paper is concerned with the development of synthetic methods for the preparation of the potentially biologically interesting 5-substituted derivatives of 7-aminopyrimido[5,4-*e*]-*as*-triazines (2-amino-7-azapteridines).[2] The investigation of both pyrimidine and *as*-triazine routes to this type of compound are described.



Previously, the rearrangement of **8** to **3** in CF_3CO_2D and of **4** to **8** in DMSO-d_6 was observed.[3] Reaction of **11**[4] with methylhydrazine gave a product that was shown by its elemental analyses and pmr spectrum in CF_3CO_2D to be a mixture of **5** and **9**. This product was converted to **9** on heating at 78°. A solution of the latter in CF_3CO_2D on standing for 72 hr showed the presence of **5** and a new component, presumably **6**. When this product was isolated and heated at 78°, the pmr spectrum of the resulting solid showed the presence of **9** containing only a trace amount of **5**. The structure of **9** was confirmed by benzylation to give the benzylthio derivative **17**. Our attention was now directed toward the preparation of **7**. The alkylation of **12**[5] with CH_3I, $C_6H_5CH_2Cl$, and $HOCH_2CH_2Br$ gave, respectively, **13**, **14**, and **15**. Treatment of **13** with hydrazine gave a 20% yield of **7**. None of **7** was isolated from the reaction of **14** and **15** with hydrazine, although the $HOCH_2CH_2S^-$ group of **15** was expected to be a better leaving group than the CH_3S^- group of **13**.[6] The major product from **14** was purified and identified as the pyrimidine **1**, which results from cleavage of the thiazolo ring. Ultraviolet spectral data indicated that the corresponding pyrimidines were also obtained in the reactions of both **13** and **15** with hydrazine. Similarly, the hydrochloride salt of **7** was refluxed in H_2O to open the thiazolo ring to give **2**, identified by comparison of its uv spectrum with that of 2,4,5-triaminopyrimidine-6(1*H*)-thione.[7]

The rearrangement of **7** to **10** was unsuccessful in DMSO. However, treatment of a DMSO solution of **7** with aqueous NaOH gave, not **10**, but a mixture of **7** and a compound identified as the 9-aminopurine **16** by comparison of its uv spectrum with that of thioguanine.[8] Presumably **16** results from anion formation at the 1

(1) This investigation was supported by funds from the C. F. Kettering Foundation and Chemotherapy, National Cancer Institute, National Institutes of Health, Contract NIH-71-2021.

(2) For a key reference to the pyrimido[5,4-*e*]-*as*-triazine antibiotics, see E. C. Taylor and F. Sowinski, *J. Amer. Chem. Soc.*, **91**, 2143 (1969).

(3) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, **34**, 3161 (1969).

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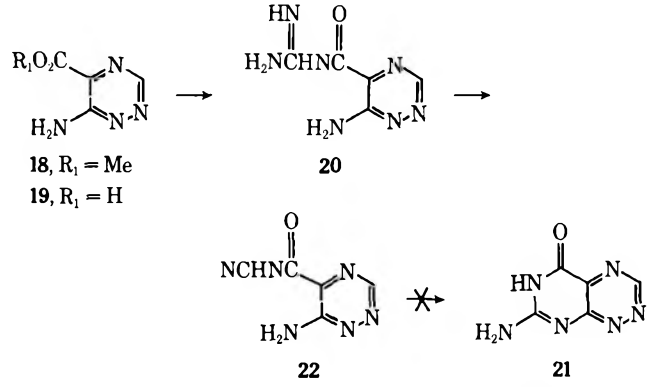
(7) G. B. Elion, W. H. Lange, and G. H. Hitchings, *ibid.*, **78**, 2858 (1956).

(8) G. B. Elion and G. H. Hitchings, *ibid.*, **77**, 1676 (1955).

nitrogen of an intermediate hydrazinopyrimidine.[9] In contrast, the rearrangement of **4** to **8** in a neutral medium involved the 2 nitrogen of an intermediate hydrazinopyrimidine.[3]

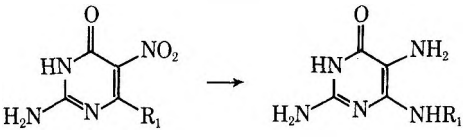
Reaction of **18**[10] with guanidine gave **20**, which was heated at 120° and then refluxed in 2-methoxyethanol to give a sample that was tentatively assigned the structure of either **21** or **22** based on elemental analyses. The tlc of this sample was similar to that of **21** described below; however, the pmr spectrum showed two CH peaks which were attributed to two tautomeric forms of **22**. Support for the latter was provided by the ir and



18, R_1 = Me
19, R_1 = H
20
22
21

uv spectra. The former exhibited two CN bands (2185, 2150 cm^{-1}), and the latter was similar to other *as*-triazines in an acidic medium in that the high wavelength uv peak decreased with time because of covalent hydration of the *as*-triazine ring.[10,11] Also, the conversion of **20** to **21** was unsuccessful when either **20** was heated at 160° or a suspension of **20** in toluene was refluxed. The guanidino group of **20** was hydrolyzed to give the corresponding carboxylic acid **19**[12] in either hot H_2O or PrOH.

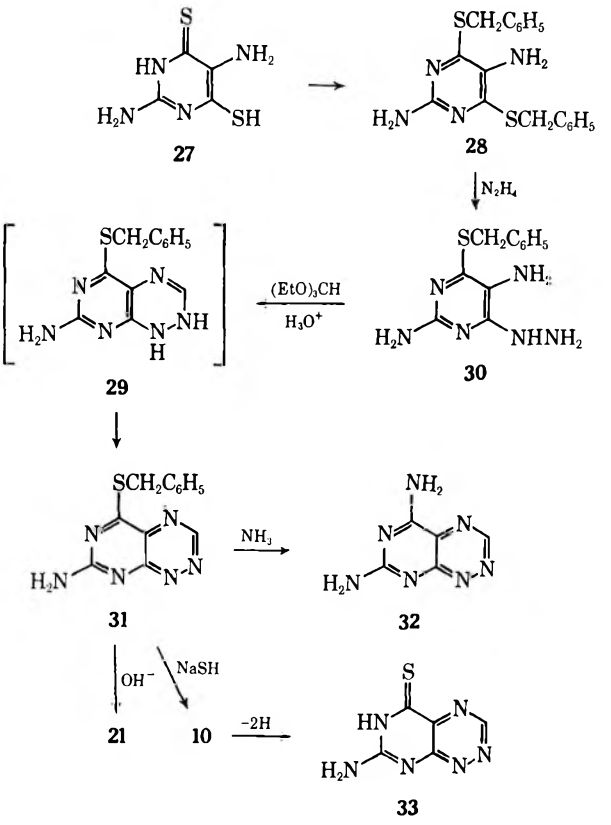
The preparation and cyclization of **25** to give the dihydro derivative of **21** was also unsuccessful. The hydrazinopyrimidine **24** was prepared by treatment of **23**[13] with hydrazine. Reduction of the nitro group of



23, R_1 = Cl
24, R_1 = $NHNH_2$
25, R_1 = NH_2
26, R_1 = H

24 was effected with $Na_2S_2O_4$, but this reagent also cleaved the hydrazino group to give **26**.[14] The catalytic hydrogenation of **24** with either a palladium or rhodium catalyst resulted in the absorption of more than the theoretical amount of hydrogen, presumably also to give **26**.

To circumvent the difficulties encountered with the 5-nitropyrimidine **24**, the 5-aminopyrimidine **27**[5] was used as an intermediate. The benzylation of **27** with benzyl chloride in DMF in the presence of K_2CO_3 gave **28** which was treated with anhydrous hydrazine at 65° to give **30**. The cyclization of **30** was effected with ethyl orthoformate in the presence of hydrochloric acid to give **31**.[9] Presumably **31** was formed by air oxidation of the dihydro intermediate **29**. The cyclization of **30** to either an 8-amino-*s*-triazolo[4,3-*c*]pyrimidine[15]



27
28
29
30
31
32
21
10
33

or a 9-aminopurine[9,16] was excluded by the integrated intensities of the peaks in the pmr spectrum of **31**. Reaction of **31** with aqueous sodium hydroxide in dioxane at 60° replaced the benzylthio group to give **21**. Similarly, treatment of **31** with 10% ethanolic ammonia gave the diamino compound **32**. The interaction of **31** with sodium hydrosulfide not only replaced the benzylthio group but also reduced the *as*-triazine ring to give **10**. The air oxidation of **10** to **33** was attempted by recrystallization of **10** from H_2O. The pmr spectrum indicated that the recovered material was a mixture of **33** and an unidentified compound. The presence of **33** was shown by alkylation of the mixture with $C_6H_5CH_2Cl$ to again give **31**. The oxidation of **10** in DMSO containing aqueous NaOH appeared to give mainly **33**, but the pmr spectrum (overlapping CH peaks) and elemental analyses suggested that hydrolysis of the amino group might have occurred.

The uv and pmr spectra and selected bands in the ir spectra for the new compounds are presented in Table I. The uv spectra of the 7-aminopyrimido[5,4-*e*]-*as*-triazines and the corresponding 2-aminopteridines[17] are dissimilar in that the long wavelength band in the

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TABLE I

Compd	Uv absorption[a] spectra at pH 7, λ_{max}, nm ($\epsilon \times 10^{-3}$)	Ir absorption[b] spectra in KBr, selected bands, cm^{-1}	Pmr spectral assignments,[c] chemical shift, δ (rel area)	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	261 (16.1), 382 (18.8)[d]	1620, 1550		$C_{11}H_{12}N_4S_2$	49.98	4.56	21.19	50.06	4.58	21.12
5			4.25 (3, CH_3), 8.83, 9.33 (1, 1, CH)[e]	$C_6H_7N_5O \cdot 0.5H_2O$[f]	37.88	4.24	36.83	37.77	3.86	36.92
				$C_6H_7N_5O$[f]	39.77	3.89	38.64	40.01	4.07	38.51
7	286 (12.5)	1615, 1610, 1570	4.5 br (2, NH_2), 6.3 br (2, NH_2), 8.62 (1, CH), 8.8 m (1, NH)	$C_5H_6N_6S$	32.95	3.32	46.12	33.03	3.35	46.35
9	252 (10.4), 354 (6.91)[d]	1630, 1585, 1560	3.12 (3, CH_3), 6.78, 7.73 (1, 1, CH)[e]	$C_6H_7N_5S$	39.77	3.89	38.64	39.47	4.10	38.92
10	343 (4.13), 440 (5.66)[d]	1615, 1580	6.28 d, 6.4, ~6.7 br (4, CH, J_{23} = 3.6 Hz, NH_2, 2-NH), 8.58, 10.42 (1, 1, NH)[g]	$C_5H_6N_6S \cdot 0.12\text{-}C_2H_6O$	33.53	3.61	44.76	33.87	3.52	44.89
13	220 (18.5), 256 (14.1), 282 (8.05), 316 (9.45)	1640, 1540, 1515	2.58 (CH_3),[h] 6.90 br (2, NH_2), 8.86 (1, CH)	$C_6H_6N_4S_2$	36.34	3.05	28.26	36.41	3.13	28.43
14	258 (13.5), 285 sh (8.66), 317 (10.4)	1610, 1600, 1535		$C_{12}H_{10}N_4S_2$	52.53	3.67	20.42	52.31	3.80	20.61
15	255 (13.5), 285 sh (8.14), 316 (9.18)	1625, 1540, 1515		$C_7H_8N_4OS_2$	36.83	3.53	24.54	36.72	3.46	24.35
16[i]	264, 341[d]	1645, 1635, 1560	5.8, 6.7, ~11 (NH_2, NH), 7.72 (CH), 8.62 (CH, 7)	$C_5H_6N_6S$	32.95	3.32		32.87	3.32	
17	241 sh (10.1), 358 (4.55)	1640, 1560, 1515	2.75 (3, CH_3), 4.30 (2, CH_2), 6.28 d (1, CH, J_{23} = 3.6 Hz), 7.31 (5, C_6H_5), 7.7 m, 7.77 (2, NH, CH)	$C_{13}H_{13}N_5S$	57.54	4.83	25.82	57.34	4.92	25.51
20	237 (9.28), 363 (2.65)	1695, 1670, 1640	4.9 br (4, NH_2), 7.17 (1, CH), 7.6 br (2, NH)	$C_5H_7N_7O$	33.15	3.89	54.12	33.06	4.08	54.15
21	261 (19.3), 313 sh (1.75), 384 (4.14)[d]	1720, 1660	7.2 br (2, NH_2), 9.55 (1, CH), ~11.7 br (1, NH)	$C_5H_4N_6O$	36.59	2.46	51.20	36.70	2.42	51.22
22	257 sh (4.12), 345 (1.65)	2185, 2150, 1650	7.4 br (NH, NH_2), 8.92 br, 9.31 br (CH)	$C_5H_4N_6O$	36.59	2.46	51.20	36.75	2.35	51.26
24	221 (15.6), 333 (10.2)	1685, 1630, 1540		$C_4H_6N_6O_3 \cdot H_2O$	23.50	3.92	41.20	23.18	3.92	41.67
				$C_4H_6N_6O_3$	25.80	3.23		25.63	3.32	
26	262 (14.6)[j]			$C_4H_7N_5O \cdot H_2SO_4$	20.05	3.76	13.40[k]	19.32	3.88	13.62[k]
28	251 (17.5), 350 (13.3)	1635, 1595, 1520		$C_{18}H_{18}N_4S_2$	60.99	5.12	15.81	60.80	5.29	15.43
30	319 (8.04)	1620, 1600, 1540		$C_{11}H_{14}N_6S$	50.36	5.38	32.03	50.64	5.38	31.77
31	268 (12.4), 352 sh (3.55), 414 (7.15)	1650, 1630, 1565	4.55 (2, CH_2), 7.4 m (5, C_6H_5), 8.0 br (2, NH_2), 9.63 (1, CH)	$C_{12}H_{10}N_6S$	53.32	3.73	31.09	53.13	3.86	31.22
32	263 (16.7), 315 (2.09), 395 (4.07)[d]	1670, 1630, 1580	7.0 br, 8.1 br (2, 2, NH_2), 9.48 (1, CH)	$C_5H_5N_7$	36.81	3.09	60.10	36.65	3.12	59.87

[a] Cary Model 14 and 17 spectrophotometers. [b] Perkin-Elmer Model 521 and 621 spectrophotometers. [c] Pmr spectra of samples were determined on DMSO-d_6 solutions (3–10% w/v), unless otherwise noted, on a Varian A-60A spectrometer with TMS as an internal reference; peak positions quoted in the case of multiplets are measured from the approximate center, and the relative peak areas are given to the nearest whole number. [d] Solvent contains 0.8% DMSO, 9.2% MeOH, and 90% pH 7 buffer. [e] Determined from the spectrum of a mixture of **5** and **9** in CF_3CO_2D (10% w/v). [f] Mixture of **5** and **9**, see Experimental Section. [g] This spectrum also exhibited a weak peak near δ 1.2, which was attributed to the CH_3 of EtOH. [h] This peak overlapped the DMSO-d_5 peak. [i] Determined on a sample that contained both **7** and **16**. [j] Determined in 0.1 *N* HCl in the presence of cysteine. [k] Sulfur.

pyrimidotriazines is more than 25 nm higher than the corresponding band in the pteridines.

Part B

Experimental Section[18]

2,5-Diamino-4-(benzylthio)pyrimidine-6(1*H*)-thione (1).—A solution of **14** (1.0 g) in dioxane (50 ml) containing 95+% hydrazine (1.0 ml) was refluxed for 16 hr. The mixture was filtered, and the filtrate was evaporated to dryness *in vacuo*. The resulting residue was washed with Et_2O (40 ml), then 0.2 *N* HCl (17 ml), and recrystallized from EtOH: yield 0.26 g (27%); mp ~247° dec and presoftening.

7-(1-Methylhydrazino)thiazolo[5,4-*d*]pyrimidine (5) and 1,2-Dihydro-1-methylpyrimido[5,4-*e*]-*as*-triazine-5(6*H*)-thione (9).—A cold solution of **11** (1.0 g)[4] in MeOH (30 ml) was added to a cold solution of methylhydrazine (0.70 ml) in MeOH (10 ml). The mixture was stirred in an ice bath for 1.5 hr, and the solid that deposited was collected by filtration and dried *in vacuo* over P_2O_5, yield 0.42 g. The pmr spectrum in CF_3CO_2D indicated that this product was a mixture of **5** (57%) and **9** (43%). This sample analyzed as the one-half hydrate (see Table I). The filtrate from above was refrigerated for 18 hr to give a second crop, yield 0.16 g. The pmr spectrum indicated that this sample contained both **5** (80%) and **9** (20%). Elemental analyses indicated that an anhydrous mixture was obtained (see Table I). A second run was carried out in ethanol at room temperature. The mixture of **5** (61%) and **9** (39%) was stirred in 1 *N* HCl for 0.5 hr and then dried *in vacuo* over P_2O_5 at 78° for 18 hr to give an 84% yield of anhydrous **9**, mp >264°.

5-Amino-7-hydrazinothiazolo[5,4-*d*]pyrimidine (7).—A solution of **13** (500 mg) and 95+% hydrazine (0.4 ml) in PrOH (20 ml) was refluxed for 2 hr. The solid that deposited was collected by filtration, washed with hot petroleum ether (bp 85–105°), and dried *in vacuo* over P_2O_5, yield 92 mg (20%), mp >264°.

Reactions with 5-Amino-7-hydrazinothiazolo[5,4-*d*]pyrimidine (7).—A solution of **7** (100 mg) in DMSO (20 ml) containing 1 *N* NaOH (0.15 ml) was stirred at room temperature for 18 hr, neutralized with 1 *N* HCl (0.15 ml), and evaporated to dryness *in vacuo*. The resulting residue was washed with H_2O and dried *in vacuo* over P_2O_5 at 78° for 4 hr to give a 1:3 mixture of **7** and **16**, yield 65 mg, mp >264°.

Solid **7** (25 mg) was added to concentrated HCl (2 ml), and the mixture was stirred at room temperature for 18 hr. The HCl salt of **7**, identified by its uv spectrum, was collected by filtration and refluxed in water (10 ml) for 4 hr. After filtration the residue (11 mg) obtained from the filtrate was identified as **2** by comparison of its uv spectrum (0.1 *N* HCl, 310 nm) with that of 2,4,5-triaminopyrimidine-6(1*H*)-thione (0.1 *N* HCl, 310 nm).[7] No reaction was observed when a solution of **7** in 4:1 DMSO–H_2O was heated at 75° for 5 hr.

7-Amino-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine-5(6*H*)-thione (10).—A mixture of **31** (1.0 g) and hydrated NaSH (1.0 g) in H_2O (40 ml) was heated with stirring at 80° for 2.5 hr. After filtration the filtrate was extracted with Et_2O (discarded) and acidified with 1 *N* HCl. The solid that deposited was collected by filtration, washed with C_6H_6 and then with warm EtOH (25 ml), and dried *in vacuo* over P_2O_5 at 140°, yield 0.29 g (43%), mp >264°.

Reactions with 7-Amino-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine-5(6*H*)-thione (10).—A sample of **10** (180 mg) was recrystallized from a large volume of H_2O and dried *in vacuo* over P_2O_5 at 140°, yield 90 mg, mp >264°.

Anal. Calcd for $C_5H_6N_6S$: C, 32.96; H, 3.32; N, 46.12. Found: C, 32.79; H, 3.38; N, 46.33.

Although this sample analyzed correctly for **10**, the pmr spectrum showed that this product was about a 2:1 mixture [δ 9.6 and 7.8 (CH)] of **33** and an unidentified component. The presence of **33** was confirmed by alkylation of the mixture (50 mg) with $C_6H_5CH_2Cl$ in 0.1 *N* NaOH to deposit **31**, yield 44 mg, mp 225° dec.

When a solution of **10** in H_2O was refluxed for 18 hr, the pmr spectrum of the product showed weak CH peaks at δ 9.6 and 7.8 and a strong unidentified peak at δ 9.37.

Treatment of a DMSO solution of **10** (50 mg) with aqueous NaOH gave a mixture (32 mg) that appeared to contain **33** and another unidentified component [δ 9.6, 9.7 (CH)]. Elemental analyses suggested that the second component resulted from hydrolysis of the 7-amino group.

5-Amino-7-(methylthio)thiazolo[5,4-*d*]pyrimidine (13).—A mixture of **12** (1.0 g),[5] CH_3I (0.38 ml), and K_2CO_3 (1.0 g) in DMF (20 ml) was stirred at room temperature for 4 hr, then diluted with 0.1 *N* HCl (90 ml), and evaporated to dryness *in vacuo*. The residue was washed with H_2O (25 ml) and recrystallized from petroleum ether (bp 85–105°), yield 0.64 g (59%), mp 146°.

5-Amino-7-(benzylthio)thiazolo[5,4-*d*]pyrimidine (14) was similarly prepared by stirring a mixture of **12** (1.0 g),[5] K_2CO_3 (0.75 g), and $C_6H_5CH_2Cl$ (0.65 ml) in DMF (30 ml) at room temperature for 18 hr. The resulting residue was extracted with hot $CHCl_3$ (three 60-ml portions); the solid obtained from the combined extracts was recrystallized from benzene–petroleum ether (bp 85–105°), yield 0.69 g (46%), mp 145–146°.

5-Amino-7-[2-(hydroxyethyl)thio]thiazolo[5,4-*d*]pyrimidine (15) was similarly prepared by stirring a mixture of **12** (1.0 g),[5] 2-bromoethanol (0.38 ml), and anhydrous K_2CO_3 (0.75 g) in DMF (10 ml) at room temperature for 18 hr. The resulting residue was extracted with hot C_6H_6 (200 ml), which was cooled to deposit the product in two crops, yield 0.48 g (39%), mp 118–119°.

5-(Benzylthio)-1,2-dihydro-1-methylpyrimido[5,4-*e*]-*as*-triazine (17).—A mixture of **9** (1.6 g), $C_6H_5CH_2Cl$ (1.1 ml), and anhydrous K_2CO_3 (1.3 g) in DMF (20 ml) was stirred at room temperature for 18 hr. The mixture was evaporated to dryness *in vacuo*, and the residue was extracted with ether (three 100-ml portions). The solid obtained from the combined extracts was recrystallized from petroleum ether (bp 85–105°), yield 1.47 g (59.5%), mp 131° dec.

***N*-Amidino-6-amino-*as*-triazine-5-carboxamide (20).**—A mixture of **18** (2.0 g),[10] guanidine HCl (1.4 g), and NaOMe (0.76 g) in MeOH (25 ml) was stirred at room temperature for **18** hr. The solid was collected by filtration, washed with EtOH, and dried *in vacuo* over P_2O_5 at 56°, yield 1.7 g (72%), mp >264°.

***N*-Cyano-6-amino-*as*-triazine-5-carboxamide (22).**—Solid **20** (146 mg) was heated at 120° for 1 hr and then dissolved in 2-methoxyethanol (10 ml). The resulting solution was refluxed for 7 hr and evaporated to dryness *in vacuo*. This hygroscopic residue was washed with ether to give **22**, yield 127 mg (96%), melting point indefinite.

7-Aminopyrimido[5,4-*e*]-*as*-triazin-5(6*H*)-one (21).—A solution of **31** (1.1 g) in 1:2 dioxane–H_2O (60 ml) containing 1 *N* NaOH (8.0 ml) was heated with stirring at 60° for 2 hr. The reaction mixture was filtered, and the filtrate was neutralized with 1 *N* HCl (8.0 ml). The precipitate that deposited was collected by filtration and washed with Et_2O (two 50-ml portions). This solid was recrystallized twice from HOAc and dried *in vacuo* over P_2O_5 at 100° for 4 hr, yield 0.20 g (30%), mp >264°.

2-Amino-4-hydrazino-5-nitropyrimidin-6(1*H*)-one (24).—Anhydrous hydrazine (0.1 ml) was added to a suspension of **23** (200 mg)[13] in MeOH (10 ml), and the mixture was stirred at room temperature for 2.5 hr. The solid was collected by filtration, washed with MeOH, and dried *in vacuo* over P_2O_5 to give the hydrate, yield 200 mg (93%), mp >264°. This material was reprecipitated from DMSO with EtOH and dried at 100° to give anhydrous **24**.

Reduction of 24.—Solid $Na_2S_2O_4$ (4 g) was added with stirring over a 10-min period to a refluxing suspension of **24** (1.0 g) in H_2O (30 ml). The hot mixture was filtered directly into cold 4 *N* H_2SO_4. After 1.5 hr the solid that deposited was collected by filtration and recrystallized from 2 *N* H_2SO_4 to give **26**·H_2SO_4, yield 0.26 g (20%), mp >264°.

2,5-Diamino-4,6-bis(benzylthio)pyrimidine (28).—A mixture of the semisulfate hydrate of **27** (9.0 g),[5] K_2CO_3 (16 g), and $C_6H_5CH_2Cl$ (8.7 ml) in DMF (180 ml) was stirred at room temperature for 18 hr and then diluted with H_2O (900 ml). The oil that deposited was extracted with ether (three 1000-ml portions). The combined extracts were dried ($MgSO_4$), evaporated to dryness *in vacuo*, and the resulting oil stirred vigorously in ice–water to give a pink solid, yield 9.0 g (68%), mp ~73°. The analytical sample was obtained by recrystallization from hexane, mp 75°.

2,5-Diamino-4-(benzylthio)-6-hydrazinopyrimidine (30).—A solution of **28** (3.0 g) in 95+% hydrazine (30 ml) was heated with stirring at 65° for 18 hr and evaporated to dryness *in vacuo*. This residue was washed with hot petroleum ether (three 100-ml portions) and then extracted with $CHCl_3$ (300 ml). The extract was evaporated to dryness *in vacuo* to give practically pure **30**, yield 1.4 g (63%). For analyses a sample (390 mg) was recrys-

(18) Melting points were determined in a Kofler–Heizbank apparatus.

tallized from H_2O, yield 145 mg (50% recovery), mp 144° dec with presoftening from 139°.

7-Amino-5-(benzylthio)pyrimido[5,4-*e*]-*as*-triazine (31).—To a suspension of **30** (5.0 g) in H_2O (250 ml) containing 1 *N* HCl (2.5 ml) was added $(EtO)_3CH$ (75 ml) with vigorous stirring. The mixture became oily and then resolidified. After 3 hr the crude product was collected by filtration and dried *in vacuo* over P_2O_5, yield 4.4 g (85%). For analyses a sample (860 mg) was recrystallized from MeCN, yield 650 mg (76% recovery), mp 226° dec.

5,7-Diaminopyrimido[5,4-*e*]-*as*-triazine (32).—Solid **31** (2.0 g) was added with stirring to 10% ethanolic ammonia (40 ml), which was cooled in an ice bath. After 30 min the ice bath was removed, and the reaction mixture was stirred at room temperature for 18 hr. The solid was collected by filtration, recrystallized from a large volume of H_2O, and dried *in vacuo* over P_2O_5 at 78°, yield 0.50 g (41%), mp >264°.

Registry No.—**1**, 31739-65-8; **5**, 31739-66-9; **7**, 31739-67-0; **9**, 31739-68-1; **10**, 31791-00-1; **13**, 31739-69-2; **14**, 31739-70-5; **15**, 31739-71-6; **16**, 31739-72-7; **17**, 31791-01-2; **20**, 31736-42-2; **21**, 31791-02-3; **22**, 31736-43-3; **24**, 31736-44-4; **26**, 23706-18-5; **28**, 31736-46-6; **30**, 31736-47-7; **31**, 31736-48-8; **32**, 31736-49-9.

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Bridgehead Nitrogen Heterocycles. I. The 2*H*(and 4*H*)-Pyrimido[1,2-*b*]pyridazin-2(and 4)-one, 3*H*-Imidazo[1,2-*b*]pyridazin-2-one, and 7*H*-1,3,4-Thiadiazolo[3,2-*a*]pyrimidin-7-one Systems

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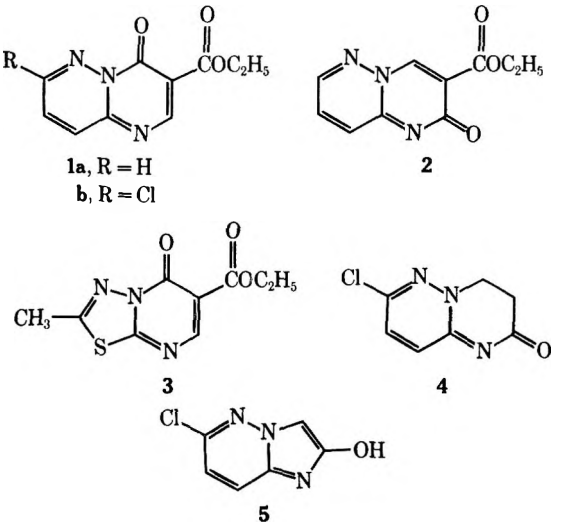
The title compounds have been synthesized by condensation of 3-amino-6-chloropyridazine and 2-amino-1,3,4-thiadiazole with several 3-chloroacrylic and atropic acids (and acid chlorides). Nucleophilic replacement reactions of some chloro-substituted 2*H*-pyrimido[1,2-*b*]pyridazin-2-ones are reported. Structural assignments are based on chemical evidence, ir, nmr, and mass spectral data. A brief analysis of the results is reported.

Of the isomeric pyrimido[1,2-*b*]pyridazinone and the 1,3,4-thiadiazolo[3,2-a]pyrimidone systems, only representatives of 4*H*-pyrimido[1,2-*b*]pyridazin-4-one[2] and 4*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-4-one[3,4] are known. The first report of the synthesis of the pyrimido[1,2-*b*]-pyridazinone ring system appeared in 1968 and came to our attention during the course of our own investigations. The condensation of 3-aminopyridazine with ethyl ethoxymethylenemalonate was reported by Stanovnik and Tišler[2] to afford ethyl 3-pyridazinylaminomethylenemalonate, which cyclized in refluxing diphenyl ether to give 3-ethoxycarbonyl-4*H*-pyrimido-[1,2-*b*]pyridazin-4-one (**1a**). The corresponding intermediate was prepared from 3-amino-6-chloropyridazine, but efforts to cyclize it to **1b** were unsuccessful. Structure **2**, resulting from initial condensation of 3-aminopyridazine with the ester carbonyl of ethyl ethoxymethylenemalonate, was rejected on the basis of the evidence for the intermediate and upon examination of spectroscopic data. An earlier report[3] describes a similar route to the 4*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-4-one system starting with 2-amino-5-methyl-1,3,4-thiadiazole and ethyl ethoxymethylenemalonate. Levin, *et al.*,[4] described these two reactants as yielding ethyl 5-methyl-1,3,4-thiadiazol-2-ylaminomethylenemalonate, which ring closed to the bicyclic product **3** on prolonged heating at elevated temperature under reduced pressure. Tišler and coworkers[5] have recently described the preparation of 6-chloro-2-hydroximidazo-[1,2-*b*]pyridazine (**4**) and 7-chloro-3,4-dihydropyrimido-[1,2-*b*]pyridazin-2-one (**5**) by fusion of 3-amino-2-(ethoxycarbonylalkyl)-6-chloropyridazinium bromides.



We wish to report the reaction of chlorinated acrylic and atropic acids (and acid chlorides) with 3-amino-6-chloropyridazine and 2-amino-5-(methylthio)-1,3,4-thiadiazole, which gave derivatives of 2*H*(and 4*H*)-pyrimido[1,2-*b*]pyridazin-2-(and 4)-one, 3*H*-imidazo-[1,2-*b*]pyridazin-2-one, and 7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one.

(1) To whom correspondence should be addressed.

(2) B. Stanovnik and M. Tišler, *Tetrahedron Lett.*, 33 (1968).

(3) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, I. F. Tinker, and J. A. Van Allan, *J. Org. Chem.*, **24**, 779 (1959).

(4) Ya. A. Levin, N. A. Shvink, and V. A. Kukhtin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **8**, 1481 (1964); *Chem. Abstr.*, **64**, 19595 (1966).

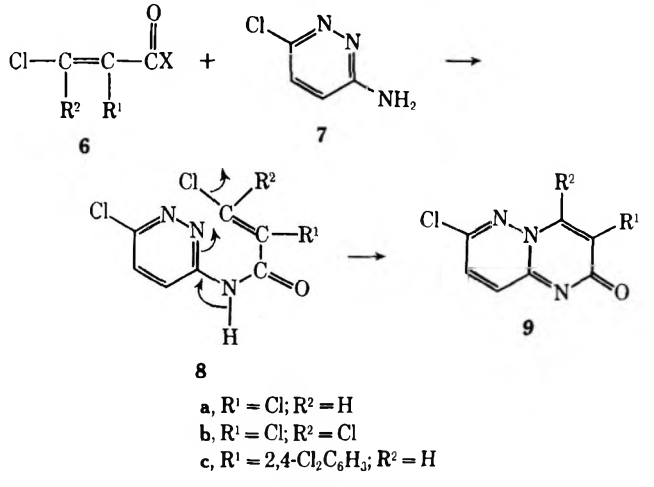
(5) S. Ostroversnik, B. Stanovnik, and M. Tišler, *Croat. Chem. Acta*, **41**, 135 (1969); *Chem. Abstr.*, **72**, 12684 (1970).

Results and Discussion

2*H*(and 4*H*)-Pyrimido[1,2-*b*]pyridazin-2(and 4)-one Systems.—A literature[6] synthesis of 2*H*-pyrido[1,2-*a*]pyrimidin-2-one suggested to us that entry into the desired pyrimido[1,2-*b*]pyridazinone system might be obtainable through a similar condensation involving a suitable substituted derivative of β-chloroacrylic or β-chloroatropic acid (**6**) and 3-amino-6-chloropyridazine (**7**). The reaction of heterocyclic amines having the amidine structure with derivatives of **6** is complicated by the presence in both molecules of two centers of similar reactivity, and it is frequently difficult to present unequivocal proof of structure of the reaction products.

The first β-chloroacrylic acid examined was the readiy available α,β-dichloroacrylic acid **6a** (X = OH). Fusion with **7** at 190° led to isolation of **9a** in 16% yield; when, however, the intermediate acrylamide **8a** was first prepared by conventional means and cyclization of the latter was carried out in refluxing xylene (2.5 hr), the yield of **9a** rose to 84%. Compound **9a** is colorless, melts at 277–278° with decomposition, is insoluble in hexane and benzene, and may be recrystallized from water. Analytical, spectroscopic, and mass spectral data (see Experimental Section) clearly establish that ring closure has occurred. Structures with NH or OH groups can be eliminated from consideration since bands for these groups are absent from both the ir and nmr spectra.

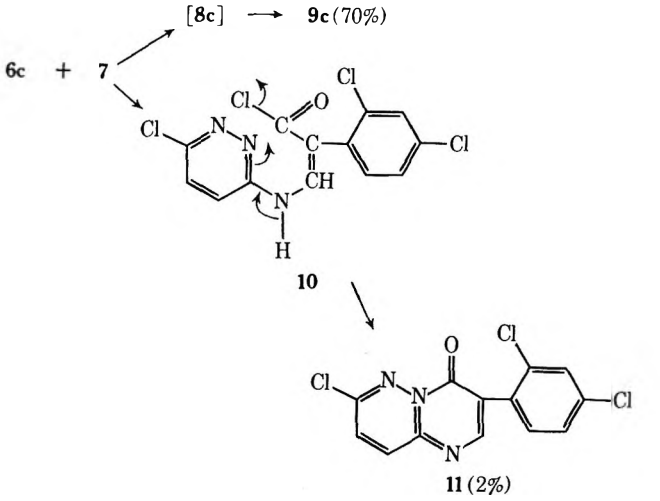
Fusion of the similarly constituted trichloroacrylamide **8b** proceeded more sluggishly (18 hr in refluxing xylene) to give the expected heterocycle **9b** in 69% yield. At higher temperature, cyclodehydrochlorination of **8b** took a different course, the results of which will be discussed in the next section.



6 **7** **8** **9**

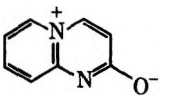
a, $R^1 = Cl$; $R^2 = H$
b, $R^1 = Cl$; $R^2 = Cl$
c, $R^1 = 2,4\text{-}Cl_2C_6H_3$; $R^2 = H$

Both (*Z*)-β-2,4-trichloroatropic acid **6c** (X = OH) and the corresponding atropoyl chloride **6c** (X = Cl) reacted with **7** to give the fused heterocycle **9c**. Thus, when **7** and **6c** (X = OH) were fused at 170–180° for 10 min, **9c** was obtained in 31% yield; intermediates such as **8c** and **10** could not be detected in the reaction mixture. When the reaction described above was carried out in polyphosphoric acid (3 hr at 170°), the only product obtained (34%) was **9c**. However, when **7** was allowed to react with **6c** (X = Cl) in tetrahydrofuran at 66° in the presence of triethylamine, reaction conditions which normally provided the intermediate amides **8**, the products isolated were **9c** (70%) and **11** (2%). The formation of **9c** from **6c** (X = Cl) and **7** indicates that



the fused ring system is most likely formed *via* intermediate **8c**. As **6c** (X = Cl) is an acid chloride, it would be expected to form the hypothetical amide **8c** first, followed by an extremely facile ring closure. The formation of **9c** from **6c** (X = OH) and **7** can also be rationalized as proceeding *via* intermediate **8c**.[7] The formation of **11** may involve nucleophilic displacement by the amino group of **7** of the β-chlorine atom in **6c** (X = Cl) to give the β-aminoatropic acid derivative **10**, which would cyclize to the 4*H*-pyrimido[1,2-*b*]pyridazin-4-one (**11**) system.

Both **9c** and **11** are colorless compounds. Compound **11**, the 4-one, melts at 195–198° with decomposition, has a high R_f value in nonpolar solvents, and may be recrystallized from benzene and hexane. Compound **9c**, the 2-one, on the other hand, melts at 240–243°, is only sparingly soluble in refluxing benzene, and has a low R_f value in polar solvents. Adams and Pachter[6] report similar differences in physical properties for the similarly constituted pyrido[1,2-*a*]pyrimidin-4-one and pyrido[1,2-*a*]pyrimidin-2-one; these authors suggest that fully aromatic structures such as **12** contribute



12

largely to the resonance hybrid of the 2-one. The structural dissimilarity of **9c** and **11** is also indicated by differences in their ir spectra. Ir absorption at $\nu_{C=O}$ 1643 cm^{-1} for **9c** and $\nu_{C=O}$ 1708 cm^{-1} for **11** is in agreement with and confirms[9] the expectation that the isomeric 2-one (**9c**) would be expected to absorb at a longer wavelength than the 4-one **11**.

(6) R. Adams and I. Pachter, *J. Amer. Chem. Soc.*, **74**, 5491 (1952).

(7) In agreement with this mechanism it has been found[8] that carboxylic acids react with weakly basic amines in the presence of polyphosphoric acid to yield the corresponding amides.

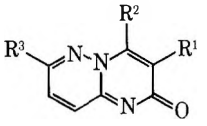
(8) H. R. Snyder and C. T. Elston, *J. Amer. Chem. Soc.*, **76**, 3039 (1954).

(9) According to ref 3 members of the 2-one series have carbonyl absorption at 1667 cm^{-1}, whereas the 4-one series has a band at shorter wavelengths.

The displacement of chlorine in both the 4 and 7 positions of **9** was quite facile, and reactions of methylamine and sodium methylmercaptide with **9a–c** led to additional products **17–21** listed in Table I. Monosubstituted products of **9b** were not isolated and the 3-chlorine atom in **9a** and **9b** was inert under the conditions employed.

TABLE I

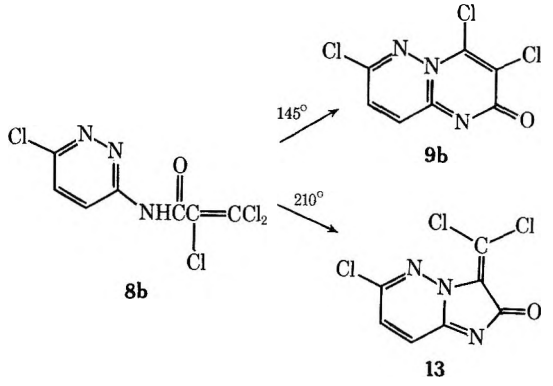
2*H*-PYRIMIDO[1,2-*b*]PYRIDAZIN-2-ONES[a]



Compd	R¹	R²	R³	Mp, °C	Ir data, $\nu_{C=O}$, cm⁻¹
9a	Cl	H	Cl	275–277[b]	1652
17	Cl	H	CH_3S[c]	240[b]	1645
9b	Cl	Cl	Cl	285–289[b]	1650
18	Cl	CH_3S	CH_3S[c]	203–206	1641
9c	2,4-$Cl_2C_6H_3$	H	Cl	235	1643
19	2,4-$Cl_2C_6H_3$	H	$NHCH_3$	>300	1635
20	2,4-$Cl_2C_6H_3$	H	CH_3S	192–194	1642
21	2,4-$Cl_2C_6H_3$	H	CH_3SO_2	130[b]	1650

[a] Satisfactory analytical data (±0.3% for C and H) were reported for all compounds in this table; Cl analyses were reported for all except **17**; N analyses for all except **21**; S analyses were reported for **18** and **20**: Ed. [b] With decomposition. [c] Oxidation with 33% H_2O_2 in CH_3CO_2H afforded water-soluble products from which sulfone could not be isolated.

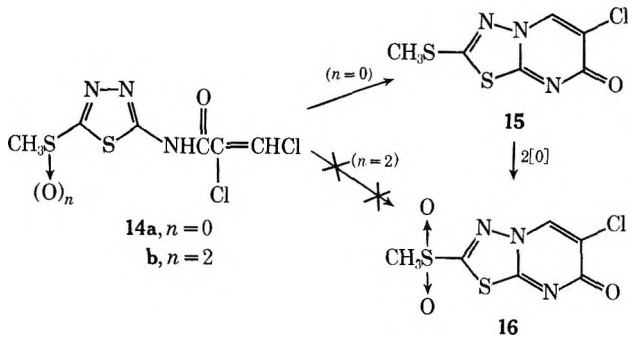
The 3*H*-Imidazo[1,2-*b*]pyridazin-2-one System.—Entry into the 3*H*-imidazo[1,2-*b*]pyridazin-2-one system was obtained unexpectedly when it was discovered that fusion of **8b** led to cyclization involving either the α or β chlorine atom, depending upon the reaction temperature. Thus, when **8b** was refluxed in xylene at 140° for a period of 6 hr, the heterocycle **9b** described above was obtained. However, when the cyclization was carried out in 1,2,4-trichlorobenzene at 210° for 20 min, **9b** could not be isolated from the reaction mixture. Instead, 6-chloro-3-dichloromethylene-3*H*-imidazo[1,2-*b*]pyridazin-2-one (**13**) was formed.



Since **9b** and **13** are not in practice thermally interconvertible (at 210°), it is concluded that the former is not a precursor in the formation of **13**. The structural dissimilarity of **9b** and **13** is indicated by differences in melting point, R_f value, and ir and mass spectrum. The 1700-cm⁻¹ region in the ir spectra proved to be of analytical interest. From the location of the carbonyl absorption bands, it was possible to characterize the ring size. For example, ir absorption at $\nu_{C=O}$ 1650 cm⁻¹ for **9b** and $\nu_{C=O}$ 1710 cm⁻¹ for **13** is in agreement[10] with the expectation that an increased ring strain will result in a shift toward higher frequencies as one proceeds from a six-membered ring such as **9b** to a more strained five-membered ring structure such as **13**.

The nmr spectrum of **13** is simple, showing the expected proton count and shifts of two aromatic protons at 7.9 and 8.15 ppm. Mass spectra were shown to be a valuable and reliable tool in the deduction of the structures of the isomers **9b** and **13**. The fragmentation patterns are in accord with their structural assignment and indicate the molecular arrangement of the respective C_2Cl_2 fragments in both isomers. For example, the prominent ion *m/e* 94 (C_2Cl_2) from **13** is not observed in the mass spectrum of **9b**. Because of its high degree of symmetry, dichloroacetylene (ClC≡CCl) may leave the ionization chamber without apparent ionization. This is no doubt due to the higher ionization potential and the reluctance of this molecule to hold a formal positive charge.

The 7*H*-1,3,4-Thiadiazolo[3,2-*a*]pyrimidin-7-one System.—5*H*-1,3,4-Thiadiazolo[3,2-*a*]pyrimidin-5-ones have previously been synthesized from a 5-substituted 2-amino-1,3,4-thiadiazole and ethyl ethoxymethylenemalonate.[3,11] We have now investigated an approach which builds up the 7-one system from a β-chloro-*N*-1,3,4-thiadiazol-2-ylacrylamide. 2-Amino-5-(methylthio)-1,3,4-thiadiazole (mp 174–178°) is readily prepared from 2-amino-5-mercapto-1,3,4-thiadiazole[12] by methylation and yielded the acrylamide **14a** on treatment with 2,3-dichloroacryloyl chloride in 96% yield. When **14a** was heated for 45 min in refluxing 1,2,4-trichlorobenzene, **15** was obtained in 35% yield; oxidation gave the corresponding sulfone **16** (62%). All efforts to achieve cyclization of sulfone **14b** to the corresponding heterocycle **16** directly were unfruitful. The failure of **14b** to cyclize is presumably due to the electronegativity of the methylsulfonyl group, which prevents the development of a negative charge on the hetero amidine nitrogen atom, whereas the methylthio group does not prevent this cyclization.



Experimental Section

Reaction of 3-Amino-6-chloropyridazine (7) with 2,3-Dichloroacrylic Acid 6a (X = OH).—An intimate mixture of 6a (6.5 g,

(10) L. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 213.

(11) L. B. Dashkevich and E. S. Korbelainen, *Khim. Geterotsikl. Soedin.*, 441 (1968); *Chem. Abstr.*, **69**, 96645 (1968).

(12) T. Sandstrom, *Acta Chem. Scand.*, **15**, 1295 (1961).

46 mmol) and **7** (2.6 g, 20 mmol) was heated with stirring in an oil bath at 150°. When the temperature of the melt reached 140°, an exothermic reaction accompanied by evolution of hydrogen chloride took place and the internal temperature rose rapidly to 190°. The reaction was complete within 10 min and the temperature dropped to 160°, at which point gas evolution ceased. The cooled reaction mixture was extracted with 150 ml of boiling benzene, and the extract was dried ($MgSO_4$) and decolorized (Norit). Evaporation of the solvent provided 2 g of an oil. Trituration with 5 ml of methanol gave 0.7 g (16%) of **9a**, a brown solid melting at 271–272° dec. Recrystallization from boiling water gave **9a** as a colorless solid melting at 277–278° dec: ir (KBr) 3050 (CH=), 1652 (C=O), and 1631 cm^{-1} (C=N); nmr (DMSO-d_6) δ 7.75 (s, 2, CH=CH) and 9.0 ppm (s, 1, NCH=); nmr (CF_3CO_2H) δ 8.30 (d, 2, J = 9 Hz, CH=CH) and 8.93 ppm (s, 1, NCH=); mass spectrum (70 eV) m/e 215 and 217 (M^+).

2,3-Dichloro-*N*-(6-chloropyridazin-3-yl)acrylamide (8a).—A solution of 6.5 g (46 mmol) of **7** in 50 ml of DMF, prepared by warming to 50°, was added dropwise during an interval of 15 min to a stirred solution of **6a** (X = Cl) (4.0 g, 25 mmol) in 25 ml of DMF. The addition was exothermic, the temperature rising rapidly to 65°. Heating at 70° was continued for 15 min, whereupon the reaction mixture was poured into 150 ml of cold water with brisk agitation. The solid was collected by filtration and washed with cold water. The crude product was recrystallized from benzene to give 6.0 g (95%) of **8a**, yellow solid melting at 161–163°.

Compound **8a** was also prepared in 64% yield using a 2:1 molar ratio of **7** and **6a** (X = Cl), and in 71% yield from equimolar amounts of the reagents in DMF in the presence of triethylamine as an acid acceptor: ir (KBr) 3440, 3375 (NH), 3085 (CH=), 1690 (C=O), 1640 (C=, weak), 1590, 1575 cm^{-1} (amide II); nmr ($CDCl_3$) δ 7.5 (d, 1, J = 9 Hz, CH=), 8.5 (d, 1, J = 9 Hz, CH=), and 7.8 (s, 1, CHCl=).

Anal. Calcd for $C_7H_4Cl_3N_3O$: C, 33.3; H, 1.6; Cl, 42.2; N, 16.6 Found: C, 33.1; H, 1.7; Cl, 42.6; N, 16.7.

Fusion of 8a. A. With 1,2,4-Trichlorobenzene as Solvent.—A solution of **8a** (10.0 g, 39.6 mmol) in 75 ml of 1,2,4-trichlorobenzene was heated to 200–210° for 1 hr. Evolution of HCl was detected. The dark reaction mixture was cooled to 20° and filtered. The filter cake (6.5 g) was recrystallized from boiling water to give 6.0 g (70.5%) of **9a** melting at 277–278° dec. The identity of this product with that described above was confirmed by tlc (different solvent systems) and a mixture melting point and verified by identical mass and ir spectra.

B. With Xylene as Solvent.—A suspension of **8a**, 45.0 g (0.178 mol), in 250 ml of xylene was heated to reflux for 2.5 hr. The mixture became increasingly darker as HCl evolved. The reaction mixture was cooled to 20°, filtered, and washed with hexane, yield 32 g (84%) of tan solid melting at 275–277°. This product was identical (tlc, mixture melting point, ir) with **9a**.

3-Chloro-7-(methylthio)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (17).—To a solution of 9.0 g (41.6 mmol) of **9a** in 100 ml of dimethylsulfoxide containing 5.0 g (104 mmol) of methyl mercaptan sodium methoxide (2.4 g, 44.5 mmol) in 25 ml of dimethyl sulfoxide was added dropwise within 10 min, causing an exothermic reaction which was controlled at 30° with an ice bath. The mixture was stirred at 25–30° for 1.5 hr and then poured over ice water and filtered. The solid was recrystallized from methanol to yield 3.0 g (32%) of **17**, tan crystalline solid, mp 240° dec.

2,3,3-Trichloro-*N*-(6-chloropyridazin-3-yl)acrylamide (8b).—A suspension of **7** (32.4 g, 0.25 mol) and triethylamine (25.3 g, 0.25 mol) in 500 ml of tetrahydrofuran was stirred and controlled at 30° during the dropwise addition of **6b** (X = Cl). After completion of the addition, the mixture was heated to 60° for 1 hr and then poured into ice water. The products were extracted into methylene chloride, dried ($MgSO_4$), filtered, and concentrated to dryness. Recrystallization from methanol afforded 48.4 g (66%) of **8b**, colorless crystalline solid melting at 124–126°: ir (KBr) 3380, 3200 (NH), 1705 (C=O), and 1510 cm^{-1} (amide II).

Anal. Calcd for $C_7H_3Cl_4N_3O$: Cl, 49.5; N, 14.6. Found: Cl, 49.5; N, 14.6.

Fusion of 8b. A. With Xylene as Solvent.—A solution of **8b** (14.0 g, 0.05 mol) in 100 ml of xylene was heated at reflux for 6 hr. The mixture was cooled and filtered. Recrystallization from methanol afforded 3.0 g (24%) of **9b**, white crystalline solid melting at 285–289°: ir (KBr) 3080, 3050 (CH=), 1650 (C=O), 1609, 1585 cm^{-1} (C=); nmr (CF_3CO_2H) δ 8.28 ppm (q, J = 9 Hz, CH=CH), very similar to that of **9a**; mass spectrum (70 eV) (ions with a relative abundance of >5%) 249, 221, 214, 186, 155, 108, 99, 73, 64.

B. With 1,2,4-Trichlorobenzene as Solvent.—A solution of 13.0 g (45 mmol) of **8b** in 50 ml of 1,2,4-trichlorobenzene was heated at reflux for 20 min. Acidic gases evolved and the mixture became a dark solution. The mixture was cooled to 25° and diluted with 50 ml of hexane. The resultant precipitate (9.5 g) was filtered and recrystallized from methanol to yield 6.5 g (59%) of **13**, tan crystalline solid melting at 207–210°: ir (KBr) 1710 cm^{-1} (C=O); nmr (CF_3CO_2H) δ 7.8 (d, 1, J = 9.5 Hz, CH=) and 8.15 ppm (d, 1, J = 9.5 Hz, CH=); mass spectrum (70 eV) (ions with a relative abundance >5%) 249, 221, 214, 186, 108, 94, 73, 64.

Anal. Calcd for $C_7H_2Cl_3N_3O$: Cl, 42.5; N, 16.8. Found: Cl, 42.3; N, 16.5.

3-Chloro-4,7-bis(methylthio)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (18).—A solution of 12.5 g (0.05 mol) of **9b** in 150 ml of methanol was stirred during the dropwise addition of a previously prepared solution of 2.3 g of metallic sodium in 100 ml of methanol and 6 g (0.125 mol) of methyl mercaptan. The addition was exothermic to 45° and the reaction mixture was heated to 60° for 1.5 hr. The product was chilled to 5° and filtered. The filter cake was recrystallized from methanol to yield 12.0 g (88%) of **18**, tan crystalline solid melting at 203–206°: ir (KBr) 1641 (C=O), 1610, 1557 cm^{-1}; (C=); nmr (CF_3CO_2H) δ 2.8, 2.9 (s, 3, SCH_3), and 8.0 ppm (s, 1, CH=).

2,4-Dichloro-α-(chloromethyl)mandelonitrile.—A 105-g portion (0.47 mol) of 2,2′,4′-trichloroacetophenone (mp 56–59°) and approximately 0.5 ml of saturated, aqueous potassium cyanide were placed in a 1-l. three-necked flask equipped with a water-cooled dropping funnel and efficient reflux condenser. Liquid hydrogen cyanide (50 ml) was added rapidly producing almost immediate solution of the solid ketone. A mild exothermic reaction occurred and the HCN refluxed gently at 32°. After about 15 min, the reaction subsided, and external warming was provided to maintain reflux at 30–32° for 30 min longer. The colorless solution was cooled at 25° and a few drops of concentrated sulfuric acid were added to stabilize the cyanohydrin. Excess HCN was removed under reduced pressure into a KOH trap, causing the residual cyanohydrin to solidify. The product was triturated with hexane to remove traces of unreacted ketone and used without further purification after being dried *in vacuo*. The yield was 113 g (96%), mp 97–98°.

Anal. Calcd for $C_9H_6Cl_3NO$: Cl, 42.5. Found: Cl, 42.9.

(*Z*)-β,2,4-Trichloroatropamide.—2,4-Dichloro-α-(chloromethyl)-mandelonitrile (15 g, 0.05 mol) was suspended in 100 ml of concentrated sulfuric acid and heated on the steam bath, causing the solid to dissolve rapidly. After 30 min at 95°, the dark colored, opaque solution was collected by filtration and recrystallized from CCl_4, yielding 12 g (96%): mp 101–102°; ir (KBr) 3450, 3220 (NH), and 1669 cm^{-1} (C=O); nmr ($CDCl_3$) δ 6.2, 7.2 (s, 2, NH), 6.55 (s, 1, CH=), and 7.3 ppm (m, 3, C_6H_3).

Anal. Calcd for $C_9H_6Cl_3NO$: Cl, 42.5; N, 5.6. Found: Cl, 42.8; N, 5.2.

(*Z*)-β,2,4-Trichloroatropic Acid (6c, X = OH).—To a solution of 25.1 g (0.1 mol) of β,2,4-trichloroatropamide in 95 ml of concentrated sulfuric acid was added gradually at 0–15° a solution of 9.0 g of sodium nitrite in 30 ml of water. The mixture was then heated over the steam bath at 95° for 4 hr until gas evolution ceased. The cooled solution was poured over ice and the solid product was recrystallized from CCl_4. The colorless crystalline acid, 15.1 g (60%), melted at 94–97°: nmr ($CDCl_3$) δ 6.83 (s, 1, CH=) and 7.25 and 7.43 ppm (m, 3, C_6H_3).

Anal. Calcd for $C_9H_5Cl_3O_2$: Cl, 42.3; acid equiv, 250.5. Found: Cl, 42.4; acid equiv, 226.

Reaction of 3-Amino-6-chloropyridazine (7) with (*Z*)-β,2,4-Trichloroatropic Acid (6c, X = OH). A. Without Solvent.—An intimate mixture of **6c** (X = OH) (5.0 g, 0.02 mol) and **7** (2.6 g, 0.02 mol) was heated in an oil bath at 170–180° for 10 min, the solid mass melting with evolution of gas to form a dark liquid melt. The product was extracted with boiling benzene, dried ($MgSO_4$), and concentrated to dryness. Trituration with hexane gave 2.0 g (31%) of **9c**, yellow solid melting sharply at 235° (238–239° dec): ir (KBr) 3090, 3055 (CH=), 1643 (C=O), 1601, 1590 cm^{-1} (C=); nmr (DMSO-d_6) δ 7.3–7.7 (m, 3, C_6H_3), 7.73 (s, 2, CH=), and 8.62 ppm (s, 1, CH=).

B. With Polyphosphoric Acid as Solvent.—When the reaction described above was carried out in 30 ml of polyphosphoric acid

at 170° over a period of 3 hr, the only product isolated (34%) was **9c**.

Reaction of 3-Amino-6-chloropyridazine (7) with β-2,4-Trichloroatropoyl Chloride (6c, X = Cl).—A solution of 16.0 g (0.059 mol) of **6c**[13] (X = Cl) in 50 ml of tetrahydrofuran was added dropwise with stirring to a slurry of 8.0 g (0.061 mol) of **7** and 6.0 (0.061 mol) of triethylamine in 350 ml of tetrahydrofuran at 55°. During the period of addition (30 min), the temperature was maintained at 55°. Heating was then resumed at reflux (66°) for 2.5 hr. Triethylamine hydrohloride was removed by filtration, and the residual solution was concentrated and poured into water. The product was extracted with cold benzene; the insoluble solid, 13.6 g (70%) of **9c**, melted at 238–241° dec. Evaporation of the benzene provided 2 g of a brown solid which was purified by column chromatography over silica gel using acetone as eluent: yield 0.4 g (2%) of **11**; pale yellow solid melting at 195–198° dec; ir (KBr) 3095 (CH=) and 1708 cm^{-1} (C=O); nmr (DMSO-d_6) δ 7.5, 7.7 (m, 3, C_6H_3), 8.0 (d, 2, J = 9 Hz, CH=CH) and 8.35 ppm (s, 1, CH=).

Anal. Calcd for $C_{13}H_6Cl_3N_3O$: Cl, 32.7. Found: Cl, 32.5.

The reaction repeated at a lower temperature (30°) on a larger scale (0.1 mol) gave 15 g (46%) of **9c**, mp 240–243° dec. No other product was isolated. The identity of this product and **9c** (see above) was confirmed by tlc (different solvent systems) and mixture melting point and verified by identical ir spectra.

3-(2,4-Dichlorophenyl)-7-(methylamino)-2*H*-pyrimido[1,2-*b*]-pyridazin-2-one (19).—A suspension of **9c** (0.5 g, 1.5 mmol in 70 ml of 40% aqueous methylamine was heated on a water bath at 60–82° (final temperature) for 1 hr. The product was filtered and washed successively with water and acetone to give 0.45 g (94%) of **19**, tan solid melting at >300°: ir (KBr) 3240 (NH), 3060 (CH=), 1635 (C=O), 1600, 1580 cm^{-1} (C=).

3-(2,4-Dichlorophenyl)-7-(methylthio)-2*H*-pyrimido[1,2-*b*]-pyridazin-2-one (20).—A solution of **9c** (3.0 g, 12.7 mmol), 50 ml of dimethyl sulfoxide, and methyl mercaptan (2.0 g 41.6 mmol) was stirred at 25–30° during the dropwise addition of 0.6 g of sodium hydroxide in 5 ml of water. The mixture was stirred at ambient temperature for 1 hr and then poured into 400 ml of ice water. The precipitate was filtered and recrystallized from benzene–hexane to yield 2.5 g (80%) of yellow-brown crystalline solid, mp 192–194°.

Oxidation of 20.—To a solution of **20** (2.0 g, 6 mmol) in 50 ml of chloroform was added a solution of 2.5 g (12 mmol) of 85% *m*-chloroperbenzoic acid in 25 ml of chloroform. The mixture was stirred at ambient temperature for 18 hr and then extracted with 10% sodium carbonate solution. The chloroform layer was dried ($MgSO_4$), filtered, and concentrated. The residue was washed well with ether to give 1.0 g (45%) of **21**, brown crystalline solid melting at 130° dec.

2,3-Dichloro-*N*-[5-(methylthio)-1,3,4-thiadiazol-2-yl]acrylamide (14a).—To a solution of 29.4 g (0.2 mol) of 2-amino-5-(methylthio)-1,3,4-thiadiazole and 20.2 g (0.2 mol) of triethylamine in 200 ml of tetrahydrofuran was added dropwise, with stirring, 31.9 g (0.2 mol) of **6a** (X = Cl). The addition was exothermic to 50°. After completion of the addition, the mixture was heated to 66° for 1 hr and then drowned in ice water and filtered to yield 52 g (96%) of **14a**, cream-colored crystalline solid: mp 198–200°; ir (KBr) 3140 (NH), 1668 (C=O), 1532 cm^{-1} (amide II); nmr (DMSO-d_6) δ 2.8 (s, 3, SCH_3), 8.0 (s, 1, CHCl=), and 12.5 ppm (s, 1, NH).

Anal. Calcd for $C_6H_5Cl_2N_3S_2O$: Cl, 26.3; S, 23.7. Found: Cl, 26.6; S, 23.4.

Fusion of 14a.—A suspension of 30.0 g (11.1 mmol) of **14a** in 100 ml of 1,2,4-trichlorobenzene was heated to 210° for 45 min. The mixture was cooled and filtered. The filter cake was dissolved in hot dimethylformamide and allowed to cool to 25°. Filtration yielded 9 g (35%) of **15**, yellow-green crystalline solid: mp >320°; ir 3075 (C=), 1615 cm^{-1} (C=O).

Anal. Calcd for $C_6H_4ClN_3S_2O$: Cl, 15.2; N, 18.0. Found: Cl, 15.4; N, 17.8.

Oxidation of 15.—A mixture of 11.6 g (0.05 mol) of **15** in 100 ml of glacial acetic acid was treated with 25 ml of 30% hydrogen peroxide at 90° for 2 hr. The product was poured over ice water, filtered, and dried to yield 8.0 g (62%) of **16**, colorless crystalline solid: mp 235–238° dec; ir (KBr) 1680 (C=O), 1630 (C=), 1330, 1155 cm^{-1} (SO_2); nmr (DMSO-d_6) δ 3.65 (d, 3, CH_3), 6.9, 7.2 ppm (s, 1, CH=).

Anal. Calcd for $C_6H_4ClN_3S_2O_3$: N, 15.8; S, 24.1. Found: N, 15.6; S, 24.4.

2,3-Dichloro-*N*-[5-(methylsulfonyl)-1,3,4-thiadiazol-2-yl]acrylamide (14b).—A solution of 5.0 g (18.5 mmol) of **14a** in 30 ml of glacial acetic acid was treated with 20 ml of 30% hydrogen peroxide at 90° for 15 min. This solution was left standing for 2 hr, poured over ice water, and filtered to yield 4.0 g (72%) of **14b**, colorless crystalline solid: mp 217–220°; ir (KBr) 3450, 3250 (NH), 1675 (C=O), 1520 (amide II), 1315, 1155 cm^{-1} (SO_2); nmr (DMSO-d_6) δ 3.6 (s, 3, CH_3), 8.15 (s, 1, CHCl=), and 12.75 ppm (s, 1, NH).

Anal. Calcd for $C_6H_5Cl_2N_3S_2O_3$: Cl, 23.5; N, 21.2. Found: Cl, 23.1; N, 21.1.

Registry No.—**6c** (X = OH), 31579-71-2; **6c** (X = NH_2), 31579-72-3; **8a**, 31578-98-0; **8b**, 31578-99-1; **9a**, 31579-00-7; **9b**, 31579-01-8; **9c**, 31579-02-9; **11**, 31579-03-0; **13**, 31615-25-5; **14a**, 31568-46-4; **14b**, 31568-47-5; **15**, 31568-48-6; **16**, 31568-49-7; **17**, 31568-50-0; **18**, 31568-51-1; **19**, 31568-52-2; **20**, 31568-53-3; **21**, 31568-54-4; 2,4-dichloro-α-(chloromethyl)mandelonitrile, 24123-74-8.

Acknowledgment.—We wish to thank E. K. Francis for the mass spectrometric data, G. E. Pollard for the ir and nmr data, and P. M. Saliman for elemental analyses.

(13) Prepared from **6c** (X = OH) and thionyl chloride in the presence of catalytic amounts of dimethylformamide. The crude acid chloride was used without purification.

Neighboring-Group Participation by Oxirane Oxygen during Oxymercuration of 1,5-Diene Monoxides[1a,b]

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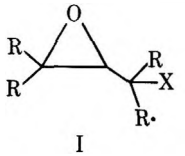
Oxymercuration of the monoepoxides of *cis,cis*-1,5-cyclooctadiene and 1,5-hexadiene takes place with neighboring-group participation of the oxirane oxygen, resulting in formation (after demercuration) of bicyclic and monocyclic ether–alcohols, respectively, in high yield. The rate acceleration caused by this participation is appreciable but less than that of a similarly located hydroxyl group. A stepwise mechanism involving prior hydrolysis to a diol and then oxymercuration is clearly ruled out by the nature of the products and the inertness of similar saturated oxiranes to the reaction conditions. Effects of structure on the oxymercuration rates of a number of substituted *cis*-cyclooctenes are reported.

Neighboring-group participation by ether oxygen has been a topic of interest for more than a decade,[2] but, except for a brief study of the tetrahydrofuran system,[3] participation by the oxygens of cyclic ethers (except for numerous examples of 1-3 participation) has received little attention. A particularly interesting case would be participation by oxirane oxygen. Ethylene oxide is the weakest base toward hydrogen bonding[4] and iodine complexation[5] of the simple cyclic ethers, resembling in this respect ethylenimine.[6] On this basis one might expect oxirane oxygen to be a relatively poor neighboring group during solvolysis reactions. Recently, however, Richey and Kinsman reported evidence for considerable anchimeric assistance by oxygen during solvolysis of esters of substituted 2,3-epoxy-1-propanols (I).[7] The products were substituted 3-oxetanyl derivatives, and 1-oxabicyclobutonium ions (II) were proposed as intermediates.[7] We wish to report additional cases of oxirane oxygen participation which involve epoxy groups quite distant (4,5 position) from the site of the electron-deficient carbon.



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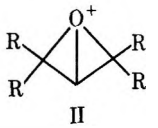
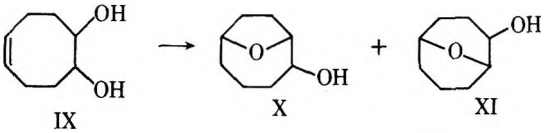


II

During the course of some synthetic investigations we noted that the monoepoxide of *cis,cis*-1,5-cyclooctadiene (III) reacted with the complex formed from mercuric acetate in THF–water[8] much more rapidly than expected. Thus, while cyclooctene requires *ca.* 2 hr for decolorization of the complex,[8] III decolorized the reaction mixture in about 5 sec at 25°. (It has been pointed out that this "time to color disappearance" is at least roughly related to the actual oxymercuration rate.[8]) The products from III, after demercuration with sodium borohydride,[8] were shown to consist of the bicyclic ether alcohols IV and V, in a ratio of 1:3. The same products were obtained in the same ratio when the mercuration reaction was carried out in glacial acetic acid. The structures of IV and V were determined by Jones oxidation of the mixture of alcohols and Wolff–Kishner reduction of the ketone mixture to a mixture of the bicyclic ethers VI and VII, which were identified by comparison with known samples obtained by the method of Bordwell and Douglass.[9] The stereochemistry of the hydroxyl groups in IV and V was shown to be trans to the ether oxygen by formation of the same two alcohols through oxymercuration–demercuration of the trans diol VIII. The ratio of IV to V from this route was distinctly different from that obtained from III, being 72:28, almost exactly reversed. (Oxymercuration of VIII with mercuric nitrate in water, however, is an excellent way to prepare pure V. See Experimental Section.) The interrelations are shown in Scheme I. As a further check, the oxymercuration–demercuration of the cis diol IX was examined and found to yield two different ether alcohols, the exo isomers X and XI in a ratio of 88:12.[10]



IX X XI

A mechanism involving rapid prior hydrolysis of III to diol VIII, followed by rapid oxymercuration of VIII, can easily be ruled out, since both cyclooctene oxide and styrene oxide were found to be inert to brief exposure to the reaction conditions. Also, the gross difference in ratio of the two alcohols from III and VIII makes this mechanism untenable.

Another mechanism, suggested by a referee, would involve normal addition of mercuric ion to give the hydroxy epoxide XII, followed by cyclization either at this stage or after demercuration. While such a *trans*-hydroxy epoxide as XII would almost certainly cyclize to a bicyclic ether alcohol,[11] we feel that this mechanism is

(1) (a) Supported in part by the Alfred P. Sloan Foundation. (b) presented before the Organic Division at the 159th National Meeting of the American Chemical Society, Houston, Tex., Feb 1970. (c) Alfred P. Sloan Research Fellow, 1968–1970.

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(3) G. T. Kwiatkowski, S. J. Kavarnos, and W. D. Closson, *J. Heterocycl. Chem.*, **2**, 11 (1965).

(4) S. S. Searles and M. Tamres, *J. Amer. Chem. Soc.*, **73**, 3704 (1951).

(5) M. Brandon, M. Tamres, and S. Searles, *ibid.*, **82**, 2129 (1960); M. Tamres and M. Brandon, *ibid.*, **82**, 2134 (1960).

(6) H. C. Brown and M. Gerstein, *ibid.*, **72**, 2926 (1950).

(7) H. G. Richey, Jr., and D. V. Kinsman, *Tetrahedron Lett.*, 2505 (1969).

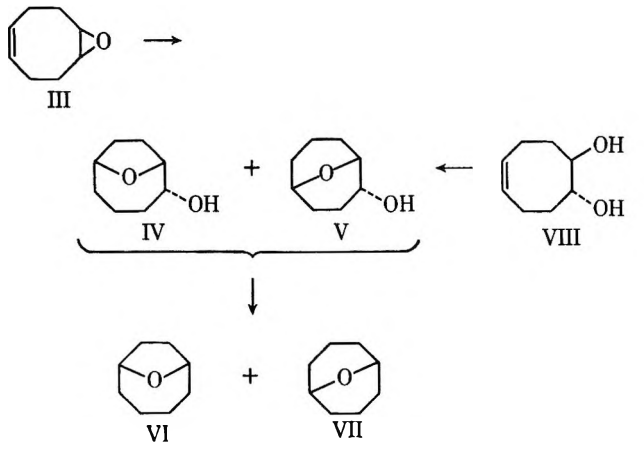
(8) H. C. Brown and P. Geoghegan, Jr., *J. Amer. Chem. Soc.*, **89**, 1522 (1967); *J. Org. Chem.*, **35**, 1844 (1970).

(9) F. G. Bordwell and M. L. Douglass, *J. Amer. Chem. Soc.*, **88**, 993 (1966).

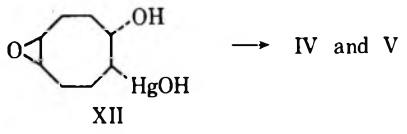
(10) Authentic samples of IV, V, and X were obtained from Professor Leo Paquette of the Department of Chemistry, The Ohio State University, and were shown to be identical with our compounds by comparison of gc retention times on several columns. We thank Professor Paquette for his generous help. See L. A. Paquette and P. C. Storm, *J. Amer. Chem. Soc.*, **92**, 4295 (1970).

(11) Epoxidation of 4-cyclooctenol with *m*-perbenzoic acid yields directly a mixture of IV and V, and *cis*-4-cycloocten-1-ol oxide: unpublished work of J. L. Jernow. See also J. K. Crandall, J. P. Arrington, and C. F. Mayer, *J. Org. Chem.*, **36**, 1428 (1971).

SCHEME I



also unlikely. First, it would require very stereospecific oxymercuration to give exclusively XII, since the *cis*-hydroxy epoxide would probably survive and be easily detectable. Second, such a mechanism would not explain the enhanced reaction rate of III (*vide infra*). Third, oxymercuration of III in anhydrous methanol yields a mixture of ethers, after demercuration, which appear to be simply the methoxy analogs of IV and V. No evidence for a cyclooctene oxide group, easily detectable by nmr (δ 3.0–3.1), could be found in this latter reaction product. Clearly, one would not expect a methoxy group to open an epoxide ring under these mild conditions. (The *trans*-4,5-epoxycyclooctyl acetate is known to be fairly stable.)[12]



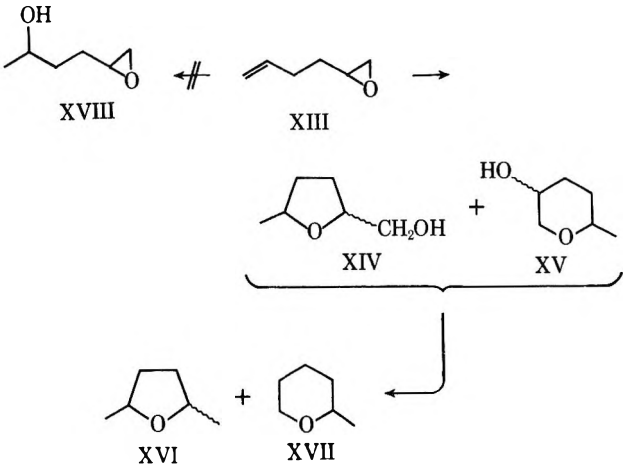
To test whether oxirane-oxygen participation would compete with normal oxymercuration in an acyclic system, the reaction of the monoxide of biallyl (1,5-hexadiene) (XIII) was examined. From treatment of XIII with mercuric acetate in THF–water and demercuration of the products was obtained a complicated mixture of alcohols. The nmr spectrum of this mixture was devoid of the characteristic terminal epoxide proton resonances in the δ 2.5–3.0 region.[13] Conversion of the alcohol mixture to tosylates and reduction with lithium aluminum hydride yielded a mixture of *cis*- and *trans*-2,5-dimethyltetrahydrofuran (XVI) and 2-methyltetrahydropyran (XVII) in about 60:40 ratio, implying that the initially obtained alcohol products are probably XIV and XV, as indicated in Scheme II. It should be noted that the tosylates of XIV and XV could conceivably equilibrate under the conditions of reduction, and that epoxy alcohol XVIII, if present, might also be converted to XVI and/or XVII under these conditions. Clearly, though, the bulk of the reaction must proceed generally as indicated in Scheme II.

Neighboring-group participation during oxymercuration often leads to considerable rate acceleration, *e.g.*, *endo*-5-hydroxymethyl-2-norbornene (XIX), which

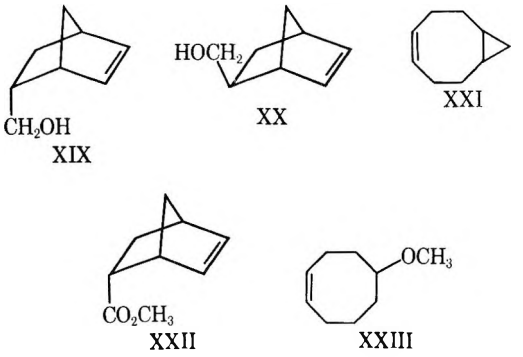
(12) A. C. Cope, B. S. Fisher, W. Funke, J. M. McIntosh, and M. A. McKervey, *J. Org. Chem.*, **34**, 2231 (1969).

(13) N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1963, Spectra No. 193, 558.

SCHEME II



yields a ring-closed ether, reacts at least 10^2 times faster than its exo epimer (XX),[14] and both 4-penten-1-ol and 5-hexen-1-ol undergo oxymercuration at accelerated rates relative to unsubstituted 1-alkenes and yield cyclic oxymercuri ethers.[15] The approximately 10^3-fold increase in reactivity of III over that of *cis*-cyclooctene, mentioned previously, is probably not a good measure of the anchimeric effect of the oxirane oxygen, however.



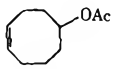
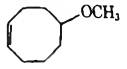
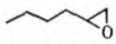
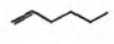
This is clearly indicated by the relative rate data in Table I. From the *ca.* 10^2-fold acceleration of bicyclo[6.1.0]non-4-ene (XXI) over *cis*-cyclooctene, it is clear that a major portion of the reactivity of III must be geometric in origin. It should be noted that XXI yields only a mixture of normal oxymercuration products and the cyclopropane ring survives intact.[16] The geometries about the double bonds in III and XXI should be essentially identical. The 50-fold difference in rate between III and XXI is probably much closer to a true measure of the anchimeric effect, but does not take into account the rate-retarding inductive effect of the oxygen in III. Halpern and Tinker report that oxymercuration in aqueous acid media is rather sensitive to inductive effects ($\rho^* = -3.3$)[15] and one would expect a modest effect in III. Crude kinetic data also indicate that the acyclic epoxy olefin XIII exhibits enhanced reactivity relative to an unsubstituted terminal alkene, but is apparently less reactive than analogous

(14) A. Factor and T. G. Traylor, *J. Org. Chem.*, **33**, 2607 (1968).

(15) J. Halpern and H. B. Tinker, *J. Amer. Chem. Soc.*, **89**, 6427 (1967).

(16) Strained cyclopropanes have been observed to react with mercuric ion in water; see V. I. Sokolov, N. B. Rodina, and O. A. Reutov, *J. Organometal. Chem.*, **17**, 477 (1969), and R. Y. Levina, V. N. Kostin, D. G. Kim, and T. K. Ustynyuk, *Zh. Obshch. Khim.*, **29**, 1956 (1959). Also, at higher temperatures unstrained cyclopropyl rings may be oxymercurated; see R. J. Ouellette and C. Levin, *J. Amer. Chem. Soc.*, **93**, 471 (1971).

TABLE I
RELATIVE RATES OF OXYMERCURATION AT 25° [a]

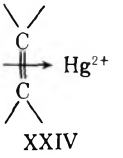
Compd	Registry no.	Relative rate[b]	Time, sec[c]	K_{Ag^+}, $1/M$[d]
	931-87-3	0.0005	7200[e]	0.005[f]
	1552-12-1		15	
	31598-69-3	0.02	60	
	31598-70-6		840	1.30
	31598-71-7	1.0	5	0.10
	31598-73-9		5650	<0.10
	31598-72-8		1680	
	31598-74-0		2	29
	1436-34-6	1.1		
	821-41-0	3.3[g] 0.92[h]		29
			90	0.095[i]

[a] Reactions run in 50% THF–water, unless otherwise specified. [b] From competition reactions; precision is about ±20%. [c] Time required for decolorization of mercuric complex in THF–water; determined under conditions specified in ref 8. [d] Formation constants for silver ion π complex in water at 25°; from ref 20b unless otherwise specified. [e] From ref 8. [f] J. G. Traynham and J. R. Olechowski, *J. Amer. Chem. Soc.*, **81**, 571 (1959). [g] Absolute rate in 0.01 *M* aqueous perchloric acid is 10^6 l. mol sec^{-1}; see ref 14. [h] Competition against 1,5-cyclooctadiene monoxide in glacial acetic acid. [i] S. Winstein and H. J. Lucas, *J. Amer. Chem. Soc.*, 60, 836 (1938).

hydroxyalkenes. One interesting feature is that participation by oxirane oxygen appears to be relatively independent of solvent, XIII and III both yielding cyclic products in glacial acetic acid as well as in the THF–water mixture, unlike participation by the ester carbonyl in XXII, which occurs only in aqueous media.[14]

The data in Table I also give interesting information on the effects of other neighboring groups and trigonal atoms in the cyclooctane ring. Neither reaction rate nor products reflect participation in the case of a 5-acetoxy substituent, no bicyclic material being observed after demercuration. Presumably the carbonyl oxygen, the more basic site in the acetoxy group, is too remote to interact. The slightly greater reactivity of *cis*-4-cyclooctenyl acetate, as measured by its rate of decolorization of the mercuric ion complex, may simply be due to greater solubility in 50% THF–water. Oxymercuration of *cis*-5-methoxycyclooctene (XXIII) is significantly enhanced, and yields a mixture of products containing about 30% of the bicyclic ethers VI and VII, after demercuration. The rest is a higher boiling fraction, presumably a mixture of 4- and 5-methoxycyclooctanols. The corresponding alcohol reacts extremely rapidly (as do the diols VIII and IX) and yields only VI and VII, as reported previously by Bordwell and Douglass.[9] Introduction of two trigonal atoms, as in *cis*-1,5-cyclooctadiene, leads to very rapid reaction as noted previously,[9] but replacing the double bond by a fused cyclopropane ring (as in XXI) is almost as efficient at enhancing reactivity. One trigonal atom, as in *cis*-4-cycloocten-1-one, is considerably less rate enhancing, but the ketone is still *ca.* ten times as reactive as cyclooctene in spite of an adverse inductive effect. These effects of trigonal or "semitrigonal" carbons in the cyclooctene ring are probably due to diminution of unfavorable torsional interactions and angle strain that normally occur when one of the trigonal carbons of cyclooctene is converted to tetrahedral geometry.[17]

In Table I the silver ion complexation constants (K_{Ag}) are given for several of the compounds investigated. These have generally been regarded as being indicative of rates of oxymercuration,[15,18] due to the similarity of the chemistry and electronic structures of Ag(I) and Hg(II), and it has often been postulated that oxymercuration proceeds through a mercurinium π-complex intermediate (XXIV).[19] Halpern and Tinker concluded that XXIV might be formed in a rapid preequilibrium, followed by rate-controlling rearrangement, or reaction with solvent, to yield product.[15] (The large value of ρ^* would favor rate-controlling formation of a carbon–mercury σ bond.) Since remote functional groups, particularly hydroxyl, often confer considerable stabilization on silver–olefin π complexes, presumably through chelation,[20] one might expect similar stabilization of the corresponding mercurinium π complexes. This could lead to rate enhancement by increasing the concentration of XXIV. This seems



XXIV

clearly *not* the case for the epoxy compounds, since III has a very low K_{Ag}, and neighboring-group participation, as discussed earlier, must be a major cause of rate acceleration. The case of the hydroxyl-substituted systems is less clear, and a portion of their enhanced reactivity may be due to stabilization of XXIV by bonding of the hydroxyl to mercuric ion, though this would require considerable reorientation of groups in the following step leading to cyclized products. Henbest and Nicholls have postulated such chelation effects to explain the stereochemistry of oxymercuration of 3-cyclohexenyl derivatives and related compounds,[21] but recent work strongly implies that the stereoselectivity of these reactions is due primarily to inductive and steric effects.[22]

(17) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, Chapter 9.

(18) C. Heathcock, *Angew. Chem., Int. Ed. Engl.*, **8**, 134 (1969).

(19) H. Lucas, F. Hepner, and S. Winstein, *J. Amer. Chem. Soc.*, **61**, 3102 (1939); N. S. Zefirov, *Russ. Chem. Rev.*, **34**, 527 (1965). For recent discussions of mercurinium ions, see W. Kitching, *Organometal. Chem. Rev.*, **3**, 61 (1968); G. A. Olah and P. R. Clifford, *J. Amer. Chem. Soc.*, **93**, 2320 (1971); and J. E. Byrd and J. Halpern, *ibid.*, **92**, 6967 (1970).

(20) (a) B. Franzus, W. C. Baird, Jr., E. I. Snyder, and J. H. Surridge, *J. Org. Chem.*, **32**, 2845 (1967); (b) D. Gray, R. A. Wies, and W. D. Closson, *Tetrahedron Lett.*, 5639 (1968); (c) See, however, C. F. Wilcox, Jr., and W. Gaal, *J. Amer. Chem. Soc.*, **93**, 2453 (1971).

(21) H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 227 (1959).

(22) (a) J. Klein and R. Levene, *Tetrahedron Lett.*, 4833 (1969); (b) M. R. Johnson and B. Rickborn, *Chem. Commun.*, 1073 (1968); (c) P. Chamberlain and G. H. Whitham, *J. Chem. Soc. B*, 1382 (1970).

Experimental Section[23]

cis,cis-1,5-Cyclooctadiene monoxide (III) was prepared by the method of Traynham and Greene[24] with the following modifications: molar ratio of diene to peracid was 2.5:1 and chloroform was used as solvent. A 63% yield of III was obtained, bp 95° (30 mm) [lit.[24] bp 97–100° (40 mm)].

cis-Cyclooctene-*trans*-5,6-diol (VIII).—A solution of 12.4 g (0.100 mol) of III in a mixture of 30 ml of tetrahydrofuran (THF), 120 ml of water, and about 0.5 ml of concentrated sulfuric acid was stirred at 25° for 24 hr. The mixture was then saturated with sodium carbonate and extracted several times with ether. The extract was dried with magnesium sulfate and concentrated, and the residual oil distilled, yielding 12.3 g (0.87 mol) of the diol: bp 84–87° (0.05 mm); nmr ($CDCl_3$) δ 1.3–2.5 (m, 8 H), 3.4–3.7 (m, 2 H), 3.8 (s, 2 H), and 5.4–5.7 (m, 2 H).

The dibrosylate, mp 132.5–133.5°, and its analysis have been described previously.[25]

cis-Cyclooctene-*cis*-5,6-diol (IX).—To a solution of 65 g (0.60 mol) of 1,5-cyclooctadiene in 100 ml of acetone, kept at −5 to −10°, was slowly added a solution of 39 g (0.20 mol) of potassium permanganate in a mixture of 1 l. of acetone and 100 ml of water. After addition was complete (1.5 hr) the solution was allowed to warm to room temperature and then filtered through Supercel. The filtrate was concentrated under reduced pressure to *ca.* 150 ml and then extracted with five 50-ml portions of ether. The ether extract was dried with magnesium sulfate and the solvent and unreacted diene were removed under reduced pressure. The residue, after recrystallization from ether, yielded 0.89 g (6.3 mmol, 3.1% yield) of diol IX: mp 104.5–106°; nmr (DMSO-d_6) δ 1.3–2.8 (m, 8 H), 3.5 (s, 2 H), 3.8 (m, 2 H), and 5.5 (m, 2 H).

The dibrosylate, mp 146–147°, and its analysis have been described elsewhere.[25] The bis phenylurethane melted at 188–190°.

Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36. Found: C, 69.27; H, 6.42.

1,5-Hexadiene monoxide (XIII) was prepared in a manner similar to that of Everett and Kon[26] from biallyl and *m*-chloroperbenzoic acid. The monoxide was obtained in 44% yield, bp 119–120° (760 mm) [lit.[26] bp 119–121° (760 mm)].

cis-Bicyclo[6.1.0]non-4-ene (XXI) was prepared by the procedure of Cope, *et al.*,[27] bp 167° (760 mm) [lit.[27] bp 65–68° (22 mm)].

cis-4-Cycloocten-1-ol, its acetate, and the corresponding ketone were available from previous work.[20b]

5-Methoxycyclooctene (XXIII).—To 2.5 g (0.020 mol) of *cis*-4-cycloocten-1-ol in 20 ml of ether was added slowly 20 ml of 5% methyllithium in ether (1.0 g, 0.040 mol) at 25° with stirring. After addition was complete, 5.5 g (0.050 mol) of dimethyl sulfate (neat) was added dropwise. The mixture was then heated at reflux for 24 hr. It was then cooled and drowned in ice–water, and the ether layer was separated, dried, and concentrated. Distillation of the residual oil gave 2.1 g (0.015 mol, 75%) of XXIII: bp 77° (26 mm); ir (neat) 1473 (m), 1097 (s), and 728 cm^{-1} (m); nmr (CCl_4) δ 1.2–2.4 (m, 10 H), 3.0–3.3 (m, 1 H), 3.2 (s, 3 H), and 5.2–5.8 (m, 2 H).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.85; H, 11.21.

Preparative oxymercuration reactions were mostly carried out by the method of Brown and Geoghegan.[8] The olefin (0.01 mol) was added neat to a rapidly stirred mixture of 0.01 mol of mercuric acetate in 20 ml of 50% (v/v) THF–water at 25°. The times required for disappearance of the yellow mercuric complex, which are roughly related to the rate and extent of reaction,[8] are reported in Table I. Reduction and isolation of products were as described previously.[8]

Oxymercuration of *cis,cis*-1,5-Cyclooctadiene Monoxide (III).—By Brown's procedure,[8] 1.3 g (92%) of material, bp 125–128° (8 mm), was obtained. Analysis by gc on a 12 ft × 0.25 in. column of 10% tris-1,2,3-cyanoethoxypropane (TCEP) showed it to be a mixture of 24% *endo*-9-oxabicyclo[4.2.1]non-2-ol (IV) and 76% *endo*-9-oxabicyclo[3.3.1]non-2-ol (V). The identities of IV and V were confirmed both by comparison of gc retention times with those of authentic samples,[10] and by removal of the hydroxyl groups (Jones oxidation, Wolff–Kishner reduction) yielding a mixture of 9-oxabicyclo[4.2.1]nonane (VI) and 9-oxabicyclo[3.3.1]nonane (VII) in *ca.* a 1:3 ratio. These ethers were identified by comparison of ir spectrum of the ether mixture and gc retention times 6 ft × 0.125 in. column of 10% diglycerol) with those of an authentic mixture of VI and VII prepared from 1,5-cyclooctadiene by the method of Bordwell and Douglass.[9]

Oxymercuration of III in acetic acid was carried out by adding 2.5 g (0.020 mol) of III to a suspension of 6.4 g (0.020 mol) of mercuric acetate in 10 ml of acetic acid at 25°. After 3 min of stirring, the solution became clear and slightly warm. After an additional 10 min of stirring, the mixture was poured into 250 ml of saturated sodium chloride solution and allowed to stand overnight. A white solid was then collected by filtration, dissolved in 40 ml of 1.5 *N* sodium hydroxide, and treated with 20 ml of 0.5 *N* sodium borohydride in 3 *N* sodium hydroxide. Work-up according to the usual procedure[8] yielded 1.9 g (0.013 mol, 65%) of a mixture of IV (29%) and V (71%), as shown by gc.

Oxymercuration of III in anhydrous methanol was carried out in a manner similar to that carried out in acetic acid, except that the reaction mixture, after 10 min, was treated directly with aqueous sodium hydroxide and sodium borohydride. Work-up in the usual procedure yielded 2.5 g (0.016 mol, 80%) of a mixture of what appeared to be methyl ethers: bp 94–96° (16 mm); nmr ($CDCl_3$) δ 1.3–2.3 (m, 10 H), 3.35 (s, 3 H), 3.8–4.1 (m, 3 H) (the region δ 2.4–3.1, where epoxide protons would be expected, was entirely clear); ir (neat) 1110 (s), 1070 (m), 1049 (w), 1002 (m), 991 (m), 901 (m), 872 cm^{-1} (m). (Compare nmr and ir with that of V, for example.)

Oxymercuration of *cis*-cyclooctene-*trans*-5,6-diol (V,III) by Brown's procedure[8] yielded 0.78 g (5.5 mmol, 55%) of a mixture of ether–alcohols, bp 130–132° (10 mm), shown to consist of 77% IV and 23% V by gc on a TCEP column.

Oxymercuration of 7.1 g (0.050 mol) of VIII by adding it neat to 16.2 g of mercuric nitrate in 120 ml of water and stirring at 25° for 2 hr yielded, after treatment with 120 ml of 3 *N* sodium hydroxide and 100 ml of a 0.5 *M* sodium borohydride in 3 *N* sodium hydroxide solution and isolation of the organic material in usual fashion, 5.2 g (0.041 mol, 82%) of *endo*-9-oxabicyclo[3.3.1]-nonan-2-ol (V), bp 130–135° (10 mm), mp 73–73.5°. Analysis by gc (TCEP column) showed a single peak with retention time identical with that of authentic V:[10] ir ($CHCl_3$) 1073 (s), 1045 (s), 992 (m), 897 (m), and 862 cm^{-1} (m); nmr (CCl_4) δ 1.4–2.2 (m, 10 H), 3.5–4.0 (m, 4 H).

Oxymercuration of *cis*-cyclooctene-*cis*-5,6-diol (IX) by Brown's procedure[8] yielded 0.85 g (6.0 mmol, 60%) of a mixture of ether–alcohols, bp 120–122° (7 mm). The major component (88%) had a gc retention time (TCEP column) identical with that of authentic[10] *exo*-9-oxabicyclo[4.2.1]non-2-ol (X). The minor component (12%) was assumed to be *exo*-9-oxabicyclo[3.3.1]-non-2-ol (XI).

Oxymercuration of bicyclo[6.1.0]non-4-ene (XXI) by Brown's procedure[8] gave a 60% yield of a mixture of alcohols, bp 117–122° (22 mm). The nmr spectrum of the mixture was identical with that of the starting material except for the absence of vinyl protons and the presence of –CHOH protons. Oxidation (Jones method) of 3.5 g (0.025 mol) of the alcohol mixture yielded a single ketone (4-bicyclo[6.1.0]nonanone)[28] (XXVI) in 60% yield (2.0 g, 0.0145 mol), bp 118–120° (35 mm), whose 2,4-dinitrophenylhydrazone melted at 160.5–161.5° (ethanol).

Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70. Found: C, 56.44; H, 5.73.

Wolff–Kishner reduction of the ketone XXV on a small scale yielded a hydrocarbon, bicyclo[6.1.0]nonane, identical (gc, nmr) with that obtained from XX by catalytic hydrogenation.

Oxymercuration of 1,5-hexadiene monoxide (XIII) by the usual procedure yielded a complicated mixture of alcohols in 65% yield, bp 85–91° (12 mm). Conversion of this mixture to

(23) All nmr spectra were recorded using a Varian A-60A spectrometer with tetramethylsilane as internal standard. Infrared (ir) spectra were recorded on a Beckman IR-10 spectrometer. Gas chromatographic (gc) analyses were performed using Hewlett–Packard 5750 and Varian A-90 gas chromatographs. Melting and boiling points are uncorrected. Unless otherwise specified, all materials were obtained from commercial sources.

(24) J. G. Trayham and P. M. Greene, *J. Amer. Chem. Soc.*, **86**, 2657 (1964).

(25) W. D. Closson, J. L. Jernow, and D. Gray, *Tetrahedron Lett.*, 1141 (1970).

(26) J. L. Everett and G. A. R. Kon, *J. Chem. Soc.*, 3131 (1950).

(27) A. C. Cope, S. Moon, and C. H. Park, *J. Amer. Chem. Soc.*, **84**, 4843 (1962).

(28) This ketone has been prepared previously [K. B. Wiberg and A. Demeijere, *Tetrahedron Lett.*, 59 (1969)], but its properties were not described.

tosylates and reduction with lithium aluminum hydride in the usual manner gave a mixture of 2,5-dimethyltetrahydrofuran (cis and trans) and 2-methyltetrahydropyran (*ca.* 6:4 ratio by gc) identical by nmr and gc with a similarly proportioned authentic mixture.

Oxymercuration of 5-methoxycyclooctene (XXIII) (Brown's procedure[8]) gave a 70% yield of a mixture consisting of about 30% of ethers VI and VII and 70% of material of longer gc retention time, presumably a mixture of 4- and 5-methoxycyclooctanols.

Oxymercuration of 5-acetoxycyclooctene was carried out in usual fashion. The product (*ca.* 60%) contained a fair amount of unreacted unsaturated acetate, no bicyclic ethers VI or VII, but a considerable amount of material of very long gc retention time. This latter fraction was presumably a mixture of various cyclooctanediols and monoacetates thereof.

Stabilities of Oxides to Reaction Conditions.—Cyclooctadiene monoxide was found to be stable to glacial acetic acid at 25° for periods of up to 2 hr, and to 50% THF–water for even longer periods of time, as measured by gc analysis of sample mixtures. Saturated olefin oxides, such as cyclooctene oxide, styrene oxide, and propylene oxide, were unaffected by several minutes of exposure to 0.005 *M* mercuric acetate in 50% THF–water. Cyclooctene oxide could be recovered in 75% yield after 72 hr of exposure to these conditions.

Competition Experiments.—In aqueous THF, a solution of *ca.* 1 mmol of each of the competing olefins in 1 ml of THF was stirred at 25° while 1.0 ml of 0.1 *M* mercuric acetate in water was added. After a period of 0.5–3 min, 1 ml of 3 *N* sodium hydroxide followed by 1 ml of sodium borohydride solution was added, the aqueous layer was saturated with sodium hydroxide pellets, and the THF layer was analyzed by gc.

In acetic acid, a mixture of the two olefins (*ca.* 1 mmol each) was added to a stirred solution of 0.2 mmol of mercuric acetate in 1 ml of acetic acid at 25°. After 3 min of stirring, the flask was chilled and 3 *N* sodium hydroxide was added until basic. Reduction was then carried out with 0.5 *M* sodium borohydride in 3 *N* sodium hydroxide, the products were extracted with ether, and analysis was performed by gc.

Variation of reaction times between 0.5 and 3 min had no apparent effect on product composition. Each reported relative rate is the average of at least two experiments using different proportions of reactants. Reproducibility was at least of the order of 20%. It has been shown that relative rates measured under these conditions correlate excellently with measured absolute rates.[22c]

Registry No.—IV, 29359-88-4; IV (methoxy analog), 31598-89-7; V, 31598-90-0; V (methoxy analog), 31662-28-9; VIII, 31598-91-1; IX, 31603-51-7; IX bisphenylurethane, 31603-52-8; X, 29359-87-3; XI, 31598-76-2; XXVI, 28405-47-2; XXVI 2,4-DNPH, 31603-54-0.

Replacement of the Carbonyl Oxygen of Hydroxy Ketones by Methylene and 1,1-Ethano Groups by Reaction with the Simmons–Smith Reagent[1]

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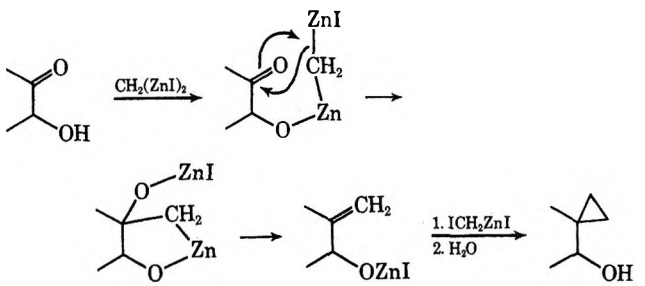
The reagent prepared from methylene iodide and zinc–copper couple replaces the carbonyl oxygen of ketones containing a neighboring hydroxyl group by the methylene and 1,1-ethano groups. Reaction conditions have been defined which allow the formation of either one of these products.

In a previous communication we reported[2] the unexpected formation of methylene and ethano derivatives **2** and **3** by reaction of 17β-acetoxy-11β-hydroxyestr-5(10)-en-3-one (**1**) with a reagent derived from methylene iodide and zinc–copper couple (Simmons–Smith reagent). Further work has shown that the reaction is not limited to hydroxy ketones; for example, 5α-androstan-3-one (**4**) was converted into a mixture of 3,3-methylene-5α-androstane (**5**), 3,3-ethano-5α-androstane (**6**), and other unidentified products. However, good yields were obtained only in the cases where assistance by hydroxyl is sterically allowed. No reaction was observed with α,β-unsaturated carbonyl groups, although the dienone **7** gave the derivatives **8a** and **8b** by by a normal cyclopropyl-forming reaction on the more nucleophilic, terminal double bond.

The reaction of α-hydroxy ketones with the Simmons–Smith reagent prepared in the usual manner led to mixtures of the methylene and ethano derivatives. For example, 17α-hydroxypregn-4-ene-3,20-dione (**9**) gave a mixture of **10** and **11**. Variation of the reaction conditions indicated that the relative yields of the two products were critically but reproducibly dependent on the procedure by which the reagent was prepared. A reagent formed *in situ* or by refluxing an ether solution of methylene iodide with zinc–copper couple for up to 1 hr reacted with the ketone **9** to give the ethano derivative **11** in high yield, whereas a reagent preformed by refluxing for 2–4 hr reacted to give the methylene derivative **10**, also in high yield. These results can be rationalized in terms of an inhomogeneous and time-variable composition for the reagent.

Olefination of aldehyde and ketone carbonyls by *gem*-dimetallic reagents of the type MCH_2M is quite general;[3] we therefore attribute the formation of ethano derivatives from hydroxy ketones to hydroxyl-assisted methylenation of the carbonyl by a species of the general structure $\cdots ZnCH_2Zn\cdots$, followed by a typical

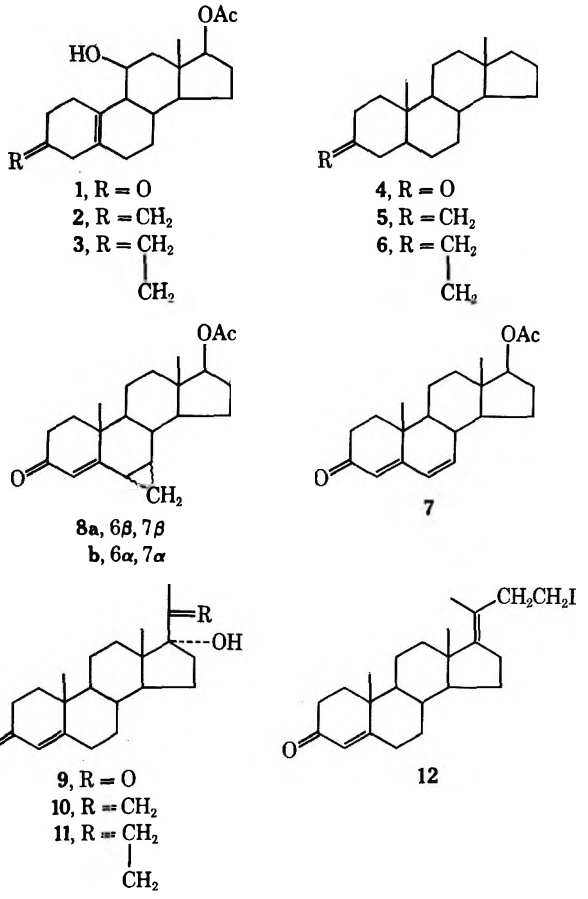


hydroxyl-assisted cyclopropyl formation. This mechanism was suggested[2] earlier for the conversion of **1** into

(1) Publication no. 385 from the Syntex Institute of Organic Chemistry. For publication no. 384, see L. Tökés, "Photochemical Cycloadducts," part VI, in press.

(2) P. Turnbull, K. Syhora, and J. H. Fried, *J. Amer. Chem. Soc.*, **88**, 4764 (1966).

(3) F. Bertini, P. Grasselli, G. Zubiani, and G. Cainelli, *Tetrahedron*, **26**, 1281 (1970).

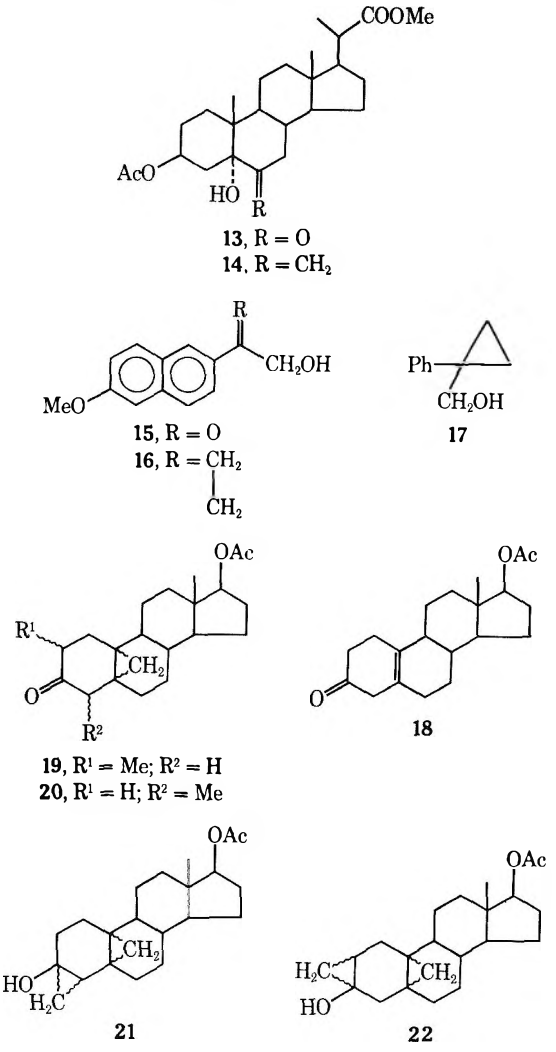


2 and 3. The less reactive reagent preformed by longer refluxing periods leads only to the methylenation product and therefore contains only minor amounts of the cyclopropyl-forming reagent ICH_2ZnI. A further reaction observed was the cleavage of the cyclopropylcarbinol **11** to the iodoethyl derivative **12** by the Lewis acid by-product ZnI_2.

The generality of the methylenation and cyclopropyl-forming reactions was further supported by application to methyl 3β-acetoxy-5α-hydroxybisnorcholan-6-on-21-oate (**13**), forming the methylene derivative **14**, and by conversion of hydroxymethyl (6′-methoxy-2′-naphthyl) ketone (**15**) to the derivative **16**. The cyclopropyl derivative **17** was formed from ω-hydroxyacetophenone.

A more complex reaction was observed on treatment of the nonhydroxylic ketone **18** with the more reactive cyclopropyl-forming zinc–methylene iodide reagent. From the products of this reaction there was isolated 17β-acetoxy-2ξ-methyl-5,19ξ-cycloandrostane (**19**) and the 4 isomer **20**. Unstable intermediates which could be isolated from the reaction mixture are considered to be the cyclopropanols **21** and **22** formed by methylenation of enol intermediates. Chromatography of **21** and **22** caused ring opening, forming the observed methyl ketones. This result is reminiscent of the reaction of lithium enolates with methylene iodide and zinc, which has been used[4] as a means of α-methylation of ketones.

After most of this work was completed, a simplified preparation of the Simmons–Smith reagent, using a mixture of zinc and cuprous halide in place of zinc–copper couple, was described.[5] This new method is also satisfactory for the preparation of methylene or ethano derivatives from hydroxy ketones.



Experimental Section[6]

General Procedure for the Reaction of Ketones with the Zinc–Methylene Iodide Reagent. A. Cyclopropyl-Forming Conditions.—A stirred mixture of zinc–copper couple[7] (3.2 g) and methylene iodide (2.5 ml) was heated under reflux in a nitrogen atmosphere for 1 hr (shorter periods of reflux also gave satisfactory results). The ketone (1.3 mmol) was then added to the cooled mixture and stirring continued at about 25° for 24 hr. The mixture was then diluted with benzene, solids were removed by filtration, and the solution was washed successively with NH_4Cl and $NaHSO_3$ solutions. Products were isolated by column chromatography on silica gel or by tlc, followed by crystallization.

B. Methylene-Forming Conditions.—The above general procedure was used except that the reagent was heated for 4 hr before reaction with the ketone. Reflux periods in the range 2–4 hr were satisfactory.

20,20-Ethano-17α-hydroxypregn-4-en-3-one (**11**).—The general procedure A converted the ketone **9** (2 g) into **11**: yield 1.84 g (89%); mp 229–231°; $[\alpha]D$ +82° ($CHCl_3$); uv max 240 nm (ε 17,500); nmr ($CDCl_3$) δ 0.4–0.8 (m, cyclopropyl). *Anal.* Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.45; H, 9.64. A minor, less polar product was identified as 20-(2′-iodoethyl)pregna-4,17(20)-dien-3-one (**12**): mp 159–161° dec; $[\alpha]D$ +99° ($CHCl_3$); uv max (dioxane) 235 nm (ε 23,400); nmr ($CDCl_3$) ε 2.52 (t, CH_2I); mass spectrum *m/e* 452 (M^+).

(4) H. W. Whitlock and L. E. Overman, *J. Org. Chem.*, **34**, 1962 (1969).
(5) R. J. Rawson and I. T. Harrison, *ibid.*, **35**, 2057 (1970).
(6) Melting points were determined on a Fisher–Johns hot stage apparatus. We wish to thank Drs. L. Throop, L. J. Tökés, and M. L. Maddox for the determination of physical data.
(7) E. LeGoff, *J. Org. Chem.*, **29**, 2048 (1964).

Anal. Calcd for $C_{23}H_{33}IO$: C, 61.04; H, 7.34; I, 28.05. Found: C, 60.95; H, 7.15; I, 27.73.

17α-Hydroxy-20-methylenepregn-4-en-3-one (10).—The ketone 9 (2 g) was converted by procedure B into 10: yield 1.84 g (93%); mp 239–241°; $[\alpha]D$ −113° ($CHCl_3$); uv max 240 nm (ε 16,700); nmr ($CDCl_3$) δ 4.92 (d, C=CH_2). *Anal.* Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.06; H, 9.85.

Methyl 3β-Acetoxy-5α-hydroxy-6-methylenebisnorcholan-21-oate (14).—The general method B converted the ketone 13 (2.0 g) into 14: yield 1.9 g (96%) mp 103–105°; $[\alpha]D$ −59° ($CHCl_3$); nmr ($CDCl_3$) δ 4.77 and 4.63 (C=CH_2). *Anal.* Calcd for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 72.10; H. 8.95.

1-Hydroxymethyl-1-(6′-methoxy-2′-naphthyl)cyclopropane (16).—The ketone 15 (2.5 g) was converted by the general method A into 16: yield 2.0 g (76%); mp 79–80°; nmr ($CDCl_3$) δ 0.86 (m, cyclopropyl) and 3.66 (s, CH_2); mass spectrum *m/e* (rel intensity) 228 (47) and 197 (100).

1-Hydroxymethyl-1-phenylcyclopropane (17).—Method A converted ω-hydroxyacetophenone (0.4 g) into the known[8] 17: yield 0.215 g (49%); nmr ($CDCl_3$) δ 0.78 (s, cyclopropyl), 2.06 (s, OH), 3.55 (s, CH_2), 7.1–7.3 (m, aromatic).

Reaction of Androstan-3-one (4) with the Zinc–Methylene Iodide Reagent.—The general procedure A, modified by the use of tetrahydrofuran as solvent, converted the ketone 4 into a mixture from which was isolated a low yield of the known[9] 3,3-ethano derivative 6: mp 76–77°; $[\alpha]D$ +6° ($CHCl_3$); nmr ($CDCl_3$) δ 0.19 (cyclopropyl). The methylene derivative 5 was also isolated: mp 89–90°; $[\alpha]D$ −9° ($CHCl_3$); nmr ($CDCl_3$) δ 4.63 (C=CH_2). *Anal.* Calcd for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found: C, 88.12; H, 11.49.

Reaction of 17β-Acetoxyandrosta-4,6-dien-3-one (7) **with the Zinc–Methylene Iodide Reagents.**—The process A, modified by the use of tetrahydrofuran as solvent, converted the ketone 7 (100 mg) into the known derivatives 8a, yield 19 mg (18%), nmr ($CDCl_3$) δ 6.00 (s, 4 H), and the isomer 8b, yield 12 mg (12%), nmr ($CDCl_3$) δ 5.94 (s, 4 H). Identification was confirmed by comparison of infrared spectra and gas chromatographic retention times with those of authentic samples.[10]

Reaction of 17β-Acetoxy-19-norandrost-5(10)-en-3-one (18) **with the Zinc–Methylene Iodide Reagent.**—The general procedure A converted the ketone 18 (0.5 g) into a mixture, ir (film) 3450 cm^{-1}. Column chromatography on silica gel or standing in methylene chloride solution converted the two major components into new compounds of different tlc polarity. The products isolated by column chromatography are considered to be the 2 (or 4) ξ-methyl ketone 19, yield 110 mg (10%), nmr ($CDCl_3$) δ 0.8 (m, cyclopropyl), 1.15 (d, J = 7 Hz, CH_3), mass spectrum *m/e* 344 (M^+), and the 4 (or 2) ξ isomer 20, 110 mg (10%), nmr ($CDCl_3$) δ 0.48 (m, cyclopropyl), 1.14 (d, J = 7 Hz, CH_3), mass spectrum *m/e* 344 (M^+).

Registry No.—**4**, 1224-95-9; **5**, 28113-74-8; **6**, 21152-61-4; **7**, 2352-19-4; **10**, 25596-88-7; **11**, 31729-63-2; **12**, 31790-94-0; **14**, 31729-64-3; **16**, 31729-65-4; **17**, 31729-66-5; **18**, 19906-32-2; **19**, 31729-68-7; **20**, 31729-69-8; zinc–methylene iodide, 31729-70-1.

(8) H. M. Hutton and T. Schaefer, *Can. J. Chem.*, **41**, 2429 (1963).

(9) N. S. Bhacca, M. E. Wolff, and W. Ho, *Tetrahedron Lett.*, 5427 (1968).

(10) G. Tarzia, N. H. Dyson, I. T. Harrison, J. A. Edwards, and J. H. Fried, *Steroids*, **9**, 387 (1967). Authentic samples were kindly supplied by Dr. N. H. Dyson.

Dechlorination of Benzotrichloride and Tolane Tetrachloride by Metals

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Contribution No. 241 from E. I. du Pont de Nemours and Company, Inc., Elastomer Chemicals Department, Wilmington, Delaware 19898

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The reductions of benzotrichloride and tolane tetrachloride to *cis*- and *trans*-α,α′-dichlorostilbene by iron, copper, and zinc are often quantitatively irreproducible owing to their heterogeneity. Only zinc caused any complete dechlorination to diphenylacetylene, while only copper preferentially converted tolane tetrachloride to the trans isomer. An authentic pure sample of *cis*-α,α′-dichlorostilbene was obtained by preparative gas chromatography, and the literature melting point was shown to be incorrect. The ir and Raman spectra of the cis and trans isomers are compared.

During a study of the oxidizing ability of organic polyhalides, it became apparent that there are discrepancies in the literature regarding the dechlorination of benzotrichloride and of tolane tetrachloride. Consequently, we have used improved analytical techniques to determine the products of dechlorination of benzotrichloride and tolane tetrachloride by iron, copper, and zinc and have found that these heterogeneous reactions are often hard to reproduce.

Results

Reduction of Benzotrichloride by Iron and Copper.—Iron powder in boiling aqueous suspension is reported[1] to reduce benzotrichloride to *trans*-α,α′-dichlorostilbene, *via* the intermediacy of tolane tetrachloride.[2] We confirmed that reduction for 1 hr gave tolane tetrachloride; however, after 24 hr we obtained 72% *cis*-α,α′-dichlorostilbene and only 28% of the trans isomer. Reduction with active copper powder[3] in pyridine at 65° for 2 hr gave only tolane tetrachloride.[4] Thus, both methods are suitable for the convenient synthesis of tolane tetrachloride.

In contrast, neat dry benzotrichloride shaken with iron powder for 1 day at 20° gave no coupled products, although a dark red solution was formed.

Reduction of Tolane Tetrachloride by Iron.—Reduction of tolane tetrachloride with iron powder for 4 hr in boiling aqueous suspension is reported to yield 64% of *trans*-α,α′-dichlorostilbene.[2] However, even after 1 day, we obtained 68% unchanged tolane tetrachloride, 23% *cis*-α,α′-dichlorostilbene, and only 9% of the trans isomer. The cis/trans ratio, 2.6, is identical with that which we obtained on reduction of benzotrichloride with iron powder. This is therefore consistent with the intermediate formation of tolane tetrachloride in this latter reaction.

Reduction of Tolane Tetrachloride by Copper.—Freshly prepared active copper powder[3] suspended in dimethylformamide at 140° completely dechlorinated tolane tetrachloride to 28% *cis*- and 72% *trans*-α,α′-dichlorostilbene in only 30 min. Reduction in pyridine

(1) Y. Ogata and R. Oda, *Bull. Inst. Phys. Chem. Res. (Tokyo)*, **21**, 616 (1942); *Chem. Abstr.*, **43**, 2194*d* (1949).

(2) Y. Ogata and H. Nakamura, *J. Org. Chem.*, **21**, 1170 (1956).

(3) A. H. Blatt, Ed., "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1953, p 446.

(4) Compare U. Hanhart, *Ber.*, **15**, 898 (1882).

at 65° was much slower;[5] after 3 hr there remained 54% unchanged tolane tetrachloride together with 38% *trans*-α,α'-dichlorostilbene and only 8% of the cis isomer. In each case the cis/trans ratio is much smaller than that for reduction by iron, and copper was the only reducing agent which produced the trans isomer preferentially.

In contrast, copper is said[6] to reduce 4,4'-dichlorotolane tetrachloride in pyridine to 72% *cis*-α,α'-dichloro-4,4'-dichlorostilbene and only 28% of the trans isomer.

Reduction of Tolane Tetrachloride by Zinc.—Blank[7] and Taylor and Murray[8] reported that zinc powder reduces tolane tetrachloride to a mixture of *cis*- and *trans*-α,α'-dichlorostilbene which can be separated with cold ethanol. However, Weis[1] claimed that reduction by zinc in dimethylformamide for 30 min at 140° gave only the cis isomer, which is not further dechlorinated to diphenylacetylene.

We have performed a number of reductions of tolane tetrachloride by zinc in dimethylformamide. A different product distribution was obtained in each case (Table I), and there was no unchanged starting material. It is apparent that the extent of dechlorination to diphenylacetylene is highly variable. Measurements at various reaction times for reaction 7 showed that the cis isomer must be initially produced in preference to the trans. However, the trans isomer is rapidly reduced to diphenylacetylene, while the cis form undergoes such further reduction only to a much smaller extent. From only two reactions, 1 and 7, did we obtain, after recrystallization from methanol, the white crystals melting sharply at 68° which were identified by Weis[6] as *cis*-α,α'-dichlorostilbene. However, we found, by vpc, that these crystals comprised two components in a 1:2 ratio, and after isolation by preparative gas chromatography these were identified as diphenylacetylene, mp 61°, and authentic *cis*-α,α'-dichlorostilbene, mp 58°, respectively (see Experimental Section). The mixture melted sharply, and at higher temperature than either component, suggesting the formation of a molecular complex. Bergmann[9] has noted such a 1:2 complex, mp 67–69°, from the chlorination of diphenylacetylene, and Iwai, *et al.*,[10] from the reaction of diphenylacetylene with nitryl chloride.

TABLE I
REDUCTION OF TOLANE TETRACHLORIDE BY ZINC DUST IN DIMETHYLFORMAMIDE AT 140°

Reaction	Reaction time, min	Product distribution by vpc, %: c-PhCCl=CClPh	t-PhCCl=CClPh	PhC≡CPh
1	30	67[a]	0	33[a]
2	30	27	0	73
3	30	53	33	14
4	30	50	24	26
5	30	42	42	16
6	30	52	18	30
7	60	58	26	16
7	90	54	13	33
7	120	50	6	44
7	150	48	Trace	52
7	180	46	0	54
7	180	67[a]	0	33[a]

[a] After recrystallization from methanol.

The ir and Raman spectra of *cis*- and *trans*-α,α'-dichlorostilbene are compared in Table II.

Discussion

The reductions of benzotrichloride and tolane tetrachloride described above are summarized in Table III. They are often irreproducible and there are many discrepancies in the published literature. This is probably due to the complete heterogeneity of the reactions, where neither the metal powder nor, in some cases, the organic substrate is soluble in the medium used. In addition the precise condition of the metal surface and the efficiency of stirring[1] are important. Another variable lies in the precautions taken against light, since we found that sunlight, even through glass, isomerizes *cis*-α,α'-dichlorostilbene in solution to the trans form within a week, although the reverse process did not occur. Our procedure of product analysis by direct gas chromatography rather than by reliance on product isolation as previous authors had done is also probably responsible for some of the differences between our results and theirs.

Comparison of the reductions of benzotrichloride and tolane tetrachloride by iron described above shows that the latter compound is more rapidly reduced when produced *in situ* from benzotrichloride than when it was used as the starting material. This may be due to more intimate contact between tolane tetrachloride formed as an intermediate and the metal, since it is partly soluble in the reaction mixture containing benzotrichloride. In contrast, when the tolane tetrachloride is the initial substrate it is insoluble in the wholly aqueous medium employed. In support of this, the converse situation prevails in the corresponding reductions with copper, when the tolane tetrachloride is completely soluble in the pyridine or dimethylformamide medium employed.

Our preparation of *cis*-α,α'-dichlorostilbene with mp 58°, lower than that reported previously, deserves comment. The compound was isolated by preparative gas chromatography and was shown by gas chromatography to be free from the trans isomer. In contrast, literature preparations of supposedly pure *cis*-α,α'-dichlorostilbene have relied on purification by solvent extraction and recrystallization. However, we found that recrystallization did not completely separate all trans isomer from the cis compound, because the latter is more soluble. Hence recrystallization is an ineffective method for the purification of *cis*-α,α'-dichlorostilbene, although the trans isomer can be obtained pure in this way. It appears that, while the "α-dichlorostilbene" of the literature[11] is the pure trans-α,α'-dichlorostilbene, the so-called "β-dichlorostilbene," with reported melting points of 61–64°,

(5) Compare L. V. Johnson, F. Smith, M. Stacey, and J. C. Tatlow, *J. Chem. Soc.*, 4710 (1952).
(6) C. D. Weis, *Helv. Chim. Acta*, **49**, 234 (1966).
(7) A. Blank, *Justus Liebigs Ann. Chem.*, **248**, 17 (1888).
(8) T. W. J. Taylor and A. R. Murray, *J. Chem. Soc.*, 2078 (1938).
(9) E. Bergmann, *ibid.*, 402 (1936).
(10) I. Iwai, K. Tomita, and J. Ide, *Chem. Pharm. Bull.*, **13**, 118 (1965). These authors erroneously identify the complex as 2:1 diphenylacetylene–*cis*-α,α'-dichlorostilbene, but their analytical results actually support a 1:2 complex.
(11) J. Heilbron, Ed., "Dictionary of Organic Compounds," 4th ed, Oxford University Press, New York, N. Y., 1965, and references cited therein.

TABLE II

IR AND RAMAN SPECTRA OF *cis*- AND *trans*-DICHLOROSTILBENES

Isomer	Ir		Raman	
	C=C, aromatic, 1600 cm^{-1}	C—Cl, 700 cm^{-1}	C=C, aromatic, 1600 cm^{-1}	C—Cl, 700 cm^{-1}
Cis	1570 (w), 1590 (w), 1610 (w)	760 (m)	1575 (s), 1600 (s), 1605 (s), 1620 (s)	775 (w)
Trans		730 (s)[a]	1575 (w), 1600 (s), 1620 (w), 1650 (s)	760 (w)

[a] Aromatic C–H deformation probably overlaps with this band.

TABLE III

DECHLORINATION OF BENZOTRICHLORIDE AND TOLANE TETRACHLORIDE BY IRON, COPPER, AND ZINC

Reductant	Conditions	Product
	Benzotrichloride	
Fe	Aqueous suspension, 100°, 1 hr	$PhCCl_2CCl_2Ph$
	Aqueous suspension, 100°, 24 hr	72% *cis*-, 28% *trans*-PhCCl=CClPh
Active Cu	Pyridine suspension, 65°, 2 hr	$PhCCl_2CCl_2Ph$
	Tolane Tetrachloride	
Fe	Aqueous suspension, 100°, 24 hr	23% *cis*-, 9% *trans*-PhCCl=CClPh 68% unchanged $PhCCl_2CCl_2Ph$
Active Cu	Dimethylformamide suspension, 140°, 30 min	28% *cis*-, 72% *trans*-PhCCl=CClPh
Active Cu	Pyridine suspension, 65°, 3 hr	38% *trans*-, 8% *cis*-PhCCl=CClPh 54% unchanged $PhCCl_2CCl_2Ph$
Zn	Dimethylformamide suspension, 140°	Mixture of *cis*- and *trans*-PhCCl=CClPh and PhC≡CPh; distribution varies with reaction time (see Table I)

is not the pure cis isomer but is probably contaminated with small amounts of the trans compound.[4,7-9,12,13]

Table II shows that our *cis*- and *trans*-α,α'-dichlorostilbenes exhibit characteristic ir and Raman spectra which are in agreement with the proposed assignment. There is no C=C stretching band in the ir of the trans isomer. The C—Cl stretching for the cis isomer is higher than that for the trans isomer (ir, cis 760 cm^{-1}, trans 730 cm^{-1}; Raman, cis 775 cm^{-1}, trans 760 cm^{-1}). This trend is also true for the analogous case of *cis*- and *trans*-dichloro-2-butene,[14] where the cis isomer showed a C—Cl stretch at 755 cm^{-1} *vs.* 730 cm^{-1} for the trans isomer. This suggests a greater single bond character in the cis isomer and agrees with the observation that the C=C stretch is at 1620 cm^{-1} for the cis isomer but at 1650 cm^{-1} for the trans isomer. A similar shift is noted in dichloroethylene, where the C=C stretch is at 1590 cm^{-1} for the cis isomer but at 1653 cm^{-1} for the trans isomer.[15]

Experimental Section

Gas Chromatographic Analysis.—Vpc analyses of reaction products and of the purity of compounds isolated were made on 6 ft of 10% OV-1 silicone gum rubber on 80–100 Supelcoport, using an all-glass system to avoid the decomposition of benzotrichloride and tolane tetrachloride which often occurs on stainless steel columns. Peaks were identified by spiking with authentic samples, by mass spectrometry, and in some cases by collection. Despite reports that *cis*- and *trans*-α,α'-dichlorostilbenes interconvert above 200°,[8] this did not occur in our system since it was possible to chromatograph pure samples of both isomers without isomerization.

Purification of Benzotrichloride.—Benzotrichloride filtered through alumina and fractionated under nitrogen at reduced pressure still contains small amounts of tolane tetrachloride and the α,α'-dichlorostilbenes. When necessary these were removed by recrystallization twice from hexane at −10°, the feathery white crystals then being remelted and purged with nitrogen to remove all residual hexane.

Preparative Methods.—Reactions were generally carried out, in subdued light, as described in the literature cited in the Results section. Vpc analyses of product distribution were performed on the reaction solutions directly after removal of the spent metal.

Tolane tetrachloride was prepared by reduction of benzotrichloride with iron[2,3] or copper[5] as previously described. It was recrystallized with activated charcoal from benzene–methanol as white, chunky crystals, mp 162°.

Anal. Calcd for $C_{14}H_{10}Cl_4$: C, 52.5; H, 3.2; Cl, 44.3. Found: C, 52.6; H, 3.2; Cl, 44.3.

***trans*-α,α'-Dichlorostilbene** was prepared by reducing benzotrichloride with iron powder in boiling aqueous suspension for 24 hr.[2] It was finally recrystallized with activated charcoal from benzene–methanol to give white crystals, mp 140° (lit.[11] mp 140–142°). The mass spectrum showed a molecular ion peak at mass number 248, together with isotopic chlorine peaks, and vpc showed that it contained none of the cis isomer. The ir spectrum was identical with that published for the trans isomer, and the ir and Raman spectra have been discussed above.

Anal. Calcd for $C_{14}H_{10}Cl_2$: C, 67.5; H, 4.1; Cl, 28.4. Found: C, 67.5; H, 4.0; Cl, 28.5.

***cis*-α,α'-Dichlorostilbene.**—Tolane tetrachloride was reduced with zinc in dimethylformamide as described by Weis[6] to obtain, in two instances, the white crystals, mp 67–68°, identified by him as *cis*-α,α'-dichlorostilbene. Vpc showed these crystals to contain two components which were separated by preparative gas chromatography on 2 ft of 25% Dow-Corning silicone 200 oil on Gas-Chrom Z at 170°.

The more volatile component melted at 61° and was identified as diphenylacetylene (lit.[11] mp 62°), since both its mass spectrum (large molecular ion peak at mass number 178) and infrared spectrum were identical with those for an authentic sample.

The second component was recrystallized from methanol to give white, feathery crystals, mp 58°. It had a mass spectrum with a molecular ion peak at mass number 248, together with satellite peaks characteristic of chlorine isotopes, and exhibited a splitting pattern almost identical with that for *trans*-α,α'-dichlorostilbene. Vpc showed that it contained none of the trans isomer. The ir and Raman spectra have already been discussed above.

Anal. Calcd for $C_{14}H_{10}Cl_2$: C, 67.5; H, 4.1; Cl, 28.4. Found: C, 67.7; H, 4.0 Cl, 28.3.

The complex of *cis*-α,α'-dichlorostilbene with diphenylacetylene had an analysis in agreement with the 2:1 proportions shown by vpc.

Anal. Calcd for $C_{42}H_{30}Cl_4$: C, 74.5; H, 4.5; Cl, 21.0. Found: C, 74.7; H, 4.3; Cl, 21.0.

Registry No.—Benzotrichloride, 98-07-7; tolane tetrachloride, 13700-81-7; *cis*-α,α'-dichlorostilbene,

(12) H. Staudinger, *Ber.*, **49**, 1971 (1916).
(13) W. Löb, *Z. Elektrochem.*, **9**, 906 (1903).
(14) L. F. Hatch and J. J. D'Amico, *J. Amer. Chem. Soc.*, **73**, 4393 (1951).
(15) L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen, London, 1968, p 32.

5216-32-0; *trans*-α,α'-dichlorostilbene, 951-86-0; iron, 7439-89-6; copper, 7440-50-8; zinc, 7440-66-6.

Acknowledgments.—We thank Mrs. A. B. Richmond for the preparative gas chromatography, Dr. T. L. Pugh for the mass spectra, Dr. E. Bromels for the Raman spectra, and Dr. E. G. Brame and Professor Bryce Crawford for advice on spectral interpretation, and Mr. L. L. Burchfield for skillfully performing the experimental work.

Regiospecificity and Stereochemistry in the Hydralumination of Unsymmetrical Acetylenes. Controlled Cis or Trans Reduction of 1-Alkynyl Derivatives[1]

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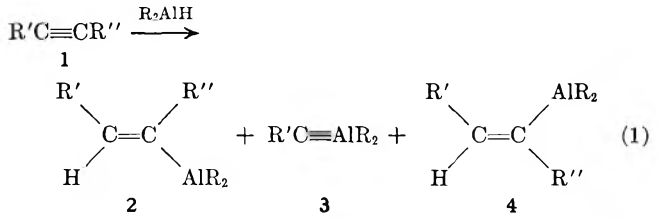
The regiospecificity and stereochemistry for the addition of aluminum–hydrogen bonds to unsymmetrical acetylenes were examined in order to evaluate the steric and electronic factors of this important reaction. Phenylethynyl derivatives of the type $C_6H_5C{\equiv}CE$ (**5**), where E = CMe_3, $SiMe_3$, $GeMe_3$, $GeEt_3$, $SnMe_3$, PMe_2, H, and Br, were treated with 1 equiv of diisobutylaluminum hydride (**6**) in hydrocarbon solution. Hydrolytic work-up was employed to determine the cis or trans nature of the addition or the extent of C–E bond cleavage; alternative work-up with deuterium oxide permitted the labeling of the carbon–aluminum bond site and hence the determination of the regiospecificity of hydralumination. With E = SiR_3 or GeR_3, the hydralumination proceeded almost completely in a trans manner; use of 1 equiv of a tertiary amine with **6** gave almost exclusively cis addition. These controlled trans or cis reductions were also found to be general for other trimethylsilyl derivatives of terminal acetylenes, and hence this method has considerable promise for stereospecific chemical transformations of acetylene derivatives. The patterns observed for the cis or trans hydraluminations and the C–E bond cleavages, taken together with the regiospecificity, are most consistent with a transition state involving electrophilic attack by the aluminum center, culminating in a cis addition. Trans hydralumination seems to ensue from the isomerization of the cis adduct.

Although the hydralumination of internal acetylenic linkages leads cleanly to the cis adduct (**2a**),[2] terminal acetylenes can yield both the hydralumination adduct (**2b**) as well as the substitution product (**3b**).[3] Since the synthetic utility of such vinylaluminum adducts (**2b**) is curtailed by contamination with varying amounts of **3b** (*ca.* 30% with $C_6H_5C{\equiv}CH$),[4] we investigated the possible use of trimethylsilyl derivatives of terminal acetylenes (**1c**) in achieving hydralumination without substitution. Such a derivative did, in fact, yield exclusively the hydralumination product,[5a]



a, R′ and R″ = alkyl
b, R′ = alkyl; R″ = H
c, R′ = alkyl or aryl; R″ = $SiMe_3$
d, R = alkyl or aryl; R″ = E

but the trans stereochemistry of the reaction,[5b] forming almost solely **4c**, was an arresting contrast to that of previously reported cis hydraluminations with dialkylaluminum hydrides.[2] Moreover, the direction or regiochemistry of Al–H bond addition to the acetylenic linkage of **1c** was opposite[5a] that observed for related disubstituted acetylenes (**1a**).[2b] These interesting orientational and stereochemical observations have encouraged us to examine the hydralumination of a series of 1-alkynyl derivatives bearing metalloidal or nonmetallic functional groups adjacent to the triple bond (**1d**). By assessing the relative amounts of hydralumination (cis and trans, **2d** and **4d**) and of metalation (**3d**), we hoped to understand better the steric and electronic factors of this important reaction.

Results

The hydraluminations of a series of phenylethynyl derivatives, $C_6H_5C{\equiv}CE$ (**5**) (where E = CMe_3, $SiMe_3$, $GeMe_3$, $GeEt_3$, $SnMe_3$, PMe_2, H, and Br) were performed in heptane solution with 1 equiv of diisobutylaluminum hydride (**6**). Hydrolytic work-up of the reaction mixtures with deuterium oxide and nmr analyses of the deuterated reduction or cleavage products permitted a determination of the proportion of aluminum derivatives, *e.g.*, **2**, **3**, and **4**. Because of the novel trans hydraluminations observed with the trialkylsilyl and -germyl derivatives of phenylacetylene, the hydraluminations of these compounds were examined under other experimental conditions. Even when the hydralumination of phenylethynyl(trimethyl)silane (**5b**) was carried out at −10° to only 5% conversion, the hydrolyzed[6] product was still 95% *trans*-β-styryl(trimethyl)silane (**9b**). However, earlier work

(1) Part XIX of the series, "Organometallic Compounds of Group III," devoted to carbometalation and hydrometalation. Previous part: J. J. Eisch and J. M. Biedermann, *J. Organometal. Chem.*, **30**, 167 (1971).

(2) (a) G. Wilke and H. Müller, *Justus Liebigs Ann. Chem.*, **629**, 222 (1960); (b) J. J. Eisch and W. C. Kaska, *J. Amer. Chem. Soc.*, **88**, 2213 (1966).

(3) H. Lehmkuhl, K. Ziegler, and H. G. Gellert in "Houben-Weyls Methoden der Organischen Chemie," Band XIII/4, E. Müller, Ed., Georg Thieme, Stuttgart, 1970, pp 159–164.

(4) J. J. Eisch and W. C. Kaska, *J. Organometal. Chem.*, **2**, 184 (1964).

(5) (a) J. J. Eisch and M. W. Foxton, *ibid.*, **11**, P24 (1968). (b) The trans hydralumination of alkynes with lithium aluminum hydride was first reported by L. H. Slaugh and E. F. Magoon [*Tetrahedron*, **23**, 4509 (1967)] and, independently, by the present authors (ref 5a). Lithium diisobutylmethylaluminum hydride has been found to effect trans hydralumination of alkynes very smoothly in nonpolar media [G. Zweifel and R. Steele, *J. Amer. Chem. Soc.*, **89**, 5085 (1967)].

(6) In this and other cases of measuring the ratio of cis and trans aluminum adducts by hydrolysis, a low temperature and vigorous stirring had to be maintained during quenching, in order to avoid thermal isomerization of the aluminum adducts. N.B: Ordinarily, vinylaluminum compounds are hydrolyzed with retention of stereochemistry.[2]

TABLE I

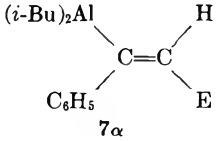
HYDRALUMINATIONS OF PHENYLETHYNYL DERIVATIVES, $C_6H_5C{\equiv}CE$ (5), BY $(i\text{-Bu})_2AlH$ (6)

Substrate $C_6H_5C{\equiv}CE$—				Products			
Compd	E	C≡C, μ	Conditions[a]	7β	9	7α	8
5a	CMe_3	4.61 (w)	50°			100	
5b	$SiMe_3$	4.65 (s)	20°	4	96		
5b	$SiMe_3$		60°, R_3N[b]	96	4		
5b	$SiMe_3$		35°, Et_2O[c]	65	35		
5c	$GeMe_3$	4.65 (m)	50°	6	94		
5c	$GeMe_3$		100°, R_3N[b]	98	2		
5d	$GeEt_3$	4.65 (m)	50°	7	93		
5e	$SnMe_3$		20°				100
5e	$SnMe_3$		20°, R_3N[b]				100
5f	PMe_2	4.63 (m)	50°	85		15	
5f	PMe_2		50°, R_3N[b]	85		15	
5g	H	4.72 (sh)	20°	71			29
5h	Br	4.55 (s)	100°				100

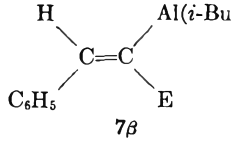
[a] In pentane or heptane using a 1:1 ratio of equivalents of 5 and 6. [b] With 1 equiv of *N*-methylpyrrolidine. [c] In diethyl ether solution.

in this laboratory had shown that tertiary amine adducts of diisobutylaluminum hydride achieved a slower but cleaner cis hydralumination of tolane (2, R′ = R″ = C_6H_5), with no trans adduct or dimerized product. Consequently, the hydraluminating properties of a 1:1 adduct of *N*-methylpyrrolidine and **6** were examined. Although *tert*-butyl(phenyl)acetylene (**5a**) simply underwent the previously observed cis addition at a slower rate, the silyl and germyl derivatives of phenylacetylene (**5b–d**) now underwent almost completely cis addition, a behavior exactly opposite that observed in the absence of the amine. Diethyl ether was not as effective in redirecting the hydralumination to a cis course, since a 65:35 cis:trans ratio resulted.

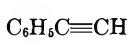
As to the regiospecificity of the addition reactions, the deuterium labeling in the hydrolysis products showed that hydralumination of *tert*-butyl(phenyl)-acetylene (**5a**) placed the diisobutylaluminum group exclusively α to the phenyl group (7α). With the silyl and germyl derivatives **5b–d**, and phenylacetylene itself, **5g**, the aluminum group was placed exclusively β to the phenyl group in both cis and trans hydraluminations (7β and **9**). Dimethyl(phenylethynyl)phosphine (**5f**) on the other hand, yielded regioselective, cis hydralumination in proportions of 85% β and 15% α to the phenyl group.



7α



7β



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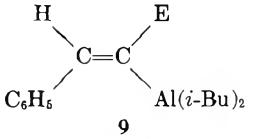
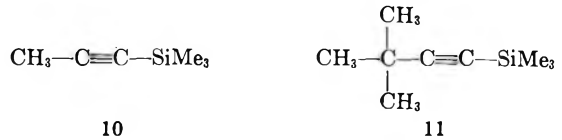


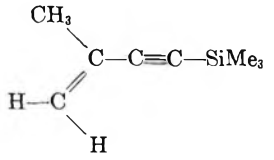
9

Cleavage of the C–E bond in $C_6H_5C{\equiv}CE$ (**1d** → **3d**) was observed only for E = $SnMe_3$ (**5e**), H (**5g**), and Br (**5h**). In **5e** and **5h** only cleavage and no discernible hydralumination was achieved; with phenylacetylene cleavage amounted to 29% of the total reaction. The behavior of these phenylethynyl derivatives is summarized in Table I.

The possible generality of the controlled cis or trans hydralumination of silyl derivatives of 1-alkynes was investigated for the cases **10–12**. Both **11** and **12**



10 11

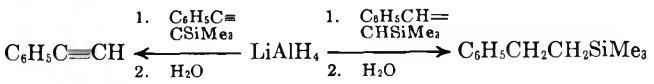


12

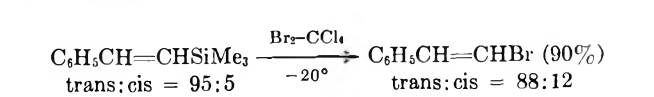
behaved exactly like **5b**, giving the trans reduction product with **6** alone and the cis product with **6** combined with *N*-methylpyrrolidine. On the other hand, for reasons not yet understood, **10** led to no detectable monomeric reduction product (cis or trans), despite diligent variation in experimental conditions. Instead, only two isomers of 1,3-bis(trimethylsilyl)-2-methyl-1,3-pentadiene were isolated.

The cis hydralumination adducts of these silyl and germyl acetylenes (**5b–d**, **11** and **12**) could be smoothly isomerized into their more stable trans structures either by adding 1 equiv of diisobutylaluminum chloride at 25° or by heating with a catalytic amount of **6**. In both cases it appears that the isomerizing agent acts as a Lewis acid toward the *N*-methylpyrrolidine.

Also bearing on the interpretation of these results are the observations that lithium aluminum hydride in THF effected only the cleavage of **5b** to yield phenylacetylene on hydrolysis, but that the same reagent smoothly hydraluminated *cis*-β-styryl(trimethyl)silane.

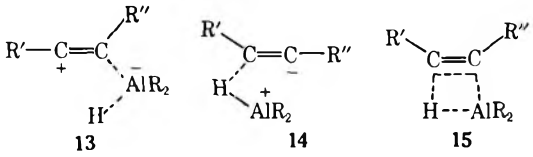


Finally, it should be mentioned that the substituted vinylsilanes resulting from these reductions show considerable promise as precursors for other organic derivatives. The highly stereoselective bromodesilylation of β-styryl(trimethyl)silane has encouraged us to continue work on the synthetic aspects of these reactions.



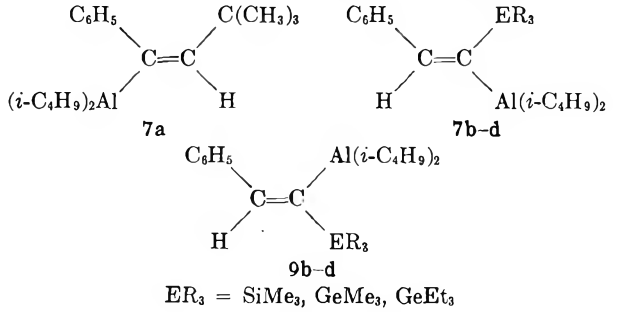
Discussion

The regiospecificity, the stereospecificity, and the isomerization processes observed in these hydraluminations call for some further mechanistic consideration. The regiospecificity or direction of Al–H bond addition to these alkynes could be rationalized, either electronically in terms of an electrophilic attack by aluminum (**13**) or a nucleophilic attack by hydrogen (**14**), or sterically in terms of a four-center trasition state (**15**). The



13 **14** **15**

pronounced retarding effect of tetrahydrofuran on the hydralumination rate of 4-octyne[7] and of *N*-methylpyrrolidine on the reactions of these alkynes (**5**) is consistent with the importance of a tricoordinate hydraluminating species, as in **13** or **15**, in nondonor media. Thus, some type of electrophilic attack by aluminum seems to be involved when **6** is used in hydrocarbon solution in the absence of Lewis bases.[8] A further choice between transition state models **13** and **15** can be made by considering the behavior of *tert*-butyl(phenyl)acetylene (**5a**) *vs.* that of its silyl and germyl counterparts (**5b–d**). If the exclusive formation of **7a** from **5a** were explained on steric grounds (*i.e.*, smaller nonbonded interactions between R″ = C_6H_5 and R = *i*-C_4H_9 in **15**), then the exclusive placement of the (*i*-C_4H_9)$_2$Al group next to the R_3Si or R_3Ge in **5b–d** (either cis or trans) to yield **7** or **9b,c** must be

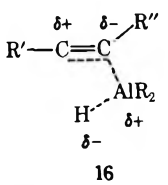


7a **7b–d**

9b–d

ER_3 = $SiMe_3$, $GeMe_3$, $GeEt_3$

a source of bewilderment. On the other hand, a superior explanation applicable to all cases is that electrophilic attack by **6** will be favored, so as to place the electron deficiency on that carbon (**15**) better able to sustain it. The polarization of the carbon–carbon linkage in the transition state, shown in **16**, would be



16

especially fostered in **5a**, where R″ = C_6H_5 and R′ = *tert*-C_4H_9, and in **5b–d**, where R′ = C_6H_5 and R″ = R_3Si, R_3Ge, R_2P, and H. For the C_6H_5, *tert*-C_4H_9, and H substituents, their σ_{para} could be invoked to rationalize their electron release; for the organometalloidal groups R_nE a particularly effective p_π–d_π interaction with E could be noted. Even in the ground state of **5b–d** and **5f**, their infrared spectral C≡C stretches display shifts and accentuated intensities consistent with dative bonding and marked polar character[9,10] (Table I).

$$C_6H_5C{\equiv}CE \longleftrightarrow C_6H_5\overset{+}{C}{=}\overset{-}{C}E \longleftrightarrow C_6H_5\overset{+}{C}{=}C{=}\overset{-}{E}$$

5, E = Me_3Si, Me_3Ge, Et_3Ge, and Me_2P

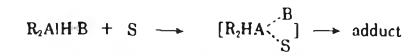
The stereochemistry and the isomerization processes of these additions deserve joint treatment, for the question arises whether the observed trans hydralumination of $C_6H_5C{\equiv}CSiMe_3$ and $C_6H_5C{\equiv}CGeR_3$ might have occurred by an initial cis addition followed by isomerization to the more stable trans adduct. If this be the actual pathway for **9b–d**, such isomerization must be very fast indeed, for at 5% conversion of **5b** at −10°, the product was already 95% trans adduct. A scrutiny of the first 5% of reaction and a complete kinetic analysis of initial rates are underway,[7] in order to distinguish the isomerization possibility from a kinetically controlled trans hydralumination,[5] presumably of different kinetic order than a cis process. However, it is clear from the present studies that cis adducts **7b–d**, in the absence of Lewis base complexation (*N*-methylpyrrolidine), are readily converted into the trans adducts **9b–d**. Addition of a Lewis acid, **6** or (*i*-C_4H_9)$_2$AlCl, to the amine adduct of **7b** causes formation of **9b**.

Two mechanistic possibilities come to mind:[2b,11] after removal of the amine by complexation with the Lewis acid, (*i*-Bu)$_2$AlCl, either Lewis acid catalyzed isomerization (path a) or uncatalyzed, thermal isomerization of **7b** by virtue of an exceptionally low C=C rotational barrier arising from combined p_π–d_π (C–Si) and p_π–p_π (C–Al) effects.[10] The observation that just 1 equiv of (*i*-C_4H_9)$_2$AlCl causes a prompt isomerization of **7b** at 25° is in better accord with path b, since the Lewis acid should be essentially tied up as its *N*-methylpyrroline complex and hence not available for path a. This rapid isomerization of uncomplexed **7b** suggests that the trans hydraluminations of **5b–d** do proceed *via* cis adducts. It is noteworthy that the phosphine derivative **5f** undergoes cis hydralumination, with or without the presence of an amine. Presumably the basic character of the Me_2P group provides the system with an internal Lewis base to protect **7f** from isomerization.

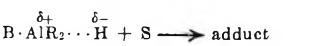
Finally, the C–E bond cleavages observed with $C_6H_5C{\equiv}CE$, where E = Me_3Sn, Br, or H, may well proceed by differing mechanisms. However, it can be observed that slight modification of transition state **16** could permit the hydridic group to attack group R″, instead of the β carbon. Another noteworthy cleavage is that of the C–Si bond in **5b** by $LiAlH_4$. This finding

(7) J. J. Eisch and S. G. Rhee, unpublished studies.

(8) In the presence of Lewis bases, an electrophilic attack by aluminum on the unsaturated hydrocarbon (S), with displacement of the base (B), may also obtain.



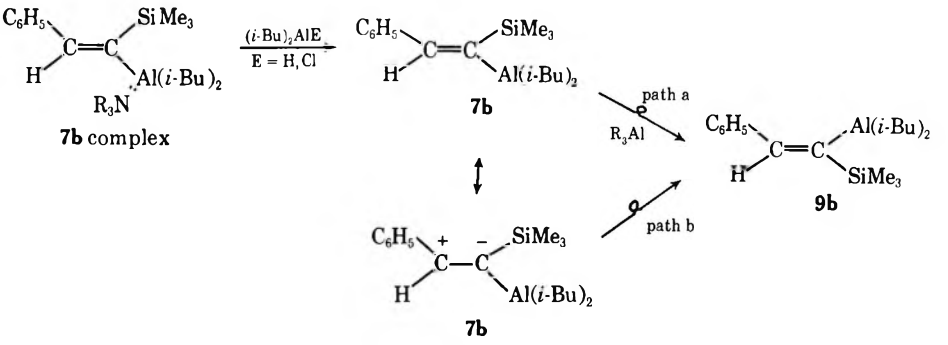
However, kinetic studies[7] have yet to rule out a nucleophilic attack by the hydridic complex.



(9) R. West and C. S. Kraihanzel, *Inorg. Chem.*, **1**, 967 (1962).

(10) J. J. Eisch and J. T. Trainor, *J. Org. Chem.*, **28**, 487 (1963).

(11) A third possibility, addition of (*i*-Bu)$_2$AlE to **7b** (ref 2b) and reelimination, seems unlikely to play a role under the relatively mild conditions employed here.



shows that a recognized nucleophilic attack by hydride takes place in an entirely different manner than the attack of **6** or **6**-NR_3 on the same substrate. This is further reason to dismiss **13** as a suitable model for these hydraluminations by reagent **6**.

Experimental Section

Melting points were determined with a Thomas–Hoover "Unimelt" apparatus and are corrected. Infrared spectra were recorded of samples as potassium bromide disks, mineral oil suspensions, or solutions in pure solvents, by means of a Perkin-Elmer spectrophotometer, Model 137. Proton magnetic resonance spectra were measured with a Varian spectrometer, Model A-60, on samples dissolved as 10% solutions in pure solvents containing tetramethylsilane as an internal standard. Signals are reported using the δ scale in parts per million, followed by the integrated intensities of the proton signals and the coupling constants (J) in hertz. Vpc analyses were performed on an F & M dual-column equipped with 2-ft columns packed with 10% silicone gum rubber on firebrick. Elemental analyses were carried out by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

All preparations and reactions involving either air- and moisture-sensitive organometallic reagents were conducted under an atmosphere of dry, oxygen-free nitrogen. Appropriate techniques for such manipulations, including the necessary purification of solvents, have already been described.[2b]

Preparation of Starting Materials.—Several of the substituted phenylacetylenes were prepared from phenylethynylmagnesium bromide and the appropriate organometalloidal halide in general accordance with the following specific procedure for phenylethynyl(trimethyl)silane. Thus, a stirred solution of ethylmagnesium bromide prepared from 12.2 g (0.50 g-atom) of magnesium turnings and 54.5 g (0.50 mol) of ethyl bromide in 250 ml of anhydrous diethyl ether was treated dropwise with 51.0 g (0.50 mol) of freshly distilled phenylacetylene and the resulting mixture was further stirred for 16 hr at 25°. Thereupon, a solution of 55.0 g (0.505 mol) of chlorotrimethylsilane in 50 ml of ether was added dropwise over the course of 4 hr. After a 24-hr reflux period, the semisolid mixture was cooled in ice and stirred while 100 ml of water was cautiously introduced. The separated organic layer was stored over anhydrous calcium sulfate, the solvent was evaporated, and the residue was distilled under reduced pressure. Phenylethynyl(trimethyl)silane (**5b**) was obtained in 80% yield, bp 46–47° (0.4 mm), $n^{22.5}$D 1.5272 [lit.[12] bp 59–60° (1.0 mm), n^{26}D 1.5255], and proved to be pure by vpc.

Phenylethynyl(trimethyl)germane (**5c**) was prepared by a similar procedure, except that tetrahydrofuran was used as the solvent. On a 0.035-molar scale, 95% of the germane was obtained, bp 54–55° (0.5 mm) [lit.[13] bp 70° (1.5 mm)].

Phenylethynyl(triethyl)germane (**5d**) was analogously synthesized in 60% yield from a 0.080-molar run, bp 90–91° (0.40 mm) [lit.[14] bp 115° (1.5 mm)].

Phenylethynyl(trimethyl)tin (**5e**) was prepared on a 0.10-molar scale in only 35% yield when diethyl ether was employed as the solvent. Better yields were subsequently obtained by conducting the reaction in tetrahydrofuran, bp 72–74° (0.50 mm) [lit.[15] bp 60° (0.2 mm)].

Dimethyl(phenylethynyl)phosphine[16] (**5f**) was synthesized on a 0.080-molar scale in 67% yield by permitting chloro(dimethyl)-phosphine to interact with phenylethynylmagnesium bromide in diethyl ether and maintaining the reaction mixture at room temperature at all times. The reaction product was worked up and then distilled under a nitrogen atmosphere, bp 58–59° (0.30 mm).

***tert*-Butyl(phenyl)acetylene** (**5a**).—A solution of 41.0 g (0.50 mol) of *tert*-butylacetylene in 200 ml of 95% ethanol was added to a solution of 71.3 g (0.50 mol) of cuprous bromide in 800 ml of concentrated ammonium hydroxide. After standing overnight the blue-green precipitate was collected and washed, in turn, with ten 100-ml portions of water and then with three 50-ml portions of ethanol. The resulting orange powder, upon drying *in vacuo*, amounted to only 5.5 g (8%) of *tert*-butylethynylcopper(I). However, its subsequent reaction with iodobenzene proceeded well.

Thus, the foregoing cuprous acetylide (0.038 mol) and 7.66 g (0.038 mol) of iodobenzene were heated for 16 hr in 100 ml of refluxing anhydrous pyridine (general procedure of Stephens and Castro).[17] The cooled solution was diluted with 300 ml of water and extracted with four 100-ml portions of ether. The ether extracts were washed successively with 2 *N* hydrochloric acid, sodium bicarbonate solutions, and water. After drying over anhydrous calcium sulfate the ether solution provided, upon fractional distillation, 5.9 g (84%) of *tert*-butyl(phenyl)acetylene, bp 76–77° (1.5 mm) [lit.[18] bp 84° (10 mm)]. A vpc examination showed the presence of <1% of iodobenzene.

An effective modification to circumvent the difficult isolation and purification of the *tert*-butylethynylcopper(I) consisted in using the silver salt. Thus, a solution of 20.5 g (0.25 mol) of *tert*-butylacetylene in 100 ml of 95% ethanol was mixed with a solution of 42.5 g (0.50 mol) of silver nitrate in 100 ml of aqueous ethanol (1:1 v/v). The precipitated *tert*-butylethynylsilver was collected, washed with water and then with ethanol, and dried *in vacuo*, yield 45 g (94%). This silver acetylide (45 g, 0.24 mol), 48 g (0.24 mol) of iodobenzene, and 30.4 g (0.24 mol) of cuprous bromide were heated for 16 hr in 800 ml of refluxing anhydrous pyridine. Usual work-up afforded 23 g (57%) of pure *tert*-butyl-(phenyl)acetylene.

Bromo(phenyl)acetylene (**5h**).—A solution of 20.4 g (0.20 mol) of phenylacetylene in 10 ml of tetrahydrofuran was added to a sodium hypobromite solution that was prepared from 11 ml of bromine, 50 ml of 10 *N* sodium hydroxide solution, and 100 g of ice. After a 5-hr stirring period, the reaction solution was treated with sufficient ammonium chloride solution to destroy the residual hypobromite ion. The solution was then extracted with ether, the extracts were dried over anhydrous calcium sulfate, and the ether solvent was evaporated. Distillation yielded 29.0 g (81%) of bromo(phenyl)acetylene as a pale yellow oil, bp 37–39° (0.35 mm), n^{24}D 1.6088 [lit.[19] bp 96° (15 mm)].

1-Propynyl(trimethyl)silane (**10**), **3,3-dimethylbut-1-ynyl(trimethyl)silane** (**11**), **and 2-methylbut-1-en-3-yn-4-yl(trimethyl)-silane** (**12**) were prepared from chlorotrimethylsilane and the corresponding alkynes, namely propyne, *tert*-butylacetylene, and

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2-methylbut-1-en-3-yne, respectively, by following the procedure for phenylethynylsilane. Because of the volatility of the alkynes, the yields of silanes ranged from 30 to 60%. Physical constants of $RSiMe_3$ follow: (a) R = $CH_3C{\equiv}C$, bp 96–97°, $n^{26}D$ 1.4153 (lit.[20] bp 100°); (b) R = $Me_3CC{\equiv}C$, bp 52–54° (55 mm) [lit.[21] 57° (60 mm)]; and [c] R = $CH_2{=}CMeC{\equiv}C$, bp 49–50° (33 mm), 120–122° (750 mm), $n^{25}D$ 1.4451 [lit.[22] bp 32° (15 mm)].

Reactions of Phenylethynyl Derivatives with Diisobutylaluminum hydride. Trans Hydralumination of Phenylethynyl(trimethyl)silane (5b).—A solution of 20.0 g (0.141 mol) of diisobutylaluminum hydride (6) in 25 ml of pentane was added dropwise to a stirred solution of **5b** (24.5 g, 0.141 mol) in 35 ml of pentane maintained at 20°. After a 15-hr stirring period, the solution was chilled in an ice bath and cautiously treated with 7.6 ml of water. The resulting suspension was filtered and the solvent was removed from the filtrate. Distillation of the residue gave 23.5 g (96%) of *trans*-β-styryl(trimethyl)silane, bp 90–91° (13 mm) [lit.[12] bp 80–83° (3 mm)]. A vpc analysis showed this sample to contain less than 5% of an equal mixture of the cis isomer and **5b**. Redistillation and spectral analysis established that trans reduction of the silylacetylene had occurred: ir (liquid film) 6.25 and 6.35 (C=C conjugated with aromatic) and 10.16 μ (*trans* CH=CH); nmr (neat) δ 0.14 [s, $(CH_3)_3Si$], 6.33 (d, 1-CH, J = 19 Hz), 6.88 (d, 2-CH, J = 19 Hz), 7.07–7.41 (m, 5 H).

When a 1:1 molar ratio of triisobutylaluminum and **5b** (0.04-molar scale) was heated at reflux in 50 ml of heptane for 15 hr, hydrolysis gave a mixture of 90% trans and 3% cis products and 7% of a higher isomeric mixture possibly involving Al–C bond addition.

Trans Hydralumination of 5b and Treatment with Deuterium Oxide.—Repetition of the foregoing hydralumination but treatment of the reaction mixture with deuterium oxide (99.8%), instead of water, yielded a monodeuterated *trans* product, nmr (neat) 6.88 (t, J = 3 Hz). There was no trace of the doublet centered at 6.33 ppm, due to the β hydrogen. Therefore, it is concluded that the aluminum was attached exclusively to the carbon adjacent to the Me_3Si group.

Trans Hydralumination of 5b at −10° under Partial Conversion.—To check whether any large amount of cis hydralumination occurred under kinetically controlled conditions, the foregoing hydraulumination was conducted at −10° (insignificant reaction <−10°), samples periodically withdrawn with a hypodermic syringe and squirted immediately into ice water. A vpc analysis showed that, even at 5% conversion of alkynylsilane into alkenylsilane, the *trans*-β-styryl(trimethyl)silane accounted for 95% of the products. It was observed that any time lag due to inefficient hydrolysis of the aliquots permitted further hydralumination during hydrolysis and led to spurious results.

Cis Hydralumination of 5b in the Presence of *N*-Methylpyrrolidine.—Admixture of 4.8 g (0.056 mol) of *N*-methylpyrrolidine with a solution of 8.0 g (0.056 mol) of diisobutylaluminum hydride in 40 ml of heptane gave a slight exotherm. This reagent solution was then added dropwise to a stirred solution of **5b** (9.8 g, 0.056 mol) in 20 ml of heptane and the resulting solution was heated for 24 hr at 55–60°. After cooling, 3.1 g of water were cautiously added, the suspension was filtered, and the filtrate was distilled. The main fraction (9.4 g, 96%) boiled at 43–45° (0.50 mm) [lit.[12] bp 50–52° (0.2 mm)] and was shown by vpc analysis to contain 96% *cis*-β-styryl(trimethyl)silane and 4% of the trans isomer. Redistillation through a 40 × 2 cm spinning-band column afforded a pure cis product: nmr (neat) δ 0.03 [s, $(CH_3)_3Si$)], 5.83 (d, 1-CH, J = 15, Hz), 7.36 (d, 2-CH, J = 15 Hz), 7.2 (s, sh, 5 H).

When a 1:1 molar ratio of **5b** and the hydride were permitted to interact in diethyl ether solution for 12 hr, a 65:35 ratio of cis and trans isomers were obtained upon hydrolysis.

Cis Hydralumination of 5b and Treatment with Deuterium Oxide.—The cis hydralumination was performed as described above, but the hydrolysis was performed with deuterium oxide (99.8%), nmr (neat) δ 7.36 (t, J = 2.2 Hz). Thus, it is concluded that again the aluminum in the hydralumination adduct was attached exclusively to the carbon adjacent to the Me_3Si group.

Trans Hydralumination of 5b *via* Cis Hydralumination. A. Diisobutylaluminum Chloride.—The cis hydralumination of **5b** was carried out on a 0.012-molar scale in the manner described above. A vpc analysis of a hydrolyzed aliquot showed the presence of 99% of the *cis*-styrylsilane and 1% of the trans isomer. Diisobutylaluminum chloride (2.0 g, 0.012 mol) was now added to the main reaction solution maintained at 20–25°. After 30 min the vpc analysis of a hydrolyzed aliquot showed a cis:trans styrylsilane ratio at 5:95; an aliquot analyzed after a further 15 hr of contact gave the same ratio of isomers.

Repetition of this isomerization experiment at −70° revealed that after 150 min a cis:trans ratio of 79:21 was obtained. Again in analyzing these aliquots care must be taken to achieve prompt hydrolysis at low temperatures (chilled CH_2OH–H_2O), in order to avoid additional, spurious isomerization.

B. Diisobutylaluminum Hydride.—As before, a 0.012-molar run of the cis hydraluminated adduct of **5b** was performed and again a vpc analysis of the hydrolyzed aliquot revealed 99% of the cis isomer. Diisobutylaluminum hydride (0.40 g, 0.003 mol) was added to the reaction solution and the solution was heated under reflux for 66 hr. Again a cis:trans styrylsilane ratio of 5:95 was obtained.

Trans Hydralumination of Phenylethynyl(trimethyl)germane (5c) and of Phenylethynyl(triethyl)germane (5d).—Conducted on a 0.017-molar scale, the individual hydraluminations of these compounds were performed as with **5b**. After 3 hr at 50° the reaction mixtures were hydrolyzed, worked up, and distilled (90–93% yield). In both cases, the vpc analysis of the distilled products showed 94 ± 1% of the *trans*-β-styryl isomer and 6% of the cis product. Redistillation through a spinning-band column (40 × 2 cm) afforded the pure *trans* isomer: (a) *trans*-β-styryl(trimethyl)germane, bp 60–62° (0.5 mm);[23] (b) *trans*-β-styryl(triethyl)germane, bp 96–97° (0.50 mm), nmr (neat) δ 0.75–1.32 [m, $(C_2H_5)_3Ge$], 6.57 (d, 1-CH, J = 18.5 Hz), 6.84 (d, 2-CH, J = 18.5 Hz), and 7.1–7.5 (m, 5 H).

Anal. Calcd for $C_{14}H_{22}Ge$: C, 63.95; H, 8.44. Found: C, 64.03; H, 8.30.

Trans Hydralumination of Phenylethynyl(triethyl)germane and Treatment with Deuterium Oxide.—Hydralumination was conducted on a 0.005-molar scale, as previously described for **5b**. Treatment with deuterium oxide (99.8%) and distillative work-up gave 93% of the *trans*-β-styryl(triethyl)germane, whose neat nmr spectrum showed a triplet at 6.84 ppm (J = 2 cps) but showed the absence of the doublet at 6.57 ppm; thus, in the hydraluminated adduct, the aluminum was attached exclusively to the carbon adjacent to the Et_3Ge group.

Cis Hydralumination of 5c or 5d in the Presence of *N*-Methylpyrrolidine.—As with **5b**, but on a 11.3-millimolar scale, the *N*-methylpyrrolidine and hydride were mixed in 20 ml of heptane. This solution was added dropwise to the germane (**5c** or **5d**) in 20 ml of heptane. After 15 hr at 60° and 5 hr at reflux, the usual work-up gave the corresponding β-styryl(trialkyl)germanes in 90–94% yield, each of which was shown by vpc to be 98% ± 1 of the cis isomer and 2% of the trans isomer. *cis*-β-Styryl(trimethyl)germane boiled at 59–60° (0.5 mm) and displayed the typical vinyl signals at 5.85 and 7.45 ppm (J = 14 Hz); *cis*-β-styryl(triethyl)germane boiled at 93–94° (0.5 mm) and had vinyl nmr signals at 5.92 and 7.50 ppm (J = 14 Hz). Only the methyl analog was analyzed for carbon and hydrogen, since the *cis*-β-styryl(triethyl)germane could be converted by an isomerization into the already analyzed *trans*-β-styryl(triethyl)germane (*cf. infra*).

Anal. Calcd for $C_{11}H_{16}Ge$: C, 59.82; H, 7.30. Found: C, 60.04; H, 7.55.

Cis Hydralumination of 5c and Isomerization of the Hydralumination Adduct.—The foregoing procedure was repeated for **5d**, but on a 22-millimolar scale. At the close of the heating period, one-half of the solution was treated with deuterium oxide and worked up in the usual way. The distilled product was identified as >98% of *cis*-β-styryl isomer by vpc analysis. Examination of its nmr spectrum (neat) showed only an unresolved triplet resonance at 7.50 ppm and hence proved that the product is fully deuterated at the vinyl carbon adjacent to the Et_3Ge group.

The remaining one-half of the reaction solution was treated with 13 mmol of diisobutylaluminum chloride and the solution was

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stirred at 20–25° for 1 hr. Customary work-up gave *trans*-β-styryl(triethyl)germane which contained 4% cis isomer.

Attempted Hydralumination of Phenylethynyl(trimethyl)tin (5e).—The interaction of 1.6 g (11 mmol) of the hydride with 2.98 g (11 mmol) of **5e** in 40 ml of heptane led to the formation of reddish solution during the 48-hr reaction period at 20–25°. No gas evolution or metal deposition was noticed. Usual work-up and solvent removal through a fractionation column gave a liquid residue (1.2 g) which by vpc analysis was shown to contain 92% of phenylacetylene, 5% of **5e**, and 3% of an unidentified component of much higher retention time.

Repetition of the experiment with a 1:1 mixture of the hydride and *N*-methylpyrrolidine at 60° for 15 hr gave identical results.

Hydralumination of *tert*-Butyl(phenyl)acetylene (5a).—A solution of 4.0 g (28.2 mmol) of the hydride and 4.40 g (28 mmol) of *tert*-butyl(phenyl)acetylene in 40 ml of heptane was heated at 50° for 18 hr. Usual hydrolytic work-up gave 3.76 g (84%) of *cis*-β-*tert*-butylstyrene:[24] bp 73–75° (13 mm); nmr (neat) δ 0.95 [s, $(CH_3)_3C$], 5.57 (d, 2-CH, J = 12.5 Hz), 6.43 (d, 1-CH, J = 12.5 Hz), and 7.12 (s, 5 H).

An identical run was performed but the hydralumination adduct was treated with deuterium oxide (99.8%). The distilled product displayed an nmr spectrum having a triplet (J = 1.5 Hz) with peaks of equal intensity centered at 5.57 ppm. Since no vinyl peaks were detectable at 6.43 ppm, the product was fully deuterated at the vinyl carbon adjacent to the phenyl group.

Hydralumination and Concurrent Metalation of Phenylacetylene.—Diisobutylaluminum hydride (8.0 g, 56.4 mmol) was added dropwise to 12.5 g (122 mmol) of fresly distilled phenylacetylene and the resulting orange liquid was stirred for 4 days at 20–25°. The excess phenylacetylene (6.4 g, 63 mmol) was then removed *in vacuo* and caught in a trap cooled in ethanol–solid carbon dioxide. The residual red syrup was treated with 3.4 g of deuterium oxide, the suspension was diluted with hexane, and the mixture was filtered. Removal of the solvent from the filtrate gave, by vpc analysis, a mixture of phenylacetylene (29%) and styrene (71%). By means of nmr analysis, the acetylene was shown to be 1-deuterio-2-phenylacetylene (free of undeuterated acetylene) and the styrene to be exclusively *trans*-β-deuteriostyrene (triplets centered at 4.77 and 5.36 ppm). No deuteron could be detected on the cis-β or the α-vinyl position.

Attempted Hydralumination of Bromo(phenyl)acetylene (5h).—No reaction occurred, as determined by vpc analysis, when 8.0 g (56.4 mmol) of the hydride and 10.2 g (56.4 mmol) of bromo(phenyl)acetylene in 25 ml of heptane was stirred at 20–25° for 5 days. Reflux for 24 hr caused darkening of the solution and usual hydrolytic work-up gave only phenylacetylene.

Hydralumination of Dimethyl(phenylethynyl)phosphine (5f).—A solution of 3.28 g (23.1 mmol) of the hydride and 3.74 g (23.1 mmol) of **5f** in 25 ml of heptane was heated for 15 hr at 45–50°, during which time a colorless precipitate formed. By warming briefly to 90°, the solid redissolved and thereupon the solution was divided into two parts. One part upon hydrolytic work-up yielded 70% of dimethyl(*cis*-β-styryl)phosphine: bp 69–71° (0.85 mm); nmr (neat) 0.98 [d, $(CH_3)_2P$, J_{HP} = 3.0 Hz], 6.00 (d of d, 1-CH, $J_{H_1H_2}$ = 12.5 Hz, J_{HP} = 1.2 Hz), 6.74 (d, 2-CH, J = 12.5 Hz), 7.15–7.4 and 7.5–7.75 (m, 5 H).

Anal. Calcd for $C_{10}H_{13}P$: C, 73.15; H, 7.98. Found: C, 73.32; H, 7.85.

The other part of the reaction mixture was treated with deuterium oxide to give 75% of this distilled styrene, whose nmr spectrum (neat, triplets centered at 6.00 and 6.74 ppm) showed deuteration on both vinylic carbon atoms in the ratio of cis-β:α 85:15 in the resulting dimethyl(*cis*-β-styryl)phosphine.

Attempts to change the stereochemistry of addition were unsuccessful. (a) A run was conducted on the foregoing scale, and then 2.3 mmol of **6** were added. Refluxing for 16 hr and hydrolytic work-up gave only the cis isomer, and no sign of the trans addition. (b) Using a 1:1 ratio of the hydride and *N*-methylpyrrolidine for the reduction of **5f** for 16 hr at reflux gave 60% of the cis product and 40% of **5f** upon hydrolytic work-up.

Hydralumination of Other Alkynylsilanes. A. 1-Propynyl(trimethyl)silane (10).—This alkyne could not be smoothly hydraluminated despite a studied variation of experimental procedures, including the use of equimolar amounts of *N*-methylpyrrolidine. Either the alkyne remained unreacted or it underwent reductive dimerization to yield a mixture of 1,3-bis(trimethylsilyl)-2-methyl-1,3-pentadienes,[25] bp 173–176°. No trace of the known, stable monomeric *cis*- or *trans*-1-propenyl(trimethyl)silanes could be detected by vpc analysis of reaction hydrolysates.

B. 3,3-Dimethylbut-1-ynyl(trimethyl)silane (11).—Hydralumination on a 28-millimolar scale in 20 ml of hexane gave a 65% yield of *trans*-dimethybut-1-en-1-yl(trimethyl)silane: bp 128–130°; nmr (neat) 0.05 [c, $(CH_3)_3Si$], 0.98 [s, $(CH_3)_3C$], 5.57 (d, 1-CH, J = 19 Hz), and 6.07 (d, 2-CH, J = 19 Hz).

Repetition on the foregoing scale with a hydrolytic work-up of deuterium oxide yielded a product which by nmr analysis was shown to have the deuteron exclusively on the vinyl carbon α to the Me_3Si group (triplet at 6.07, 2.7 Hz).

The use of a 1:1 hydride–*N*-methylpyrrolidine mixture on a 14-millimolar scale with 48-hr heating gave, upon hydrolysis, 72% of *cis*-dimethylbut-1-en-1-yl(trimethyl)silane:[26] bp 109–110°; nmr (neat) 0.14 [s, $(CH_3)_3Si$], 1.07 [s, $(CH_3)_3C$], 5.37 (d, 1-CH, J = 16 Hz), and 6.37 (d, 2-CH, J = 16 Hz).

C. 2-Methylbut-1-en-3-yn-4-yl(trimethyl)silane (12).—Treatment of an excess of the silane (16.0 g, 0.116 mol) with 8.0 g (0.056 mol) of the hydride at 20–25° produced a yellow solution exothermically. After 4 days the excess **12** was removed *in vacuo*. Hydrolysis with pentane–water and distillative work-up yielded 5.4 g (67%) of *trans*-2-methylbuta-1,3-dien-4-yl(trimethyl)silane: bp 138–139°; nmr (CCl_4) δ 0.09 [s, $(CH_3)_3Si$], 1.83 (s, CH_3), 5.03 (br s), 5.81 (d, 4-CH, J = 19.5 Hz), and 6.60 (d, 3-CH, J = 19.5 Hz).

Anal. Calcd for $C_8H_{16}Si$: C, 68.48; H, 11.50. Found: C, 68.49; H, 11.59.

A 0.10-molar run employing a 1:1 mixture of hydride and *N*-methylpyrrolidine with 12 and a heating period of 50 hr at 60° led to a 78% yield of *cis*-2-methylbuta-1,3-dien-4-yl(trimethyl)silane: bp 40° (28 mm); nmr (CCl_4) 0.10 [s, $(CH_3)_3Si$], 1.79 (s, CH_3), 4.90 (br s), 5.52 (d, 4-CH, J = 15 Hz), and 6.73 (d, 3-CH, J = 15 Hz).

Anal. Calcd for $C_8H_{16}Si$: C, 68.48; H, 11.50. Found: C, 68.57; H, 11.29.

Hydraluminations with Lithium Aluminum Hydride. A. cis-β-Styryl(trimethyl)silane.—A solution of 1.0 g (26 mmol) of lithium aluminum hydride and 4.5 g (26 mmol) of *cis*-β-styryl(trimethyl)silane in 50 ml of anhydrous tetrahydrofuran was heated at reflux for 12 hr and then hydrolyzed. Work-up gave exclusively β-phenylethyl(trimethyl)silane, identified by ir and nmr comparison with an authentic sample.

B. Phenylethynyl(trimethyl)silane.—A similar reduction of this silane gave phenylacetylene as the only product.

Bromodesilylation of *trans*,β-Styryl(trimethyl)silane (17).—A solution of bromine (4.55 g, 28.4 mmol) in 8 ml of carbon tetrachloride was added dropwise to a stirred, cold (−20°) solution of **17** (95% *trans*, 5.0 g, 28.4 g) in 45 ml of the same solvent. The color was discharged promptly and some frothing was noted. After stirring for 15 hr at 20–25°, the solution was worked up by distillation. The β-bromostyrene (4.7 g, 90%) distilled at 106–108° (19 mm) and was shown by vpc analysis to be composed of 88% *trans*- and 12% *cis*-β-bromostyrene. The nmr spectrum confirmed this conclusion.

Registry No.—**5a**, 4250-82-2; **5b**, 2170-06-1; **5c**, 4131-47-9; **5d**, 4131-48-0; **5e**, 1199-95-7; **5f**, 20505-08-2; **5g**, 536-74-3; **5h**, 932-87-6; **6**, 1191-15-7; **10**, 6224-91-5; **11**, 14630-42-3; **12**, 18387-60-5; *trans*-β-styryl(trimethyl)silane, 19372-00-0; *cis*-β-styryl(trimethyl)silane, 19319-11-0; *trans*-β-styryl(triethyl)germane, 19319-12-1; *cis*-β-styryl(trimethyl)germane, 31790-89-3; *cis*-β-styryl(triethyl)germane, 19319-00-7; *cis*-β-*tert*-butylstyrene, 3740-05-4; dimethyl(*cis*-β-styryl)phosphine, 31734-51-7; 1,3-dimethyl-2,4-bis(trimethylsilyl)butadiene, 31734-52-8; *trans*-dimethylbuten-1-yl(trimethyl)silane, 20107-37-3; *cis*-dimethylbut-1-en-1-yl(trimethyl)silane, 26567-95-3; *trans*-2-

(24) D. Seyferth and G. Singh, *J. Amer. Chem. Soc.*, **87**, 4156 (1965).

(25) The individual dimers, separated by vpc, had the following nmr absorptions: isomer A, 0.1 (Me_3Si), 0.16 (Me_3Si), 1.77 (d, CH_3, J = 7.5 Hz), 1.82 (s, CH_3), 4.98 (br, 1 H), and 6.03 (q, 1 H, J = 7.5 Hz); and isomer B, −0.04 (Me_3Si), 0.09 (Me_3Si), 1.62 (d, CH_3, J = 7.5 Hz), 1.77 (s, CH_3), 4.9 (br, 1 H), and 5.7 (q, 1 H, J = 7.5 Hz) (G. Gupta, unpublished studies).

(26) R. A. Benkeser, M. L. Burrous, L. E. Nelson, and J. V. Swisher, *J. Amer. Chem. Soc.*, **83**, 4385 (1961).

methylbuta-1,3-dien-4-yl(trimethyl)silane, 31734-55-1; *cis*-2-methylbuta-1,3-dien-4-yl(trimethyl)silane, 31734-56-2.

Acknowledgments.—The authors wish to express their appreciation for the support of this research through Grant GM-13421 of the Public Health Service.

Mass Spectrometry in Structural and Stereochemical Problems. CCIX.[1] Functional Group Interaction after Electron Impact. Anomalous Ether Cleavage in Bifunctional Benzyloxy Ethers[2]

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In a series of bifunctional benzyloxy ethers, the scope and limitations of the unexpected C–O cleavage at the ether function with charge retention on the benzyloxy moiety (*m/e* 107) has been investigated. Deuterium-labeling experiments indicated that simple C–O ether cleavage alone could not account for the formation of this ion. Its generation was found to be independent of the distance between the two functional groups. From these and other data, it was concluded that the structure of this ion was best represented as protonated benzaldehyde.

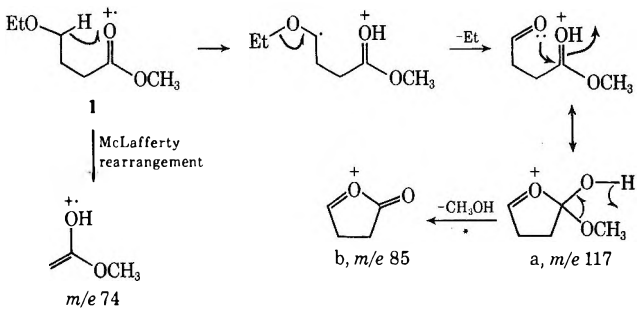
During the last decade the fragmentation patterns of almost every class of monofunctional compounds were thoroughly investigated,[4] and in the last few years the question of whether two functional groups in the same molecule would give rise to fragmentations independent of one another or to unique fragmentations resulting from direct interaction of the two groups has been the subject of several investigations.[5-14] As an extension of work reported earlier,[14] we became interested in pursuing further the nature of the process leading to the intense peaks at *m/e* 117 and 85 in the mass spectrum[15] (Figure 1) of methyl 4-ethoxybutyrate (**1**). With the

$EtO(CH_2)_3CO_2CH_3$ (1) $\quad C_6H_5CH_2O(CH_2)_3CO_2CH_3$ (2)

aid of deuterium-labeling studies, high-resolution measurements, and metastable defocusing experiments,[16] the formation of these ions was rationalized as shown in Scheme I.

It was reasoned that, if the ethyl ether portion of **1** were replaced with another substituent which would yield a radical more stable than ethyl, the process leading to ions of masses 117 and 85 should be enhanced. To this end methyl 4-benzyloxybutyrate (**2**) was synthesized and its mass spectrum (Figure 2) was

SCHEME I



recorded. These expectations were only partially fulfilled in that the peaks at *m/e* 117 and 85 were observed in Figure 2, but their intensities were no greater than in the spectrum (Figure 1) of **1**. Instead, a host of additional peaks was observed, most significant and interesting of which being the peak at *m/e* 107 (this peak becomes the base peak at 12 eV). High-resolution measurements indicated the composition of this ion to be C_7H_7O, which corresponds formally to cleavage of the C–O bond of the ether function with charge retention on the benzyloxy fragment. This finding was particularly unusual, since normally cleavage of an ether C–O bond with charge retention on the oxygen-containing fragment is a very unfavorable process[17] (in the spectrum of benzyl *n*-butyl ether, the *m/e* 107 peak is negligible—Σ_{40} 0.1%). Because of the uniqueness of this cleavage, we suspected that the ester function at the other end of the molecule was playing an unexpected role in this process and considered it of interest to determine the scope and limitations of this process.

Results and Discussion

It was felt that the two most obvious parameters which might influence the formation of the "anomalous" *m/e* 107 peak would be (a) the length of the hydrocarbon chain separating the two functions and (b) the nature of the functional group at the end of the chain. As a first step in this investigation, the effect of varying the chain length between the two functions on the relative intensity of the *m/e* 107 peak was probed. To this end

(1) For paper CCVIII, see J. R. Dias, Y. Sheikh, and C. Djerassi, *J. Amer. Chem. Soc.*, in press.

(2) Financial support from the National Institutes of Health (Grant No. AM 04257) is gratefully acknowledged.

(3) (a) National Science Foundation Postdoctoral Fellow, 1969–1970. (b) National Institutes of Health Postdoctoral Fellow, 1967–1968.

(4) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967.

(5) M. M. Green and C. Djerassi, *J. Amer. Chem. Soc.*, **89**, 5190 (1967).

(6) E. V. White and J. A. McCloskey, *J. Org. Chem.*, **35**, 4241 (1970).

(7) R. T. Gray, M. Ikeda, and C. Djerassi, *ibid.*, **34**, 4091 (1969).

(8) R. Brandt and C. Djerassi, *Helv. Chim. Acta*, **51**, 1759 (1968).

(9) J. Diekman, J. B. Thomson, and C. Djerassi, *J. Org. Chem.*, **34**, 4091 (1969).

(10) R. G. Cooks, J. Ronayne, and D. H. Williams, *J. Chem. Soc. C*, 2601 (1967).

(11) R. H. Shapiro and K. B. Tomer, *Org. Mass Spectrom.*, **3**, 333 (1970).

(12) (a) R. J. Highet and P. F. Highet, *Tetrahedron Lett.*, 1803 (1970); (b) R. E. Wolff and A. Caspar, *ibid.*, 1807 (1970).

(13) G. Remberg and G. Spiteller, *Chem. Ber.*, **103**, 3640 (1970).

(14) M. Sheehan, R. J. Spangler, M. Ikeda, and C. Djerassi, *J. Org. Chem.*, **36**, 1796 (1971).

(15) Mass spectra recorded at nominal voltages of 70 and 12 eV. Unless otherwise stated, only 70-eV spectra are shown.

(16) (a) J. H. Beynon, *Nature*, **204**, 67 (1964); (b) K. R. Jennings, "Some Newer Physical Methods in Structural Chemistry," R. Bonnett and J. G. Davis, Ed., United Trade Press, London, 1967, p 105.

(17) Reference 4, p 227.

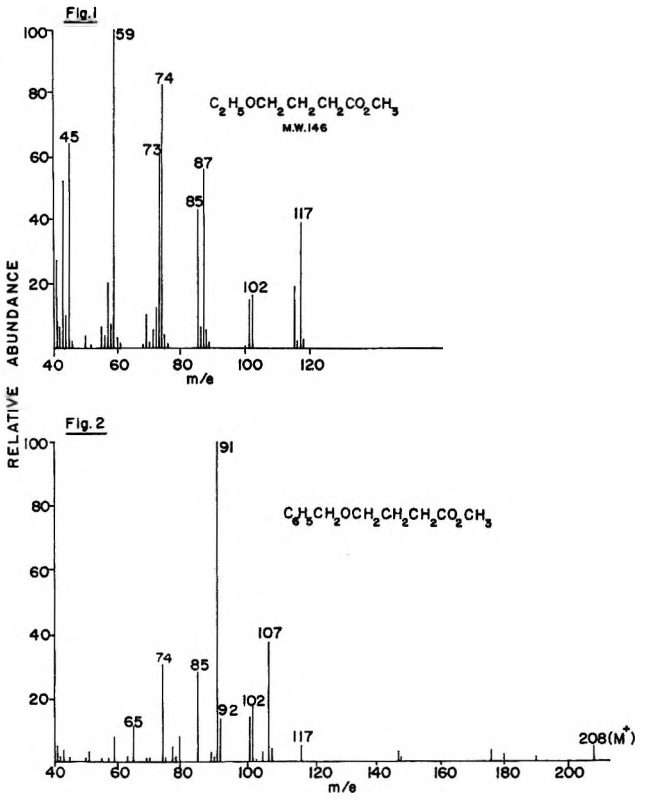


Figure 1.—Mass spectrum (70 eV) of methyl 4-ethoxybutyrate (1).

Figure 2.—Mass spectrum (70 eV) of methyl 4-benzyloxybutyrate (2).

the series of substances **3–6** were synthesized and their mass spectra recorded. Table I summarizes the pertinent spectral data regarding the *m/e* 107 peak for these compounds. From Table I it can be seen that the importance of the *m/e* 107 peak is not drastically affected by increasing the length of the hydrocarbon chain between the two functional groups. If it is assumed that the generation of the *m/e* 107 peak is a result of the interaction of the two functional groups, then analogies to solution chemistry would dictate that such interactions should be most favorable (with respect to entropy considerations) when a six-membered transition state is involved ($n = 3$) and should be very poor for a ten-membered transition state ($n = 7$). In point of fact, there is relatively little difference between these two cases. One explanation of these facts which has been previously postulated[14] is that after electron impact and expulsion of an electron from the parent molecule the resultant charge is actually shared between the two functions such that there is an attractive force holding the two ends of the molecule together, and that this force overrides any entropy consideration that might be made.

$C_6H_5CH_2OCH_2CH_2CH_2CO_2CH_3$

3, $n = 1$
4, $n = 2$
5, $n = 4$
6, $n = 7$

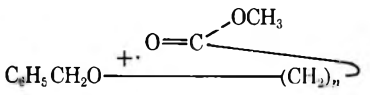
TABLE I

SPECTRAL DATA REGARDING THE *m/e* 107 PEAK FOR THE BENZYLOXY ESTERS

$C_6H_5CH_2O(CH_2)_nCO_2CH_3$

Compd no.	Σ_{40} *m/e* 107[a]	Base peak at 12 eV[b]
3, $n = 1$	21.0	107
4, $n = 2$	23.6	107
2, $n = 3$	11.5	107
5, $n = 4$	6.8	116 (*m/e* 107 is 70% of this peak)
6, $n = 7$	8.8	158 (*m/e* 107 is 50% of this peak)

[a] 70 eV. [b] Nominal voltage.



Accepting this model, it would be predicted that the spectra of substances in which the methoxycarbonyl group is replaced by another function capable of sharing charge should also exhibit prominent ions at mass 107. To test this notion, the series of substrates **7–12** was prepared and their mass spectra were recorded (Figures 3–8). Considering the first three substances (**7–9**),

$C_6H_5CH_2O(CH_2)_nR$

7, $n = 3$; R = CO_2H
8, $n = 4$; R = OH
9, $n = 4$; R = OCH_3
10, $n = 2$; R = $N(CH_3)_2$
11, $n = 2$; R = Br
12, $n = 2$; R = $OSi(CH_3)_3$

such was the case. That is, excluding the ubiquitous tropylium ion (*m/e* 91), the most intense ion in each spectrum was found at *m/e* 107 (Σ_{40} 23.0, 23.3, and 10.1%, respectively; base peak at low voltage). For R = OH and OCH_3, the effect of varying the length of the hydrocarbon chain between the two functional groups on the intensity of the *m/e* 107 peak was measured (see Table II), and again it was found that the intensity of this ion was more or less independent of the chain length. The only exception to this trend was found in the spectrum of benzyloxymethoxymethane (**17**) where no *m/e* 107 peak was encountered. In this instance, however, the two oxygen atoms are on the same carbon atom, and, hence, the compound is actually monofunctional (mixed acetal) and should be considered separately. In the spectra of the substrates **10–12** (Figures 6–8, respectively), it was found that the ion of mass 107 was either absent or unimportant. Various factors may be responsible for this deviation, but it is premature to speculate on the precise reasons at this time.

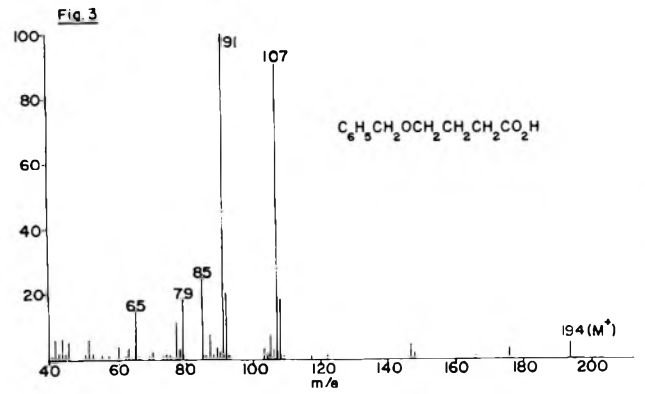
TABLE II

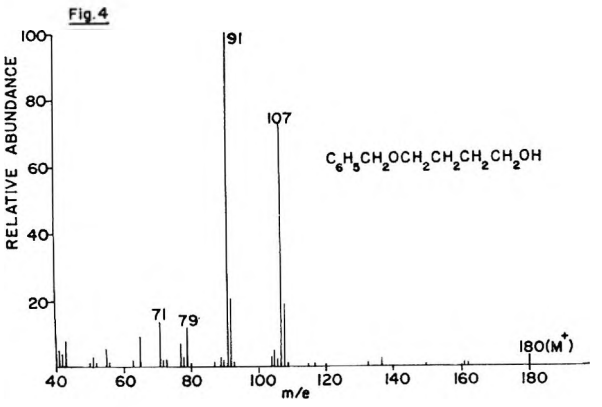
SPECTRAL DATA REGARDING THE *m/e* 107 PEAK FOR THE BENZYLOXY ALCOHOLS AND METHYL ETHERS

$C_6H_5CH_2O(CH_2)_nR$

Compd no.	Σ_{40} *m/e* 107[a]	Base peak at 12 eV, *m/e*[b]
13, R = OH; $n = 2$	10.7	152 (107 is 60% of this peak)
14, R = OH; $n = 3$	33.3	107
8, R = OH; $n = 4$	23.3	107
15, R = OH; $n = 5$	10.4	107
16, R = OH; $n = 8$	16.2	107
17, R = OCH_3; $n = 1$	0.1	91 (no 107 peak)
18, R = OCH_3; $n = 2$	11.0	107
9, R = OCH_3; $n = 4$	10.1	107

[a] 70 eV. [b] Nominal voltage.





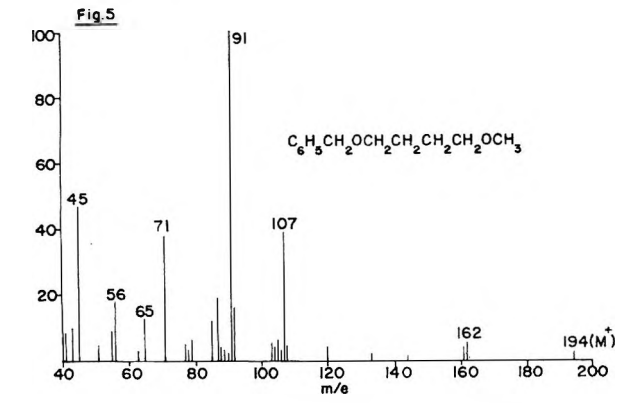
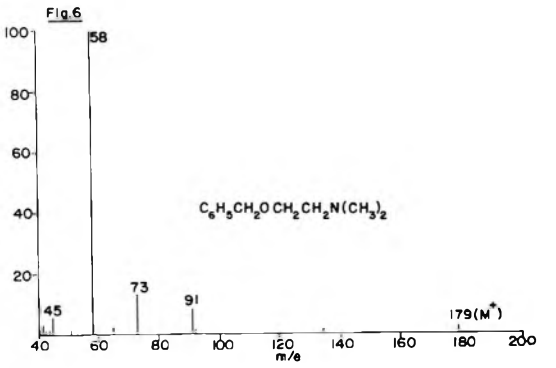
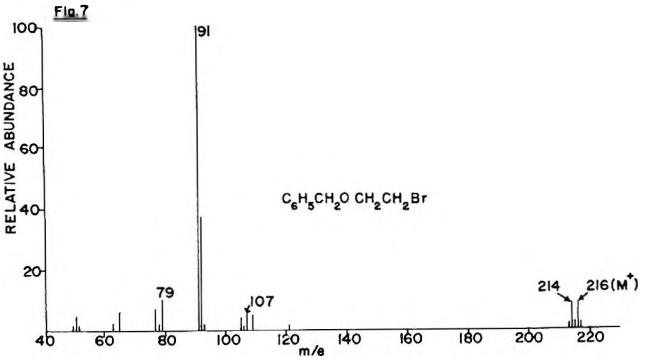


Figure 3.—Mass spectrum (70 eV) of 4-benzyloxybutyric acid (**7**).
Figure 4.—Mass spectrum (70 eV) of 4-benzyloxy-1-butanol (**8**).
Figure 5.—Mass spectrum (70 eV) of 4-benzyloxybutyl methyl ether (**9**).





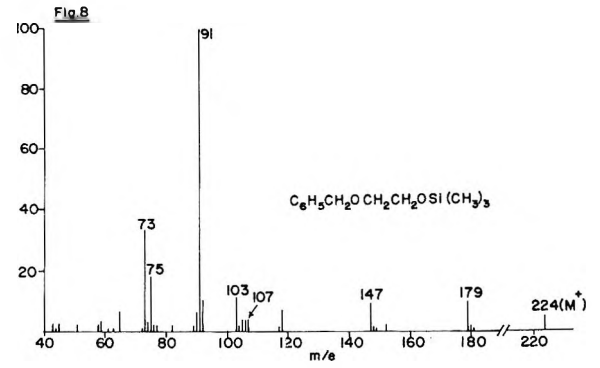


Figure 6.—Mass spectrum (70 eV) of 2-benzyloxyethyldimethylamine (**10**).
Figure 7.—Mass spectrum (70 eV) of 2-benzyloxyethyl bromide (**11**).
Figure 8.—Mass spectrum (70 eV) of 2-benzyloxyethyl trimethylsilyl ether (**12**).

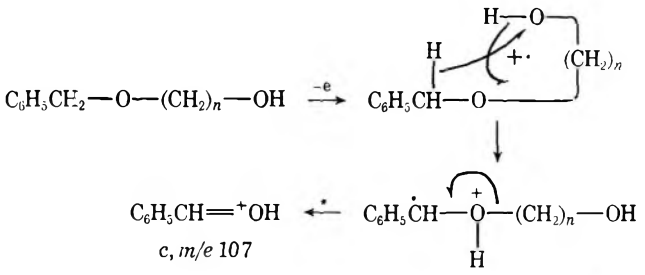
One of the requirements for the generation of the *m/e* 107 peak in bifunctional benxyloxy substances appears to be an unhindered oxygen function on the terminus of the molecule. However, so far nothing has been stated about the actual details of the process leading to this ion. It was more or less assumed at the outset that this ion was not the result of direct C–O bond cleavage to give $C_6H_5CH_2O^+$ with its unfavorable sextet on oxygen; rather, it was felt that a rearrangement or reciprocal H transfer was probably occurring. To test this hypothesis and to elucidate the details of the process or processes leading to the *m/e* 107 peak in the substances mentioned above, several D-labeled analogs of **3**–**9** were synthesized (see Syntheses of Labeled Substrates) and their mass spectra recorded. Table III gives the structures of these substrates and lists the pertinent spectral data regarding the *m/e* 107 peak for each compound. In the absence of any reciprocal hydrogen transfers or rearrangements, it would be expected that the *m/e* 107 peak would shift completely to *m/e* 109 for α-d_2 labeled substrates and remain at 107 for any label in the hydrocarbon chain or functional group. For the most part, no scrambling of the labels was encountered. However, for the substrates **21**, **25**, **26**, and **27** considerable exchange was observed. Accounting for unlabeled substrate and ^{13}C isotope contributions, the following deuterium exchange was calculated: 0.7 D in **21**, 0.4 D in **25**, 0.67 D in **26**, and 0.70 D in **27**. These data suggest some type of reciprocal hydrogen transfer between the terminal hydroxyl group and the benzyl protons in the benzyloxy alcohols. This exchange did not seem to be affected by increased chain length, since significant exchange was also observed for the α-d_2 analog of 8-benzyloxy-1-octanol. One possible mechanism for the formation of the *m/e* 107 peak which is consistent with these data for the al-

TABLE III

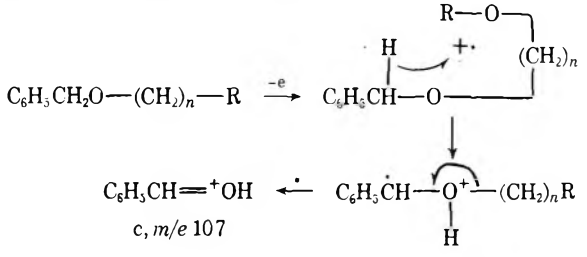
SPECTRAL DATA REGARDING THE *m/e* 107 PEAK FOR SOME DEUTERIUM-LABELED BENZYLOXY ESTERS, ALCOHOLS, AND METHYL ETHERS

Compd	No.	% isotopic purity	*m/e* (rel abundance) 105	106	107	108	109	110
$C_6H_5CH_2OCH_2CH_2CH_2CO_2CH_3$	2		3	1	37	4		
$C_6H_5CD_2OCH_2CH_2CH_2CO_2CH_3$	19	97 d_2	2			2	34	3
$C_6H_5CH_2OCD_2CH_2CH_2CO_2CH_3$	20	96 d_2	5	2	42	4		
$C_6H_5CH_2OCH_2CH_2CH_2CH_2OH$	8		5	3	72	19	1	
$C_6H_5CD_2OCH_2CH_2CH_2CH_2OH$	21	97 d_2	3	2	2	25	33	10
$C_6H_5CH_2OCD_\alpha CH_2CH_2CH_2OH$	22	96 d_2	3	2	78	20	2	
$C_6H_5CH_2OCH_2CD_2CD_2CH_2OH$	23	96 d_4	5	3	81	21	2	
$C_6H_5CH_2OCH_2CH_2CH_2CD_2OH$	24	98 d_2	5	2	48	12	1	
$C_6H_5CH_2OCH_2CH_2CH_2CH_2OD$	25	60 d_1	3	2	40	20	1	
$C_6H_5CH_2OCH_2CH_2OH$	13		2	1	20	2		
$C_6H_5CD_2OCH_2CH_2OH$	26	98 d_2			1	10	15	2
$C_6H_5CH_2OCH_2CH_2OD$	27	50 d_1	3	1	35	15	2	
$C_6H_5CH_2OCH_2CH_2OCH_3$	18		9	6	33	3		
$C_6H_5CD_2OCH_2CH_2OCH_3$	28	98 d_2	5	2	5	2	30	3
$C_6H_5CH_2OCH_2CH_2OCD_3$	29	98 d_3	8	7	35	4		

cohols is shown below. In accord with this mechanism, moderate metastable peaks were observed in the spectra



of most of these substrates for the transition $M^+ \rightarrow m/e$ 107. Whether this process is concerted or the exact structure of ion c is as shown is a matter of speculation at this point. Formation of the mass 107 ion from the benzyloxy esters, acids, and methyl ethers can be envisaged in an analogous manner, except that no reciprocal H transfer occurs (the benzyl proton protonating the benzyloxy oxygen directly).



It was felt that some driving force for the formation of the mass 107 ion in the above substances was provided by the particular stability of the intermediate benzyl radicals. Therefore, the question arose whether such intense *m/e* 107 peaks would also be observed after substitution of an alkyl group for the benzyl moiety. To answer this question, compounds **30–33** were synthesized and their mass spectra recorded (Figures 9–12). For ions of the general structure R′CH=O⁺H, peaks at masses 45 for **30**, 59 for **31**, 73 for **32**, and 101 for **33** would be expected in the spectra of these substances, and such peaks were, in fact, found in **30–32**.

$RO(CH_2)_4OH$

30, R = C_2H_5
31, R = $CH(CH_3)_2$
32, R = n-C_4H_9
33, R = n-C_6H_{13}

In each instance, however, ions of the same mass could have been formed by other cleavage processes, and as yet no deuterium-labeling studies have been carried out to distinguish these from the cleavage in question. Only in the spectrum (Figure 12) of **33** could the peak at mass 101 be formed in only one way (excluding rearrangements) and perhaps give the ion corresponding to structure c. Inspection of Figure 12, however, reveals that formation of this peak is not a very favorable process (*m/e* 101, Σ_{40} 1.8% as compared to Σ_{40} 23.3% when R = $C_6H_5CH_2$). If this peak is formed by the same process as was postulated for the *m/e* 107 peak, then it would be expected that *m/e* 101 should be proportioned between 102 and 103 in the spectrum of 1,1-dideuterio-*n*-hexyl 4-hydroxy-*n*-butyl ether (**34**). In-

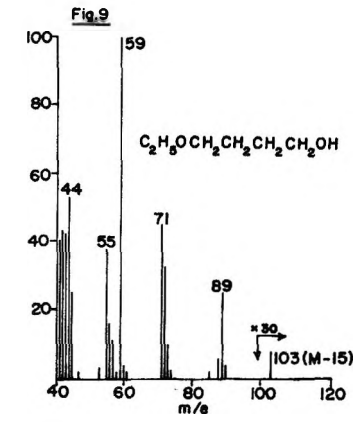
$CH_3CH_2CH_2CH_2CH_2CD_2OCH_2CH_2CH_2CH_2OH$

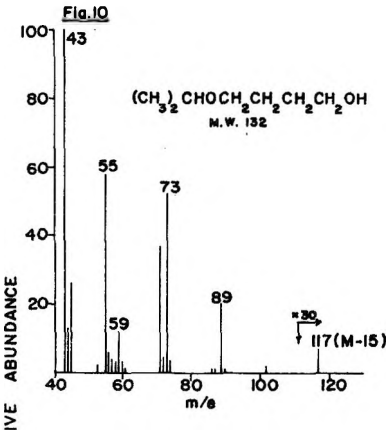
34

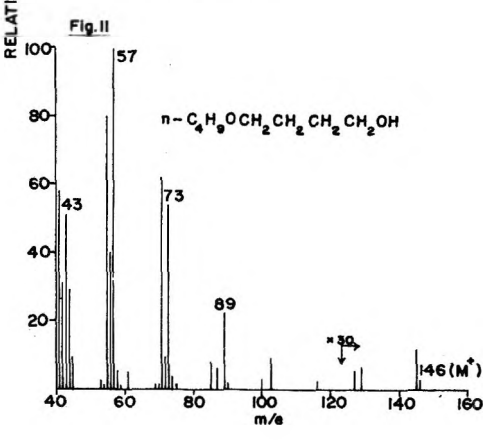
deed, the spectrum (not reproduced) of **34** shows that *m/e* 101 was shifted equally to 102 and 103 (deuterium content, 98% d_2). Whereas these data indicate that generation of ions of the general formula R′CH=⁺OH does occur, the low intensity of the *m/e* 101 peak in the spectrum of **33** suggests that a phenyl group is necessary to stabilize the incipient secondary radical.

While formation of protonated aldehyde ions of the general formula R′CH=O⁺H was not a very important process in the spectra of the 4-alkoxy-1-butanols, several interesting features were observed in these spectra which merit further discussion. In an earlier study[14] regarding the interaction of remote functional groups in acyclic systems upon electron impact, an intense peak (rel intensity 45% Σ_{40} 20%) was observed at *m/e* 58 in the spectrum of 4-methoxy-1-butanol (**35**). The structure and genesis of this ion were further studied by examining the spectra of **30–33** and of two deuterium-labeled analogs of **35**. In the spectra (not shown) of 4-methoxy-4,-4-dideuterio-1-butanol (**36**) and 4-methoxy-1,1-dideuterio-1-butanol (**37**) it was found that the position of the *m/e* 58 peak was unchanged in **37** but shifted to *m/e* 59 in **36**. Furthermore, peaks corresponding to the loss of HDO and D_2O were observed for **36** but not for **37**, suggesting that loss of water in these substrates was occurring in the normal 1,4 manner.[18] Thus, formation

(18) (a) W. Benz and K. Biemann, *J. Amer. Chem. Soc.*, **86**, 2375 (1964); (b) S. Meyerson and L. C. Leitch, *ibid.*, **86**, 2555 (1964).







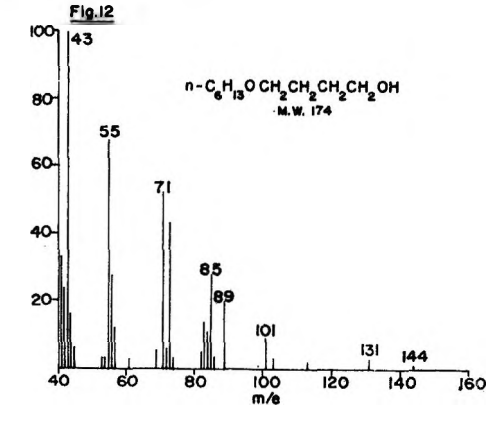


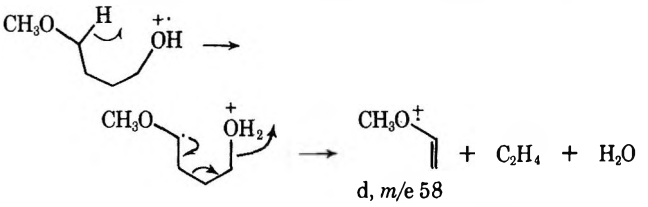
Figure 9.—Mass spectrum (70 eV) of 4-ethoxy-1-butanol (**30**).
Figure 10.—Mass spectrum (70 eV) of 4-isopropoxy-1-butanol (**31**).
Figure 11.—Mass spectrum (70 eV) of 4-*n*-butoxy-1-butanol (**32**).
Figure 12.—Mass spectrum (70 eV) of 4-*n*-hexoxy-1-butanol (**33**).

of the *m/e* 58 peak in the spectrum of **35** may be envisioned as transfer of the C-4 hydrogen atom to the

$CH_3OCH_2CH_2CH_2CH_2OH$
35

$CH_3OCD_2CH_2CH_2CH_2OH$ **36** $CH_3OCH_2CH_2CH_2CD_2OH$ **37**

terminal hydroxyl group followed by elimination of water and ethylene to give ion d, as shown below.

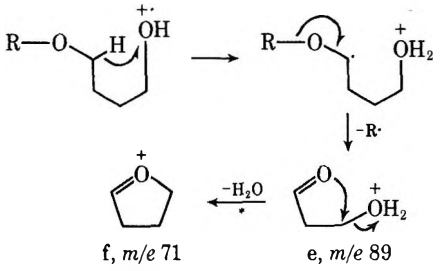


d, *m/e* 58

Metastable defocusing experiments indicated that the *m/e* 58 peak was formed from a precursor of mass 86 as well as from the molecular ion at *m/e* 104. Examination of the spectra (Figures 9–12) of **30–33** reveals that formation of ions analogous to d for these substances (*m/e* 72 for **30**, 86 for **31**, 100 for **32**, and 128 for **33**) is not general. That is, as the alkyl chain increases in length, the fragmentation process leading to these ions becomes unimportant. Instead, intense peaks were observed at *m/e* 89 and 71 (trivial peaks were observed at these values in the spectrum of **35**). Formally, loss of the ether alkyl group from the molecular ion affords the fragment of mass 89, and this fragment can then lose water to give the *m/e* 71 peak. In support of this notion, intense metastable peaks were observed at *m/e* 56.6–56.8 ($71^2/89 = 56.7$) in the spectra of **30–33**. Likewise, the position of these ions was unchanged in the spectrum **34**, whereas 89 was shifted to 91 and 71 to 73 in the spectrum of 4-*n*-butoxy-1,1-dideuterio-1-butanol (**38**). A plausible representation of

n-$C_4H_9OCH_2CH_2CH_2CD_2OH$
38

the structures and formation of these two ions is given below. It is probable that the low abundance of ions e and f in the spectrum of **35** is a reflection of the lower

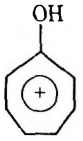


f, *m/e* 71 e, *m/e* 89

stability of the methyl radical compared to the other alkyl radicals.

Summary.—The main purpose of this work was to investigate the scope and limitations of the process leading to the ion of mass 107 in the spectrum of **2**. Based on the findings that formation of this ion (1) was independent of the chain length between the two functional groups, (2) required an oxygen atom on the terminus of the molecule, and (3) involved the benzyl hydrogen atoms, it was concluded that direct C–O bond cleavage to give $C_6H_5CH_2O^+$ did not occur. Whether this ion is best represented by structure c is a matter of conjecture, since it is entirely possible that c imme-

diately rearranges to the symmetrical tropylium alcohol ion g upon formation as was postulated for the M − 1 ion of benzyl alcohol.[19] Recently, the utility of ion



g

cyclotron resonance (icr) spectroscopy in distinguishing between isomeric ions has been dramatically proven,[20] and it is hoped that icr studies can be initiated in these laboratories to determine the exact structure of the mass 107 ion in the benzyloxy esters, alcohols, and methyl ethers.

Syntheses of Labeled Substrates.—For this investigation it was necessary to synthesize several deuterium-labeled substrates. The reaction pathways employed to obtain these substances are summarized in Scheme II, and the isotopic purity of the products is given in the appropriate table.

SCHEME II

$$HOCH_2CH_2CH_2CH_2OH \xrightarrow[2.\ C_6H_5CD_2Br]{1.\ NaH}$$

$$C_6H_5CD_2OCH_2CH_2CH_2CH_2OH \xrightarrow[2.\ CH_2N_2]{1.\ CrO_3}$$

21

$$C_6H_5CD_2O(CH_2)_3CO_2CH_3$$

19

$$CH_3O_2CCH_2CH_2CO_2CH_3 \xrightarrow{LiAlD_4}$$

$$HOCD_2CH_2CH_2CD_2OH \xrightarrow[2.\ C_6H_5CH_2Br]{1.\ NaH}$$

$$C_6H_5CH_2OCD_2CH_2CH_2CD_2OH \xrightarrow[2.\ CH_2N_2]{1.\ CrO_3}$$

$$C_6H_5CH_2OCD_2CH_2CH_2CO_2CH_3 \xrightarrow{LiAlH_4}$$

20

$$C_6H_5CH_2OCD_2CH_2CH_2CH_2OH$$

22

$$CH_3O_2CC{\equiv}CO_2CH_3 \xrightarrow[Pd/C]{D_2} CH_3O_2CCD_2CD_2CO_2CH_3 \xrightarrow{LiAlH_4}$$

$$HOCH_2CD_2CD_2CH_2OH \xrightarrow[2.\ C_6H_5CH_2Br]{1.\ NaH}$$

$$C_6H_5CH_2OCH_2CD_2CD_2CH_2O$$

23

$$n\text{-}C_5H_{11}CO_2H \xrightarrow[2.\ Br_2,\ (C_6H_5)_3P]{1.\ LiAlD_4}$$

$$n\text{-}C_5H_{11}CD_2Br \xrightarrow{Na^+OCH_2CH_2CH_2CH_2OH}$$

$$n\text{-}C_5H_{11}CD_2OCH_2CH_2CH_2CH_2OH$$

34

Experimental Section

The low-resolution mass spectra were obtained by Mr. R. G. Ross using an AEI MS-9 double-focusing mass spectrometer (heated inlet 150°, ion source temperature 180°). The high-resolution data were obtained by Mr. Ross with the same instrument, and metastable transitions in the first field free region were observed with the aid of the metastable defocusing technique.[16] All substances were purified by vpc (5 ft × 0.25 in. SE-30, 5% on Chromosorb G) prior to spectral analyses.

Infrared spectral data were recorded with a Perkin-Elmer Model 700 spectrophotometer, and the nmr spectra were secured with a Varian Model T-60 spectrometer. All nmr measurements were made in CCl_4 solutions containing 1% TMS as an internal standard. Chemical shifts are reported in parts per million downfield from the standard, and coupling constants are reported in hertz.

4-Benzyloxy-1-butanol (8).—NaH (1 equiv) was added in small batches to excess 1,4-butanediol (Matheson, reagent) covered with a layer of dry benzene. After the addition was completed, the mixture was refluxed for 4 hr, and then 1 equiv of benzyl bromide was added and reflux was continued for 18 hr. The solution was cooled, excess water added, and the resultant mixture extracted with ether. Ether extracts were washed with water and saturated NaCl solution and dried. The solvent was removed under vacuum, and the resultant viscous oil was distilled to give **8** as a colorless oil: bp 95–105° (0.5 mm); ir (CCl_4) 3350 cm^{-1} (OH); nmr δ 7.24 (s, 5 H, C_6H_5), 4.5 (s, 2 H, $C_6H_5CH_2$), 3.52 (m, 4 H, OCH_2, CH_2OH), 1.80 (m, 4 H, CH_2-CH_2); M^+ 180 ($C_{11}H_{16}O_2$).

4-Benzyloxybutyric Acid (7).—Jones oxidation[21] of **8** gave **7** as a colorless oil: bp 133–134° (0.5 mm); ir (film) 3100 cm^{-1} (broad, COOH); nmr δ 11.0 (s, 1 H, COOH), 7.2 (s, 5 H, C_6H_5), 4.4 (s, 2 H, $C_6H_5CH_2$), 3.4 (t, J = 6 Hz, 2 H, OCH_2), 2.4 (m, 2 H, CH_2CO_2), 1.9 (m, 2 H, $CH_2CH_2CH_2$); M^+ 194 ($C_{11}H_{14}O_3$).

Methyl 4-Benzyloxybutyrate (2).—Methylation of **7** with diazomethane in the usual manner gave **2** as a colorless oil: bp 110–113° (0.5 mm); ir (film) 1740 cm^{-1} (C=O); nmr δ 7.3 (s, 5 H, C_6H_5), 4.5 (s, 2 H, $C_6H_5CH_2$), 3.6 (s, 3 H, CO_2CH_3), 3.5 (t, J = 6 Hz, 2 H, OCH_2), 2.4 (m, 2 H, CH_2CO_2), 1.95 (m, 2 H, $CH_2CH_2CH_2$); M^+ 208 ($C_{12}H_{16}O_3$).

Methyl Benzyloxyacetate (3).—Potassium metal (1 equiv) was added to 1 equiv of benzyl alcohol dissolved in excess benzene. This mixture was refluxed for 3 hr, and then 1 equiv of methyl bromoacetate (Aldrich) was added slowly and the resultant solution was refluxed for an additional 12 hr. Work-up and distillation gave **3** as a colorless oil: bp 82–89° (4 mm); ir (CCl_4) 1740 cm^{-1} (C=O); nmr δ 7.3 (s, 5 H, C_6H_5), 4.6 (s, 2 H, $C_6H_5CH_2$), 4.0 (s, 2 H, CH_2CO_2), 3.7 (s, 3 H, CO_2CH_2); M^+ 180 ($C_{10}H_{12}O_3$).

Methyl Benzyloxy Esters 4, 5, and 6.—Esters **4**, **5**, and **6** were prepared from the corresponding glycols according to the procedure described above for the preparation of **2**. These esters were separated from their respective reaction mixtures by preparative vpc and were identified by their ir, nmr, and mass spectra. **Methyl 3-benzyloxypropionate (4):** ir (film) 1740 cm^{-1} (C=O); nmr δ 7.3 (s, 5 H, C_6H_5), 4.5 (, 2 H, $C_6H_5CH_2$), 3.7 (s, 3 H, CO_2-CH_3), 3.7 (m, 2 H, OCH_2), 2.5 (t, J = 6 Hz, 2 H, CH_2CO_2); M^+ 194 ($C_{11}H_{14}O_3$). **Methyl 5-benzyloxyvalerate (5):** ir (CCl_4) 1735 cm^{-1} (C=O); nmr δ 7.28 (s, 5 H, C_6H_5), 4.5 (s, 2 H, C_6H_5-CH_2), 3.6 (s, 3 H, CO_2CH_3), 3.5 (t, J = 6 Hz, 2 H, OCH_2), 2.35 (m, 2 H, CH_2CO_2), 1.9 (m, 4 H, CH_2CH_2); M^+ 222 ($C_{13}H_{18}O_3$). **Methyl 7-benzyloxyoctanoate (6):** ir (CCl_4) 1740 cm^{-1} (C=O); nmr δ 7.25 (s, 5 H, C_6H_5), 4.5 (s, 2 H, $C_6H_5CH_2$), 3.6 (s, 3 H, CO_2CH_3), 3.5 (m, 2 H, OCH_2), 2.4 (m, 2 H, CH_2CO_2), 1.8–2.0 (m, 10 H, CH_2); M^+ 264 ($C_{16}H_{24}O_3$).

4-Benzyloxybutyl Methyl Ether (9).—Treatment of **8** with 1 equiv of NaH and 1 equiv of methyl iodide in benzene for 24 hr at reflux afforded **9**: nmr δ 7.3 (s, 5 H, C_6H_5), 4.5 (s, 2 H, C_6H_5-CH_2), 3.5 (s, 4 H, OCH_2), 3.4 (s, 3 H, OCH_3), 1.7 (m, 4 H, CH_2-CH_2); M^+ 194 ($C_{12}H_{18}O_2$).

2-Benzyloxyethyldimethylamine (10).—To 1 equiv of neat 2-dimethylaminoethanol (Aldrich) was added 0.67 equiv of NaH under nitrogen and the mixture was refluxed for 1 hr. Benzyl bromide (1 equiv) in benzene was added, and reflux continued for 2 hr. Separation by vpc after work-up gave **10**: nmr δ 7.4 (s, 5, C_6H_5), 4.4 (s, 2 H, $C_6H_5CH_2$), 3.5 (t, J = 6 Hz, 2 H, OCH_2), 2.4 (t, J = 6 Hz, 2 H, CH_2N), 2.17 (s, 6 H, NCH_3); M^+ 179 ($C_{11}H_{17}NO$).

2-Benzyloxyethyl Bromide (11).—Treatment of **13** with triphenylphosphine and bromine according to the procedure of Wiley[22] afforded **11**, M^+ 214, 216 ($C_9H_{11}BrO$).

2-Benzyloxyethyl Trimethysilyl Ether (12).—A mixture of 1

(19) Reference 4, p 119.

(20) (a) G. Eadon, J. Diekman, and C. Djerassi, *J. Amer. Chem. Soc.*, **92**, 6205 (1970), and references cited therein; (b) J. L. Beauchamp and R. C. Dunbar, *ibid.*, **92**, 1477 (1970).

(21) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(22) G. A. Wiley, *et al.*, *J. Amer. Chem. Soc.*, **86**, 964 (1964).

equiv of **13** and 0.5 equiv of hexamethyldisilazane was heated under reflux with 1 drop of trimethylchlorosilane until the evolution of ammonia ceased (1 hr). After work-up, **12** was isolated from the crude reaction mixture by preparative vpc: nmr δ 7.3 (s, 5 H, C_6H_5), 4.5 (s, 2 H, $C_6H_5CH_2$), 3.6 (m, 4 H, OCH_2CH_2O), 0.08 (s, 9 H, CH_3Si); M^+ 224.

Benzyloxy Alcohols 13, 14, 15, and 16.—Benzyloxy alcohols **13**, **14**, **15**, and **16** were prepared by treatment of the corresponding glycol with 1 equiv of NaH and 1 equiv of benzyl bromide. The monobenzyl ethers were then separated from starting material and dibenzyl ethers by preparative vpc and identified by their ir, nmr, and mass spectra. **2-Benzyloxyethanol (13)**: ir (film) 3375 cm^{-1} (OH); nmr δ 7.3 (s, 5 H, C_6H_5), 4.4 (s, 2 H, $C_6H_5CH_2$), 3.6 (m, 4 H, OCH_2, CH_2OH); M^+ 152 ($C_9H_{12}O_2$). **3-Benzyloxy-1-propanol(14)**: ir (CCl_4) 3450 cm^{-1} (OH); nmr δ 7.25 (s, 5 H, C_6H_5), 4.4 (s, 2 H, $C_6H_5CH_2$); 3.6 (m, 4 H, OCH_2, CH_2OH), 1.7 (m, 2 H, $CH_2CH_2CH_2$); M^+ 166 ($C_{10}H_{14}O_2$). **5-Benzyloxy-1-pentanol (15)**: ir (CCl_4) 3350 cm^{-1} (OH); nmr δ 7.3 (s, 5 H, C_6H_5), 4.5 (s, 2 H, $C_6H_5CH_2$), 3.6 (m, 4 H, OCH_2, CH_2OH), 1.8 (m 6 H, $CH_2CH_2CH_2$); M^+ 194 ($C_{12}H_{19}O_2$). **8-Benzyloxy-1-octanol (16)**: ir (film) 3400 cm^{-1} (OH); nmr δ 7.25 (s, 5 H, C_6H_5), 4.4 (s, 2 H, $C_6H_5CH_2$), 3.5–3.6 (m, 4 H, OCH_2, CH_2OH), 1.7–1.9 (m, 12 H, CH_2); M^+ 236 ($C_{15}H_{24}O_2$).

Benzyloxymethyl Methyl Ether (17).—A mixture of 20.0 g (0.185 mol) of benzyl alcohol, 6.0 g (0.185 mol) of methanol, 5.0 g of paraformaldehyde, and a trace (*ca.* 200 mg) of *p*-toluenesulfonic acid in 30 ml of reagent chloroform was stirred at room temperature for 48 hr. The reaction mixture was worked up as usual, and **17**, was obtained as a colorless liquid by distillation: bp 70–75° (4 mm) [lit.[23] bp 74° (5 mm)]; M^+ 152 ($C_9H_{12}O_2$).

2-Benzyloxyethyl Methyl Ether (18).—Preparation of **18** was carried out by treatment of **13** with 1 equiv of NaH followed by 1 equiv of methyl iodide. Work-up and vpc separation gave **18**: nmr δ 7.3 (s, 5 H, C_6H_5) 4.4 (s, 2 H, $C_6H_5CH_2$), 3.5 (s, 3 H, OCH_3), 3.3 (s, 4 H, OCH_2CH_2O); M^+ 166 ($C_{10}H_{14}O_2$).

4-Alkoxy-1-butanols.—All 4-alkoxy-1-butanols were prepared by treating the monosodium alkoxide of 1,4-butanediol with the corresponding alkyl bromide. In a typical run *ca.* 10 equiv of 1,4-butanediol was covered with benzene, and 1 equiv of NaH (54.7% mineral oil dispersion) was added with stirring. The mixture was heated at reflux 2–4 hr, and then 1–2 equiv of the appropriate alkyl bromide was added slowly and reflux was continued for 4–6 hr. The mixture was cooled, diluted with saturated NaCl solution, and extracted with ether. The ether extracts were combined, washed with saturated NaCl solution, and dried ($MgSO_4$). The 4-alkoxy-1-butanols were then separated from the crude reaction mixtures by distillation and preparative vpc and identified by their ir, nmr, and mass spectra. **4-Ethoxy-1-butanol (30)**: bp 68–71° (6 mm) [lit.[24] bp 72° (8 mm)]; ir (film) 3380 cm^{-1} (OH); nmr δ 3.42 (m, 6 *H*, CH_2O), 1.85 (*m*, 4 H, CH_2CH_2), 1.15 (t, J = 6 Hz, 3 H, CH_3CH_2). **4-Isopropoxy-1-butanol (31)**: bp 145–150° (lit.[25] bp 149–152°); ir (CCl_4) 3445 cm^{-1} (OH); nmr 3.50 (m, 5 H, CH_2O,CHO), 1.57 (m, 4 H, CH_2CH_2), 1.08 (d, 6 H, J = 6 Hz, $(CH_3)_2CH$). **4-*n*-Butoxy-1-butanol (32)**: bp 80–84° (6 mm) (lit.[26] bp 212–214°); ir (CCl_4) 3400 cm^{-1} (OH); nmr δ 3.55 (m, 6 H, CH_2O), 1.65 (m, 8 H, CH_2CH_2), 1.10 (t, 3 H, J = 6 Hz, CH_3CH_2). **4-*n*-Hexoxy-1-butanol (33)**: bp 110° (4 mm); ir (CCl_4) 3450 cm^{-1} (OH); nmr δ 3.4 (m, 6 H, CH_2O), 1.1–1.8 (m, 12 H, CH_2CH_2), 0.9 (m, 3 H, CH_3CH_2); M^+ 174 ($C_{10}H_{22}O_2$).

Preparation of Deuterium-Labeled Substrates.—Preparation of 1,1,4,4-tetradeuterio-1,4-butanediol and 2,2,3,3-tetradeuterio-1,4-butanediol was described earlier.[14] The α-d_2 labeled substrates **19**, **21**, **26**, and **28** were prepared using 98% α-d_2 benzyl bromide following the same procedures as for the unlabeled substances. Likewise, **20** and **23** were prepared using the appropriate butanediol-d_4 in place of unlabeled butanediol. Compound **22** was synthesized from **20** by $LiAlH_4$ reduction, and **24** from **2** by $LiAlO_4$ reduction. The synthesis of **29** was the same as that of **18**, except that CD_3I was used instead of CH_3I. Compound **34** was prepared from 2,2-dideuteriohexyl bromide and 1,4-butanediol in the same manner as was **33**, and the 2,2-dideuteriohexyl bromide was generated from hexanoic acid by $LiAlD_4$ reduction followed by bromination with triphenylphosphine and bromine.

Registry No.—**1**, 29006-04-0; **2**, 31600-42-7; **3**, 31600-43-8; **4**, 4126-60-7; **5**, 31662-20-1; **6**, 31662-21-2; **7**, 10385-30-5; **8**, 4541-14-4; **9**, 31600-47-2; **10**, 27058-12-4; **11**, 1462-37-9; **12**, 31600-50-7; **13**, 622-08-2; **14**, 4799-68-2; **15**, 4541-15-5; **16**, 31600-54-1; **17**, 31600-55-2; **18**, 31600-56-3; **19**, 31600-57-4; **20**, 31600-58-5; **21**, 31600-59-6; **22**, 31600-60-9; **23**, 31600-61-0; **24**, 31600-62-1; **25**, 31600-63-2; **26**, 31600-64-3; **27**, 31600-65-4; **28**, 31600-66-5; **29**, 31600-67-6; **30**, 111-73-9; **31**, 31600-69-8; **32**, 4161-24-4; **33**, 4541-13-3.

Acknowledgments.—We wish to thank Professor A. L. Weinheimer (University of Oklahoma) for the preparation of **5** during his sabbatical leave at Stanford University.

(23) I. Jansson, *Suom. Kemistilehti, B*, **37**, 19 (1964).

(24) M. H. Palomaa and R. Jansson, *Ber.*, **64**, 1606 (1931).

(25) R. R. Schneider and W. M. Schneider, *Monatsh. Chem.*, **90**, 510 (1959).

(26) T. P. Hobin, *Polymer*, **6**, 403 (1965).

The Reaction between 2,6- and 2,7-Di-*tert*-butyl-1,4-naphthoquinone and Phenylmagnesium Bromide and Phenyllithium

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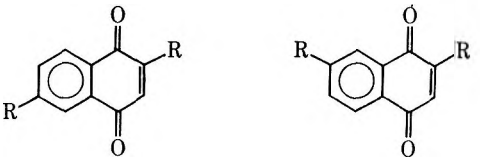
Phenylmagnesium bromide and phenyllithium reacted with 2,6- and 2,7-di-*tert*-butyl-1,4-naphthoquinone to give the expected mono- and diaddition products. Oxidation of the monoaddition products gave *tert*-butylbenzoylbenzoic acids. Two new derivatives, the 3,3-diphenylphthalides and the 3-phenyl-3-anilinophthalides, of each of these acids were prepared. The diaddition products were dehydrated with rearrangement. The two compounds obtained in largest amounts were substituted phthalides, presumably resulting from the oxidation of the 1,2–1,4-diaddition products during isolation. These phthalides reacted with phenylmagnesium bromide, phenyllithium, and lithium aluminum hydride. The 46 new compounds are described.

The study[1] of the reactions between quinones and organometallic reagents has been extended to the 2,6- and 2,7-di-*tert*-butyl-1,4-naphthoquinones.

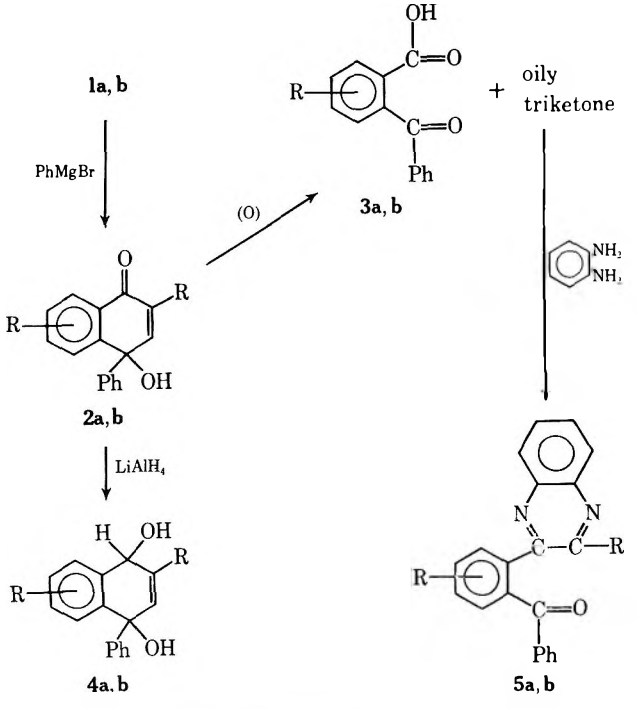
The quinones **1a** and **1b** differ only in the location



1a **1b**

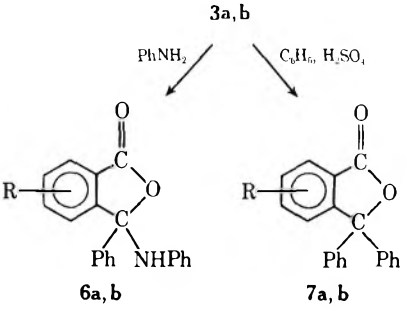
of the two *tert*-butyl groups on the naphthalene rings. When the reaction products are similar, the "a" series will refer to compounds with the *tert*-butyl group in the 6 position and the "b" series will refer to the *tert*-butyl group in the 7 position. In all formulas R will be used to represent the *tert*-butyl group and Ph to represent the phenyl group.

More reactions were carried out with the "a" series since the 2,6- and 2,7-di-*tert*-butylnaphthalenes are formed in about the ratio of 6:1 and the 2,7 hydrocarbon is very difficult to separate from the complex which it forms with the 2,6 hydrocarbon.



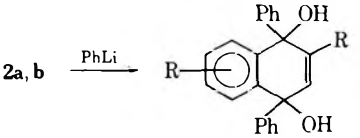
Monoaddition Products.—The only monoaddition products isolated were those resulting from the 1,2 addition to the carbonyl group in the 4 position. Oxidation of **2a,b** by chromium trioxide in glacial acetic acid gave the acids **3a,b** and oily triketones which did not crystallize but did react with *o*-phenylenediamine to give the corresponding quinoxalines **5a,b**. The acid **3b** has been prepared before[2] and its formation by the oxidation of various compounds described here establish its structure. The acid **3a** is a new compound which, on treatment with fuming sulfuric acid, gave the same 2-*tert*-butylanthraquinone[2] as **3b**.

Two new derivatives of each of these acids were made by the same procedures used for the preparation of the corresponding derivatives of *o*-benzoylbenzoic acid.[3,4]



The 3,3-diphenylphthalide and the 3-phenyl-3-anilinophthalide were also made from *o*-benzoylbenzoic acid for comparison of their ir spectra with the spectra of **6a,b** and **7a,b**.

1,2–1,2-Diaddition Products.—Compounds **2a,b** reacted with phenyllithium to give the diaddition products **8a,b**. **8b** was also obtained in small amounts by



the reaction of the quinone **1b** with phenyllithium. It did not lose water spontaneously and too little was available for dehydration experiments. When the quinone **1a** reacted with phenyllithium, a small amount of **2a** was obtained along with compound **9**. Compound **8a** lost water so readily that it could be obtained

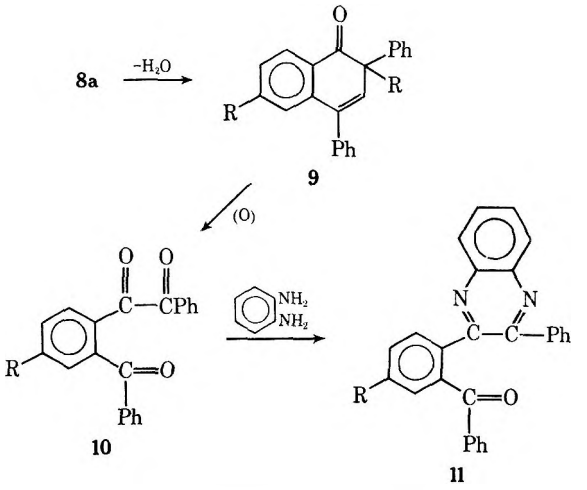
(1) H. M. Crawford, *J. Amer. Chem. Soc.*, **61**, 3310 (1939); **63**, 1070 (1941); **70**, 1081 (1948); *J. Org. Chem.*, **28**, 3082 (1963).

(2) R. B. Contractor and A. T. Peters, *J. Chem. Soc.*, 1314 (1949).

(3) *Beilstein*, 4th ed, **12**, 524 (1929).

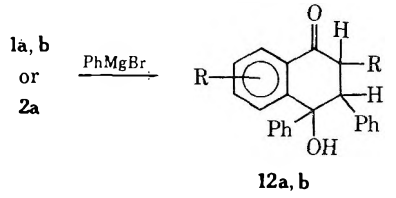
(4) S. D. Ross and M. Schwarz, *J. Amer. Chem. Soc.*, **77**, 3020 (1955).

only by the procedure described in the Experimental Section. Oxidation of **9** by chromium trioxide gave

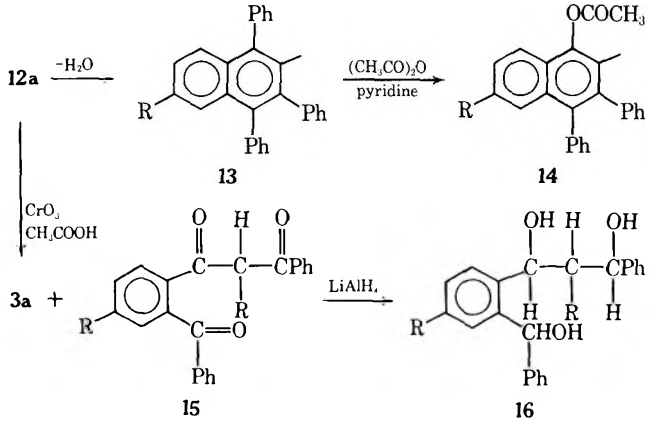


the acid **3a** and the yellow triketone **10** which reacted with *o*-phenylenediamine to give the quinoxaline **11**.

1,2–1,4-Diaddition Products.—Compounds of this type were the main products obtained from the reactions of other substituted 1,4-naphthoquinones with phenylmagnesium bromide.[1] In this study, if the same procedure was used, the main solids isolated were the phthalides **17a,b** which will be discussed later. If most of the ether was evaporated as soon as the intermediate magnesium compounds were decomposed, and the mixture was chromatographed on alumina, the expected diaddition products were obtained. The reaction of phenylmagnesium bromide with **2a** also gave **12a**. Both **12a** and **12b** were obtained in two

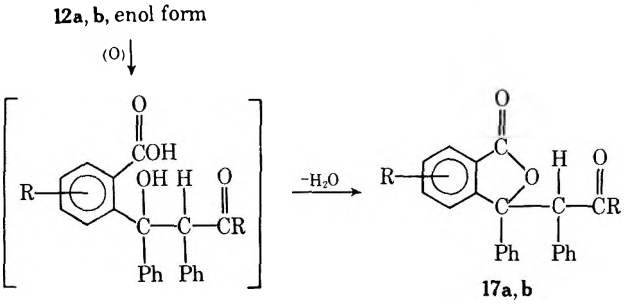


modifications. The two forms of **12a** melted at 198 and 209°, and the two forms of **12b** melted at 146 and 177°. The ir spectra of the four compounds were almost identical, and both forms of **12a** gave the same chemical reactions. Either form of **12a**, or a mixture of the two, could be dehydrated to a naphthol **13**, which on acetylation gave **14**. Either form of **12a**, or a mixture of the two, on oxidation by chromium trioxide



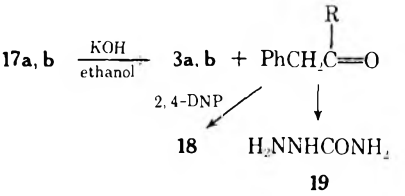
gave the acid **3a** and a triketone **15** which could be reduced to the alcohol **16**.

Two Phthalides.—When the ether solution of the products from the reaction of either quinone with phenylmagnesium bromide was allowed to evaporate slowly, the solids obtained were the two phthalides **17a,b**. A possible method for their formation is shown.

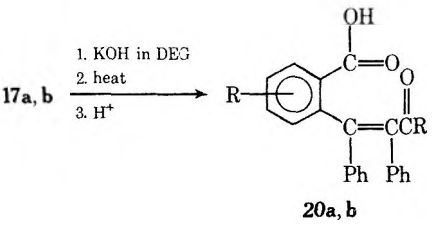


It is well known that compounds of the type written as the intermediate lose water immediately to form phthalides. The reaction of phenylmagnesium bromide with **2a** also gave **17a**.

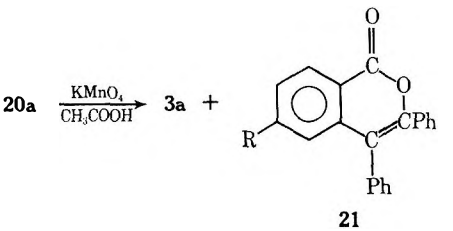
The phthalides both reacted with potassium hydroxide and the products depended on the conditions of the reaction. When they were refluxed with potassium hydroxide in ethanol the products were the corresponding acids **3a,b** and *tert*-butyl benzyl ketone.



The latter was identified as the 2,4-dinitrophenylhydrazone **18** which was identical with a known sample kindly supplied by Dr. House.[5] The semicarbazone **19** was also prepared. When the phthalides were heated to boiling with potassium hydroxide in diethylene glycol, the acids **20a,b** resulted. The acid **20a**, on

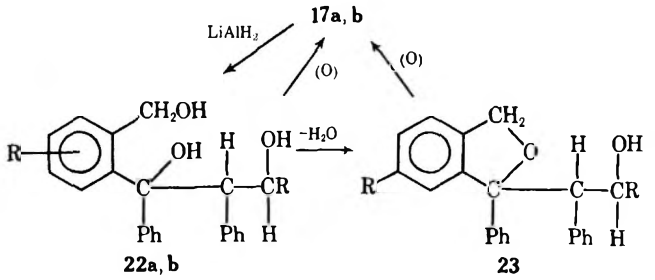


oxidation by potassium permanganate in acetic acid, gave the acid **3a** and a neutral compound for which structure **21** is proposed. The phthalides were reduced



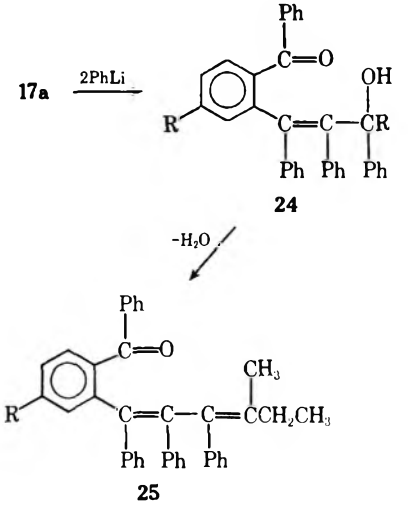
(5) H. O. House and E. J. Grubbs, *J. Amer. Chem. Soc.*, **81**, 4733 (1959).

to the corresponding alcohols **22a,b**, and **22a** was dehydrated to **23**. Oxidation of the alcohols **22a,b** gave

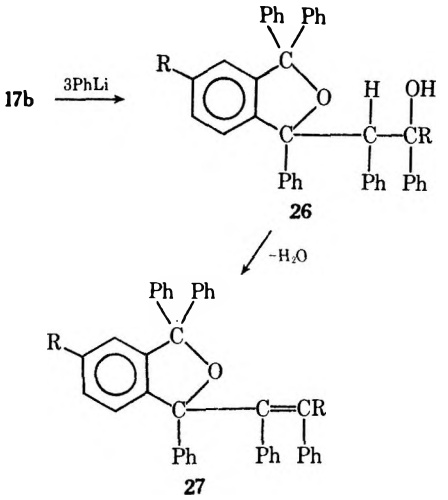


about 70% of the phthalides **17a,b** and small amounts of the acids **3a,b**. Oxidation of **23** also gave 70% of **17a** and some **3a**, which is evidence for the loss of water giving the phthalan rather than an ethylenic structure.

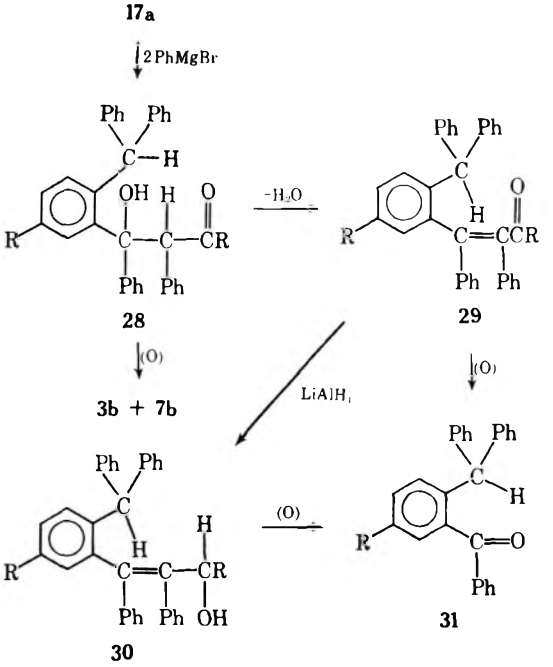
The phthalides reacted with phenyllithium and the products were quite different for the two series. **17a** reacted with 2 mol of phenyllithium to give **24**, which was dehydrated, with rearrangement to give **25**. Oxidation of both **24** and **25** gave methyl ethyl ketone



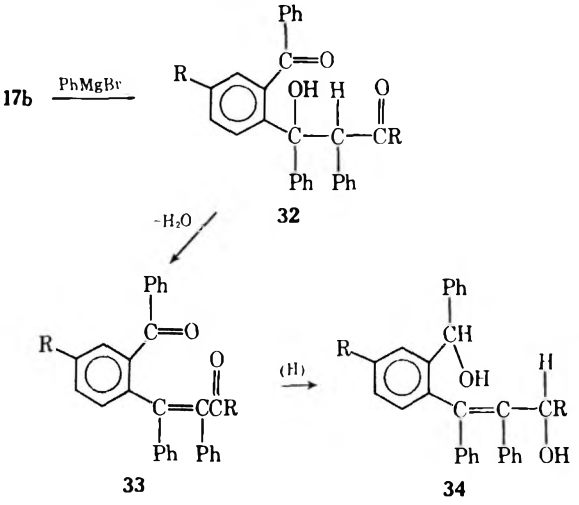
which was identified as the 2,4-dinitrophenylhydrazone. The oxidation of **24** also gave the acid **3b**. **17b** reacted with 3 mol of phenyllithium to give **26** which was dehydrated to give **27**.



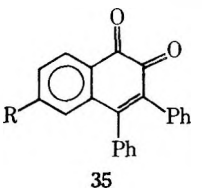
Both phthalides reacted with phenylmagnesiun bromide and again the results were quite different. Oxidation of **28** by chromium trioxide gave the acid **3b** and the phthalide **7b**. Oxidation of both **29** and **30** with chromium trioxide gave **31**. Reductive cleavage of lactones by Grignard reagents has been reported before.[6] The spectra of **31** were very similar to the



spectra of a known sample of 2-(diphenylmethyl)benzophenone kindly supplied by Dr. Bradsher.[7] The results of these oxidations established the locations of the phenyl groups. Attempts to oxidize **32** resulted only in the dehydration to **33**.



In reactions of phenylmagnesium bromide with the quinones, after separating as much of the solid products as possible, the thick, dark oils were chromatographed on alumina. This usually gave more of the compounds already obtained. In one case only, the end fractions gave a bright red solid which proved to be the *o*-quinone **35**. Analyses and comparison of its spectra



(6) R. C. Fuson and D. E. Brasure, *J. Amer. Chem. Soc.*, **77**, 3131 (1955).
(7) C. K. Bradsher and E. Studley Smith, *ibid.*, **65**, 451 (1943).

with the spectra of the known 3,4-diphenyl-1,2-naphthoquinone kindly furnished by Dr. Smith[8] established its structure. At present no suggestion can be made as to the method of its formation.

In several cases the end fractions from the chromatography gave a yellow compound. It looked and behaved like a *p*-quinone, giving a white diacetate on reductive acetylation. At present no satisfactory structures can be written for these compounds, **36** and **37**.

Experimental Section

All melting points are uncorrected. All nmr spectra were made in $CDCl_3$ with TMS as reference and are given in δ values. Most ir spectra were made in $CHCl_3$ or CS_2 with a few in KBr, and are given in reciprocal centimeters. The absorption for *tert*-butyl and for mono- and trisubstituted benzenes are not listed as they occur in all compounds.

Preparation of the Two Quinones (1a,b).—The quinones were prepared as described earlier[9] by the oxidation of the corresponding hydrocarbons by CrO_3 in glacial HOAc. The best yields (70% for **1a** and 60% for **1b**) were obtained when the hydrocarbon was finely divided and the temperature was kept at 35–45° during the addition of the oxidizing agent. The melting point of **1a** was 86–87° and of **1b**, 72–73°. Earlier[9] **1b** was reported as melting at 55–57° but after several years the sample had changed to a higher melting form and all later preparations had the higher melting point. The nmr spectrum for **1a** showed 18 H's at 1.4, 1 vinyl H at 6.9, and 3 aromatic H's at 7.8–8.1.

Reactions of the Two Quinones.—The reactions with PhMgBr and with PhLi were carried out as before[1] by adding an ether solution of the reagent to an ether solution of the quinone. A 2.5:1 ratio of the reagent to the quinone usually gave more of the monoaddition products, while a 4:1 ratio gave more of the diaddition products or the phthalides. Reactions of this type are very unpredictable[1] and yields of solid products are usually low and variable. Thick, dark oils account for a large part of the starting material. For these reasons it was best to carry out the reactions on small amounts of the quinones (2.7–5.4 g, 0.01–0.02 mol) rather than on larger amounts. The reaction mixtures were allowed to stand overnight and then decomposed with ice and NH_4Cl solution. The ether solutions were allowed to evaporate slowly and solids were filtered off and recrystallized. After no more solid could be obtained from the dark oils they were chromatographed on alumina. This usually gave more solids. The products obtained in this way (when PhMgBr was the reagent) were **2a,b** and **17a,b**. If most of the ether was distilled off as soon as the reaction mixture was worked up and the solution was then chromatographed on alumina, the products were **2a,b** and **12a,b**. The products obtained when PhLi was the reagent were **8b** or **9**.

2,6-Di-*tert*-butyl-4-hydroxy-4-phenyl-1(4*H*)-naphthalenone (2a) and 2,7-Di-*tert*-butyl-4-hydroxy-4-phenyl-1(4*H*)-naphthalenone (2b).—These monoaddition products were formed when PhMgBr reacted with the quinones **1a,b**. The yields were 10–56% for **2a** and 2–50% for **2b**. The faintly yellow **2a** was crystallized from heptane or methanol, mp 164.5–165°. **2b** was crystallized from petroleum ether, mp 144–145°. The ir spectra for both showed carbonyl absorption at 1650 and hydroxyl at 3400 cm^{-1}. The nmr spectrum for **2a** showed 18 H's at 1.23, 1 H at 3.4, 1 H at 6.8, and 8 H's at 7.0–8.1.

Anal. Calcd for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10; mol wt, 348. Found for **2a**: C, 82.5; H, 8.1; mol wt, 345 in benzene. Found for **2b**: C, 83.0; H, 8.18.

4-*tert*-Butyl-2-benzoylbenzoic Acid (3a) and 5-*tert*-Butyl-2-benzoylbenzoic Acid (3b).—**3a** was first obtained in 25% yield by refluxing 1 g of **2a** with 3 g of $K_2Cr_2O_7$ or 2 g of CrO_3 in 30 ml of glacial HOAc for 5 min. The solution was diluted with H_2O and neutralized with KOH. (The ether extract of the alkaline solution gave **5a** after treatment with *o*-phenylenediamine.) The alkaline solution was acidified and extracted with ether to give **3a**. This acid was also obtained in small amounts by the oxidation of **9**, **12a**, **20a**, and **23** by $K_2Cr_2O_7$ in glacial HOAc. Oxidation of 2 g of **22a** by refluxing for 25 min with 2 g of CrO_3 in 30 ml of glacial HOAc gave 44% of **3a**. Refluxing 3 g of **17a** with 0.5 g of KOH in 75 ml of 95% ethanol for 2 hr gave 44% of **3a**. It was crystallized from benzene and petroleum ether, mp 163–164°. **3b** was prepared by the method of Contractor and Peters,[2] mp 179°. It resulted in small amounts by the oxidation of **2b**, **22b**, and **28** by CrO_3 in glacial HOAc. Refluxing 1 g of **17b** with 0.5 g of KOH in 25 ml of 95% ethanol for 2 hr gave 70% of **3b**. The ir spectra for **3a** and **3b** were practically identical, with carbonyl absorptions at 1680 and 1700 cm^{-1} and the broad, merged band of the *tert*-butyl and hydroxyl at 2500–3500 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; mol wt, 282. Found for **3a**: C, 76.7; H, 6.5; neut equiv, 291.

Cyclization of 3a.—The acid (0.6 g) and fuming sulfuric acid (4 ml) were heated on the steam bath for 90 min and then poured into ice water. After washing the ether extract with $NaHCO_3$ solution, the ether was evaporated and the remaining solid crystallized from methanol, mp 102–103°. The ir spectrum, with carbonyl absorption at 1780 cm^{-1}, was very similar to the spectrum of anthraquinone. These data identify the cyclization product as 2-*tert*-butylanthraquinone.[2]

2,6-Di-*tert*-butyl-1,4-dihydro-4-phenyl-1,4-naphthalenediol (4a) and 2,7-Di-*tert*-butyl-1,4-dihydro-4-phenyl-1,4-naphthalenediol (4b).—These compounds were prepared by the reduction of 1 g of **2a** or **2b** by $LiAlH_4$. **4a** was crystallized from methanol or petroleum ether, mp 128–129°, yield 60%. **4b** was crystallized from petroleum ether, mp 150.5–151°, yield 25%. The ir spectra of both showed hydroxyl absorptions at 3600 cm^{-1}. The nmr spectrum of **4b** showed 9 H's at 1.2, 9 H's at 1.4, 3 H's at 2.2–3.2, 1 H at 7.0, and 8 H's at 7.4–8.2.

Anal. Calcd for $C_{24}H_{30}O_2$: C, 82.24; H,8.63. Found for **4a**: C, 82.2; H, 8.7. Found for **4b**: C, 81.8; H, 8.7.

5-*tert*-Butyl-2-(3-*tert*-butyl-2-quinoxalinyl)benzophenone (5a) and 4-*tert*-Butyl-2-(3-*tert*-butyl-2-quinoxalinyl)benzophenone (5b).—The neutral, greenish fractions from the oxidation of **2a** and **2b** were refluxed for a few minutes with 0.3 g of *o*-phenylenediamine in 10 ml of ethanol. The solids which separated on cooling were crystallized from ethanol. **5a** melted at 156–157° and accounted for 27% of the **2a** used. **5b** melted at 209–210° and accounted for 30% of the **2b**. Both ir spectra showed carbonyl absorption at 1670 cm^{-1}.

Anal. Calcd for $C_{29}H_{30}N_2O$: C, 82.43; H, 7.16. Found for **5a**: C, 82.1; H, 6.9. Found for **5b**: C, 82.8; H, 7.3.

5-*tert*-Butyl-3-anilino-3-phenylphthalide (6a) and 6-*tert*-Butyl-3-anilino-3-phenylphthalide (6b).—These two compounds were made by heating to boiling 0.3 g of the acids **3a,b** with 15 drops of aniline. After crystallization from ethanol **6a** melted at 210–211.5° and **6b** melted at 217–218°. The ir spectra for these compounds and for the known 3-anilino-3-phenylphthalide[3] were identical, except for the *tert*-butyl group, showing carbonyl absorption at 1760 and NH at 3400 cm^{-1}.

Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49. Found for **6a**: C, 80.7; H, 6.8. Found for **6b**: C, 80.4; H, 6.5.

5-*tert*-Butyl-3,3-diphenylphthalide (7a) and 6-*tert*-Butyl-3,3-diphenylphthalide (7b).—These phthalides were prepared from **3a** and **3b** by stirring a mixture of 0.4 g of the acid, 20 ml of benzene, and 15 ml of concentrated H_2SO_4 for 2 hr.[4] The mixture was poured into water, and the benzene layer was washed with Na_2CO_3 solution and allowed to evaporate. The resulting solids were crystallized for ethanol. **7a** melted at 178.5–179° and **7b** melted at 223–224°. They could also be prepared by treating the acids with $SOCl_2$, followed by benzene and anhydrous $AlCl_3$. **7b** was also obtained in 50% yield by refluxing 2 g of **28** with 5 g of CrO_3 in 50 ml of glacial HOAc for 90 min and diluting the mixture with H_2O. The ir spectra of **7a**, **7b**, and the known 3,3-diphenylphthalide[4] all showed carbonyl absorption at 1770 cm^{-1}. The nmr spectrum of **7b** showed 9 H's at 1.36 and 13 H's at 7.3–8.0.

Anal. Calcd for $C_{24}H_{22}O_2$: C, 84.18; H, 6.48; mol wt, 342. Found for **7a**: C, 84.0; H, 6.6. Found for **7b**: C, 84.4; H, 6.8; mol wt, 331 in benzene, 340 in camphor.

2,6-Di-*tert*-butyl-1,4-dihydro-1,4-diphenyl-1,4-naphthalenediol (8a) and 2,7-Di-*tert*-butyl-1,4-dihydro-1,4-diphenyl-1,4-naphthalenediol (8b).—Attempts to make **8a** by the slow evaporation of the ether solution from the reaction of PhLi with either **1a** or **2a** gave only dark oils and small amounts of **9**. If most of the ether was distilled as soon as the reaction mixture of **2a** and PhLi was worked up, and the remaining solution was chromatographed on alumina, about 10% of **8a** could be obtained. After crystallization from benzene and petroleum ether, it melted at 178–180°. On standing for some time it lost water to form **9**.

(8) L. I. Smith and H. Hoehn, *J. Amer. Chem. Soc.*, **61**, 2619 (1939).
(9) H. M. Crawford, *ibid.*, **77**, 1046 (1955).

8b was obtained once in 69% yield when 1.9 g of **1b** reacted with PhLi, and once in 61% yield when 1 g of **2b** reacted with PhLi. After crystallization from heptane it melted at 195–197°. The ir spectra of **8a** and **8b** were very similar, showing hydroxyl absorption at 3000 cm^{-1}.

Anal. Calcd for $C_{30}H_{34}O_2$: C, 84.46; H, 8.03. Found for **8a**: C, 84.0; H, 8.4. Found for **8b**: C, 84.2; H, 8.1.

2,6-Di-*tert*-butyl-2,4-diphenyl-1(2*H*)-naphthalenone (9).—This compound was formed in 20% yield by the reaction of PhLi with 2.7 g of **1a**, by the spontaneous loss of water from **8a**, and in 37% yield by the reaction of PhLi with 3.7 g of **2a**. When crystallized from heptane or ethanol, it melted with decomposition at 140°. The ir spectrum showed carbonyl absorption at 1675 cm^{-1}. The nmr spectrum showed 18 H's at 1.2, 1 H at 6.8, and 13 H's at 7.1–8.2.

Anal. Calcd for $C_{30}H_{32}O$: C, 88.19; H, 7.90; mol wt, 400. Found: C, 88.1; H, 8.0; mol wt, 389 in benzene.

4-*tert*-Butyl-2-benzoylbenzil (10).—This yellow triketone was formed in 40% yield by the oxidation of 1 g of **9** by $K_2Cr_2O_7$ in glacial HOAc. It melted at 147–147.5° after crystallization from ethanol and ethyl acetate. The ir spectrum showed carbonyl absorption at 1675 cm^{-1}. The nmr spectrum showed 9 H's at 1.2 and 13 H's at 6.9–8.0.

Anal. Calcd for $C_{25}H_{22}O_3$: C, 81.05; H, 6.0; mol wt, 370. Found: C, 81.0; H, 6.1; mol wt, 344 in benzene.

5-*tert*-Butyl-2-(3-phenylquinoxalinyl)benzophenone (11).—This compound was formed in 50% yield when 0.37 g of **10** and 0.15 g of *o*-phenylenediamine were refluxed for 30 min in 15 ml of ethanol. After crystallization from methanol or hexane and benzene it melted at 153–154°. The ir spectrum showed carbonyl absorption at 1670 cm^{-1} and was very similar to the spectra of **5a,b**. The nmr spectrum showed 9 H's at 1.35 and 17 H's at 7.0–8.2.

Anal. Calcd for $C_{31}H_{26}N_2O$: C, 84.13; H, 5.92. Found: C, 84.0; H, 6.2.

2,6-Di-*tert*-butyl-4-hydroxy-3,4-diphenyl-(2,3*H*)-naphthalenone (12a) and 2,7-Di-*tert*-Butyl-4-hydroxy-3,4-diphenyl-(2,3*H*)-naphthalenone (12b).—The quinones **1a,b** were treated with an excess (4:1) of PhMgBr and allowed to stand overnight. The reaction mixture was decomposed with NH_4Cl solution and most of the ether was removed by distillation. A little benzene was added and the solution chromatographed on alumina. This gave 54% of solid material **12a** which was separated by fractional crystallization from ethanol and ethyl acetate into the two isomeric forms melting at 198–199 and 209–210°. Both isomers were also formed (61%) when the reaction mixture from **2a** and PhMgBr was treated in the same way. By the same procedure, **1b** and PhMgBr gave 70% of two isomers which melted at 146–147 and 177–178°. The ir spectra for these four isomers were very similar showing carbonyl absorption at 1670 and hydroxyl at 3500 cm^{-1}. The nmr spectrum of the 198° compound showed 9 H's at 0.9, 9 H's at 1.22, 1 H each at 2.2, 3.2, and 3.8, and 13 H's at 6.95–7.9.

Anal. Calcd for $C_{30}H_{34}O_2$: C, 84.46; H, 8.03; mol wt, 427. Found for **12a** (198°): C, 84.2; H, 8.3; mol wt, 400 in benzene. Found for **12a** (209°): C, 84.7; H, 8.1; mol wt, 406 in benzene. Found for **12b** (146°): C, 84.9; H, 8.0. Found for **12b** (177°): C, 84.4; H, 8.2; mol wt, 404 in benzene.

6-*tert*-Butyl-3,4-diphenyl-1-naphthol (13).—Either form of **12a** could be dehydrated by heating with I_2 in glacial HOAc or *p*-toluenesulfonic acid in benzene. The naphthol darkened on standing and no satisfactory solvent for crystallization could be found. Dehydration of 2 g of the 209° isomer by refluxing for 90 min with 1 g of *p*-toluenesulfonic acid in 15 ml of benzene, washing the benzene with water, distilling about half of the solvent, and diluting with petroleum ether gave 1.7 g (80%) of a pale pink solid melting at 142–146°. The ir spectrum showed hydroxyl absorption at 3600 cm^{-1}. Acetylation gave **14**.

6-*tert*-Butyl-3,4-diphenyl-1-naphthol Acetate (14).—The acetate was made from 1 g of the crude naphthol **13** by refluxing for 1 hr with 5 ml of Ac_2O in 15 ml of pyridine. The solution was diluted with water. The resulting solid crystallized from ethanol as long, shiny white needles, mp 124–125°. The ir spectrum showed carbonyl absorption at 1750 cm^{-1}. The nmr spectrum showed 9 H's at 1.2, 3 H's at 2.4, and 13 H's at 7.0–8.0.

Anal. Calcd for $C_{28}H_{26}O_2$: C, 85.24; H, 6.64. Found: C, 85.2; H, 6.7.

2-*tert*-Butyl-3-phenyl-1-(4-*tert*-butyl-2-benzoylphenyl)-1,3-propanedione (15).—This compound was formed in 25–30% yield by refluxing either form of **12a**, or a mixture of the two, with CrO_3 in glacial HOAc. After crystallization from ethanol, it melted at 163–164°. The ir spectrum showed carbonyl absorption at 1675 and 1730 cm^{-1}. The nmr spectrum showed 9 H's at 1.05, 9 H's at 1.3, 1 H at 5.25, and 13 H's at 7.3–8.0.

Anal. Calcd for $C_{30}H_{32}O_3$: C, 81.78; H, 7.32; mol wt, 441. Found: C, 81.5; H, 7.6; mol wt, 429 in benzene.

2-*tert*-Butyl-3-phenyl-1-[4-*tert*-butyl-2-(hydroxyphenylmethyl)-phenyl]-1,3-propanediol (16).—Compound **15** (1 g) was refluxed for 1 hr with 1 g of $LiAlH_4$ in 25 ml of ether. After decomposing the excess $LiAlH_4$ with ethyl acetate and dilute HCl, the ether solution gave a white solid (70%) which was crystallized from petroleum ether and acetone and melted at 196–197°. The ir spectrum showed hydroxyl absorption at 3500 cm^{-1}.

Anal. Calcd for $C_{30}H_{38}O_3$: C, 80.68; H, 8.58. Found: C, 80.6; H, 8.8.

5-*tert*-Butyl-3-phenyl-3-(α-pivaloylbenzyl)phthalide (17a) and 6-*tert*-Butyl-3-phenyl-3-(α-pivaloylbenzyl)phthalide (7b).—These phthalides were the main products isolated from the slow evaporation of the ether solutions from the reactions of **1a,b** with PhMgBr. Yields varied, with a maximum of 52% for **17a** and 32% for **17b**. After crystallization from ethyl acetate **17a** melted at 222–223° and **17b** at 213–214°. Neither of these could be oxidized by refluxing with CrO_3 in glacial HOAc. The ir spectra for both showed carbonyl absorptions at 1700 and 1750 cm^{-1}. The nmr spectra for both showed 9 H's at 0.8, 9 H's at 1.4, 1 H at 5.23, 12 H's at 7.0–7.8, and 1 H at 8.5.

Anal. Calcd for $C_{30}H_{32}O_3$: C, 81.78; H, 7.32; mol wt, 441. Found for **17a**: C, 81.7; H, 7.2; mol wt, 426 in benzene. Found for **17b**: C, 81.4; H, 7.4; mol wt, 436 in benzene.

2,4-Dinitrophenylhydrazone of *tert*-Butyl Benzyl Ketone (18).—This compound resulted when the neutral fraction, from the reaction of either **17a** or **17b** with KOH in ethanol, was treated with 2,4-dinitrophenylhydrazine. It melted at 140–141° and was not depressed when mixed with a known sample.[5]

Semicarbazone of *tert*-Butyl Benzyl Ketone (19).—The semicarbazone was prepared in the usual way from the neutral fraction from the reaction of **17a** with KOH in ethanol. After crystallization from 10% ethanol it melted at 149–150°.

Anal. Calcd for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21. Found: C, 66.7; H, 8.3.

4-*tert*-Butyl-2-(4,4-dimethyl-1,2-diphenyl-1-penten-3-onyl)benzoic Acid (20a) and 5-*tert*-Butyl-2-(4,4-dimethyl-1,2-diphenyl-1-penten-3-onyl)benzoic Acid (20b).—These acids were formed when the phthalides (1 g) were heated to boiling with KOH (0.3 g) in 7.5 ml of diethylene glycol. The solution was poured on ice and the clear solution acidified. The heavy, white precipitate was filtered and crystallized from ethanol. The yield of **20a** was 90% and it melted at 178–180°. It was unchanged by heating to 250°, and oxidation by CrO_3 gave 44% of **3a**. The yield of **20b** was very small and it melted at 176–177°. The ir spectra were very similar showing the broad, merged band of the acid hydroxyl and the *tert*-butyl groups at 2500–3500 cm^{-1}, and the carbonyl groups at 1680 and 1740 cm^{-1}. The nmr spectrum for **20b** showed 9 H's at 0.8, 9 H's at 1.2, 13 H's at 6.8–7.8, and the acid H at 11.0. The acid H disappeared after D_2O exchange.

Anal. Calcd for $C_{30}H_{32}O_3$: C, 81.78; H, 7.32; mol wt, 441. Found for **20a**: C, 81.8; H, 7.4; mol wt, 453 in camphor; neut equiv, 431. Found for **20b**: C, 81.8; H, 7.4.

6-*tert*-Butyl-3,4-diphenylisocoumarin (21).—The acid **20a** (1 g) was refluxed for 10 min with $KMnO_4$ (0.5 g) in 5 ml of glacial HOAc and then poured on ice. The solution was decolorized by $NaHSO_3$ and filtered, and the precipitate was dissolved in ether and extracted with $NaHCO_3$ solution. After evaporating the ether, the solid was crystallized from ethanol and ethyl acetate, mp 175–176°, yield 25%. The ir spectrum showed carbonyl absorption at 1760 cm^{-1}. The nmr spectrum showed 9 H's at 1.1 and 13 H's at 7.2–8.0.

Anal. Calcd for $C_{26}H_{22}O_2$: C, 84.72; H, 6.26. Found: C, 84.8; H, 6.5.

4,4-Dimethyl-1,2-diphenyl-1-(2-hydroxymethyl-5-*tert*-butylphenyl)-1,3-pentanediol (22a) and 4,4-Dimethyl-1,2-diphenyl-1-(2-hydroxymethyl-4-*tert*-butylphenyl)-1,3-pentanediol (22b).—Reduction of **17a** (4 g) by refluxing for 45 min with $LiAlH_4$ (3 g) in 100 ml of ether gave 95% of **22a**. After crystallization from ethanol it melted at 225–227°. Reduction of 2 g of **17b** in the same way gave 66% of **22b**. It was crystallized from benzene and melted at 198–199°. The ir spectra of both showed hydroxyl absorption at 3400 cm^{-1} and no carbonyl. The nmr spectra

showed 9 H's at 0.8, 9 H's at 1.4, 2 H's at 2.0, 5 H's at 3.8–4.7, and 13 H's at 6.9–7.8.

Anal. Calcd for $C_{30}H_{38}O_3$: C, 80.68; H, 8.58; mol wt, 447. Found for **22a**: C, 80.8; H, 8.8; mol wt, 425 in bromoform. Found for **22b**: C, 80.7; H, 8.22.

5-*tert*-Butyl-3-(3,3-dimethyl-1-phenyl-2-butanolyl)-3-phenylphthalan (23).—The dehydration of **22a** (0.7 g) was carried out by refluxing for 2 hr with *p*-toluenesulfonic acid (1 g) in 20 ml of benzene. The benzene solution was washed with H_2O and the solvent was allowed to evaporate. Crystallization from ethanol gave 60% of **23**, mp 155–156°. The ir spectrum showed hydroxyl absorption at 3500 cm^{-1} and a broad ether band at 1100 cm^{-1}. The nmr spectrum showed 9 H's at 0.7, 9 H's at 1.4, 2 H's at 3.7, 1 H at 4.1, 2 H's at 5.2, and 13 H's at 6.9–7.65.

Anal. Calcd for $C_{30}H_{36}O_2$: C, 84.07; H, 8.47. Found: C, 84.0; H, 8.7.

4,4-Dimethyl-1,2,3-triphenyl-1-(2-benzoyl-5-*tert*-butylphenyl)-1-penten-3-ol (24).—This compound resulted from the reaction of PhLi with the phthalide **17a** in yields of 50–80%. It was crystallized from ethyl acetate, mp 198–199°. Oxidation of 1 g by refluxing for 15 min with CrO_3 (2 g) in 30 ml of glacial HOAc gave the acid **3b** (100%) and a neutral fraction from which the 2,4-dinitrophenylhydrazone of methyl ether ketone was isolated. The ir spectrum showed hydroxyl absorption at 3400 and carbonyl at 1650 cm^{-1}. The nmr spectrum showed 9 H's at 0.8, 9 H's at 1.1, 1 H at 6.0, and 23 H's at 6.5–7.8.

Anal. Calcd for $C_{42}H_{42}O_2$: C, 87.14; H, 7.32; mol wt, 579. Found: C, 87.0; H, 7.4; mol wt, 562 in camphor.

4-Methyl-1,2,3-triphenyl-1-(2-benzoyl-5-*tert*-butylphenyl)-1,3-hexadiene (25).—Compound **24** (1.3 g) was refluxed for 90 min with 20 ml of Lucas reagent and 20 ml of benzene. The benzene layer was washed with water and evaporated, and the resulting solid was crystallized from ethanol and ethyl acetate. It melted at 158–160° and the yield was 75%. Oxidation by CrO_3 gave only benzoic acid from the acid fraction and the 2,4-dinitrophenylhydrazone of methyl ethyl ketone from the neutral fraction. The ir spectrum showed carbonyl absorption at 1670 cm^{-1}. The nmr spectrum showed 17 H's at 0.82–1.6 and 23 H's at 6.2–8.2.

Anal. Calcd for $C_{42}H_{40}O$: C, 89.95; H, 7.19. Found: C, 89.9; H, 7.3.

5-*tert*-Butyl-1-(3,3-dimethyl-1,2-diphenyl-2-butanolyl)-1,3,3-triphenylphthalan (26).—The phthalide **17b** reacted with 3 mol of PhLi to give 42% of **26**. After crystallization from ethanol and benzene it melted at 226–227°. The ir spectrum showed hydroxyl absorption at 3500 and the broad ether band at 1000–1200 cm^{-1}. The nmr spectrum showed 18 H's at 1.1, 1 H at 3.5, 1 H at 4.9, and 28 H's at 6.5–7.7.

Anal. Calcd for $C_{48}H_{48}O_2$: C, 87.76; H, 7.37; mol wt, 657. Found: C. 87.5; H, 7.3; mol wt, 631 in camphor.

5-*tert*-Butyl-1-(3,3-dimethyl-1,2-diphenyl-1-butenyl)-1,3,3-triphenylphthalan (27).—This compound was formed in 50% yield by the dehydration of **26** (0.4 g) by refluxing for 2 hr with *p*-toluenesulfonic acid (0.2 g) in 10 ml of benzene. After crystallization from $CHCl_3$ it melted, with decomposition, at 236–238°. The ir spectrum showed the wide ether band at 1075–1200 cm^{-1}. The nmr spectrum showed 9 H's at 0.9, 9 H's at 1.1, and 28 H's at 6.8–7.5.

Anal. Calcd for $C_{48}H_{46}O$: C, 90.24: H, 7.26. Found: C, 90.4; H, 7.0.

4,4-Dimethyl-1,2-diphenyl-1-[5-*tert*-butyl-2-(diphenylmethyl)-phenyl]-1-pentanol-3-one (28).—The phthalide **17a** reacted with 2 mol of PhMgBr to give 50–80% of **28**. After crystallization from benzene it melted at 252–253°. The ir spectrum showed carbonyl absorption at 1652 and hydroxyl at 3400 cm^{-1}. The nmr spectrum showed 9 H's at 1.0, 9 H's at 1.4, 1 H at 2.2, and 25 H's at 6.7–7.5.

Anal. Calcd for $C_{42}H_{44}O_2$: C, 86.83; H, 7.64; mol wt, 581. Found: C, 86.8; H, 7.3; mol wt, 592 in bromoform.

4,4-Dimethyl-1,2-diphenyl-1-[5-*tert*-butyl-2-(diphenylmethyl)-phenyl]-1-penten-3-one (29).—This compound was obtained (62%) by refluxing **28** (2.5 g) for 1 hr with *p*-toluenesulfonic acid (1 g) in 25 ml of glacial HOAc. The solution was diluted and filtered, and the resulting solid was crystallized from ethyl acetate, mp 266–267°. **28** also lost water when refluxed with I_2 in HOAc or with Lucas reagent or *p*-toluenesulfonic acid in benzene, but the yields were lower and the compound was more difficult to purify. The ir spectrum showed carbonyl absorption at 1670 cm^{-1}. The nmr spectrum showed 9 H's at 0.4, 9 H's at 0.9, 1 H at 2.17, and 23 H's at 6.55–7.7.

Anal. Calcd for $C_{42}H_{42}O$: C, 89.62; H, 7.52. Found: C, 89.8; H, 7.2.

4,4-Dimethyl-1,2-diphenyl-1-(5-*tert*-butyl-2-diphenylmethyl)-phenyl-1-penten-3-ol (30).—Reduction of **29** (0.7 g) by $LiAlH_4$ in ether gave 90% of **30**. After crystallization from ethyl acetate and $CHCl_3$, it melted at 281–282°. The ir spectrum showed hydroxyl absorption at 3550 cm^{-1}.

Anal. Calcd for $C_{42}H_{44}O$: C, 89.30; H, 7.85. Found: C, 89.1; H, 7.8.

5-*tert*-Butyl-2-(diphenylmethyl)benzophenone (31).—This compound was formed by the oxidation of either **29** (50%) or **30** (31%) by refluxing with CrO_3 in glacial HOAc. In both cases small amounts of benzoic acid were formed. After crystallization from hexane it melted at 140–141°. The ir spectrum showed carbonyl absorption at 1670 cm^{-1}. The nmr spectrum showed 9 H's at 1.34, 1 H at 2.2, and 18 H's at 7.0–8.5. Both the ir and the nmr spectra showed close agreement with a sample of 2-benzoyltriphenylmethane kindly supplied by Dr. Bradsher.[7]

Anal. Calcd for $C_{30}H_{28}O$: C, 89.07; H, 6.98, mol wt, 405. Found: C, 89.0; H, 6.6; mol wt, 383 in benzene.

4,4-Dimethyl-1,2-diphenyl-1-(4-*tert*-butyl-2-benzoylphenyl)-1-pentanol-3-one (32).—The phthalide **17b** reacted with 1 mol of PhMgBr to give 58% of **32**. Solutions that were left over the summer gave only the dehydration product **33**. Crystallization of **32** from acetic acid or petroleum ether gave a melting point of 181–182°. The ir spectrum showed carbonyl absorption at 1700 and hydroxyl at 3400 cm^{-1}. The nmr spectrum showed 9 H's at 0.95, 9 H's at 1.37, 1 H at 5.2, 1 H at 5.8, and 18 H's at 7.2–8.2.

Anal. Calcd for $C_{36}H_{38}O_3$: C, 83.36; H, 7.39. Found: C, 83.4; H, 7.6.

4,4-Dimethyl-1,2-diphenyl-1-(4-*tert*-butyl-2-benzoylphenyl)-1-penten-3-one (33).—This compound was formed by spontaneous loss of water from **32**. After crystallization from benzene and petroleum ether, it melted at 222–223°. The ir spectrum showed carbonyl absorption at 1700 cm^{-1}.

Anal. Calcd for $C_{36}H_{36}O_2$: C, 86.36; H, 7.25; mol wt, 501. Found: C, 86.9; H, 7.6; mol wt, 527 in benzene.

4,4-Dimethyl-1,2-diphenyl-1-[4-*tert*-butyl-2-(α-hydroxybenzyl)-phenyl]-1-penten-3-ol (34).—Reduction of **33** (0.4 g) by $LiAlH_4$ gave 78% of **34**. Crystallization from ethanol and ethyl acetate gave a melting point of 197–198°. The ir spectrum showed hydroxyl absorption at 3400 cm^{-1}. The nmr spectrum showed 9 H's at 0.6, 9 H's at 1.23, 1 H at 2.17, 1 H at 3.65, 1 H at 4.35, and 18 H's at 6.9–8.1.

Anal. Calcd for $C_{36}H_{40}O_2$: C, 85.67; H, 7.99. Found, C, 85.6; H, 7.8.

6-*tert*-Butyl-3,4-diphenyl-1,2-naphthoquinone (35).—This bright red compound was isolated from the end fractions after chromatographing mixtures from the reaction of PhMgBr with the quinone **1a**. It melted at 183–184° after crystallization from ethanol. The ir spectrum showed carbonyl absorption at 1670 cm^{-1} and was very similar to the spectrum of a sample of 3,4-diphenyl-1,2-naphthoquinone kindly supplied by Dr. Smith.[8] The nmr spectrum showed 9 H's at 1.2 and 13 H's at 6.9–7.7.

Anal. Calcd for $C_{26}H_{22}O_2$: C, 85.21; H, 6.05. Found: C, 85.6; H, 6.1.

Yellow Quinone (36).—This compound was obtained several times in chromatographing the residues from the reaction of PhMgBr with the quinone **1a**. It crystallized from ethanol as soft, cottony, yellow needles melting at 204–205°. The ir spectrum showed carbonyl absorption at 1675 cm^{-1}. The nmr spectrum showed 9 H's at 1.4 and 13 H's at 6.8–8.3. These data suggest a *tert*-butyldiphenyl-1,4-naphthoquinone, but the percentages of carbon and hydrogen are too low.

Anal. Calcd for $C_{26}H_{22}O_2$: C, 85.21; H, 6.05, mol wt, 366. Calcd for $C_{26}H_{22}O_3$; C, 81.65; H, 5.8; mol wt, 382. Found: C, 81.6; H, 5.9; mol wt, 373 in bromoform.

Diacetate of 36 (37).—Compound **36** (1.5 g) was refluxed for 10 min with Zn powder (5 g), anhydrous NaOAc (1 g), and 15 ml of $(CH_3CO)_2O$. The clear, colorless solution was poured on ice and most of the acid neutralized with KOH, and the solution was extracted with ether. Evaporation of the solvent gave an oil which solidified when rubbed with petroleum ether. The white solid was crystallized from hexane and melted at 125–127°, yield 80%. Later this material changed to a form melting at 144–145°. The spectra and analyses were the same for both forms. The ir spectra showed carbonyl absorption at 1770 cm^{-1}. The nmr spectra showed 9 H's at 1.35, 3 H's at 1.95, 3 H's at 2.05, and 13 H's at 6.5–7.9.

Anal. Calcd for $C_{30}H_{28}O_4$: C, 79.6; H, 6.24; mol wt, 452. Calcd for $C_{30}H_{28}O_5$: C, 76.90; H, 6.02; mol wt, 468. Found: C, 76.6; H, 6.1; mol wt, 453 in benzene.

Registry No.—**1a**, 31592-22-0; **1b**, 10239-91-5; **2a**, 31592-24-2; **2b**, 31592-25-3; **3a**, 31592-26-4; **3b**, 31592-27-5; **4a**, 31592-28-6; **4b**, 31592-29-7; **5a**, 31592-30-0; **5b**, 31592-31-1; **6a**, 31592-32-2; **6b**, 31592-33-3; **7a**, 31592-34-4; **7b**, 31592-35-5; **8a**, 31592-36-6; **8b**, 31592-37-7; **9**, 31592-38-8; **10**, 31592-39-9; **11**, 31592-40-2; **12a**, 31592-41-3; **12b**, 31592-42-4; **13**, 33189-77-4; **14**, 33189-78-5; **15**, 31592-45-7; **16**, 31592-46-8; **17a**, 31592-47-9; **17b**, 31592-48-0; **18**, 31592-49-1; **19**, 31592-50-4; **20a**, 31592-51-5; **20b**, 31662-33-6; **21**, 31592-52-6; **22a**, 31592-53-7; **22b**, 31592-54-8; **23**, 31592-55-9; **24**, 31592-56-0; **25**, 31592-57-1; **26**, 31592-58-2; **27**, 31592-59-3; **28**, 31592-60-6; **29**, 31592-61-7; **30**, 31592-62-8; **31**, 31592-63-9; **32**, 31592-64-0; **33**, 31592-65-1; **34**, 31592-66-2; **35**, 31592-67-3; phenylmagnesium bromide, 100-58-3; phenyllithium, 591-51-5.

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Reaction of Nitriles with Hydrazine Hydrate and Raney Nickel[1]

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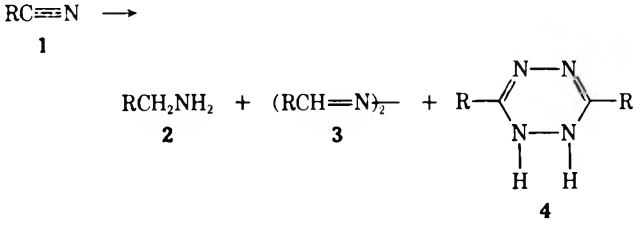
The reaction of ethanolic solutions of nitriles with hydrazine hydrate and catalytic amounts of Raney nickel was investigated as a possible general synthesis of aldehydes (isolated as the aldazines). The types of nitriles investigated were mono-, di-, and trisubstituted acetonitriles, carbocyclic nitriles, aromatic nitriles, α,β-unsaturated nitriles, and some heterocyclic nitriles. Depending upon the structure of the nitrile, it was found that either a primary amine, an aldazine, or a 3,6-disubstituted 1,2,4,5-tetrazine derivative was the major product. The reaction of α,β-unsaturated nitriles is further complicated by reactions of the double bond. Some experiments aimed at elucidating the reaction path were also performed. As a general aldehyde synthesis, the reaction appears to be limited to benzonitrile and substituted benzonitriles.

Hydrazine hydrate and Raney nickel are an effective combination for the reduction of aromatic nitro compounds to amines.[3] These same reagents have been employed by Pietra and Trinchera[4] for the partial reduction of 20 substituted benzonitriles to the corresponding aldazines which upon hydrolysis affords the corresponding aldehydes. We extended the hydrazine–Raney nickel reducing system to 2-(arylmethyl)benzonitriles and obtained aldazines which upon heating with acid give excellent yields of polynuclear aromatic hydrocarbons.[5] Terent'ev, *et al.*,[6] reported that phenylacetonitrile, 3-indoleacetonitrile, and 5-methoxy-2-methyl-1-benzyl-3-indoleacetonitrile are reduced to the primary amines with hydrazine and Raney nickel. In another investigation using these reducing agents, Dallacker[7] reported that the three isomeric cyanopyridines and 3,4-methylenedioxybenzonitrile yield the corresponding 3,6-disubstituted 1,2-dihydro-1,2,4,5-tetrazines. However, it was later reported by Butte and Case[8] that Raney nickel is not necessary for the formation of the tetrazines as had been reported by Dallacker.

In view of the results of the various studies, we undertook an examination of the effect of structure in determining the nature of the product from the reaction of nitriles with hydrazine hydrate and catalytic amounts of Raney nickel.



The results of the reactions of the 34 nitriles studied are tabulated in Table I.

Some nonkinetic methods of investigation were also used to study the course of the reduction of nitriles with hydrazine and Raney nickel. Preparatively, benzaldazine is obtained from benzonitrile by evaporation of the solvent from the reaction mixture followed by addition of aqueous acid to the residual oil. The oil was thought to be either the impure hydrazone or aldazine or a mixture of both. The ultraviolet spectrum of this oil (before acidification) was found to be consistent with that which would be obtained from a mixture of benzaldehyde hydrazone and benzaldazine. The presence of benzaldehyde hydrazone was confirmed by acidifying the oil, thus converting the hydrazone to benzaldazine, and this was observed spectroscopically. The presence of benzylamine (15%) and benzonitrile (a trace) was confirmed by vapor phase chromatograms of the reaction mixture both before and after conversion of the hydrazone to the aldazine.

Robinson and Brown[9] had found that hydrazine–Raney nickel effected the cleavage of N,N′-diacylated hydrazines to produce the corresponding amides. This suggested that the benzylamine found in the reaction

(1) This work was presented in part at the Second Middle Atlantic Regional Meeting of the American Chemical Society, New York, N. Y., Feb 1967.

(2) Abstracted in part from the M.S. theses of J. F. Siuda, 1964, M. J. Nolan, 1964, and T. M. Santosusso, 1966, Villanova University.

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TABLE I

YIELD OF PRODUCTS FROM THE REACTION OF NITRILES WITH HYDRAZINE HYDRATE AND RANEY NICKEL

No.	1, R	Registry no.	Product (yield, %)	No.	1, R	Registry no.	Product (yield, %)	Registry no.
1	$CH_3CH_2CH_2$–	109-74-0	**2** (75)	20	$C_6H_5(CH_3CH_2)_2C$–		*a*	
2	$C_6H_5CH_2$–	140-29-4	**2** (75)	21	$CH_3CH_2(C_6H_5)_2C$–		*a*	
3	4-C_6H_5-$C_6H_4CH_2$–	31603-77-7	**2** (75)	22	$(C_6H_5)_3C$–		*a*	
4	$C_6H_5CH_2CH_2$–	645-59-0	**2** (75)	23	CH_2=CHCN	107-13-1	*c*	
5	$C_6H_5CH_2CH_2CH_2$–	2046-18-6	**2** (75)	24	CH_3CH=CHCN	4786-20-3	*c*	
6	1-$C_{10}H_7CH_2$–	132-75-2	**2** (75)	25	C_6H_5CH=CHCN	4360-47-8	**3** (15)[c]	1568-11-2
7	$(CH_3)_2CH$–		*a*	26	*p*-HOC_6H_4—	767-00-0	**3** (74)	5466-23-9
8	$C_6H_5(CH_3)CH$–	1823-91-2	**2** (35)	27	*o*-NCC_6H_4–		*a*	
9	$C_6H_5(CH_3CH_2)CH$–	769-68-6	**2** (30)	28	*p*-NCC_6H_4–		*a*	
10	$(C_6H_5)_2CH$–	86-29-3	**2** (40), **3** (50)					
				29	2-(2′-Methylbenzyl)phenyl	782-13-8	**3** (98)	
11	9-Fluorenyl	1529-40-4	**2** (45), **3** (50)					
12	Cyclopropyl	5500-21-0	*b*	30	9-Phenanthryl	2510-55-6	**2** (66), **3** (10)	
13	3-Methylcyclobutyl	31603-86-8	**2** (5)[b]	31	2-Fluorenyl	2523-48-0	**2** (15)	
14	Cyclopentyl		*a*	32	2-Pyridyl	100-70-9	**4** (61)[d]	1671-86-9
15	Cyclohexyl		*a*	33	3-Pyridyl	100-54-9	**4** (70)[d]	31599-23-2
16	Cycloheptyl		*a*					
17	Bicyclo[2.2.1]heptyl	74-90-8	**2** (10)					
18	$(CH_3)_3C$–		*a*	34	4-Pyridyl	100-48-1	**4** (80)[d]	31599-25-4
19	$(CH_3CH_2)_3C$–		*a*					

[a] >95% of unreacted starting nitrile. [b] Products isolated from ring-opening reactions. [c] Products isolated from additions to the double bond. [d] Raney nickel is not necessary for this reaction; *cf.* ref 8.

mixture might arise as the result of reductive cleavage of benzaldazine or benzaldehyde hydrazone. In order to determine if this were the case, benzaldazine and benzaldehyde hydrazone were each allowed to react with hydrazine–Raney nickel under the reaction conditions. With benzaldazine, it was found that reductive cleavage did occur under these conditions, benzylamine being formed.

In should be noted that the conditions under which this cleavage occurred did not conform exactly to those found in the reduction of benzonitrile. In the cleavage reaction, there were relatively large concentrations of benzaldazine, hydrazine, and fresh Raney nickel simultaneously present, while, in the reduction of benzonitrile, is formed only after decomposition of the hydrazine has begun. Nevertheless, in the reduction of benzonitrile, some benzaldazine is present while hydrazine is undergoing decomposition, and, therefore, it seems likely that some reductive cleavage of the aldazine should occur.

Under the reaction conditions benzaldehyde hydrazone was converted to a mixture of benzaldazine and benzylamine. Because of the ease with which the hydrazone is converted to the aldazine by heat or moist air,[10] it could not be determined by a simple examination of products if the benzylamine found in the reaction mixture were formed directly from the hydrazone or indirectly through the aldazine or from both sources. Similar results were obtained in the investigation of the reaction of 9-cyanophenanthrene. As with benzaldazine, 9-phenanthrenecarboxaldazine underwent reductive cleavage to yield the corresponding amine under the reaction conditions. The extent of the reaction in this case was limited by the relative low solubility of the aldazine in the reaction mixture.

The final part of the investigation dealt with the reaction of benzonitrile with the separate components of the hydrazine–Raney nickel reducing system.

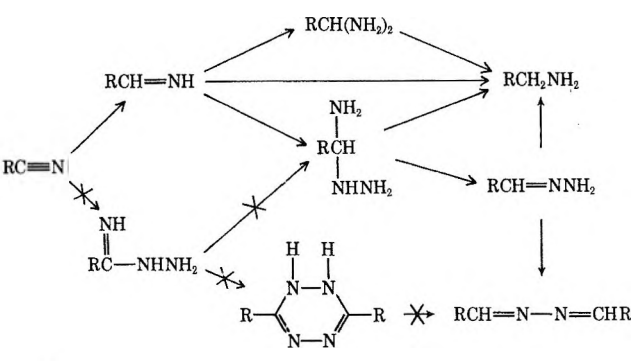
(10) G. Lock and K. Stach, *Chem. Ber.*, **76B**, 1252 (1943).

In all cases, benzonitrile remained unreacted. Hydrazine alone did not effect a reduction nor did Raney nickel alone, whether the active catalyst or the modified "reacted" catalyst was used, or whether the ammonia normally found in the reaction mixture was present or not. These results show that reduction of benzonitrile in this system can be accomplished only in the presence of active Raney nickel and excess decomposing hydrazine.

The formation of a hydrazone from an aromatic nitrile by initial nucleophilic attack of hydrazine to give the intermediate amidrazone (proposed by Pietra and Trinchera[4]) seems unlikely in view of the fact that under the usual reaction conditions hydrazine does not react with benzonitrile in the absence of Raney nickel. However, the cyanopyridines seem to exhibit a marked reactivity toward hydrazine, since these nitriles yield the corresponding 3,6-disubstituted 1,2-dihydro-1,2,4,5-tetrazines[7,8] presumably by initial formation of the amidrazone.[11]

The results of our investigation are consistent with a mechanism also proposed by Pietra and Trinchera[4] (Scheme I). In the presence of Raney nickel and de-

SCHEME I



(11) D. G. Nelson, R. Roger, J. W. M. Heatlie, and L. R. Newlands, *Chem. Rev.*, **70**, 151 (1970).

composing hydrazine, the nitrile is reduced to the aldimine. Addition of hydrazine to the aldimine followed by loss of ammonia yields the hydrazone. However, the present evidence indicates that this description of the course of the reaction should be extended to account for the formation of primary amine from the aldazine which need not be the only source of primary amine, since either direct reduction, as in catalytic hydrogenation, or addition of ammonia to the aldimine or hydrazone followed by reductive cleavage would also yield the primary amine. The relative importance of the different reactions as sources of the primary amine has yet to be determined. Furthermore, this reaction scheme also accounts for the fact that in those cases where primary amine is the major product, no secondary amine formed by reaction of the aldimine and primary amine is obtained.

$$RCH{=}NH + RCH_2NH_2 \longrightarrow$$

$$RCH(NH_2)NHCH_2R \xrightarrow{H_2} (RCH_2)_2NH + NH_3$$

In catalytic hydrogenation Schwoegler and Adkins[12] reported that the extent of the reaction between the primary amine and aldimine to form secondary amine could be diminished by conducting the hydrogenation in the presence of ammonia. Since it appears that the hydrazine hydrate reduction of nitriles may also proceed through the aldimine intermediate, the yield of pure primary amine by this method might then be explained as a result of preferential reaction of the ammonia produced by hydrazine decomposition with the aldimine.

One of the original intents of this investigation was to determine the reaction limitations as an aldehyde synthesis. From our results it is obvious that good yields of aldazine can be expected only with benzonitriles providing they do not contain strongly electron-withdrawing groups. It has also been demonstrated that the reaction is useful as a preparative method for converting monosubstituted acetonitriles to the corresponding primary amines.

Experimental Section

Elemental analyses were carried out by Alfred Bernhardt, Mülheim (Ruhr), Germany. Melting points were determined in capillaries in a Thomas–Hoover apparatus and are uncorrected. Infrared spectra were obtained using a Perkin-Elmer Model 337. Ultraviolet spectra were obtained using a Perkin-Elmer Model 202. Nmr spectra were determined on a Varian A-60 nmr spectrometer with tetramethylsilane as an internal standard. Gas chromatographic analyses were carried out on an F & M model 720 using a 6 × $^3/_8$ in. column packed with 5% 20M Carbowax–1% KOH on a Diatoport S support.

The Raney nickel used during this work was prepared by the method of Dominguez, Lopez, and Franco[13] and was periodically tested for activity by running the reaction with benzonitrile and 85% hydrazine hydrate in 95% ethanol.

All the nitriles used were commercially available except for the following, which were synthesized by published procedures: *cis*- and *trans*-3-methylcyclobutanecarbonitrile,[14] 9-cyanofluorene,[15] and 2-(2′-methylbenzyl)benzonitrile.[16]

9-Phenanthrenecarboxaldazine was prepared from 9-phenanthrenecarboxaldehyde and hydrazine hydrate as a yellow solid: mp 239–240° (benzene–ethanol); uv max (DMF) 352 and 366 nm; ir (KBr) 1625 cm^{-1} (C=N); nmr ($CDCl_3$) δ 7.6 (s, 1, -CH=N-).

Anal. Calcd for $C_{30}H_{20}N_2$: C, 88.21; H, 4.94; N, 6.85. Found: C, 88.47; H, 5.07; N, 6.45.

2-(2′-Methylbenzyl)benzaldazine was prepared in 98% yield from the reaction of 2-(2′-methylbenzyl)benzonitrile[16] with hydrazine hydrate and Raney nickel as yellow needles: mp 153–155° (benzene–95% ethanol); uv max (95% ethanol) 309 nm; ir (KBr) 1613 cm^{-1} (C=N); nmr ($CDCl_3$) δ 7.55 (s, 1, CH=N-).

Anal. Calcd for $C_{30}H_{28}N_2$: C, 86.49; H, 6.77; N, 6.73. Found: C, 86.93; H, 6.80; N, 6.44.

Reaction of Nitriles with Hydrazine Hydrate in the Presence of Raney Nickel.—Two general sets of reaction conditions were used in conjunction with several methods of separation, purification, and identification of products (Table II). After filtration to remove the Raney nickel the resulting solution was treated in one of the following ways.

TABLE II

	Method A	Method B
Nitrile	1–2 g	1–2 g
Solvent (95% ethanol)	15 ml	50 ml
Hydrazine hydrate (85%)	5 ml	48 ml
Raney nickel[13]	50 mg	0.50 g
Time of reaction	18 hr	7 hr
Temperature	50–55°	70–80°

(a) The solution was distilled and various fractions were subjected to vapor phase chromatographic analysis. If it was determined that only amine was present it was then isolated and characterized by spectroscopic methods as well as conversion to the benzoyl derivatives.

(b) After removal of volatile material by distillation under reduced pressure the residual oil was acidified with hydrochloric acid. Any solid material which precipitated was collected while the mother liquor was examined by vpc.

The solid residue was treated with dilute sodium hydroxide and then extracted under the ether. When the ether extract was analyzed by glpc and determined to have amine then the amine was isolated as the benzoyl derivative. Any solid aldazine residue was recrystallized and characterized by spectroscopic means and comparison with authentic samples.

Registry No.—Hydrazine hydrate, 7803-57-8; 9-phenanthrenecarboxaldazine, 31603-73-3; 2-(2′-methylbenzyl)benzaldazine, 31603-74-4.

Acknowledgment.—The authors wish to thank Dr. Aldan Josey, E. I. du Pont de Nemours and Co., Wilmington, Del., for the generous sample of 3-methylenecyclobutanecarbonitrile.

(12) E. J. Schwoegler and H. Adkins, *J. Amer. Chem. Soc.*, **61**, 3499 (1939).

(13) A. Dominguez, I. C. Lopez, and R. Franco, *J. Org. Chem.*, **26**, 1625 (1961).

(14) E. Gil-Av and J. Shabtal, *ibid.*, **29**, 257 (1964).

(15) W. Wislicenus and K. Russ, *Ber.*, **43**, 2719 (1910).

(16) F. A. Vingiello and J. G. van Oot, *J. Amer. Chem. Soc.*, **73**, 5070 (1951).

Synthesis and Reaction of α-Chlorostyryl Isocyanates[1]

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The reaction of arylacetonitriles, bearing at least two methyl groups on the 2 and 6 position of the benzene ring, *p*-nitrophenylacetonitrile, and α-chlorophenylacetonitrile with phosgene in the presence of hydrogen chloride was investigated. α-Chlorostyryl isocyanates thus obtained were isolated as urea derivatives in 5–48% yield. The pyrolysis and hydrolysis reaction of the ureas were also studied. On heating α-chloro-2,3,5,6-tetramethylstyryl isocyanate (**2a**) and α-chloro-2,3,4,5,6-pentamethylstyryl isocyanate (**2c**) with hydrogen chloride in acetonitrile at 100–105°, the demethylation reaction occurred to yield 3-chloro-5,6,8-trimethylisocarbostyril and 3-chloro-5,6,7,8-tetramethylisocarbostyril in 70 and 68% yield, respectively. In the reaction of α-chloro-*p*-nitrostyryl isocyanate (**2e**) with acetonitrile in the presence of hydrogen chloride at 55–60°, 6-chloro-2-(*p*-nitrobenzyl)-4(3*H*)-pyrimidone was formed in 22% yield.

In a preceding paper,[2] we reported the facile one-step synthesis of 1,3-dichloroisoquinoline derivatives by reacting arylacetonitriles with phosgene in the presence of hydrogen chloride and also clarified the formation of α-chlorostyryl isocyanate as an intermediate.

α,β-Unsaturated isocyanates have been synthesized by several methods; the Curtius rearrangement of acrylic acid azides,[3] reaction of ketimine with phosgene,[4] dehydrochlorination of polychloroalkyl isocyanates,[5] and elimination of ethanol from *N*-ethoxycarbonyl ketimines.[6] However, they are elaborative and require many steps.

In view of the proposed mechanism for isoquinoline formation,[2] it is speculated that some nitriles may react with phosgene in the presence of hydrogen chloride to give α,β-unsaturated isocyanates exclusively.

This paper deals with the reaction of phosgene with duryl-, isoduryl-, pentamethylphenyl-, and mesitylacetonitrile, which seem to be unable to yield isoquinolines, and then *p*-nitrophenylacetonitrile and α-chlorophenylacetonitrile, which are reluctant to cyclize owing to the presence of the electron-attracting group.[2] The reactions of isocyanates prepared with hydrogen chloride in acetonitrile are also discussed.

Results and Discussion

Synthesis of Isocyanates.—In a sealed glass tube, arylacetonitriles **1a–f** were allowed to react with phosgene in the presence of hydrogen chloride at 105–125° for 6 days. Isocyanates were obtained as isomeric mixtures of cis and trans. Nmr spectra of **2a**, **2c**, **2d**, and **2e** showed two olefinic proton signals (Table I), but assignments of these peaks to the cis and trans isomers were not made.

Isolation of pure isocyanates from reaction mixtures was difficult, because large amounts of unreacted nitriles were present. Thus, all the isocyanates were converted to phenylurea derivatives **3a–f** by reacting with aniline; the isolation yields as ureas were 5–48% (Scheme I).

The structure of **3** was determined on the basis of ir spectra and elemental analysis. The results are summarized in Table II.

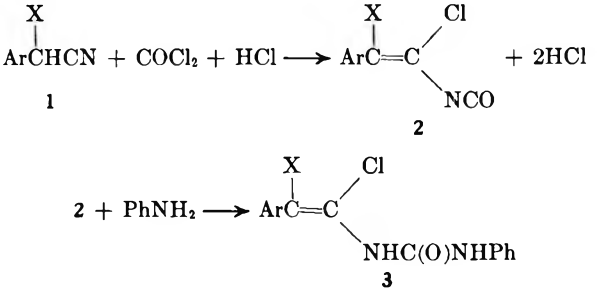
TABLE I

OLEFINIC PROTON SIGNALS OF ISOCYANATES

Compd[a]	Solvent	Chemical shift, τ (area ratio)
2a	CCl_4	3.76, 3.91 (4.7:1)
2c	$CDCl_3$	3.68, 3.84 (3.6:1)
2d	CCl_4	3.82, 3.96 (4.4:1)
2e	$CDCl_3$	3.54, 3.82 (1.1:1)

[a] The mixture of isocyanate and the starting nitrile was examined.

SCHEME I



a, Ar = duryl; X = H
b, Ar = isoduryl; X = H
c, Ar = pentamethylphenyl; X = H
d, Ar = mesityl; X = H
e, Ar = *p*-nitrophenyl; X = H
f, Ar = phenyl; X = Cl

Raw products of **3a–e** are very unstable and decompose gradually into the nitriles **1**, phenyl isocyanate, and hydrogen chloride at room temperature. After purification, **3a–c** were stable at room temperature, and no change in ir absorption bands was observed. **3d** and **3e**, however, were unstable even after purification. All of the ureas decomposed at their melting points even after purification.

The pyrolysis of **3a**, **3d** and **3e** at 80° for 15 min in acetonitrile indeed gave the nitrile **1**, phenyl isocyanate, and hydrogen chloride (Scheme II). Phenyl isocyanate was isolated as *sym*-diphenylurea in 73, 82, and 66% yield, respectively.

Thermal dissociation of symmetrically disubstituted ureas in aniline, alcohol, and fatty acid has been reported to form amines and isocyanates,[7] which further

(1) (a) The reaction of nitriles with phosgene series, part VI. (b) Part V: S. Yanagida, M. Yokoe, M. Ohoka, and S. Komori, *Bull. Chem. Soc. Jap.*, **44**, 2182 (1971).

(2) S. Yanagida, M. Ohoka, and S. Komori, *J. Org. Chem.*, **34**, 4127 (1969).

(3) P. A. S. Smith, *Org. React.*, **3**, 337 (1946).

(4) L. I. Samaraj, O. W. Wischnewskij, and G. I. Derkatsch, *Angew. Chem.*, **80**, 620 (1968).

(5) K. H. Koenig and H. Pommer, *Chem. Abstr.*, **59**, 454 (1963).

(6) J. Hoch, *C. R. Acad. Sci.*, **201**, 773 (1935); *Chem. Abstr.*, **30**, 1362 (1936).

(7) (a) T. L. Davis and K. C. Blanchard, *J. Amer. Chem. Soc.*, **45**, 1816 (1923); (b) T. Hoshino, T. Mukaiyama, and H. Hoshino, *ibid.*, **74**, 3094 (1952); (c) T. Hoshino, T. Mukaiyama, and H. Hoshino, *Bull. Chem. Soc. Jap.*, **25**, 392 (1952); (d) T. Mukaiyama, *ibid.*, **28**, 253 (1955); (e) T. Mukaiyama and Y. Fujita, *ibid.*, **29**, 54 (1956).

Table II

Synthesis of α-Chlorostyryl Isocyanates and Isolation as Urea Derivatives

Urea	Amounts of reactants, mmol: Nitrile	$COCl_2$	HCl	Aniline	Yield,[a] %	Mp,[b] °C	$\nu_{C=O}$ (Nujol), cm^{-1}	Found, % (calcd, %)
3a[c]	15	94	20	13	48	139	1647	C, 69.65 (69.40) H, 6.08 (6.44) N, 8.66 (8.52)
3b[d]	7.5	45	8	4	36	124–125.5	1643	C, 69.72 (69.40) H, 6.24 (6.44) N, 8.68 (8.52)
3c[e]	7.5	44	8	5	48	134–136	1642	C, 69.79 (70.06) H, 6.66 (6.76) N, 7.85 (8.17)
3d	15	92	19	9	33	101.5[g]	1645	Cl, 11.2[h] (11.26)
3e	15	154	0[f]	9	43	106–108[g]	1645	Cl, 11.5[h] (11.16)
3f[c]	10	88	8	3	5	182–185	1647	C, 58.78 (58.65) H, 4.12 (3.94) N, 9.24 (9.12)

[a] Based on the nitrile used. [b] All of the ureas decomposed at their melting points. [c] Recrystallized from THF–CH_3CN (3:1, v/v). [d] Recrystallized from THF–CH_3CN (1:4, v/v). [e] Recrystallized from THF–CH_3CN (1:1, v/v). [f] MeOH (1 ml) was added to evolve HCl. [g] Melting point of raw product. [h] Raw product was analyzed.

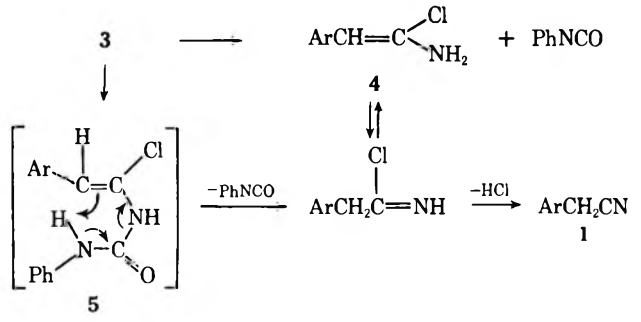
Table III

Preparation of Acylureas by Hydrolysis of 3

Acylurea	Yield, %	Mp, °C	$\nu_{C=O}$ (KBr), cm^{-1}	Nmr[a] (methylene proton), τ	Found, % (calcd, %)
6a[b]	87	228–230	1715	6.13	C, 73.41 (73.52) H, 7.17 (7.14) N, 9.05 (9.03)
6b[b]	91	196–201	1716[d]	6.19	C, 73.78 (73.52) H, 7.13 (7.14) N, 9.14 (9.03)
6c[b]	94	216–218	1719[d]	6.15	C, 73.73 (74.04) H, 7.39 (7.46) N, 8.88 (8.64)
6d[b]	73	193–196	1715	6.24	C, 72.84 (72.95) H, 6.59 (6.80) N, 9.37 (9.45)
6e[c]	78	219.5–223[e]	1710	6.08	C, 60.14 (60.20) H, 4.11 (4.38) N, 13.97 (14.04)
6f[b]	82	205–211	1702		C, 62.47 (62.40) H, 4.39 (4.54) N, 9.77 (9.70)

[a] DMSO-d_6 was used as solvent. [b] Recrystallized from CH_3CN. [c] Recrystallized from DMSO–CH_3CN (6:1, v/v). [d] Nujol. [e] Mp 235°: S. Basterfield and M. E. Greig, *Can. J. Res.*, **8**, 450 (1933); *Chem. Abstr.*, **27**, 4223 (1933).

Scheme II



react with the solvents used to give ureas, urethanes, and N-substituted carboxamides, respectively. Based

$$RNHCNHR \rightleftharpoons RNCO + RNH_2$$

on this fact, the pyrolysis of **3** is possible to proceed *via* α-chloroenamine **4**. An alternative mechanism including cyclic intermediate **5** is also possible. The cyclic intermediate similar to **5**, for example, has been reported in the pyrolysis of ethyl vinyl ether to ethylene and acetaldehyde.[8]

3a–f were also identified by hydrolyzing them to acylureas **6a–f** in dimethyl sulfoxide at room temperature (Table III).

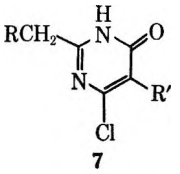
$$3 \xrightarrow{H_2O\text{–DMSO}} ArCH(X)C(=O)NHC(=O)NHPh \quad (6)$$

Reaction of Isocyanates.—In this investigation the pyrimidone **7** (R = R′ = Ar), expected to form in view of the previous work,[2,9] was not isolated. We have found that *N*-(α-chlorobenzylidene)carbamoyl chloride (**8**) reacts with alkyl cyanide in the presence of hydro-

(8) A. T. Blades and G. W. Murphy, *J. Amer. Chem. Soc.*, **74**, 1039 (1952).

(9) (a) S. Yanagida, M. Ohoka, M. Okahara, and S. Komori, *Tetrahedron Lett.*, 2351 (1968); (b) S. Yanagida, M. Ohoka, M. Okahara, and S. Komori, *J. Org. Chem.*, **34**, 2972 (1969).

gen chloride to give the pyrimidone **9** and the pyrimidine **10**.[1b]



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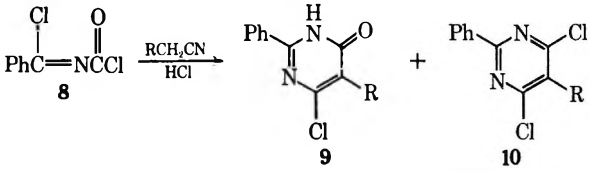
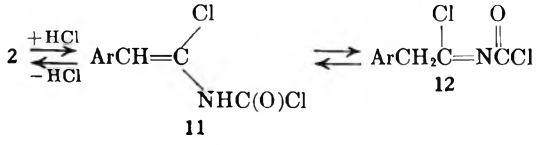


8 **9** **10**

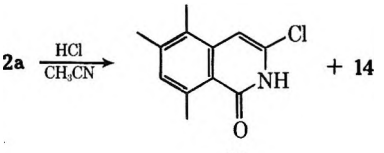
In the presence of hydrogen chloride, the isocyanate **2** is considered to be in equilibrium with **11** and **12**. The structure of **12** is analogous to that of **8**. Thus



11 **12**

expecting the formation of the pyrimidone **7** (R = Ar; R′ = H), the reaction of **2** with acetonitrile in the presence of hydrogen chloride was attempted. In this investigation, the isocyanates **2** containing the starting nitriles were allowed to react with acetonitrile and hydrogen chloride.

On heating **2a** with acetonitrile and hydrogen chloride in a sealed glass tube at 100–105° for 110 hr, the expected pyrimidone **7** (R = duryl; R′ = H) was not obtained, but unexpectedly the demethylation reaction occurred to give 70% yield of 3-chloro-5,6,8-trimethylisocarbostyril (**13**) and a small amount of 1,3-dichloro-5,6,8-trimethylisoquinoline (**14**) (7%). The structure of **13** was confirmed on the basis of microanalysis and spectral properties, and moreover by converting it to **14**. The reaction at 55–60° for 93 hr gave a 9% yield of **13** and 26% of unreacted **2a** was recovered.



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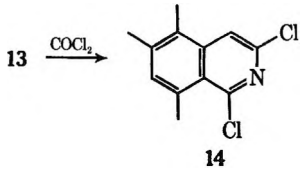

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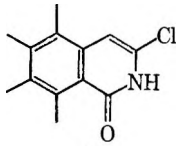
Treatment of **2c** with hydrogen chloride at 100–105° for 70 hr yielded 3-chloro-5,6,7,8-tetramethylisocarbostyril (**15**) (68%) and 1,3-dichloro-5,6,7,8-tetramethylisoquinoline (**16**) (13%).



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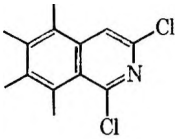
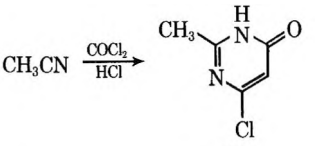


16

From **2b**, trace amounts of isocarbostyril and 6-chloro-2-methyl-4(3*H*)-pyrimidone (**17**), and moreover dichloroisoquinolines **18** (7.6%) and **19** (0.8%), were isolated.



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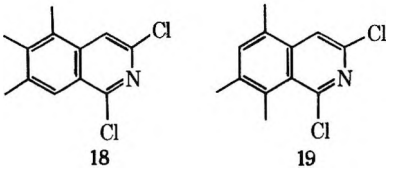
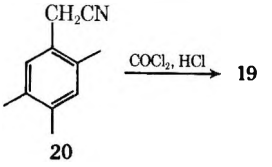


18 **19**

The structure of **19** was confirmed by comparing its ir spectrum with that of an authentic sample, prepared from 2,4,5-trimethylphenylacetonitrile (**20**),[2] and the mixture melting point showed no depression.



20

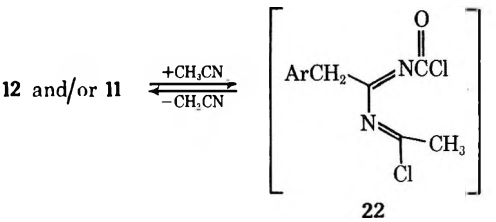
From **2d**, neither pyrimidone **7** (R = mesityl; R′ = H) nor isocarbostyril was isolated, but 1,3-dichloro-5,7-dimethylisoquinoline (**21**) (8%) and a trace amount of **17** were obtained, and **2d** was not recovered.

In view of the previous papers,[9] **17** was evidently formed by the reaction of acetonitrile with hydrogen chloride and phosgene, formed by decomposition of the carbamoyl chloride (**11** and/or **12**).

Dichloroisoquinoline derivatives (**14**, **16**, **18**, **19**, and **21**) were formed by the reaction of phosgene with the corresponding isocarbostyrils; they might be formed in part during the preparation of **2**. In fact, a small amount of **14** (1.4%) was isolated from the filtrate of **3a** by chromatography over alumina.

On heating **2e** with acetonitrile and hydrogen chloride at 100–105° for 140 hr, a trace amount of 3-chloro-7-nitroisocarbostyril was isolated. On the other hand, treatment of **2e** with acetonitrile and hydrogen chloride at 55–60° for 7 days afforded the expected 6-chloro-2-(*p*-nitrobenzyl)-4(3*H*)-pyrimidone (**7**, R = *p*-nitrobenzyl; R′ = H) in 22% yield.

This suggests that at higher temperature the intermediate **22** for pyrimidone formation is unstable. The



22

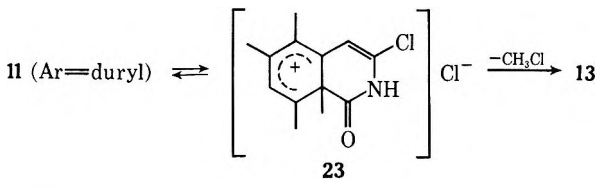
failure of **2a** to form the expected pyrimidone even at 55–60° is probably due to the steric hindrance of two methyl groups on the 2 and 6 position of the benzene ring in the step of forming **22** (Ar = duryl).

As mentioned above, in cases of **2a** and **2c**, the dramatic increase in the yield of isocarbostyrils was ob-

served. This is ascribed to higher electron density at the ortho position in **2a** and **2c** than in **2b**, **2d**, and **2e**.

Isocarbostyrils are probably formed *via* σ complex **23** followed by elimination of methyl chloride, the formation of which was confirmed by glpc analysis of gaseous product.

An analogous σ complex has been suggested by Olah and Kuhn[10] as an intermediate for dealkylating nitration of polyalkylbenzenes. To our knowledge, such a



23

demethylation reaction in the absence of Lewis acid catalyst has not been reported.

Experimental Section

Melting points were determined on a Yanagimoto micro melting point apparatus and were corrected. The nmr spectra were obtained using a Model JNM-G-60 spectrometer (Japan Electronic Optics Laboratory, Co.) with tetramethylsilane as an internal reference. The ir spectra were recorded with a Japan Electroscopic IR-E spectrophotometer. The mass spectra were recorded with a Hitachi mass spectrometer, Model RMU-6E.

Preparation of Isocyanates 2 and Isolation as Ureas 3. General Procedure.—The amounts of reactants are listed in Table II. The nitrile **1** and chlorobenzene (5 ml) were placed in a 100-ml glass tube, and dry hydrogen chloride was allowed to be absorbed in the mixture. A chlorobenzene–phosgene solution (7 ml of chlorobenzene) was then added and the glass tube was stoppered, cooled in Dry Ice–acetone, and sealed. The sealed glass tube was heated at 105–125° in an oil bath for 6 days. After heating, the sealed glass tube was chilled in Dry Ice–acetone and opened carefully. After purging HCl and phosgene from the reaction mixture, chlorobenzene was removed *in vacuo*. The residue was dissolved in benzene (15 ml) and treated with aniline under cooling to form a white precipitate of **3**, which was filtered, washed with a small portion of benzene, dried *in vacuo*, recrystallized, and analyzed. The results are summarized in Table II. In cases of **1b** and **1c**, the reaction was carried out in a 50-ml sealed glass tube.

In the case of **1e**, instead of dissolving HCl, MeOH (1 ml) was added to the mixture of **1e**, phosgene, and chlorobenzene (12 ml) to evolve HCl, because the solubility of HCl in the nitrile–chlorobenzene mixture was very low.

Hydrolysis of Ureas 3.—A typical procedure is as follows. To a solution of 131 mg (0.34 mmol) of **3a** in DMSO (4 ml) was added 0.4 ml of water. The mixture was allowed to stand for 5 days at room temperature. To the reaction mixture was added 5 ml of water to form a white precipitate, which was filtered and dried *in vacuo* to give 107 mg (87%) of **6a**. The results are summarized in Table III.

Pyrolysis of 3.—A typical procedure is described. The suspension of 92 mg (0.24 mmol) of **3a** in 5 ml of acetonitrile was heated at 80° for 15 min on a water bath. To the resulting solution was added 71 mg (0.76 mmol) of aniline in 0.5 ml of acetonitrile at room temperature and the solvent was evaporated *in vacuo*. The residual solid was suspended in benzene, filtered, washed with water to remove aniline hydrochloride, and dried to give 43 mg (73%) of *sym*-diphenylurea.

Reaction of 2a with Acetonitrile and HCl at 100–105°.—In a 20-ml sealed glass tube, 0.9 g of the mixture of **2a** and **1a** (the content of **2a** is *ca.* 0.43 g), acetonitrile (3 ml), and HCl (0.65 g) were heated at 100–105° for 110 hr. After purging HCl, the precipitate formed was filtered, washed with a small portion of acetonitrile, and dried *in vacuo* to yield 286 mg (70%) of **13**. Recrystallization from THF–CH_3CN (3:1, v/v) gave colorless fine needles: mp 259–262°; ir (KBr) 1635 cm^{-1} (C=O); nmr (CF_3COOH) τ 2.49 (s, 1 H), 2.59 (s, 1 H), 7.14 (s, 3 H), 7.44 (s, 3 H), and 7.47 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 223 (34, $M^+ + 2$), 221 (100, M^+), 186 (45), 185 (43), 157 (19), 131 (38), and 115 (24).

Anal. Calcd for $C_{12}H_{12}NOCl$: C, 65.01; H, 5.46; N, 6.32. Found: C, 64.96; H, 5.34; N, 6.30.

Acetonitrile was evaporated from the filtrate and the residue was chromatographed over alumina. The elutions with petroleum ether gave 30 mg of **14** (7%), but the expected pyrimidone **7** (R = duryl; R′ = H) was not obtained.

Chlorination of 13 with Phosgene.—**13** (123 mg, 0.56 mmol) and chlorobenzene (3 ml) were placed in a 20-ml glass tube and 1.5 g of phosgene was allowed to be absorbed. After sealing the glass tube, it was heated at 100–105° for 40 hr. The reaction mixture was evaporated to dryness to yield a tan crystalline residue, which was sublimed under reduced pressure to give 101 mg (76%) of **14** as colorless needles: mp 115–117°; ir (KBr) 1560 (ring), 1290, and 838 cm^{-1}; nmr ($CDCl_3$) τ 3.39 (s, 1 H), 2.86 (s, 1 H), 7.14 (s, 3 H), and 7.60 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 241 (66, $M^+ + 2$), 239 (100, M^+), 224 (48, $M^+ - CH_3$) and 158 (36).

Anal. Calcd for $C_{12}H_{11}NCl_2$: C, 60.02; H, 4.62; N, 5.83. Found: C, 60.21; H, 4.84; N, 5.86.

Reaction of 2a with Acetonitrile and HCl at 55–60°.—The mixture of **2a** and **1a** (0.7 g, the content of **2a** is *ca.* 0.33 g), acetonitrile (3 g), and HCl (0.4 g) were heated in a 20-ml sealed glass tube at 55–60° for 93 hr. The precipitate formed was filtered, washed with acetonitrile, and dried to give 27 mg (9%) of **13**. The filtrate was concentrated, and to the residue (CH_3CN solution) was added 0.2 g of aniline to yield a yellow precipitate of **3a** (0.12 g, 26%).

Reaction of 2c with Acetonitrile and HCl.—In a 20-ml sealed glass tube, 1.7 g of the mixture of **2c** and **1c** (the content of **2c** is *ca.* 0.93 g), CH_3CN (3 g), and HCl (0.6 g) were heated at 100–105° for 70 hr. The precipitate formed was filtered, washed with a small portion of CH_3CN, and dried to yield 0.60 g (68%) of **15**, which was sublimed under reduced pressure to give white powder: mp 300–303°; ir (Nujol) 1635 cm^{-1} (C=O); nmr (CF_3COOH) τ 2.46 (s, 1 H), 7.13 (s, 3 H), 7.43 (s, 6 H), and 7.50 (s, 3 H).

Anal. Calcd for $C_{13}H_{14}NOCl$: C, 66.24; H, 5.99; N, 5.94. Found: C, 66.02; H, 5.94; N, 5.85.

The filtrate was concentrated and chromatographed over alumina. The elutions with petroleum ether gave **16** (0.12 g, 13%), which was sublimed under reduced pressure to give colorless needles: mp 117–118.5°; nmr ($CDCl_3$) τ 2.41 (s, 1 H), 7.24 (s, 3 H), 7.55 (s, 3 H), and 7.63 (s, 6 H).

Anal. Calcd for $C_{13}H_{13}NCl_2$: C, 61.43; H, 5.16; N, 5.51. Found: C, 61.42; H, 5.01; N, 5.58.

Reaction of 2b with Acetonitrile and HCl.—In a 20-ml sealed glass tube, 1.65 g of the mixture of **2b** and **1b** (the content of **2b** is *ca.* 0.62 g), CH_3CN (3.5 g), and HCl (0.8 g) were heated at 100–105° for 110 hr. The precipitate formed was filtered, dried, and sublimed under reduced pressure to yield 10 mg of **17**, which was identified by comparing its ir spectrum with that of an authentic sample.[9] The filtrate was concentrated and a small portion of benzene was added, and the benzene-insoluble material was filtered, washed with acetone and water, dried, and sublimed under reduced pressure to give 8 mg of isocarbostyril: mp 280–288°; ir (KBr) 1630 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 223 (36, $M^+ + 2$), 221 (100, M^+), and 186 (28).

Anal. Calcd for $C_{12}H_{12}NOCl$: C, 65.01; H, 5.46; N, 6.32. Found: C, 65.03; H, 5.42; N, 6.31.

The benzene-soluble material was chromatographed over alumina. The elutions with petroleum ether gave **19** (7 mg, 0.8%), and further elutions with petroleum ether gave **18** (65 mg, 7.6%). **19** was sublimed under reduced pressure to give colorless needles: mp 146.5–150°; mass spectrum (70 eV) *m/e* (rel intensity) 241 (64, $M^+ + 2$), 239 (100, M^+), and 224 (57).

Anal. Calcd for $C_{12}H_{11}NCl_2$: C, 60.02; H, 4.62; N, 5.83. Found: C, 60.33; H, 4.57; N, 5.71.

18 was recrystallized twice from acetone to give colorless needles: mp 167–175°; nmr ($CDCl_3$) τ 2.20 (s, 1 H), 2.36 (s, 1 H), 7.55 (s, 6 H), and 7.62 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 241 (66, $M^+ + 2$), 239 (100, M^+), and 224 (70).

Anal. Calcd for $C_{12}H_{11}NCl_2$: C, 60.02; H, 4.62; N, 5.83. Found: C, 59.79; H, 4.62; N, 6.06.

Preparation of the Authentic Sample of 19.—In a 150-ml sealed glass tube, the mixture of **20**, HCl (1.0 g), $COCl_2$ (4.2 g), and chlorobenzene (11 ml) was heated at 100–105° for 93 hr. After

(10) G. A. Olah and S. J. Kuhn, *J. Amer. Chem. Soc.*, **86**, 1067 (1964).

purging unreacted $COCl_2$ and HCl, the reaction mixture was cooled in Dry Ice–acetone, and the precipitate formed was filtered, washed with a small portion of CCl_4, and dried *in vacuo* to give 2.6 g (51%, based on $COCl_2$) of **19**, which was recrystallized twice from acetone to give pale yellow plates: mp 151–153°; nmr ($CDCl_3$) τ 2.44 (s, 1 H), 2.72 (s, 1 H), 7.22 (s, 3 H), 7.52 (s, 3 H), and 7.61 (s, 3 H).

Anal. Calcd for $C_{12}H_{11}NCl_2$: C, 60.02; H, 4.62; N, 5.83. Found: C, 59.88; H, 4.57; N, 5.68.

Reaction of 2d with CH_3CN and HCl.—In a 20-ml sealed glass tube, 0.8 g of the mixture of **2d** and **1d** (the content of **2d** is *ca.* 0.31 g), CH_3CN (3 g), and HCl (0.5 g) were heated at 100–105° for 5 days. The precipitate formed was filtered, washed with CH_3CN, dried *in vacuo*, and sublimed under reduced pressure to give 7 mg of **17**. The filtrate was concentrated and chromatographed over alumina. Petroleum ether eluted 25 mg of **21** (8%): mp 111–117°; mass spectrum (70 eV) *m/e* (rel intensity) 227 (66, $M^+ + 2$), 225 (100, M^+), 210 (43), 190 (36), 154 (32), and 127 (26).

Reaction of 2e with CH_3CN and HCl at 100–105°.—In a 20-ml sealed glass tube 0.5 g of the mixture of **2e** and **1e** (the content of **2e** is *ca.* 0.28 g), CH_3CN (4 g), and HCl (0.4 g) were heated at 100–105° for 140 hr. From the reaction mixture 6 mg of brown powder was isolated by filtration. It was sublimed under reduced pressure to give the yellow powder of 3-chloro-7-nitroisocarbostyril: mp above 300°; ir (KBr) 1675 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 226 (29, $M^+ + 2$), 224 (85, M^+), 194 (93), 178 (40), 150 (51), 130 (100), 123 (49), and 114 (65).

Reaction of 2e with CH_3CN and HCl at 55–60°.—In a 20-ml sealed glass tube 0.67 g of the mixture of **2e** and **1e** (the content of **2e** is *ca.* 0.37 g), CH_3CN (4 g), and HCl (0.5 g) were heated at 55–60° for 7 days. The precipitate formed was filtered, washed with CH_3CN, and dried *in vacuo* to give brown powder of 6-chloro-2-(*p*-nitrobenzyl)-4(3*H*)-pyrimidone (81 mg, 22%), which was recrystallized from CH_3CN to give yellow plates: mp 250–259° dec; ir (KBr) 1675 cm^{-1} (C=O); nmr (CF_3COOH) τ doublets centered at 1.65 (2 H) and 2.35 (2 H, A_2B_2 system), 3.10 (s, 1 H), and 5.47 (s, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 267 (26, $M^+ + 2$), 265 (70, M^+), 264 (100), 116 (68), 106 (50), 89 (92), 68 (78), and 63 (50).

Anal. Calcd for $C_{11}H_8N_3O_3Cl$: C, 49.73; H, 3.04; N, 15.82. Found: C, 49.79; H, 2.77; N, 16.01.

Registry No.—**2a**, 31579-10-9; **2c**, 31579-11-0; **2d**, 31579-12-1; **2e**, 31579-13-2; **3a**, 31579-14-3; **3b**, 31579-15-4; **3c**, 31579-16-5; **3d**, 31579-17-6; **3e**, 31579-18-7; **3f**, 31579-19-8; **6a**, 31579-20-1; **6b**, 31579-21-2; **6c**, 31579-22-3; **6d**, 31579-23-4; **6e**, 31579-24-5; **6f**, 31579-25-6; **13**, 31579-26-7; **14**, 31579-27-8; **15**, 31579-28-9; **16**, 31579-29-0; **18**, 31579-30-3; **19**, 31579-31-4; **21**, 31579-32-5; isocarbostyryl, 31579-33-6; 3-chloro-7-nitroisocarbostyryl, 24633-93-0; 6-chloro-2-(*p*-nitrobenzyl)-4(3*H*)-pyrimidone, 31579-35-8.

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A Novel Reaction of Acetylsulfenyl Chloride with Activated Aromatic Compounds

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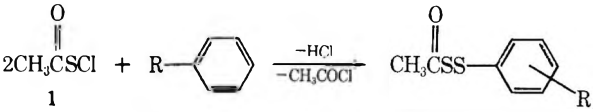
A novel aromatic sulfuration reaction is described. The reaction of acetylsulfenyl chloride with activated aromatic compounds such as anisole, *m*-xylene, toluene, and phenol yields acetyl aryl disulfides. A mechanism involving a tetravalent sulfur intermediate is proposed.

Preceding papers on aromatic sulfurations have shown that a catalytic amount of iron powder promotes the reaction of aromatics with the compounds containing bivalent sulfur–chlorine bonds. The reactions with sulfur chlorides[1] and sulfenyl chlorides[2] yield symmetric sulfides and asymmetric sulfides, respectively. On the other hand, benzenethiosulfenyl chlorides give disulfide or monosulfide depending on whether or not they have an ortho group.[3]

With a view to extending the scope of the aromatic sulfuration reaction, our attention was attracted to acetylsulfenyl chloride (**1**) which also has a sulfur–chlorine bond. **1** was first synthesized by Böhme and Clement,[4] and since then there have been several reports on the chemical behavior of **1**. However, previous works have dealt almost entirely with the reaction between **1** and such functional groups as active hydrogen[4–6] and olefinic double bonds.[7,8] The only example involving the reaction of **1** with aromatic compounds is the one with phenols[9] (*vide infra*).

In the present paper a novel reaction of **1** with activated aromatic compounds is described, which results in the formation of acetyl aryl disulfide (**2**). To



2a, R = 4-CH_3O
b, R = 2,4-di-CH_3
c, R = 2-CH_3
d, R = 4-CH_3
e, R = 4-HO

our knowledge this is the first example of asymmetric disulfide formation in aromatic sulfuration with sulfenyl halides.

A methylene chloride solution of a 1:1 mixture of acetylsulfenyl chloride (**1**) and anisole was stirred for 40 hr at room temperature and then refluxed for 2 hr. The main product was acetyl *p*-anisyl disulfide (**2a**) instead of acetyl *p*-anisyl sulfide, the product expected on the basis of analogy with previous studies. Confirmation of structure **2a** was obtained from ele-

(1) T. Fujisawa, N. Ohtsuka, T. Kobori, and G. Tsuchihashi, *Tetrahedron Lett.*, 4533 (1968).
(2) T. Fujisawa, T. Kobori, N. Ohtsuka, and G. Tsuchihashi, *ibid.*, 5071 (1968).
(3) T. Fujisawa, T. Kobori, and G. Tsuchihashi, *ibid.*, 4291 (1969).
(4) H. Böhme and M. Clement, *Justus Liebigs Ann. Chem.*, **576**, 61 (1952).
(5) H. Böhme and G. Zinner, *ibid.*, **585**, 142 (1954).
(6) H. Böhme, F. Freimuth, and E. Mundlos, *Chem. Ber.*, **87**, 1661 (1954).
(7) H. Böhme, H. Bezzenberger, and H. D. Stachel, *Justus Liebigs Ann. Chem.*, **602**, 1 (1957).
(8) S. Z. Ivin and V. K. Promonenkov, *Otd. Obshch. Tekh. Khim.*, 139 (1967); *Chem. Abstr.*, **68**, 114701p (1968).
(9) H. Böhme and H. W. Goubeaud, *Chem. Ber.*, **92**, 366 (1959).

mental analysis and ir, nmr, and mass spectra in addition to independent synthesis from **1** and *p*-methoxythiophenol. Di-*p*-anisyl sulfide and di-*p*-anisyl disulfide were obtained simultaneously as by-products. When acetonitrile was employed as the reaction medium, a somewhat higher yield of **2a** resulted.

Compared to aromatic sulfurations with sulfur chlorides[1] and common sulfenyl chlorides,[2] this reaction was less affected by catalysts. As shown in Table I, aluminum chloride and concentrated sulfuric

TABLE I

REACTION OF ACETYLSULFENYL CHLORIDE (1) WITH ANISOLE[a]

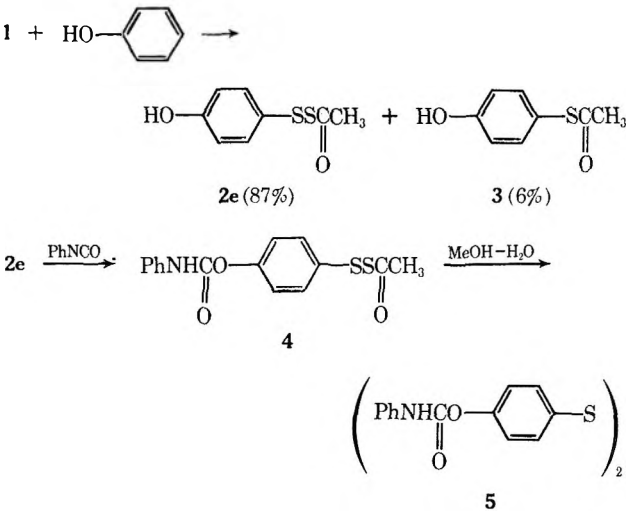
Catalyst	Medium	Product[b] yield, %[c]				
		AcAn	AcSAn	AcSSAn	AnSAn	AnSSAn
	CH_2Cl_2	0	0	61	2	9
	CH_3CN	0	0	75	2	13
$AlCl_3$	CH_2Cl_2	0	0	74	3	2
H_2SO_4	CH_2Cl_2	0	0	70	4	8
Fe	CH_2Cl_2	6	6	66	3	15
$FeCl_3$	CH_2Cl_2	7	4	45	2	25

[a] Reaction conditions: 1:anisole = 1:1; 25° (40 hr), reflux (2 hr). [b] Ac = CH_3CO–, An = *p*-$CH_3OC_6H_4$–. [c] Based on 1.

acid did not catalyze the reaction. Iron powder and ferric chloride, which are known to be effective catalysts in aromatic sulfuration, only promoted the side reactions, *i.e.*, the formation of *p*-methoxyacetophenone[10] and acetyl *p*-anisyl sulfide.

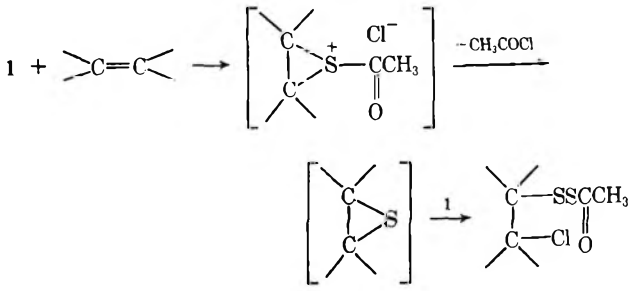
Other activated aromatic compounds also underwent a similar reaction. When a *m*-xylene solution of **1** was gradually heated up to 125° in 12 hr, acetyl 2,4-xylyl disulfide (**2b**) was obtained in 49% yield. Acetyl tolyl disulfide was obtained as a mixture of the ortho isomer **2c** and the para isomer **2d** in 26% combined yield by heating a toluene solution of **1** in the presence of iron powder. Benzene did not give any identifiable product under more drastic conditions. The properties of **2** thus obtained are summarized in Table II. The ir spectrum of **2** contains two characteristic bands in the region 1735–1700 cm^{-1}, assignable to a carbonyl group. In addition, two other absorption frequencies are observed, one at ~1105 cm^{-1} and the other at ~935 cm^{-1}. These bands would generally be assigned to a –C–C(O)– stretch and a –C(O)–S– stretch, respectively from analogy with the case of thiol esters.[11] The nmr chemical shifts of the protons ortho to the sulfur atom of **2** are observed at lower field than those of the corresponding acetyl aryl sulfide. A similar effect of the polysulfide linkage has already been observed for aryl polysulfides.[12]

The literature contains only one reference to the reaction of **1** with aromatic compounds (*vide supra*). It has been reported that the reaction product of **1** and phenol was acetyl 4-hydroxyphenyl sulfide (**3**).[9] In view of our results mentioned above, however, it would be reasonable to expect the formation of acetyl 4-hydroxyphenyl disulfide (**2e**) in the reaction of **1** with phenol. Accordingly, we reinvestigated the reaction. As will now be seen, this prediction is amply fulfilled. An ether solution of **1** and excess phenol was stirred at room temperature for 40 hr, then refluxed for 5 hr. An oily material was obtained by removal of the solvent and excess phenol. The nmr spectrum of the oil contains two AB quartets. Signals consistent with **2e** [δ 6.71 (d, J = 9.0 Hz), 7.39 (d, J = 9.0 Hz)] indicate its presence in this crude product, and the other AB quartet [δ 6.71 (d, J = 9.0 Hz), 7.15 (d, J = 9.0 Hz)] is consistent with structure **3**. In addition, the mass spectrum of the oil supports the presence of **2e** (*m/e* 200) and **3** (*m/e* 168). The yields of **2e** and **3** were estimated as 87 and 6%, respectively, from the nmr integral ratio. Subsequent treatment of the crude product with phenyl isocyanate in the presence of a catalytic amount of aluminum chloride gave the urethane derivative of **2e**, 4-acetyldithiophenyl phenylcarbamate (**4**). The physical properties of **4** are also listed in Table II. **4** was rather unstable and decomposed to a symmetric disulfide (**5**) when boiled in methanol–water. Consequently, it is concluded that aromatic sulfuration by



1 leads predominantly to the formation of acetyl aryl disulfides.

Concerning the reaction of **1**, another case of disulfide formation has been found in the reaction with olefins.[7,8,13] Böhme and coworkers proposed a mechanism in which ethylene sulfide was suggested as a possible intermediate.[7] It seems that both reactions, aromatic substitution by **1** and addition of **1** to olefins,



ought to proceed by a similar mechanism, since they are electrophilic reactions. In the former case, how-

(10) Control experiments proved that the formation of *p*-methoxyacetophenone can be ascribed to the reaction of anisole with acetyl chloride, which may be formed during the reaction of **1** with anisole, in the presence of iron powder or ferric chloride.

(11) R. A. Nyquist and W. J. Potes, *Spectrochim. Acta*, **7**, 514 (1959).

(12) T. Fujisawa and G. Tsuchihashi, *Bull. Chem. Soc. Jap.*, **43**, 3615 (1970).

(13) Chlorocarbonylsulfenyl chloride also adds to olefins in a molar ratio of 2:1 to form 2-chloroalkyl chlorocarbonyl disulfides with elimination of phosgene: G. Zumach and E. Kühle, *Angew. Chem., Int. Ed. Engl.*, **9**, 54 (1970).

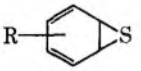
TABLE II
PROPERTIES OF ACETYL ARYL DISULFIDES (2)

CH_3COSS—C$_6$H$_4$—R

	R	Bp, °C (mm)	ν_{max}, cm^{-1} C=O	-C-C<	>C-S-	Nmr (in CCl_4, δ)
2a	4-Methoxy	132 (1.5)	1730 1705[a]	1105	935	2.32 (s, 3 H), 3.70 (s, 3 H), 6.69 (d, J = 9 Hz, 2 H), 7.41 (d, J = 9 Hz, 2 H)
2b	2,4-Dimethyl	146–147 (7)	1735 1705[a]	1105	938	2.22 (s, 3 H), 2.28 (s, 3 H), 2.42 (s, 3 H) 6.81 (d, J = 8 Hz, 1 H), 6.86 (s, 1 H), 7.37 (d, J = 8 Hz, 1 H)
2c	2-Methyl	109–110 (1)	1730 1705[a]	1105	935	2.31 (s, 3 H), 2.46 (s, 3 H), 6.95–7.05 (m, 3 H), 7.40–7.50 (m, 1 H)
2d	4-Methyl	114–116 (1)	1730 1705[a]	1105	935	2.27 (s, 3 H), 2.32 (s, 3 H), 6.97 (d, J = 8.5 Hz, 2 H), 7.31 (d, J = 8.5 Hz, 2 H)
4	4-Phenylcarbamoyloxy	(109–112)[b]	1735 1715	1108	935	2.44 (s, 3 H), 7.06–7.75 (m, 5 H), 7.10 (d, J = 9.4 Hz, 2 H), 7.53 (d, J = 9.4 Hz, 2 H)[c]

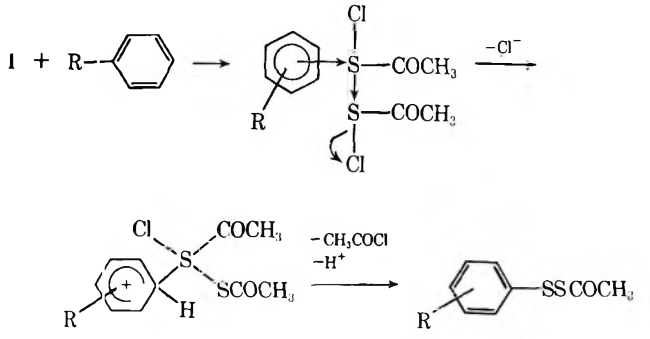
[a] Shoulder. [b] Mp, °C. [c] In $CDCl_3$.

ever, the formation of an episulfide such as **6** would be energetically unfavorable. The following three



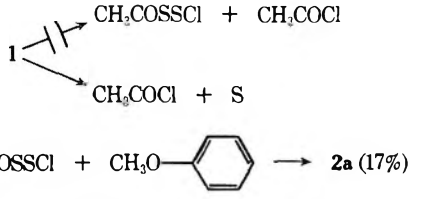
6

pathways (A–C) are conceivable for the formation of **2**. (A) **1** disproportionates to acetylthiosulfenyl chloride and acetyl chloride. The former reacts with aromatics to give **2**. (B) Acetyl aryl sulfide is formed at first and then it reacts rapidly with another molecule of **1** to give **2**. A similar reaction has been reported by Douglass:[14] methanesulfenyl chloride reacts readily with methyl thiolacetate, forming methyl disulfide and acetyl chloride. (C) Elimination of acetyl chloride from an intermediate containing tetravalent sulfur[15] results in the formation of **2**. A control experiment

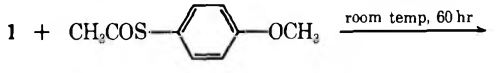


2

proved that **1** does not disproportionate but degrades to acetyl chloride with the elimination of elemental sulfur. A second control experiment revealed that acetylthiosulfenyl chloride is less reactive than **1** toward anisole, and the yield of **2a** is only 17% under conditions similar to those employed for the uncatalyzed reaction of **1** with anisole. Thus path A



seems unlikely. When acetyl anisyl sulfide was allowed to react with **1** in methylene chloride at room temperature for 60 hr, the yield of **2a** was 44%. Sub-



sequent refluxing for 2 hr caused an increase of the yield to 47% and **1** still remained in the reaction mixture. If the reaction in path B were operative, the reaction should be very fast and quantitative, because acetyl anisyl sulfide was not found in the reaction products of **1** and anisole in the absence of catalysts. Since this is not what was observed, selective formation of **2a** in the present study cannot be completely accounted for by path B. Then we prefer path C, although the evidence is not conclusive. Following this mechanism, the formation of disulfide in the reaction of **1** with olefins can also be understood by simply replacing the aromatic structure in path C by a carbon–carbon double bond.

Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra were run on a Perkin-Elmer 337 spectrophotometer. All nmr spectra were recorded on a Varian HA-100 spectrometer. Chemical shifts of nmr spectra are reported in parts per million downfield from internal TMS (δ). Mass spectra were obtained on a Hitachi mass spectrometer for all compounds. Fragments are reported as *m/e*. Glpc analyses were conducted using a Hitachi K 53 chromatograph with a 3% SE-30 column at 180°. For analytical determinations correction factors for weight ratio/area ratio data were determined with standards containing the same compounds. Acetylsulfenyl chloride (**1**) was prepared by treating diacetyl sulfide with sulfuryl chloride according to the method of Böhme and Clement.[4] Acetylthiosulfenyl chloride was prepared by treating thiolacetic acid with chlorine.[4]

Reaction of 1 with Anisole. A. In Methylene Chloride.—

(14) I. B. Douglass, *J. Org. Chem.*, **24**, 2004 (1959).

(15) For recent discussions of tetravalent sulfur intermediates see B. M. Trost, R. LaRochelle, and R. C. Atkins, *J. Amer. Chem. Soc.*, **91**, 2175 (1969); D. C. Owsley, G. K. Helmkamp, and M. F. Rettig, *ibid.*, **91**, 5239 (1969); C. R. Johnson and J. J. Rigau, *ibid.*, **91**, 5389 (1969); R. Tang and K. Mislow, *ibid.*, **91**, 5644 (1969).

To a solution of anisole (4.0 g, 37 mmol) in methylene chloride (20 ml) cooled to −20° was added slowly a solution of acetylsulfenyl chloride (1) (4.0 g, 36 mmol) in methylene chloride (20 ml). The mixture was stirred for 40 hr at room temperature and then heated under reflux for 2 hr. Distillation of the solvent and unreacted anisole under reduced pressure gave 3.3 g of a yellow liquid. The products were determined and identified by glpc. The retention times were identical with those of authentic samples. The compounds identified were acetyl *p*-anisyl disulfide (**2a**) (61%), di-*p*-anisyl sulfide (2%), and di-*p*-anisyl disulfide (9%). Distillation of the reaction mixture gave 1.6 g of pure **2a**, bp 132–134° (2 mm); ir, nmr, and mass spectra are identical with those of an authentic sample (*vide infra*).

Anal. Calcd for $C_9H_{10}O_2S_2$: C, 50.44; H, 4.70; S, 29.92. Found: C, 49.86; H, 4.83; S, 29.94.

B. In Acetonitrile.—The reaction between **1** (4.5 g, 41 mmol) and anisole (4.4 g, 41 mmol) in acetonitrile (40 ml) was carried out essentially as in methylene chloride. The products were analyzed by glpc (Table I).

C. In Methylene Chloride in the Presence of Aluminum Chloride.—The reaction between **1** (5.0 g, 45 mmol) and anisole (5.0 g, 46 mmol) in the presence of aluminum chloride (*ca.* 50 mg) was carried out essentially as in the absence of the catalyst. The identified products were listed in Table I.

D. In Methylene Chloride in the Presence of Concentrated Sulfuric Acid.—To a solution of anisole (5.0 g, 46 mmol) and concentrated sulfuric acid (*ca.* 50 mg) in methylene chloride (20 ml) cooled to −20° was added dropwise a solution of **1** (5.0 g, 45 mmol) in methylene chloride (20 ml). The mixture was stirred for 40 hr at room temperature and then heated under reflux for 2 hr. After removal of the solvent and unreacted anisole under reduced pressure, the residual liquid was dissolved in benzene, washed several times with water, and dried; the benzene was removed. The products were analyzed by glpc (Table I).

E. In Methylene Chloride in the Presence of Iron Powder.—A solution of **1** (5.0 g, 45 mmol) in methylene chloride (20 ml) was added slowly to a cooled (−20°) mixture of anisole (5.0 g, 46 mmol), iron powder (*ca.* 50 mg), and methylene chloride (20 ml). The system was stirred for 40 hr at room temperature and then heated under reflux for 2 hr. After work-up the products were analyzed by glpc. The compounds identified were *p*-methoxyacetophenone (6%), acetyl *p*-anisyl sulfide (6%), **2a** (66%), di-*p*-anisyl sulfide (3%), and di-*p*-anisyl disulfide (15%).

F. In Methylene Chloride in the Presence of Ferric Chloride.—The reaction between **1** (5.0 g, 45 mmol) and anisole (5.0 g, 46 mmol) in the presence of ferric chloride (*ca.* 50 mg) was carried out essentially as in the presence of iron powder. The products were analyzed by glpc (Table I).

Reaction of 1 with *m*-Xylene.—A solution of **1** (4.2 g, 38 mmol) in *m*-xylene (26.0 g, 245 mmol) was stirred for 10 hr at room temperature and then heated gradually up to 125° in 12 hr. The solvent was removed under reduced pressure to give 2.8 g of a dark brown liquid. Glpc indicated the presence of 2,4-dimethylacetophenone (2%), acetyl 2,4-xylyl sulfide (2%), acetyl 2,4-xylyl disulfide (**2b**) (49%), and bis(2,4-xylyl) sulfide (7%). The ir and nmr spectra of **2b** isolated by preparative glpc were identical with those of an authentic sample (*vide infra*).

Reaction of 1 with Toluene.—Iron powder (*ca.* 50 mg) was added to a solution of **1** (9.2 g, 83 mmol) in toluene (40.0 g, 430 mmol). The mixture was stirred for 7 hr at room temperature and then heated to 85° in 18 hr. Distillation of the solvent under reduced pressure and filtration of solid materials gave 2.7 g of a black liquid. Glpc indicated the presence of *o*- and *p*-methylacetophenone (1%), acetyl tolyl sulfide (3%), and the acetyl tolyl disulfides **2c** and **2d** (26% combined).

Reaction of 1 with Phenol.—A solution of **1** (4.2 g, 38 mmol) in ether (20 ml) was added dropwise to a solution of phenol (11.0 g, 117 mmol) in ether (20 ml). The mixture was stirred for 40 hr at room temperature and then heated under reflux for 5 hr. A pale yellow oil (3.7 g) was obtained by removal of ether and excess phenol under reduced pressure: ir (neat) 3400 (ν_{OH}), 1760 (shoulder), 1740, 1700 ($\nu_{C=O}$), 1110 ($\nu_{CC(O)}$), and 940 cm^{-1} ($\nu_{C(O)S}$); nmr ($CDCl_3$) δ 2.40 (s), 6.06 (s), 6.35 (s), 6.71 (d, J = 9 Hz), 7.15 (d, J = 9 Hz), and 7.39 (d, J = 9 Hz); mass spectrum (70 eV) m/e (rel intensity) 200 M^+ (8), 168 (1), 158 (18), 136 (13), 128 (9), 125 (14), 95 (8), 94 (100), 65 (17), 43 (91).

4-Acetyldithiophenyl Phenylcarbamate (4).—A mixture of the adduct from above (3.4 g, 17 mmol as **2e**), phenyl isocyanate (2.1 g, 17 mmol), a catalytic amount of aluminum chloride, and ether (30 ml) was stirred for 2 hr at room temperature and then heated under reflux for 15 hr. The reaction mixture was filtered and concentrated, and the resulting white solid was triturated with *n*-hexane to give 3.9 g of **4** (72%). Recrystallization from *n*-hexane gave **4** in pure form: mp 109–112°; mass spectrum (70 eV) m/e 319 M^+ (<1), 119 (100); ir and nmr data are listed in Table II.

Anal. Calcd for $C_{15}H_{13}NO_3S_2$: C, 56.41; H, 4.10; N, 4.38; S, 20.08. Found: C, 56.61; H, 4.31; N, 4.49; S, 19.87.

Attempts to recrystallize **4** from methanol–water resulted in the formation of bis(4-phenylcarbamoyloxyphenyl) disulfide (**5**): mp 190–191°; ir (KBr) 3275 (ν_{NH}), 1715 ($\nu_{C=O}$); nmr (DMSO-d_6) δ 7.00–7.82 (m).

Anal. Calcd for $C_{26}H_{20}N_2O_4S_2$: C, 63.91; H, 4.12; N, 5.73; S, 13.12. Found: C, 63.90; H, 4.16; N, 5.64; S, 13.15.

Independent Synthesis of 2.—Authentic acetyl aryl disulfides were synthesized by the reaction of **1** with the corresponding thiols. Ir and nmr data are summarized in Table II.

Acetyl *p*-Anisyl Disulfide (2a).—To a solution of *p*-methoxythiophenol (3.2 g, 23 mmol) in ether (25 ml) cooled to −20° was added dropwise a solution of **1** (2.5 g, 23 mmol) in ether (15 ml). After stirring for 6 hr at room temperature, the reaction mixture was heated under reflux for 1 hr. Removal of ether yielded **2a** (4.0 g, 83%) after distillation, bp 132° (1.5 mm), mass spectrum (70 eV) m/e 214 M^+.

Anal. Calcd for $C_9H_{10}O_2S_2$: C, 50.44; H, 4.70; S, 29.92. Found: C, 50.49; H, 4.70; S, 29.94.

Acetyl 2,4-Xylyl Disulfide (2b).—The reaction of **1** (2.5 g, 23 mmol) with 2,4-thioxylenol (2.5 g, 18 mmol) in ether (40 ml) afforded 2.3 g of **2b** (60%) after distillation, bp 146–147° (7 mm), mass spectrum (70 eV) m/e 212 M^+.

Anal. Calcd for $C_{10}H_{12}OS_2$: C, 56.57; H, 5.70; S, 30.20. Found: C, 56.42; H, 5.69; S, 30.08.

Acetyl *o*-Tolyl Disulfide (2c).—A solution of *o*-thiocresol (4.5 g, 36 mmol) in ether (20 ml) was treated with a solution of **1** (4.0 g, 36 mmol) in ether (20 ml) at −20°. Distillation gave 6.0 g of **2c** (84%), bp 109–110° (1 mm), mass spectrum (70 eV) m/e 198 M^+.

Anal. Calcd for $C_9H_{10}OS_2$: C, 54.51; H, 5.08; S, 32.34. Found: C, 54.49; H, 5.07; S, 32.34.

Acetyl *p*-Tolyl Disulfide (2d).—This disulfide was prepared by treating **1** (5.0 g, 45 mmol) with *p*-thiocresol (5.6 g, 45 mmol) in ether (40 ml). After reflux, work-up, and distillation, 7.8 g (87%) of product was obtained, bp 114–116° (1 mm), mass spectrum (70 eV) m/e 198 M^+.

Anal. Calcd for $C_9H_{10}OS_2$: C, 54.51; H, 5.08; S, 32.34. Found: C, 54.59; H, 5.06; S, 32.30.

Decomposition of 1.—Spontaneous decomposition of **1** in carbon tetrachloride was followed by nmr at room temperature. After 7 days 27% of **1** was changed to acetyl chloride, and formation of acetylthiosulfenyl chloride was not observed.

Reaction of Acetylthiosulfenyl Chloride with Anisole.—A solution of acetylthiosulfenyl chloride (4.1 g, 29 mmol) in methylene chloride (20 ml) was added dropwise to a cooled (−20°) solution of anisole (3.2 g, 29 mmol) in methylene chloride (30 ml). The system was stirred for 40 hr at room temperature and then heated under reflux for 2 hr. Distillation of the solvent and unreacted anisole gave a yellow liquid (4.3 g). Glpc indicated the presence of **2a** (17%), di-*p*-anisyl sulfide (2%), and di-*p*-anisyl disulfide (42%).

Reaction of 1 with Acetyl *p*-Anisyl Sulfide.—A solution of **1** (0.4 g, 3.3 mmol) and acetyl *p*-anisyl sulfide (0.6 g, 3.3 mmol) in methylene chloride (5 ml) was stirred at room temperature. After 60 hr the yield of **2a** was determined as 44% by glpc. Subsequent refluxing of the reaction mixture for 2 hr caused an increase in the yield up to 47%. Gradual coloring was observed when potassium iodide was added to the reaction mixture, suggesting that **1** still remained in the system.

Registry No.—**1**, 6405-82-9; **2a**, 31570-54-4; **2b**, 31570-55-5; **2c**, 31171-99-0; **2d**, 14227-19-1; **4**, 31570-58-8; **5**, 31570-59-9; anisole, 100-66-3; *m*-xylene, 108-38-3; toluene, 108-88-3; phenol, 108-95-2.

Acknowledgment.—We are indebted to Dr. G. Tsuchihashi for helpful comments and suggestions. This investigation was partially supported by the Kawakami Memorial Foundation.

Photoelimination of a β-Keto Sulfide with a Low-Lying π–π* Triplet State

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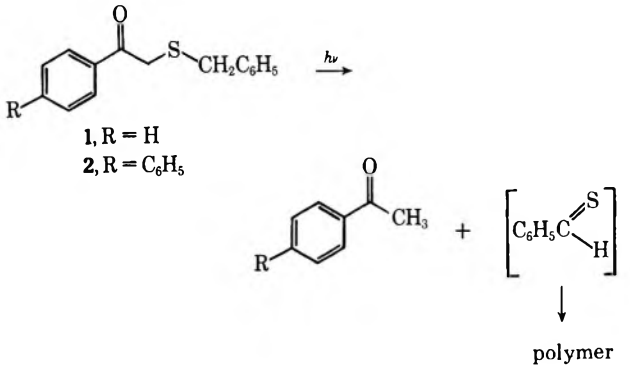
The type II photoelimination of α-benzylthioacetophenone (1) and α-benzylthio-4-acetylbiphenyl (2) has been studied. A kinetic analysis of the two systems shows that the two ketones differ in quantum efficiency and triplet reactivity. The low quantum yield and inability to quench the π–π* excited state of 2 is compatible with an electron-transfer mechanism.

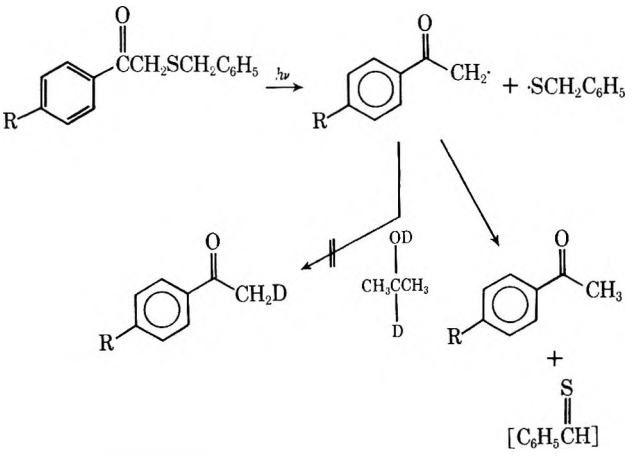
The first step in the photoelimination reaction of α-amino acetophenones has been suggested to proceed by transfer of an electron from the nitrogen atom to the excited carbonyl group.[2] As a continuation of our investigations on the photochemistry of carbonyl compounds that possess a heteroatom, we sought to define the role of the nonbonding electrons of sulfur in the type II photoelimination of β-keto sulfides. It has been reported that β-keto sulfides that possess a hydrogen bearing γ carbon[3–5] undergo conversion to ketones on photolysis by a mechanism similar to that obtained in the photochemistry of alkanones (Norrish type II elimination).[6] The present work was initiated with the hope of demonstrating the importance of electron transfer in the photochemistry of α-alkyl thioaryl ketones.

The major products of the solution-phase photolysis of α-benzylthioacetophenone (1) in benzene were acetophenone and a sulfur-containing polymer. The quantum yield at 3130 Å for the production of acetophenone in benzene is 0.35. Irradiation of α-benzylthio-4-acetylbiphenyl (2) gave comparable results, with the quantum yield for ketone formation being 0.04. The



sulfur-containing polymer is presumably derived by further polymerization of the initially derived thiobenzaldehyde.[7] In striking contrast to the photolytic behavior of the analogous β-keto ether system,[8] no thietanol formation was noted on photolysis of keto sulfides 1 and 2. The different behavior noted in the two systems may be related to the relative weakness of the C–S bond (65 kcal) as compared to the C–O bond (85 kcal).

β-Keto sulfides that do not possess γ hydrogens are reported to give disulfides by homolysis of the carbon–sulfur bond.[9,10] Although a related mechanism can be written to account for the formation of acetophenone, we have found that irradiation of 1 or 2 in deuterio-2-



propanol-2-d_1 did not lead to the incorporation of deuterium in the acetophenone produced. A mechanism involving homolytic C–S bond cleavage (see above) would be expected to lead to some deuterium incorporation by abstraction from solvent. Consequently, it would appear as though the intramolecular Norrish type II scheme is the dominant path with thioketones 1 and 2. Similar results have been noted by Caserio and coworkers with related systems.[5]

The lowest lying triplet state of 1 was demonstrated to be n–π* as evidenced from its phosphorescene emission spectrum in a methanol–ethanol glass (4:1) at 77°K. The 0–0 band of 1 corresponds to a triplet energy of 72 kcal and the vibrational spacing between the 0–0 and 0–1 band is 1660 cm^{-1}. The 77°K lifetime was determined as *ca.* 2.0 msec. In sharp contrast, the triplet energy of 2 was determined to be 61 kcal and the radiative lifetime was 0.18 sec. These observations verify that the low-lying triplet state of 2 is π–π* in nature.

Although the *p*-phenyl-substituted thioketone has a low lying ^{3}(π–π*) state, it still is capable of undergoing photocycloelimination. This observation is somewhat unusual since the ability of an aryl alkyl ketone to undergo photoelimination is dependent on the nature of the lowest lying triplet state, with ^{3}(n–π*) states being reactive and ^{3}(π–π*) states being generally unreactive. By way of illustration, *p*-phenylbutyro-

(1) Fellow of the Alfred P. Sloan Foundation, 1968–1970.

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(3) H. Hogeveen and P. J. Smit, *Recl. Trav. Chim. Pays-Bas*, **85**, 489 (1966).

(4) R. H. Fish, L. C. Chow, and M. C. Caserio, *Tetrahedron Lett.*, 1259 (1969).

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(7) E. Campaigne, *Chem. Rev.*, **39**, 1 (1946).

(8) F. D. Lewis and N. J. Turro, *J. Amer. Chem. Soc.*, **92**, 311 (1970).

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phenone has a low-lying π–π^* triplet state and has been reported to be stable to irradiation.[11]

Photolysis of 1 in degassed benzene solution in the presence of varying amounts of piperylene resulted in the linear Stern–Volmer plot shown in Figure 1. The slope of the Stern–Volmer plot equals $k_q\tau$ where k_q is the rate constant for quenching the ketone triplet by piperylene and τ is the ketone triplet lifetime. Assumption of the value of 5×10^9 M^{-1} sec^{-1} for k_q[12] allows calculation of $1/\tau$ (7.0×10^9 sec^{-1}). The large value of $1/\tau$ is very similar to the value obtained by Lewis and Turro for α-ethoxyacetophenone[8] and is indicative of a very reactive triplet state. On the other hand, photoelimination of ketone 2 could not be quenched by piperylene or 1,3-cyclohexadiene even though its quantum efficiency is one-eighth that of ketone 1. The failure to quench the excited state implies that the reaction of the triplet of 2 is faster than diffusional control quenching (>10^{10} sec^{-1}).[13] The lack of correlation between quantum yield and rate constant for photoelimination of ketones 1 and 2 is similar to the results reported by Wagner with simple alkyl phenyl ketones.[14]

The behavior of thioketone 2 is distinctly different from 1 in two regards: lower quantum efficiency and higher triplet reactivity. The difference in behavior suggests different photoelimination mechanisms for the two ketones. The sensitivity of 1 to triplet quenchers indicates direct hydrogen atom abstraction by the n–π^* state. The low quantum yield and inability to quench the π–π^* excited state of 2 suggests that the excited state interacts with an electron on sulfur (k_1) to form an ion pair or a charge-transfer complex. Once formed,

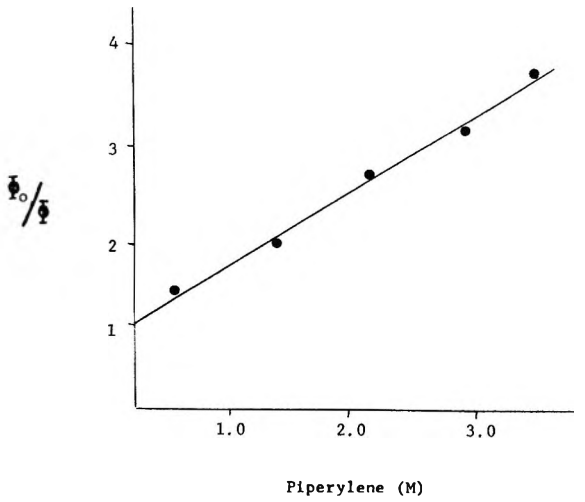
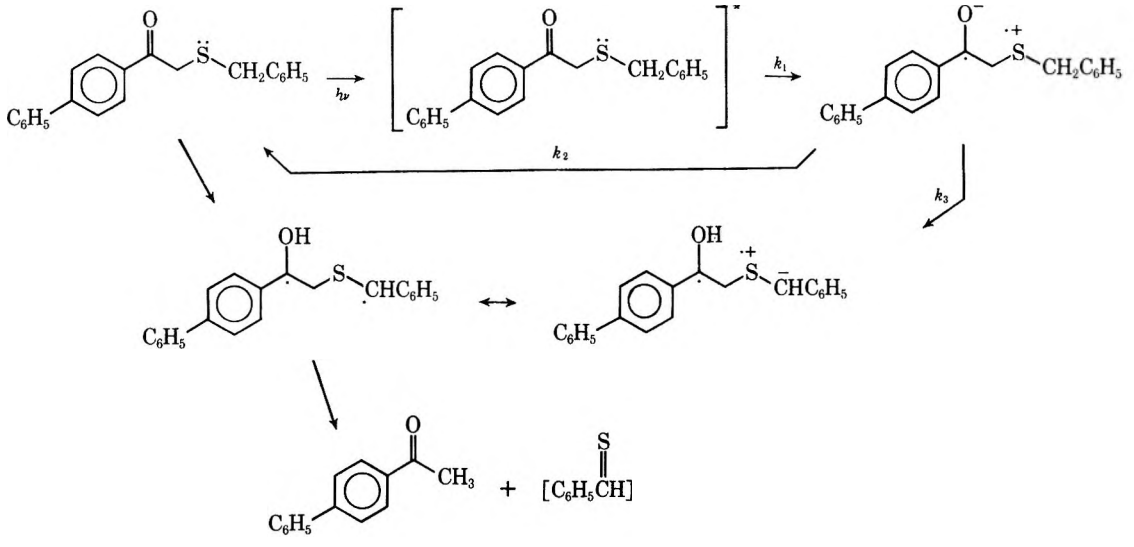


Figure 1.—Stern–Volmer plot for quenching of acetophenone formation from α-benzylthioacetophenone (1) in benzene.

ketones by amines.[15,16] In the charge-transfer complex of the thioketone system, charge destruction and quenching appears to be greater than hydrogen transfer (*i.e.*, $k_2 \gg k_3$). In the amine system, the rates of the two reactions of the complex are comparable ($k_2 \sim k_3$) and consequently the quantum efficiency of photoelimination is larger in this system. Recently Cohen and Guttenplan noted that aliphatic sulfides are good physical quenchers for excited benzophenone and have also suggested efficient interaction of the excited ketone with the nonbonding electrons of sulfur.[17]



the charge-transfer complex can transfer a proton from the benzylic carbon (k_3) or regenerate starting ketone by back transfer of the electron (k_2). Reverse electron transfer (k_2) accounts for the less than maximum quantum yield. This scheme is similar to the charge-transfer mechanism suggested to occur in the photoelimination of α-amino ketones[2] and for the photoreduction of

We have also studied the photoreduction of 4-acetylbiphenyl with aliphatic sulfides. Irradiation of 0.02 M 4-acetylbiphenyl and 0.1 M di-*n*-butyl sulfide led to a high yield of pinacol. While this ketone undergoes appreciable photoreduction with aliphatic sulfides, it is not photoreduced by alcohols or hydrocarbons. This

(11) E. J. Baum, J. K. S. Wan, and J. N. Pitts, Jr., *J. Amer. Chem. Soc.*, **88**, 2652 (1966).

(12) P. J. Wagner and G. S. Hammond, *ibid.*, **88**, 1245 (1966).

(13) An alternate possibility is that the photoelimination of **2** proceeds by way of a n–π^* singlet state.

(14) P. J. Wagner and A. E. Kemppainen, *ibid.*, **90**, 5896 (1968).

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(16) R. S. Davidson, P. F. Lambeth, F. A. Younis, and R. Wilson, *J. Chem. Soc.*, 2203 (1969); R. S. Davidson and P. F. Lambeth, *Chem. Commun.*, 511 (1968), 732 (1969).

(17) S. G. Cohen and J. Guttenplan, *ibid.*, 247 (1969).

observation provides further support for charge-transfer interaction of the nonbonding electrons on sulfur with excited $\pi-\pi^*$ triplet states.

Experimental Section[18]

α-Benzylthioacetophenone (1).—To a stirred solution containing 15 g of α-bromoacetophenone in 100 ml of benzene was added a solution containing 9.4 g of benzyl mercaptan and 8.0 g of triethylamine in 100 ml of benzene. After 12 hr the precipitated salts were filtered and the filtrate was concentrated under reduced pressure. Recrystallization of the crude solid from 95% ethanol gave 16 g (88%) of **1**, mp 85–87°. The infrared spectrum was characterized by bands at 5.99, 6.92, 7.20, 8.34, 10.00, 13.32, 14.25, and 14.65 μ. The ultraviolet spectrum (95% ethanol) had maxima at 242 mμ (ε 14,300), 278 (2000), and 330 (200). The nmr spectrum ($CDCl_3$) showed singlets at τ 6.38 (2 H) and 6.27 (2 H), and multiplets centered at τ 2.68 (8 H) and 2.10 (2 H). The mass spectrum exhibited the parent ion at *m/e* 274 and had major peaks at 105, 91, and 77.

Anal. Calcd for $C_{15}H_{14}OS$: C, 74.35; H, 5.82; S, 13.23. Found: C, 74.33; H, 5.77; S, 13.58.

α-Benzylthio-4-acetylbiphenyl (2).—To a stirred solution containing 15.2 g of α-bromo-4-acetylbiphenyl in 100 ml of benzene was added a solution containing 9.4 g of benzyl mercaptan and 6.5 g of triethylamine in 100 ml of benzene. After 12 hr the precipitated salts were filtered and the filtrate was evaporated to give a crude solid. Recrystallization of the solid from 95% ethanol gave 10.5 g of **2** (61%), mp 110–111°. The infrared spectrum was characterized by bands at 5.99, 6.23, 7.17, 8.38, 9.98, 12.02, 13.17, and 14.32 μ. The ultraviolet spectrum (95% ethanol) showed a maximum at 283 mμ (ε 28,000). The nmr spectrum ($CDCl_3$) showed singlets at τ 6.37 (2 H) and 6.27 (2 H) and had a multiplet centered at τ 2.60 (14 H). The mass spectrum exhibited a molecular ion at *m/e* 318 and had major peaks at 196, 181, 153, 91, and 77.

Anal. Calcd for $C_{21}H_{18}OS$: C, 79.21; H, 5.70; S, 10.07. Found: C, 79.06; H, 5.67; S, 9.85.

Coirradiation of 4-Acetylbiphenyl with Di-*n*-butyl Sulfide.—A solution containing 4.0 g of 4-acetylbiphenyl and 20 g of di-*n*-butyl sulfide in 250 ml of benzene was irradiated for 3 hr with a 550-W Hanovia lamp using a Pyrex filter. Removal of the solvent left a crude solid which was recrystallized from ethyl acetate to give 1.9 g (47%) of 1,2-dibiphenyl-1,2-dimethylethane-1,2-diol, mp 223–225°. The infrared spectrum of this material was identical with that of the pinacol prepared by the reaction of aluminum amalgam with 4-acetylbiphenyl.

Anal. Calcd for $C_{28}H_{26}O_2$: C, 85.24; H, 6.64. Found: C, 84.96; H, 6.65.

Quantum Yield Determinations.—All quantitative measurements were made on a rotating assembly with a central light source (internal water-cooled mercury arc lamp, Hanovia type L-450-W). Samples in 13-mm Pyrex ampoules were placed in holders on the assembly approximately 6 cm from the immersion well. The light was filtered by circulation of a solution containing 46 g of nickel sulfate hexahydrate and 14 g of cobaltous sulfate heptahydrate per 100 ml of water through the inner jacket.[12] This solution permitted the following wavelength distribution to pass through: 6%, 2967; 20%, 3025; 62%, 3130, 3340 Å. All studies were made at room temperature. Samples in 13-mm Pyrex test tubes were degassed to 5×10^{-3} mm in three freeze–thaw cycles and then sealed. Benzophenone–benzhydrol actinometry was used for quantum yield determinations. An actinometer quantum yield of 0.69 was used when the concentration of benzophenone and benzhydrol in benzene was 0.1 *M*.[19] Reliably reproducible output rates of 4.86×10^{16} quanta sec were recorded. After the irradiation the degree of reaction was determined by vapor phase chromatography (6 ft × 0.25 in. 10% SE-30 methylsilicone gum rubber on Diatoport S). The conversions were run to 15% or less. The mass balance in these runs was generally better than 96%. For the quenching studies samples were prepared and analyzed as for quantum yield determinations except that varying amounts of piperylene were added to the solutions. Five concentrations of piperylene, in addition to blanks containing no piperylene, were used for the Stern–Volmer plot.

Phosphorescence Emission Studies.—The emission spectra were made on an Aminco-Bowman spectrophotofluorometer with a phosphoroscope and transmission attachments. The spectrophotofluorometer was equipped with a 1P21 photomultiplier and a high-pressure xenon lamp, as supplied by the manufacturer. All emission spectra were recorded using EPA (ethyl ether–isopentane–ethanol, 5:5:2 volume ratio) as solvent. The solvent was checked for emission each time a spectrum was recorded. No interference due to solvent was found at any time. All compounds having relatively long radiative lifetimes were recorded on a xy plotter. Samples having short radiative lifetimes (<100 msec) were measured by photographing the decay curve on an oscillograph. The chopper was rotated manually to obtain the decay curve. The logarithmic intensities of the decay curve were plotted *vs.* time and the slope of the line at a logarithmic value of 2.303 gave the mean lifetime (τ_0).

Registry No.—**1**, 2408-88-0; **2**, 31593-31-4; 1,2-dibiphenyl-1,2-dimethylethane-1,2-diol, 10426-00-3.

Acknowledgment.—Support of this work by the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

(18) Nmr spectra were recorded on a Varian A-60 spectrometer using carbon tetrachloride as solvent. Infrared spectra were obtained on a Perkin-Elmer Infracord spectrophotometer, Model 137. The ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm matched cells. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. Gas–liquid partition chromatographic analyses and preparative separations were carried out using an F & M Model 5720 instrument equipped with a 6 ft × 0.25 in. 20% Apiezon M on 60–80 mesh Chromosorb W column. Irradiations were carried out using Hanovia 450- and 550-W, medium-pressure mercury lamps with water-cooled quartz immersion wells.

(19) W. M. Moore, G. S. Hammond, and R. P. Foss, *J. Amer. Chem. Soc.*, **83**, 2789 (1961).

Oxidative Hydrolysis of 1,3-Dithiane Derivatives to Carbonyl Compounds Using *N*-Halosuccinimide Reagents

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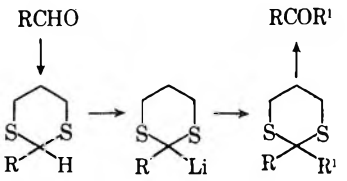
Specific and effective procedures are described for the conversion of a variety of substituted 1,3-dithianes to carbonyl compounds by means of mercury(II)-promoted hydrolysis or oxidative cleavage by *N*-bromo- or *N*-chlorosuccinimide. The conditions required for the mercury(II)-promoted hydrolysis of 1,3-dithianes may be correlated with the ease of C–S heterolysis and the electron-supplying ability of the substituents at C(2). The hydrolysis by the mercury method of 2,2-dialkyl derivatives is generally very facile and more rapid than that of 2-monoalkyl-1,3-dithianes, while the hydrolysis of 2-acyl-1,3-dithianes is very slow. For the latter cases especially the use of the *N*-halosuccinimides is advantageous, and three reagents of this type have been devised for use in aqueous acetonitrile or acetone: (1) *N*-bromosuccinimide alone, (2) *N*-bromosuccinimide with silver ion, and (3) *N*-chlorosuccinimide with silver ion. The use of the *N*-chlorosuccinimide–silver ion reagent is advantageous for unsaturated dithianes, since olefinic linkages are unaffected by it. 2,6-Lutidine and 2,4,6-collidine may be employed to buffer the three reagents in applications to acid-sensitive substrates. A number of aldehydes and ketones have been obtained in 70–100% yields using the halosuccinimide reagents.

1,3-Dithiane derivatives are versatile intermediates in the synthesis and interconversion of monocarbonyl and 1,2-dicarbonyl compounds. For example, numerous synthetic operations have been performed that involve the 2-acyl-1,3-dithiane moiety, including the extension of carbon chains, the masking and unmasking of carbonyl groups, the blocking and unblocking of activated methylene groups, the nucleophilic acylation of carboxylic acid derivatives,[1,2] the reduction of carbonyl groups to methylene groups, and the interchange[3] of a carbonyl group with an adjacent methylene group. Temporary inversion of the electrophilic reactivity of the aldehydic carbonyl group permits the synthesis of carbonyl compounds by the coupling of a nucleophilic aldehyde derivative with electrophiles. A useful procedure[1,2] for accomplishing this synthetic operation involves (1) conversion of the aldehyde to the 1,3-dithiane derivative, (2) metalation of this derivative with *n*-butyllithium in tetrahydrofuran, (3) reaction of the 2-lithio-1,3-dithiane derivative with an electrophile, and (4) hydrolysis of the resulting 1,3-dithiane derivative to the carbonyl compound using mercuric chloride. Among the many carbonyl compounds synthesized by this lithiodithiane procedure are 1-deuterioaldehydes,[4] acylsilanes and -germanes,[5,6] cyclic monoketones anddi ketones,[7,8] optically active aldehydes and ketones,[9] metacyclophanes,[10] acyclic monoterpenes,[11] and 21-keto steroids.[12] The present paper reports the oxidative hydrolysis of 1,3-dithiane derivatives to carbonyl compounds using *N*-halosuccinimide reagents. These oxidative reagents, unlike the mercury(II) reagents, permit the efficient hydrolysis of 2-acyl-1,3-dithiane derivatives to 1,2-dicarbonyl compounds and thus significantly extend the synthetic utility of the lithiodithiane method.



Hydrolysis Using Mercuric Chloride.—Mercuric chloride usually forms a sparingly soluble complex[13] with 1,3-dithiane derivatives that can be hydrolyzed in good yield (60–90%) when heated at 60–90° for 1–8 hr in an aqueous polar organic solvent (methanol,[2,4,5,7–10] ethanol,[11] ethylene glycol,[7] tetrahydrofuran,[10] acetone[6,11]). Insoluble bases (mercuric oxide, cadmium carbonate,[14] calcium carbonate[15]) are often added to neutralize the HCl formed during hydrolysis. Other reagents that also function as Lewis acids to promote the hydrolysis of 1,3-dithiane derivatives include acidic mercuric acetate,[16] mercuric oxide–boron trifluoride etherate,[17] and silver nitrate.[11] Although 2-aryl- and 2,2-dialkyl-1,3-dithianes undergo hydrolysis with mercuric chloride more readily than do the 2-alkyl derivatives,[2] even the latter are slowly hydrolyzed at 25°. 2-Benzyl-1,3-dithiane, for example, is hydrolyzed about 100 times slower at 25° than at 60° (Table I).

A variety of ketones bearing interrelated functional groups can be economically prepared by the lithiodithiane method using mercury(II)-promoted hydrolysis to generate the carbonyl group. The synthesis of 3-acetyl-2-cyclohexenone (6) by the indirect coupling of acetaldehyde and 2-cyclohexenone is exemplary. 2-Methyl-1,3-dithiane, prepared from acetaldehyde and

(1) E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075, 1077 (1965).

(2) For a recent review, see D. Seebach, *Syn.*, **1**, 17 (1969).

(3) J. A. Marshall and H. Roebke, *J. Org. Chem.*, **34**, 4188 (1969).

(4) D. Seebach, B. W. Erickson, and G. Singh, *ibid.*, **31**, 4303 (1966).

(5) E. J. Corey, D. Seebach, and R. Freedman, *J. Amer. Chem. Soc.*, **89**, 434 (1967).

(6) A. G. Brook, J. M. Duff, P. F. Jones, and N. R. Davis, *ibid.*, **89**, 431 (1967); A. G. Brook, D. G. Anderson, J. M. Duff, P. F. Jones, and D. M. MacRae, *ibid.*, **90**, 1076 (1968); A. G. Brook, P. F. Jones, and G. J. D. Peddle, *Can. J. Chem.*, **46**, 2119 (1968); P. R. Jones and R. West, *J. Amer. Chem. Soc.*, **90**, 6978 (1968).

(7) D. Seebach, N. R. Jones, and E. J. Corey, *J. Org. Chem.*, **33**, 300 (1968).

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(9) D. Seebach and D. Steinmüller, *Angew. Chem., Int. Ed. Engl.*, **7**, 619 (1968); D. Seebach, D. Steinmüller, and F. Demuth, *ibid.*, **7**, 620 (1968).

(10) T. Hylton and V. Boekelheide, *J. Amer. Chem. Soc.*, **90**, 6887 (1968).

(11) C. A. Reece, J. O. Rodin, R. G. Brownlee, W. G. Duncan, and R. M. Silverstein, *Tetrahedron*, **24**, 4249 (1968).

(12) J. B. Jones and R. Grayshan, *Chem. Commun.*, 741 (1970).

(13) Infrared data suggest that the Hg–S σ bonds in mercuric halide complexes of 1,3-dithiane and related sulfides are formed by donation of an equatorial sulfur electron pair, whereas both axial and equatorial electron pairs are involved in the Ag–S bonds of the silver nitrate adducts: see J. A. W. Dalziel, M. J. Hitch, and S. D. Ross, *Spectrochim. Acta, Part A*, **25**, 1055, 1061 (1969).

(14) M. L. Wolfrom, *J. Amer. Chem. Soc.*, **51**, 2188 (1929).

(15) The use of inexpensive $CaCO_3$ powder avoids the fresh precipitation of hydrated $CdCO_3$ and the difficulty of keeping heavy HgO powder in suspension.

(16) J. Z. Gougoutas, Ph.D. Thesis, Harvard University, 1964; R. B. Woodward, *Harvey Lect.*, **59**, 31 (1965).

(17) E. Vedejs and P. L. Fuchs, *J. Org. Chem.*, **36**, 366 (1971).

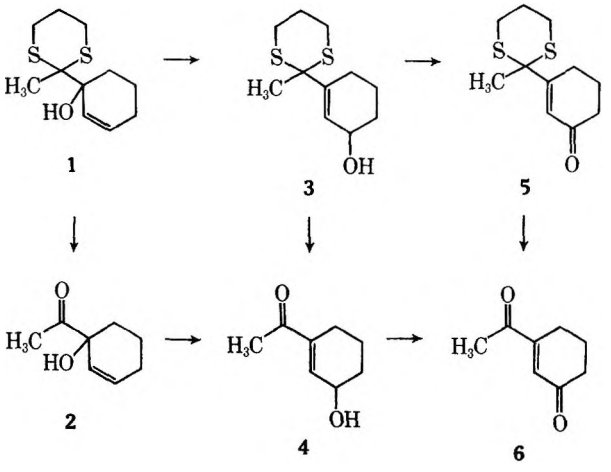
TABLE I

MERCURY(II)-PROMOTED HYDROLYSIS OF 2-BENZYL-1,3-DITHIANE TO PHENYLACETALDEHYDE[a]

Temp, °C	Time, hr	Yield,[b] %
25	48	19
25	192	62
60	2	66
60	4	77

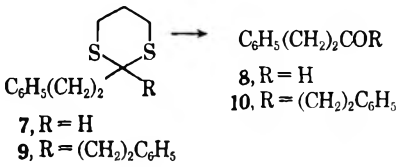
[a] Dithiane (1.0 mol), $HgCl_2$ (2.2 mol), and HgO (2.2 mol) in 90% aqueous CH_3OH. [b] Isolated as the 2,4-dinitrophenylhydrazone.

1,3-propanedithiol (91%), was treated sequentially with *n*-butyllithium and 2-cyclohexenone to afford the α-hydroxy dithiane **1** (70%). The γ-hydroxy dithiane **3**, prepared by the isomerization of **1** with acid, has been hydrolyzed with mercuric chloride–cadmium carbonate to the γ-hydroxyenone **4** (80%).[8] In extending this work, the mercuric chloride hydrolysis of the α-hydroxy dithiane **1** to the α-hydroxy enone **2** required the presence of a buffer ($CaCO_3$) to prevent the HCl liberated

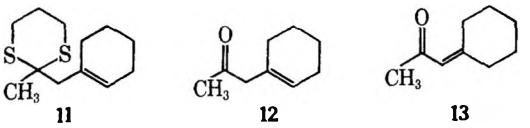


during hydrolysis from catalyzing the partial isomerization[18] of **2** to **4**. Further, hydrolysis of the γ-keto dithiane **5** with the usual 2 mol of mercuric chloride was very slow; the use of 4 mol, however, provided the enedione **6** in 84% yield. As oxidation of the allylic alcohols **3** and **4** with active MnO_2 has afforded the corresponding enones in high yield,[8,19] conversion of the adduct **1** into the enedione **6** has been accomplished by three routes, each in about 70% yield overall.

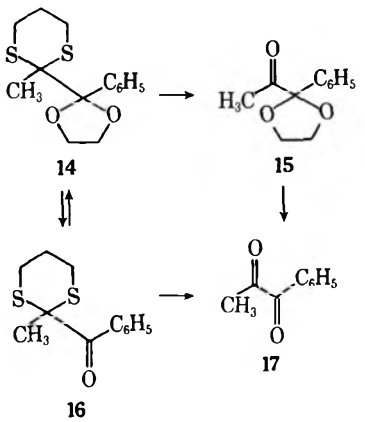
The hydrolysis of several other 1,3-dithiane derivatives with mercuric chloride was examined to test the generality of the method. Several examples that proceeded in good yield are summarized in Table II. Initially run in aqueous alcohol, the hydrolyses were later conducted in aqueous 80% acetonitrile due to the greater solubility of both mercuric chloride and the dithiane substrates in this medium. Treatment of the dithiane **7** with mercuric chloride–mercuric oxide in aqueous methanol produced mainly the dimethyl



ketal,[20] which gave the desired aldehyde on acid hydrolysis. The reaction of cyclohexenyl acetone, a 9:1 mixture of the enone **12** and the conjugated isomer **13**, with acidic 1,3-propanedithiol furnished only the dithiane **11** bearing an endocyclic double bond (85%). Mercury(II)-promoted hydrolysis of this dithiane afforded solely the unconjugated enone **12** by nmr, ir, and tlc criteria; use of these reactions allowed complete removal of the conjugated isomer from the initial enone mixture.



The slow ketalization of the α-keto dithiane **16** with ethylene glycol and nmr evidence that the dithiane ring of the product **14** is frozen in one chair conformation both attest to the steric congestion at the adjacent tetrasubstituted carbon atoms of **14**. Yet the dithiane ring was readily cleaved with twice the usual proportion of mercuric chloride and calcium carbonate.



Two of the dithianes examined, the 2-acyl-1,3-dithianes **16** and **18**, were relatively resistant to hydrolysis with mercuric chloride (Table III). Even prolonged hydrolysis of the α-keto dithiane **16** did not increase significantly the low yield of the α-dione **17** observed under the usual hydrolysis conditions.[22] Previous attempts[23] to hydrolyze α-keto dithioacetals with buffered mercuric chloride were unsuccessful; further, the reaction[17] of 2-benzoyl-1,3-dithiane with $HgO–BF_3$ etherate afforded not phenylglyoxal but benzoic acid (73%). Although mercuric acetate in aqueous acetic acid has been used

(18) This facile isomerization was accomplished preparatively by treatment of the α-hydroxyenone **2** with trifluoroacetic acid (25°, 20 hr) to give the trifluoroacetate of rearranged alcohol **4** (85%) and solvolysis of the latter in methanolic sodium bicarbonate (25°, 25 hr) to liberate **4** (95%); see Experimental Section.

(19) Dithioketals are also stable to oxidation with chromium trioxide in pyridine; see N. Pappas and H. R. Nace, *J. Amer. Chem. Soc.*, **81**, 4556 (1959).

(20) 1,3-Dithiane derivatives have been converted into ketals using $HgCl_2$–anhydrous alcohol[10,21] and into *gem*-diacetates using $Hg(OAc)_2$–BF_3 etherate–acetic acid.[17]

(21) E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Amer. Chem. Soc.*, **90**, 3245 (1968); A. G. Brook and P. J. Dillon, *Can. J. Chem.*, **47**, 4347 (1969).

(22) An indirect conversion of the acyldithiane **16** into the dione **17** was accomplished in 55% yield overall by (1) vigorous ketalization of **16** with acidic ethylene glycol (90%), (2) hydrolysis of the dithiane ring of the bis ketal **14** with mercuric chloride (76%), and (3) prolonged hydrolysis of the acyldioxolane **15** with 9 *M* sulfuric acid in aqueous THF (87%); see Experimental Section.

(23) F. Weygand and H. J. Bestmann, *Z. Naturforsch., B*, **10**, 296 (1955).

Table II

Hydrolysis of Six 1,3-Dithianes Using Mercuric Chloride[a]

Dithiane substrate	Buffer, mol	Aqueous solvent (%)	Time, hr	Carbonyl product	Yield, %
1	$CaCO_3$, 2.5	CH_3CN (80)	5.0	α-Hydroxyenone 2	93
5	None	CH_3CN (80)	6.0	Enedione 6	84
7	HgO, 1.1	CH_3OH (95)	4.5	3-Phenylpropional (8)	68
9	None	CH_3OH (90)	4.2	Ketone 10	86
11	$CaCO_3$, 2.2	CH_3CN (80)	5.0	Nonconjugated enone 12	90
14	$CaCO_3$, 4.4	CH_3CN (80)	4.0	α-Keto ketal 15	76

[a] Dithiane (1.0 mol), mercuric chloride (2.2 mol, except 4.0 mol for 5 and 14), buffer, and solvent were heated at reflux under nitrogen.

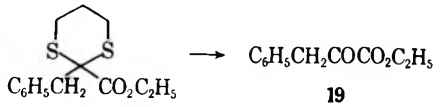
Table III

Hydrolysis of Two 2-Acyl-1,3-dithianes Using Mercuric Chloride, Mercuric Acetate, or Bromine

Dithiane substrate	Reactant, ratio[a]	Aqueous solvent (%)	Temp, °C (time, hr)	Yield,[b] %
16	$HgCl_2$, 2.2	CH_3CN (80)	80 (4)	13 (78)
16	$HgCl_2$, 2.2	CH_3CN (80)	80 (24)	20 (55)
18	$HgCl_2$, 2.2	C_2H_5OH (95)	80 (4)	0 (89)
16	$Hg(OAc)_2$, 2.0	HCO_2H (95)	75 (2.5)	37 (0)
16	$Hg(OAc)_2$, 2.2	HOAc (80)	90 (4)	40 (0)
16	Br_2, 2.0	0.33 *M* HCl, HOAc (65)	50 (1.5), 25 (36)	48 (40)
16	Br_2, 4.0	0.17 *M* HCl, HOAc (65)	25 (21)	47 (7)
16	Br_2, 4.0	0.33 *M* HCl, HOAc (65)	50 (1), 25 (21)	34 (5)
18	Br_2, 2.0	0.33 *M* HCl, HOAc (65)	50 (0.7)	33 (55)

[a] Moles per mole of dithiane. [b] Recovered dithiane (%) in parentheses.

to prepare a 1,2-cycloheptanedione derivative from a 2-acyl-1,3-dithiane,[16] hydrolysis of the α-keto dithiane **16** with mercuric acetate proceeded in only 40% yield (Table III).



18 **19**

A great variety of 2-acyl-1,3-dithianes are available by the acylation of 2-lithio-1,3-dithiane derivatives[1,2] or by the reaction of ketones bearing an enolizable methylene group with 1,3-propylene bis(*p*-toluenethiolsulfonate).[24,25] First applied in the Woodward–Barton synthesis of lanosterol,[26] the thiolsulfonate route has been used for the preparation of 2-acyl-1,3-dithianes from 3-keto steroids,[27] 11-keto steroids,[28] 2-decalones,[3,29] 17-yohimbone,[30] cyclohexanones,[31] and cycloheptanones.[16,32] Direct hydrolysis of these readily available 2-acyl-1,3-dithiane derivatives to 1,2-dicarbonyl compounds is a useful synthetic operation; the inefficiency of mercury(II) reagents in promoting this transformation emphasized the need for a more general method of 1,3-dithiane hydrolysis.

Oxidative Hydrolysis Using *N*-Halosuccinimides.—Dithioacetals and acyclic dithioketals undergo oxidative hydrolysis on treatment with bromine,[24,33–38] chlorine,[35] or iodine.[39] The oxidative hydrolysis of acyclic α-acyldithioacetals to α-ketoaldehydes using 2 mol of bromine in hydrochloric acid–acetic acid[34] proceeds in 75–90% yield; this method is useful for the hydrolysis of sugar dithioacetals.[37] Yet only moderate yields of 1,2-dicarbonyl compounds were obtained on hydrolysis of the model 2-acyl-1,3-dithianes using either 2 or 4 mol of bromine (Table III).

One mole of *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide (NCS) in anhydrous methanol rapidly oxidizes organic sulfides to sulfoxides (60–90%),[40] but carbon–sulfur bond cleavage predominates in the reaction of alkyl sulfides with 2 mol of NBS or NCS in dry methanol[40] or with aqueous NBS.[41] The latter observation suggested the use of the *N*-halosuccinimides for 1,3-dithiane hydrolysis, for this reaction requires a reagent that cleaves C–S bonds more readily than it oxidizes divalent sulfur.

2-Benzoyl-2-methyl-1,3-dithiane (**16**) was hydrolyzed to the α-dione **17** in high yield using NBS or NCS, especially in the presence of a silver(I) salt (Table IV).

(24) J. C. A. Chivers and S. Smiles, *J. Chem. Soc.*, 697 (1928).

(25) The enamine derivatives of certain ketones also couple with this thiolsulfonate reagent to form 2-acyl-1,3-dithiane derivatives (M. L. Scheinbaum, Ph.D. Thesis, Harvard University, 1963).

(26) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1131 (1957).

(27) J. L. Beton, T. G. Halsall, E. R. H. Jones, and P. C. Phillips, *ibid.*, 753 (1957); J. S. G. Cox, F. E. King, and T. J. King, *ibid.*, 514 (1959); S. Binns, J. S. G. Cox, E. R. H. Jones, and B. G. Ketcheson, *ibid.*, 1161 (1964); Y. M. Y. Haddad, W. T. Pike, G. H. R. Summers, and W. Klyne, *ibid.*, 6117 (1965); J. M. Midgley, W. B. Whalley, G. F. Katekar, and B. A. Lodge, *Chem. Commun.*, 169 (1965); J. M. Midgley, B. J. Millard, W. B. Whalley, and J. C. Smith, *ibid.*, 84 (1969).

(28) C. Djerassi, O. Halpern, G. R. Pettit, and G. H. Thomas, *J. Org. Chem.*, **24**, 1 (1959).

(29) B. Gaspert, T. G. Halsall, and D. Willis, *J. Chem. Soc.*, 624 (1958); F. Sondheimer and S. Wolfe, *Can. J. Chem.*, **37**, 1870 (1959).

(30) P. D. Pacht, Ph.D. Thesis, Harvard University, 1960.

(31) C. Djerassi, J. Osiecki, and E. J. Eisenbraun, *J. Amer. Chem. Soc.*, **83**, 4433 (1961).

(32) T. A. Crabb and K. Schofield, *J. Chem. Soc.*, 643 (1960).

(33) E. Fischer, *Chem. Ber.*, **27**, 673 (1894).

(34) F. Weygand and H. J. Bestmann, *ibid.*, **90**, 1230 (1957).

(35) The acylthio moiety is successively oxidized by chlorine to the disulfide, the thiosulfonate, and the sulfonyl chloride; see S. W. Lee and G. Dougherty, *J. Org. Chem.*, **5**, 81 (1940).

(36) C. B. Gauthier and C. Vaniscotte, *Bull. Soc. Chim. Fr.*, [5] **23**, 30 (1956), and previous papers.

(37) F. Weygand, H. J. Bestmann, and H. Ziemann, *Chem. Ber.*, **91**, 1040 (1958); F. Weygand, H. J. Bestmann, H. Ziemann, and E. Klieger, *ibid.*, **91**, 1043 (1958); H. Baganz and H. J. May, *ibid.*, **99**, 3771 (1966); R. Kuhn, W. Baschang-Bister, and W. Dafeldecker, *Justus Liebigs Ann. Chem.*, **641**, 160 (1961).

(38) W. E. Truce and F. E. Roberts, *J. Org. Chem.*, **28**, 961 (1963).

(39) G. A. Russell and L. A. Ochrymowycz, *ibid.*, **34**, 3618 (1969).

(40) R. Harville and S. F. Reed, Jr., *ibid.*, **33**, 3976 (1968).

(41) W. Tagaki, K. Kikukawa, K. Ando, and S. Oae, *Chem. Ind. (London)*, 1624 (1964).

TABLE IV

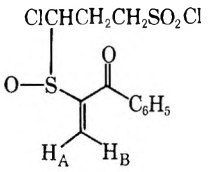
OXIDATIVE HYDROLYSIS OF 2-BENZOYL-2-METHYL-1,3-DITHIANE TO 1-PHENYL-1,2-PROPANEDIONE USING *N*-BROMOSUCCINIMIDE AND *N*-CHLOROSUCCINIMIDE

Reactant, ratio[a]					
Haloimide	Additives	Aqueous solvent (%)	Temp, °C	Time, min	Yield,[b] %
NBS, 4.0		$(CH_3)_2CO$ (97)	−5	2	48 (40)
NBS, 4.0		THF (90)	35	10	63 (27)
NBS, 6.0		$(CH_3)_2CO$ (97)	−5	2	85 (0)
NBS, 8.0		$(CH_3)_2CO$ (97)	0	2	91 (0)
NCS, 4.0		$(CH_3)_2CO$ (90)	30	10	38 (0)
NCS, 6.0		$(CH_3)_2CO$ (90)	30	10	60 (0)
NCS, 4.0	$Cd(NO_3)_2 \cdot 4H_2O$, 4.0	CH_3CN (90)	40	5	50 (0)
NCS, 8.0	$Cd(NO_3)_2 \cdot 4H_2O$, 8.0	CH_3CN (90)	10	5	50 (0)
NCS, 4.0	$CuCl_2 \cdot 2H_2O$, 4.0	CH_3CN (80)	30	10	60 (0)
NCS, 1.0	$AgClO_4$, 1.2	$(CH_3)_2CO$ (90)	30	10	34 (56)
NCS, 2.0	$AgClO_4$, 2.3	$(CH_3)_2CO$ (90)	30	10	75 (15)
NCS, 3.0	$AgNO_3$, 3.5	CH_3CN (90)	2	7	80 (0)
NCS, 4.0	$AgClO_4$, 4.5	$(CH_3)_2CO$ (90)	30	10	92 (0)
NCS, 8.0	$AgNO_3$, 8.1	CH_3CN (80)	32	5	62 (0)
NBS, 2.2	$AgClO_4$, 2.2	$(CH_3)_2CO$ (97)	20	15	55 (43)
NBS, 4.1	$AgClO_4$, 5.0	$(CH_3)_2CO$ (97)	20	15	85 (0)
NBS, 7.0	$AgNO_3$, 7.5; DMP, 16	CH_3CN (80)	5	17	85 (0)
NBS, 6.0	$AgNO_3$, 6.3; TMP, 12	CH_3CN (85)	30	10	100 (0)

[a] Moles per mole of dithiane (DMP, 2,6-dimethylpyridine; TMP, 2,4,6-trimethylpyridine). [b] Recovered dithiane (%) in parentheses.

Aqueous 90–97% acetone and aqueous 80% acetonitrile were suitable solvent systems when NBS or NCS was used alone or with silver perchlorate. Reactions using silver nitrate were conducted in aqueous 80% acetonitrile, for this salt is only sparingly soluble in aqueous acetone. In each case, a solution of the dithiane was added *to* a homogeneous solution containing the *N*-halosuccinimide and additives; when the reagents were added to the dithiane, the yield of ketone was consistently lower and occasionally vanishing.

In contrast to the 2 mol of bromine[34] needed to hydrolyze acyl dithioacetals to α-ketoaldehydes and to the single mole of chlorine[35] or bromine[36] required to convert other dithioacetals to aldehydes, about 6 mol of NBS was necessary for complete hydrolysis of **16** in the absence of silver ion. Hydrolysis using NBS (6 mol) in aqueous acetone, which occurred even at −20°, was complete within 2 min at 0°; a similar reaction in aqueous 70% dioxane was 83% complete in 4 min at 30° and complete in 9 min (nmr). Four moles of NBS or NCS was sufficient when the molar amount of silver ion present exceeded that of the haloimide; this decrease in stoichiometry may be due to a change in the electrophilic halogen species caused by the presence of silver ion.[42] The use of NCS alone or with cadmium nitrate or cupric chloride furnished only moderate yields of the α-dione; the major by-product (30% yield) with or without cupric chloride was the highly functionalized α-chlorosulfoxide **20**.[35,43]



20

A buffer system compatible with silver ion and the *N*-halosuccinimides was desired to prevent the rapid rise in acidity that occurs during hydrolysis. High recovery of the 2-acyl-1,3-dithiane **16** was observed on attempted hydrolysis with NBS in the presence of triethylamine (pK_a = 10.8) or sodium succinimide (pK_a = 9.3), for these bases are evidently incompatible with protonated NBS. In the presence of potassium acetate or an equimolar mixture of sodium acetate and acetic acid, the dithiane was completely consumed but the α-dione was formed in low yield (12 and 24%, respectively). Though the use of pyridine[44] (pK_a = 5.17[45]) as buffer afforded only moderate yields of the dione, 2,6-dimethylpyridine (pK_a = 6.75[45]) or 2,4,6-trimethylpyridine (pK_a = 7.3[46]) furnished the dione **17** in excellent yield (Table IV). These sterically hindered pyridines had little effect on the rate of hydrolysis or the role of silver ion; even though both pyridines form crystalline complexes with silver ion, a moderate concentration[47] of uncomplexed silver ion is still available during hydrolysis.

Oxidative hydrolysis of the seven other model dithianes with NBS or NCS–silver nitrate was also successful (Table V), the isolated yield of the carbonyl product generally being greater for the oxidative procedure than

(42) (a) The presence of Ag(I) salts during the oxidation of anisole by HOCl reduces the chloride ion concentration sufficiently to suppress completely any reaction through Cl_2 [P. B. D. de la Mare, A. D. Ketley, and C. A. Vernon, *J. Chem. Soc.*, 1290 (1954)]. (b) The NBS oxidation of secondary alcohols to ketones, which initially proceeds with NBS as oxidant, mainly occurs by oxidation with bromine generated rapidly *in situ;* the oxidation by Br_2 is completely suppressed in the presence of Hg(II) salts [N. Venkatasubramanian and V. Thiajarajan, *Can. J. Chem.*, **47**, 694 (1969)]. (c) The rate-limiting step in the oxidation of secondary alcohols with NCS in aqueous HCl is the generation of Cl_2, the major oxidant, by reaction of chloride ion with protonated NCS [N. S. Srinivasan and N. Venkatasubramanian, *Tetrahedron Lett.*, 2099 (1970)].

(43) The ratio of α-halogenation to C–S bond cleavage observed on reaction of the following electrophilic halogen reagents with dibenzyl sulfide ($CDCl_3$, 35°) was 3.6 for NCS, 0.78 for Br_2, and 0.29 for NBS: see G. E. Wilson, Jr., and M. G. Huang, *J. Org. Chem.*, **35**, 3002 (1970).

(44) C. Walling and M. J. Mintz, *ibid.*, **32**, 1286 (1967).

(45) W. J. Peard and R. T. Pflaum, *J. Amer. Chem. Soc.*, **80**, 1593 (1958).

(46) H. Lunden, *Chem. Zentralbl.*, 788 (1908).

(47) The concentration of uncomplexed silver ion in a saturated (0.2 *M*) solution of $Ag(2,6\text{-dimethylpyridine})_2NO_3$ in 4:1 acetonitrile–water is near 5×10^{-3} *M*, for the dissociation constant of the complex ion $Ag(2,6\text{-dimethylpyridine})^+$ is 3.4×10^{-6} *M* in acetonitrile.[45]

Table V
Oxidative Hydrolysis of Seven 1,3-Dithianes with *N*-Bromosuccinimide or *N*-Chlorosuccinimide–Silver Nitrate

Dithiane substrate	Reactant, ratio[a]	Aqueous solvent (%)	Temp, °C	Time, min	Carbonyl product	Yield, %
1	NCS, 4.0 $AgNO_3$, 4.5	CH_3CN (80)	55	5	α-Hydroxyenone **2**	71
5	NCS, 4.0 $AgNO_3$, 4.5	CH_3CN (71)	0	25	Enedione **6**	100[b]
7	NBS, 6.0	CH_3CN (80)	5	5	3-Phenylpropional (**8**)	90
9	NBS, 8.0	$(CH_3)_2CO$ (96)	−5	5	Ketone **10**	97
11	NCS, 4.0 $AgNO_3$, 4.5	CH_3CN (80)	25	10	Nonconjugated enone **12**	94
14	NBS, 6.0	CH_3CN (80)	15	10	α-Keto ketal **15**	100
18	NBS, 9.0	$(CH_3)_2CO$ (97)	−5	3	α-Keto ester **19**	78

[a] Moles per mole of dithiane. [b] Reference 8.

for the mercuric chloride method.[48] Even 2-benzoyl-2-ethoxycarbonyl-1,3-dithiane (**18**), which gave no ethyl phenylpyruvate on treatment with mercuric chloride, afforded this α-keto ester in 78% yield on reaction with NBS for 3 min at −5°.

Hydrolysis of the olefinic dithiane **11** using NBS and silver nitrate proceeded with concomitant reaction of the double bond.[49] Even though silver bromide precipitated immediately and the usual transient red color of molecular bromine was absent, the resulting methyl ketone showed no olefinic protons by nmr assay. In contrast, each of the olefinic dithianes tested was converted to the unsaturated ketone in high yield using *N*-chlorosuccinimide–silver nitrate. Evidently the presence of silver ion during the NCS hydrolysis reduced the chloride ion concentration sufficiently to suppress completely the reaction of the olefinic bond with molecular chlorine.[42] In addition, neither NCS nor its O-protonated conjugate acid was effective in attacking the olefinic bond under these conditions.

N-Bromosuccinimide or *N*-chlorosuccinimide–silver nitrate has thus proven suitable for the oxidative hydrolysis of 1,3-dithiane derivatives bearing a variety of unsaturated and oxygenated substituents. The corresponding carbonyl compound is rapidly formed in high yield at low temperatures; the reaction is readily buffered near neutrality with a 2,6-dimethylpyridine. In contrast to the mercury(II) salts and bromine, these *N*-halosuccinimide reagents efficiently hydrolyze 2-acyl-1,3-dithianes to 1,2-dicarbonyl compounds. Unlike the oxidative hydrolysis with bromine or NBS, the NCS–silver nitrate procedure is compatible with olefinic substrates.

Experimental Section

Melting points and boiling points are uncorrected. Thin layer chromatography (tlc) was performed with Merck fluorescent silica gel plates (0.25 mm for analytical and 2.0 mm for preparative work) using one solvent development unless otherwise stated; compounds were visualized with 254-nm light, with iodine vapor, or by spraying with 2% 2,4-dinitrophenylhydrazine in acidic ethanol followed by heating. Ultraviolet (uv spectra were recorded with a Cary Model 14 spectrophotometer and infrared (ir) data were obtained using a Perkin-Elmer Model 137 (Infracord) spectrophotometer. Nuclear magnetic resonance (nmr) spectra were measured with a Varian Associates A-60 or T-60 spectrometer; chemical shifts are expressed in parts per million (ppm) downfield from internal tetramethylsilane (b = broad). The ir and nmr spectra were observed in CCl_4 solution. Mass spectra (ms) were determined in these laboratories with an AEI-MS 9 spectrometer at 70 eV. *n*-Butyllithium solutions (Foote Mineral Co.) were periodically assayed for active alkyl by titration with 2-butanol in xylene using 1,10-phenanthroline as indicator.[50] NBS was recrystallized from benzene or nitromethane and NCS was recrystallized from CCl_4; both reagents assayed for >98% available halogen by titration with sodium thiosulfate.

General Procedures for the Hydrolysis of 1,3-Dithiane Derivatives. A. Mercuric Chloride Method.—A solution of the dithiane (1.0 mmol) in aqueous 80% acetonitrile (10 ml), unless otherwise state, was added at 25° to an efficiently stirring solution of mercuric chloride (2.2 mmol) in the same solvent mixture (15 ml). Mercuric oxide (1.1 mmol) or powdered calcium carbonate (2.2 mmol) often was added to buffer the reaction mixture near pH 7. The dithiane–mercuric chloride complex usually separated as a flocculent white precipitate. The mixture was stirred and heated at reflux under nitrogen for 4–6 hr, cooled, and filtered through Super Cel; the filter cake was washed thoroughly with 1:1 hexane–dichloromethane. The organic phase of the filtrate was washed with 5 *M* aqueous ammonium acetate, water, and brine, dried ($MgSO_4$), and freed of solvent. Specific reaction conditions are listed in Tables II and III.

B. *N*-Bromosuccinimide Method.—A solution of the dithiane (1.0 mmol) in acetonitrile or acetone (1–5 ml) at 25° was added dropwise *to* a solution of NBS (6–8 mmol) in aqueous 80% acetonitrile or 90–97% acetone (10–25 ml) stirring at −5 to 30°. The solution quickly turned red (bromine) but soon faded to yellow-orange; it was stirred for 5–10 min and shaken with a mixture of saturated aqueous sodium sulfite and 1:1 hexane–dichloromethane. The organic phase was washed with 1.0 *M* aqueous sodium bicarbonate, water, and brine, dried ($MgSO_4$), and freed of solvent. When a 2,6-dimethylpyridine (12–16 mmol) was initially present to buffer the reaction mixture near neutrality, the organic phase was also washed well with 5 *M* aqueous cupric nitrate. Specific reaction conditions are shown in Tables IV and V.

C. *N*-Chlorosuccinimide–Silver Nitrate Method.—A solution of the dithiane (1.0 mmol) in acetonitrile (0.5–2 ml) was added quickly *to* a well-stirred solution of NCS (4.0 mmol) and silver nitrate (4.5 mmol) in aqueous 80% acetonitrile (10–25 ml) at 25°. Silver chloride separated immediately as a voluminous white precipitate and the liquid phase became yellow. The mixture was stirred for 5–10 min and treated successively at 1-min intervals with saturated aqueous sodium sulfite, saturated aqueous sodium carbonate, and brine (1 ml each); 1:1 hexane–dichloromethane (20 ml) was added; and the mixture was filtered through Super Cel. After the filter cake was washed thoroughly with 1:1 hexane–dichloromethane, the organic phase of the filtrate was dried ($MgSO_4$) and freed of solvent. Specific reaction conditions are given in Tables IV and V.

2-Benzyl-1,3-dithiane.—2-Lithio-1,3-dithiane (120 mmol) in dry THF (200 ml) under nitrogen at 0° was treated with benzyl bromide (108 mmol) in dry THF (100 ml) and kept at 0° for 3

(48) Either or both ketal groups of the doubly masked derivative **14** can be hydrolyzed in excellent yield. Reaction of **14** with 2.5 *M* sulfuric acid in aqueous THF (25°, 104 hr) gave the acyldithiane **16** (99%), which was oxidatively hydrolyzed to the α-dione **17** in quantitative yield. Alternatively, NBS hydrolysis of **14** quantitatively yielded the acyldioxolane **15**, which on acid hydrolysis also furnished **17** (87%); see Experimental Section.

(49) Olefins are readily converted to bromohydrins with aqueous NBS; see C. O. Guss and R. Rosenthal, *J. Amer. Chem. Soc.*, **77**, 2549 (1955); E. E. van Tamelen and T. J. Curphy, *Tetrahedron Lett.*, 121 (1962).

(50) S. C. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967).

hr. The oil obtained on extractive work-up was sublimed at 120° (0.6 Torr) to remove 1,3-dithiane and the residue was distilled at 112–115° (0.25 Torr) to afford 2-benzyl-1,3-dithiane (65%), pure by nmr assay, as a pale yellow oil. Crystallization from pentane at 0° furnished white needles: mp 34.5–34.9°; ir 6.69 (m), 6.88 (m), 14.42 (vs) (all C_6H_5), 6.97 (m), 7.04 (s), 7.84 (s), 8.06 (m), 8.43 (m), and 8.52 (m), 10.97 (m), and 11.52 μ (w) (all dithiane[51]); nmr 1.83 (m, 2 H, CCH_2C), 2.63 (m, 4, CH_2S), 2.88 (d, 2 H, J = 7.0 Hz, $CH_2C_6H_5$), 4.07 (t, 1 H, J = 7.0 Hz, SCHS), and 7.15 ppm (s, 5 H, C_6H_5).

Anal. Calcd for $C_{11}H_{14}S_2$: C, 62.80; H, 6.71; S, 30.49. Found: C, 62.99; H, 6.73; S, 30.61.

Phenylacetaldehyde 2,4-Dinitrophenylhydrazone.—2-Benzyl-1,3-dithiane was hydrolyzed with mercuric chloride and mercuric oxide in aqueous 95% methanol (see Table I). The crude product in ethanol was treated with 2,4-dinitrophenylhydrazine (1.2 equiv) in 7 M aqueous sulfuric acid; crystallization of the resulting precipitate from ethanol furnished the title compound as yellow plates, mp 117–118° (lit.[52] mp 121°).

2-Methyl-1,3-dithiane.—A stirring solution of acetaldehyde (23.6 g, 0.54 mol) and 1,3-propanedithiol (49 ml, 0.48 mol) in trichloromethane (300 ml) was treated with a moderate stream of HCl gas for 40 min, during which time the temperature rose to 60° and an aqueous phase separated. The organic phase was washed with water, 2.5 M aqueous sodium hydroxide, water, and brine, dried (K_2CO_3), and freed of solvent. Distillation afforded 2-methyl-1,3-dithiane (58.3 g, 91%) as a colorless liquid: bp 53–54° (1.1 Torr) [lit.[53] bp 79–80° (8–10 Torr); lit.[54] bp 66° (5 Torr)]; ir 6.87, 7.30, and 9.43 (all m, CH_3) and 6.99 (m), 7.03 (s), 7.08 (m), 7.84 (m), 8.09 (m), 8.40 (m), 8.54 (w), 10.99 (m), and 11.55 μ (w) (all dithiane[51]); nmr, identical with the published spectrum.[2]

Anal. Calcd for $C_5H_{10}S_2$: C, 44.77; H, 7.52; S, 47.71. Found: C, 44.76; H, 7.31; S, 48.04.

1-Acetyl-2-cyclohexenol (2) was prepared from the α-hydroxy dithiane 1[8] (a) in 93% yield with mercuric chloride and calcium carbonate and (b) in 71% yield with NCS–silver nitrate at 55° for 5 min. The filtered reaction solution from (a) was freed of acetonitrile before extraction, as the title alcohol was moderately water soluble. Short-path distillation afforded the analytical sample: bp 83° (10 Torr), 32° (0.08 Torr); tlc R_f 0.30 ($CHCl_3$); ir 2.87 (m, OH), 5.84 (vs, C=O), 7.40 (s), 8.59 (s), 9.10 (s), 9.75 (m), and 10.42 μ (m); nmr 1.3–2.3 (m, 6 H, $(CH_2)_3$), 2.17 (s, 3 H, CH_3), 3.95 (s, 1 H, OH), 5.46 (d, 1 H, J_1 = 10 Hz, C=CH), and 6.02 ppm (dt, 1 H, J_1 = 10, J_2 = 3.5 Hz, CH_2CH=C).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.39; H, 8.59.

Alcohol 2 was recovered unchanged after being heated at reflux for 45 min with 0.4 M methanolic sodium methoxide (1.1 mol).

3-Acetyl-2-cyclohexenyl Trifluoroacetate.—A solution of 1-acetyl-2-cyclohexenol (2, 0.280 g, 2.00 mol) in trifluoroacetic acid (0.75 ml, 10 mmol) was kept at 25° for 20 hr, diluted with dichloromethane, washed with 1 M aqueous sodium bicarbonate–brine (1:1), dried ($NaHCO_3$–$MgSO_4$), and freed of solvent to furnish the title ester (0.399 g; 85%), pure by ir and nmr assay. Distillation afforded the analytical sample: bp 52° (0.09 Torr); uv max (95% EtOH) 225 nm (ϵ 11,600); ir 5.62 (s, CF_3C=O), 5.96 (s, CH_3C=O), 8.17, 8.51, and 8.69 μ (all vs, CF_3CO); nmr 1.5–2.4 (m, 6 H, $(CH_2)_3$), 2.26 (s, 3 H, CH_3), 5.4–5.7 (m, 1 H, OCH), and 6.5–6.7 ppm (m, 1 H, C=CH); mass spectrum m/e (rel intensity, assignment) 236 (100, molecular ion M), 221 (41, M − CH_3), 193 (70, M − $COCH_3$), and 139 (47, M − $COCF_3$).

Anal. Calcd for $C_{10}H_{11}F_3O_3$: C, 50.85; H, 4.69. Found: C, 50.89; H, 4.84.

3-Acetyl-2-cyclohexenol (4).—A solution of the trifluoroacetate of 4 (64 mg, 0.27 mmol) and sodium bicarbonate (32 mg, 0.38 mmol) in methanol (1.0 ml) was stirred at 25° for 25 hr and freed of solvent. Trituration of the residue with dichloromethane and evaporation of the resulting solution provided the title alcohol (36 mg, 95%) as a liquid: ir 2.91 (m, OH), 5.96 (s, C=O), 6.07 (sh, C=C), 7.30, 7.45, 8.03, 8.15, 9.37, 9.55, and 10.55 μ (all m–s); nmr 1.2–2.4 (m, 6 H, $(CH_2)_3$), 2.25 (s, 3 H, CH_3), 4.0–4.5 (b s, 2 H, CHOH), and 6.72 ppm (b s, 1 H, C=CH). This product was identical with an authentic sample[8] by ir and nmr assay.

Treatment of the α-hydroxyenone 2 with CCl_4 saturated with HCl (25°, 23 hr) gave a mixture of 2 and the title alcohol 4 in the ratio of 2/4 = 6:4 (nmr).

3-Acetyl-2-cyclohexenone (6).—3-(2-Methyl-1,3-dithianyl-2)-2-cyclohexenone[8] (5), R_f 0.61 ($CHCl_3$, 3 developments), was hydrolyzed for 6 hr with mercuric chloride (4 mol); the product was crystallized from 1:1 hexane–benzene to afford the enedione 6 in 84% yield as light yellow plates: mp 48.8–49.8° (lit.[8] mp 49.9–50.4°); tlc R_f 0.52 ($CHCl_3$, 3 developments); ir 5.92 (s, C=O), 8.0 (m), 8.23 (s), 8.46 (m), and 10.35 μ (m). This product was identical with an authentic sample[8] by ir and tlc assay. Treatment of 5 with 2 mol of mercuric chloride for 4 hr gave a mixture containing 5/6 = 1:3. The quantitative hydrolysis of 5 to the title enedione 6 using NCS and silver nitrate (0°, 25 min) has been described.[8]

2-(2-Phenylethyl)-1,3-dithiane (7).—1,3-Dithiane[7] (5.75 g, 47.4 mmol) in dry THF (90 ml) under nitrogen was cooled to −75° and treated with 1.60 M n-butyllithium in hexane (30 ml, 48 mmol). The solution was kept at −10° for 2.5 hr, cooled to −90° with an ether–ethanol slush, and treated dropwise over 3 min with (2-bromoethyl)benzene. The solution was stored at −10° for 10 hr, diluted with 1:1 pentane–dichloromethane (200 ml), and washed with 0.5 M aqueous ammonium chloride, water, and brine; the organic phase was dried (K_2CO_3) and freed of solvent. Short-path distillation afforded the dithiane 7 (7.4 g, 69%) as a colorless liquid: bp 130° (0.06 Torr); ir 7.03 (s), 7.06 (m), 7.84 (s), 8.04 (m), 8.34 (m), 8.47 (m), 11.01 (s), and 11.50 μ (m) (all dithiane[51]); nmr 1.8–2.2 (m, 4 H, CCH_2C), 2.6–2.9 (m, 6 H, CH_2S and $CH_2C_6H_5$), 3.88 (t, 1 H, SCHS), and 7.15 ppm (s, 5 H, C_6H_5).

Anal. Calcd for $C_{12}H_{16}S_2$: C, 64.23; H, 7.19. Found: C, 64.33; H, 7.30.

3-Phenylpropanal (8).—Treatment of the dithiane 7 with mercuric chloride–mercuric oxide in aqueous 95% methanol afforded an oil that was primarily 1,1-dimethoxy-3-phenylpropane: nmr 1.7–2.1 (m, 2 H, $CH_2CH_2C_6H_5$), 2.5–2.8 (m, 2 H, $CH_2C_6H_5$), 3.28 (s, 6 H, CH_3), 4.30 (t, 1 H, OCHO), and 7.18 ppm (m, 5 H, C_6H_5). It was hydrolyzed with 2:1 dioxane–1.0 M aqueous hydrochloride acid (50°, 1.0 hr) to furnish 3-phenylpropanal (68% yield overall) as a colorless liquid: ir 3.49, 3.61 (both m, O=CH), and 5.86 μ (vs, C=O); nmr 2.3–3.0 (A_2B_2 m, 4 H, CH_2CH_2), 7.12 (s, 5 H, C_6H_5), and 9.57 ppm (s, 1 H, CHO); 2,4-dinitrophenylhydrazone, mp 152–153° (lit.[55] mp 149°; lit.[56] mp 155–157°).

Reaction of the dithiane 7 with NBS (6 mol) in aqueous 80% acetonitrile at 5° provided the title aldehyde in 90% yield.

2,2-Bis(2-phenylethyl)-1,3-dithiane (9).—1,3-Dithiane[7] (9.00 g, 75 mmol) in dry THF (140 ml) was cooled to −50° under nitrogen, treated with 1.60 M n-butyllithium in hexane (56 ml, 82 mmol), and stored at 0°. Anion formation was judged complete after 2 hr by adding part of the solution to D_2O and measuring the deuterium incorporation at C-2 by nmr. The solution was cooled to −50°, treated with (2-bromoethyl)benzene (15.2 g, 82 mmol) in dry THF (25 ml), and stored at 0°. After 15 hr (80% alkylation by the above assay) the solution was cooled to −60°, treated with 1.60 M n-butyllithium in hexane (60 ml, 96 mmol), and stored at 0°. After 2 hr (complete anion formation) the solution was cooled to −60°, treated with (2-bromoethyl)-benzene (17.7 g, 96 mmol) in dry THF (20 ml), stored at 0° for 40 hr, diluted with water, and extracted with 1:1 pentane–dichloromethane. The extracts were washed with 1.0 M aqueous hydrochloric acid, water, and brine, dried (K_2CO_3), and freed of solvent.

Vacuum distillation of the remaining oil provided, after a forerun containing the monoalkyl dithiane 7, the title dithiane (8.6 g, 35% yield), pure by tlc, as a viscous oil: bp 220° (0.20 Torr); tlc R_f 0.5 (1:1 pentane–benzene). Filtration through silica gel and crystallization four times from pentane at −20° afforded small white crystals: mp 46.4–46.6°; ir 7.03 (m), 7.07 (m), 7.84 (m), 8.07 (w), 10.98 (m), and 11.47 μ (w) (all di-

(51) Examination of the ir spectra of over 100 1,3-dithiane derivatives bearing C-2 substituents has permitted assignment of the following bands to this ring system: ir max (rel intensity) 6.99 (m), 7.02 (m–s), 7.06 (m), 7.84 (m–s), 8.06 (w–m), 10.98 (m–s), and 11.5 μ (w–m). In addition, bands are seen at 8.44 and 8.53 μ (w–m) when C-2 bears one proton (N. H. Andersen and B. W. Erickson, unpublished results).

(52) "Tables for Identification of Organic Compounds," 2nd ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1964, p 86.

(53) L. Autenrieth and K. Wolff, *Chem. Ber.*, **32**, 1375 (1899).

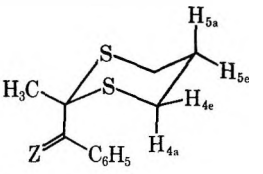
(54) E. E. Campaigne and G. F. Schaefer, *Bol. Col. Quim. P. R.*, **9**, 25 (1952); *Chem. Abstr.*, **46**, 10884 (1952).

(55) C. F. H. Allen and J. H. Richmond, *J. Org. Chem.*, **2**, 222 (1937).

(56) M. Stiles and A. J. Sisti, *ibid.*, **25**, 1691 (1960).

Table VI

220-MHz Nmr Data for Two Compounds with Conformationally Rigid 1,3-Dithiane Rings[a]



Compd	Chemical shift, ppm: δ_{4a} (ddd)	δ_{4e} (ddd)	δ_{5a} (dtt)	δ_{5e} (dtt)	Coupling constant, Hz: $J_{4a,4e}$	$J_{4a,5a}$	$J_{4a,5e}$	$J_{4e,5a}$	$J_{4e,5e}$	$J_{5a,5e}$
Ketal 14[b]	3.23	2.65	1.88	2.08	13.8	10.4	3.0	3.4	6.1	13.8
Ketone 16[c]	3.32	2.71	1.89	2.15	14.2	12.4	2.7	3.2	4.4	14.0

[a] Varian HR-220 spectrometer, $CDCl_3$ solvent. [b] Also 1.50 (s, 3 H, CH_3), 3.5–4.3 (A_2B_2 m, 4 H, OCH_2CH_2O), and 7.1–7.6 ppm (m, 5 H, C_6H_5). [c] Plus 1.75 (s, 3 H, CH_3) and 7.2–8.1 ppm (m, 5 H, C_6H_5).

thiane[61]); nmr 1.6–2.4 (m, 6 H, CCH_2C). 2.5–2.9 (m, 8 H, CH_2S and $CH_2C_6H_5$), and 7.13 ppm (s, 5 H, C_6H_5).

Anal. Calcd for $C_{20}H_{24}S_2$: C, 73.11; H, 7.36; S, 19.52. Found: C, 73.07; H, 7.24; S, 19.65.

1,5-Diphenyl-3-pentanone (10) was prepared from the dithiane **9** (a) in 86% yield with mercuric chloride in aqueous 90% methanol and (b) in 97% yield with NBS (8 mol) in aqueous 96% acetone at −5°. Short-path distillation afforded the ketone **10** as a colorless oil: bp 160° (0.1 Torr); ir 5.80 (s, C=O), 6.70, 6.90 (both m, CH_2 bend), and 14.30 μ (s, C_6H_5); nmr 2.68 (A_2B_2 sextet, 4 H, CH_2CH_2) and 7.12 ppm (s, 5 H, C_6H_5).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.68; H, 7.61. Found: C, 85.51; H, 7.60.

2-Methyl-2-(1-cyclohexenyl)methyl-1,3-dithiane (11).—Cyclohexenyl acetone and 1,3-propanedithiol were condensed by the procedure described above for the preparation of 2-methyl-1,3-dithiane to provide the title dithiane in 85% yield as a colorless liquid: bp 125–127° (0.12 Torr); tlc R_f 0.17 (CCl_4), R_f 0.74 (CH_2Cl_2); ir 7.00, 7.06, 7.86, 8.09, 10.98, and 11.53 μ (all m, dithiane[61]); nmr 1.57 (s, 3 H, CH_3), 1.4–2.3 (m, 10 H), 2.50 (s, 2 H, CH_2C=O), 2.7–2.9 (m, 4 H, CH_2S), and 5.48 ppm (b s, 1 H, C=CH).

Anal. Calcd for $C_{12}H_{20}S_2$: C, 63.10; H, 8.83. Found: C, 62.92; H, 8.87.

1-Cyclohexenyl-2-propanone (12) was prepared by hydrolysis of the dithiane **11** (a) in 90% yield with mercuric chloride and calcium carbonate and (b) in 94% yield with NCS and silver nitrate (25°, 10 min). These methods furnished identical samples of the nonconjugated ketone **12**: tlc R_f 0.36 (CH_2Cl_2); ir 5.81 μ (s, C=O); nmr 1.4–2.2 (m, 8 H, $(CH_2)_4$), 2.02 (s, 3 H, CH_3), 2.93 (s, 2 H, CH_2C=O), and 5.49 ppm (b s, 1 H, C=CH). Neither sample contained any trace of the conjugated ketone **13** by tlc, nmr, or ir assay; **13** is readily detected in 1-cyclohexenylacetone, a mixture of **12**/**13** = 90:10 (nmr), by a tlc spot at R_f 0.12 (CH_2Cl_2), by an nmr peak at 5.94 ppm (b s, C=CH), and by ir bands at 6.00 (C=O), 6.17 (C=C), and 10.40 μ.

2-(2-Methyl-1,3-dithianyl-2)-2-phenyl-1,3-dioxolane (14).—A mixture of 2-benzoyl-2-methyl-1,3-dithiane (**16**; 3.58 g, 15.0 mmol), ethylene glycol (4.2 g, 75 mmol), *p*-toluenesulfonic acid (0.2 g), and benzene (60 ml) was heated at reflux in a flask equipped with a Dean-Stark water separator. After 24 and 48 hr, additional 0.2-g portions of the acid catalyst were added; after 72 hr the mixture showed no ir carbonyl adsorption. It was cooled, diluted with 1:1 pentane–dichloromethane, washed with 0.5 *M* aqueous sodium bicarbonate, water, and brine, dried, and freed of solvent. The residue was recrystallized from cyclohexane to afford the dioxolane **14** (3.96 g, 90%) as white needles: mp 118.4–119.0°; tlc, R_f 0.43 (CH_2Cl_2); ir 7.00, 7.02, 7.08, 7.82, 10.99, 11.46 (all m, dithiane[61]), 9.09, and 9.24 μ (both s, dioxolane); nmr, see Table VI; mass spectrum *m/e* (rel intensity, assignment) 282 (0.25, molecular ion M), 149 (100, M − $C_5H_9S_2$), and 133 (8, M − $C_9H_9O_2$).

Anal. Calcd for $C_{14}H_{18}O_2S_2$: C, 59.54; H, 6.42; S, 22.71. Found: C, 59.84; H, 6.48; S, 22.73.

2-Acetyl-2-phenyl-1,3-dioxolane (15) was obtained from the dioxolane **14** (a) in 76% yield using mercuric chloride (4.0 mol) and calcium carbonate (4.4 mol) and (b) in quantitative yield with NBS (6 mol) at 15°. Short-path distillation provided the analytical sample, bp 79–80° (0.06 Torr). On standing at 0° it crystallized as colorless plates: mp 27–29°; tlc R_f 0.16 (CH_2Cl_2); ir 5.75 (s, C=O), 9.05, 9.68 (both s, dioxolane), and 14.33 μ (s, C_6H_5); nmr 2.02 (s, 3 H, CH_3), 3.8–4.0 (m, 4 H, CH_2CH_2), and 7.1–7.6 ppm (m, 5 H, C_6H_5).

Hydrolysis of the ketal-dithioketal **14** to the acyldioxolane **15** was slow and incomplete using 2.2 or 3.0 mol of mercuric chloride (Table VII).

Table VII

Mercuric Chloride Hydrolysis of Ketal-Dithioketal 14 to Acyl Ketal 15

Reactant ratios[a]: $HgCl_2$	$CaCO_3$	Time,[b] hr	Yield,[c] %
2.2	2.3	5	51 (29)
2.2	2.3	24	52 (17)
3.0	3.1	10	69 (7)
4.0	4.4	1	74 (14)
4.0	4.4	4	81 (5)

[a] Moles per mole of **14**. [b] Aqueous 80% CH_3CN at reflux under N_2. [c] Recovery of **14** (%) in parentheses.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.70; H, 6.23.

2-Benzoyl-2-methyl-1,3-dithiane (16). A. Addition of 2-Lithio2-methyl-1,3-dithiane to Benzonitrile.—The published procedure[1] was modified. 2-Methyl-1,3-dithiane (28.0 g, 0.208 mol) in dry THF (400 ml) was cooled under nitrogen to −75°, treated with 1.60 *M* *n*-butyllithium in hexane (135 ml, 0.216 mol), stored at −20° for 16 hr, cooled to −75°, and treated dropwise with benzonitrile (22.7 g, 0.220 mol). The bright orange solution was maintained at −75° for 1.0 hr, warmed to 0° over 1.0 hr, treated with 3 *M* aqueous HCl (80 ml), and heated at reflux (65°) for 1.0 hr. The mixture was freed of organic solvents and extracted with 1:1 dichloromethane–ether; the extract was washed with 2 *M* aqueous sodium hydroxide, 1 *M* aqueous HCl, water, and brine, dried, and freed of solvent. The crystalline residue was treated with charcoal and recrystallized from methanol to furnish the acyldithiane **16** (46.9 g, 94.5%) as white crystals: mp 98.6–98.9° (lit.[1] mp 98.4–98.8°); tlc R_f 0.52 (CH_2Cl_2), R_f 0.80 (acetone); ir 5.95 (s, C=O), 6.99, 7.02, 7.08, 7.84, 11.01, and 11.54 μ (all m, dithiane[61]); nmr, see Table VI.

Anal. Calcd for $C_{12}H_{14}OS_2$: C, 60.50; H, 5.92; S, 26.86. Found: C, 60.33; H, 5.99; S. 27.10.

B. Selective Hydrolysis of the Dioxolane 14.—Compound **14** (0.283 g, 1.00 mmol), THF (6 ml), and aqueous 48% sulfuric acid (2 ml) were stirred at 25° for 4.3 days, treated with 1.2 *M* aqueous sodium hydroxide (16 ml), and extracted with ether. The extract was washed with 1 *M* aqueous sodium bicarbonate and brine, dried, and freed of solvent to furnish the acyldithiane **16** (0.236 g, 99%), pure by nmr assay, as white crystals, mp 96.8–98.0°.

1-Phenyl-1,2-propanedione (17). A. Hydrolysis of 2-Benzoyl-2-methyl-1,3-dithiane (16).—The reaction conditions and results are listed in Tables III and IV.

B. Hydrolysis of 2-Acetyl-2-phenyl-1,3-dioxolane (15).—The acyldioxolane **15** (0.335 g, 1.74 mmol), THF (10 ml), and aqueous 48% sulfuric acid (10 ml) were stirred at 25° for 48 hr and extracted with 1:1 pentane–dichloromethane; the extract was washed with 2 *M* aqueous ammonium acetate, water, and brine, dried, and freed of solvent. Short-path distillation of the residual liquid afforded the diketone **17** (0.224 g, 87%), pure by

nmr, as a clear yellow liquid: bp 100° (15 Torr) [lit.[57] bp 123° (23 Torr)]; ir 5.83 (s, $CH_3C{=}O$), 5.95 (s, $C_6H_5C{=}O$), 8.63 (s), 11.41 (s), and 14.33 μ (s, C_6H_5); nmr 2.45 (s, 3 H, CH_3) and 7.3–8.1 ppm (m, 5 H, C_6H_5). Lower acidity or a shorter reaction period resulted in incomplete conversion (see Table VIII).

TABLE VIII

ACID HYDROLYSIS OF α-KETO KETAL 15 TO α-DIONE 17[a]

Sulfuric acid, M	Time, hr	Yield,[b] %
6	75	44 (46)
9	12	78 (12)
9	18	81 (9)
9	48	87 (1)

[a] THF–water (2:1, 10 ml/mmol of 15) at 25°. [b] Recovery of 15 (%) in parentheses.

2-Benzyl-2-ethoxycarbonyl-1,3-dithiane (18).—2-Benzyl-1,3-dithiane (4.37 g, 20.8 mmol) in dry THF (100 ml) was cooled under nitrogen to −50°, treated with 1.60 M n-butyllithium in hexane (14 ml, 23 mmol), and warmed to −20° over 2 hr. The resulting anion solution was cooled to −75° and added over 1 hr through a narrow stainless steel tube to a solution of ethyl chloroformate (31 ml, 0.33 mol) in dry THF (31 ml) stirring under nitrogen at −75°. The reaction mixture was stored at 0° for 12 hr and freed of most solvent; ether extracts of the residual oil were washed with 1 M aqueous sodium bicarbonate, water, and brine, dried, and freed of solvent. Short-path distillation furnished the ester 18 (4.40 g, 75%), pure by nmr assay, as a colorless oil: bp 144° (0.01 Torr); ir 5.79 (s, C=O), 7.02, 7.07, 7.85, and 11.00 (all m, dithiane[51]), 8.32, and 8.47 μ (both s, CO); nmr 1.25 (t, 3 H, J = 7 Hz, CH_3), 1.5–2.1 (m, 2 H, H_{5a} and H_{5e}), 2.50 (dt, 1 H, H_{4e}), 3.29 (ddd, 1 H, H_{4a}), 3.29 (s, 2 H, $CH_2C_6H_5$), 4.15 (q, 2 H, J = 7 Hz, CH_2O), and 7.19 ppm (s, 5 H, C_6H_5) with $J_{4a,4e}$ = 14, $J_{4a,5a}$ = 12, and $J_{4a,5e} = J_{4e,5a} = J_{4e,5e}$ = 4 Hz.

Anal. Calcd for $C_{14}H_{18}O_2S_2$: C, 59.54; H, 6.42; S, 22.71. Found: C, 59.82; H, 6.58; S, 22.50.

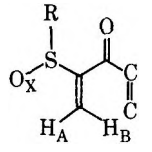
Ethyl 3-Phenylpyruvate (19).—Reaction of the acyldithiane 18 with NBS (8 mol) in aqueous 95% acetone at −5° provided the α-keto ester 19 in 78% yield as a colorless liquid: ir 5.76 μ (s, C=O); nmr 1.20 (t, 3 H, J = 7.0 Hz, CH_3), 3.95 (s, 2 H, $CH_2C_6H_5$), 4.11 (q, 2 H, J = 7.0 Hz, CH_2O), and 7.11 ppm (s, 5 H, C_6H_5). On treatment with 1:1 pyridine–CCl_4 the keto ester was mainly converted to an enol tautomer[58] [partial nmr 1.25 (t, 3 H, J = 7.0 Hz, CH_3), 4.23 (q, 2 H, J = 7.0 Hz, CH_2O), and 6.47 ppm (s, 1 H, $C{=}CHC_6H_5$)]; the equilibrium ratio was keto/enol = 3:17 by nmr assay.

(57) I. Smedley, *J. Chem. Soc.*, **95**, 218 (1909).

(58) Ester **19** is reported to exist in two enol forms [α, mp 52°; β, bp 152° (15 Torr)] and a keto form (γ, mp 79°): see H. Gault and R. Weick, *Bull. Soc. Chim. Fr.*, [4] **31**, 867 (1922).

3-Chloro-3-(1-oxo-1-phenyl-2-propenyl-2-sulfinyl)propanesulfonyl Chloride (20).—Treatment of the acyldithiane 16 with NCS (4.0 mol) and cupric chloride dihydrate (4.0 mol) in aqueous 80% acetonitrile (30°, 10 min) afforded an oil that was subjected to preparative tlc. The polar material (R_f 0.09, $CHCl_3$) was predominately the title compound: ir 6.08 (m, C=O), 6.28 (w, C=C), 7.29 (s, asym SO_2Cl), 8.58 (s, sym SO_2Cl), 9.55 (m, S=O), and 14.5 μ (m, C_6H_5); nmr 2.2–4.1 (m, 5 H, CH_2CH_2CH), 6.65 (s, 1 H, H_A), 6.82 (s, 1 H, H_B), and 7.3–7.9 ppm (m, 5 H, C_6H_5); mass spectrum m/e (rel intensity) 338 (45), 339 (8), 340 (32), 341 (6), and 342 (9) [calcd for $C_{11}H_{12}Cl_2O_4S_2$: 338 (44), 339 (8), 340 (34), 341 (6), and 342 (8)] plus m/e 302 (molecular ion − HCl), 105 ($C_7H_5O^+$), and 77 ($C_6H_5^+$).

Use of the tables of Pascual, Meier, and Simon,[59] which correlate chemical shifts of olefinic protons with their chemical environment, predicts that the vinylic protons A and B in the partial structure 21 will appear at 5.99 and 6.25 ppm, respectively, when X = 0 and at 7.38 and 7.24 ppm, respectively, when X = 2. By interpolation, protons A and B should appear at 6.68 and 6.74 ppm, respectively, when X = 1. The observed values for the vinylic protons of the sulfoxide 20 (6.65 and 6.82 ppm) are in good accord with this prediction.



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Registry No.—2, 31593-36-9; 4, 15040-95-6; 6, 15040-96-7; 7, 31593-39-2; 8, 104-53-0; 9, 31593-41-6; 10, 5396-91-8; 11, 31593-43-8; 12, 768-50-3; 14, 31593-45-0; 15, 31593-46-1; 16, 4883-01-6; 17, 579-07-7; 18, 4882-96-6; 19, 6613-41-8; 20, 31593-50-7; mercuric chloride, 7487-94-7; N-bromosuccinimide, 128-08-5; N-chlorosuccinimide, 128-09-6; silver nitrate 7761-88-8; 2-benzyl-1,3-dithiane, 31593-52-9; 2-methyl-1,3-dithiane, 6007-26-7; 3-acetyl-2-cyclohexenyl trifluoroacetate, 31593-54-1; 1,1-dimethoxy-3-phenylpropane, 30076-98-3.

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Solvolysis of 1-Chloro-1-nitro-1-phenylethane and Its Derivatives[1]

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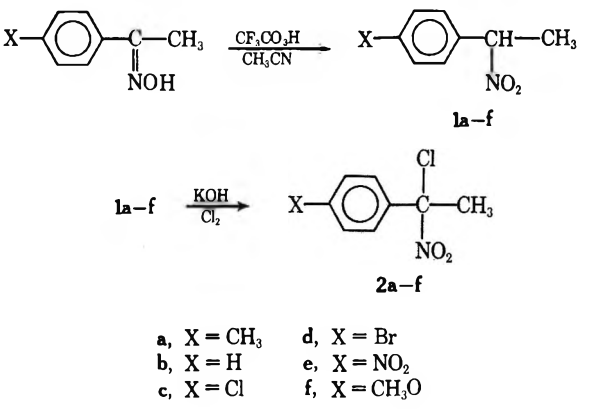
The solvolyses of five 1-chloro-1-nitro-1-(*p*-X-phenyl)ethanes (X = CH_3, H, Cl, Br, NO_2), **2a–e**, respectively, have been studied in 50 and 80% aqueous ethanol and in 90% formic acid. A linear Hammett correlation utilizing σ^+ values was obtained in 50% ($\rho = -1.52$; $r = -0.9976$) and 80% ($\rho = -1.62$; $r = -0.9959$) aqueous ethanol for **2b–e**. The methyl derivative **2a** hydrolyzed faster in these solvents than predicted from its σ^+ value and the ρ values mentioned. In 90% formic acid, however, the rates of solvolysis of **2a**, **2b**, **2d**, and **2e** were all correlated well with σ^+ values ($\rho = -3.73$; $r = -0.9951$). It is suggested that, as is the case in the solvolysis of other benzylic systems, two mechanisms are involved in the more nucleophilic aqueous ethanol solvents, with those compounds containing electron-withdrawing substituents requiring nucleophilic involvement of solvent molecules. In the less nucleophilic but highly ionizing formic acid solvent, a single mechanism involving a high degree of carbonium ion character prevails for all compounds. Anchimeric assistance by the nitro group is apparently not involved in these solvolyses.

A nitro group conjugated with a reaction center strongly inhibits carbonium ion formation in SN1 solvolyses. In alcoholysis, *p*-nitrobenzyl halides react at a rate one-tenth to one-twentieth that of the corresponding benzyl halides.[2,3] Similarly, *p*-nitrobenzhydryl chloride undergoes alcoholysis much more slowly than benzhydryl chloride, the relative rate being 0.00069.[4,5] These findings lead to the expectation that α-halonitro compounds, in which the nitro group is attached directly to the reaction site, should solvolyze very sluggishly. This expectation is substantiated by the work of Simonetta, Favini, and Carra with 2-chloro-2-nitropropane, which ionizes very slowly even at 90° in the presence of an excess of silver ion.[6] In contrast, however, Norten and Slater found that α-nitrobenzhydryl chloride (**3**) ionizes in 80% ethanol at about the same rate that *p*-nitrobenzhydryl chloride would be expected to ionize.[7] This unanticipated finding prompted the present exploration of the possibility of anchimeric assistance to ionization by the nitro group. Nitro group participation has been utilized to explain unexpectedly large differences in reactivity between *o*-nitro and *p*-nitro benzyl and benzhydryl systems. Kim, Friedrich, Andrews, and Keefer report that for the acetolysis at 25° of *o*-nitrobenzhydryl bromide and *p*-nitrobenzhydryl bromide the rate constant ratio, k_{ortho}/k_{para}, is approximately 3000.[8] Similarly, for the dissociation rates of the isomeric nitroiodobenzene dichlorides, the rate constant ratio in acetic acid at 25° is of the order of 1000.[9] From this work it is apparent that nitro group participation can be expected in those systems in which the geometry is favorable, although the solvolysis in ethanol–water mixtures of *o*-nitrobenzyl chloride represents an apparent anomaly in this respect.[10]

The work of Kemp and Metzger[11] and of Bordwell and Knipe[12,13] suggested a possible approach to the problem. The ρ value for hydrolysis of substituted α-bromophenylacetates was shown to be relatively insensitive to salt and medium effects, and this was interpreted as resulting from intramolecular electrostatic interaction of the carboxylate ion with the incipient carbonium ion center. Accordingly, a study of solvent effects on the magnitude of ρ for the hydrolysis of a series of 1-chloro-1-nitro-1-(*p*-X-phenyl)ethanes might provide information bearing on the possibility of nitro group participation.

Results and Discussion

Six 1-chloro-1-nitro-1-(*p*-X-phenyl)ethanes, **2a–f**, were prepared as shown in the following equations. Oxidation of the appropriate oximes of para-substituted acetophenones gave 1-nitro-1-(*p*-X-phenyl)ethanes, **1a–f**, which were converted to the nitronate anions in basic solution and allowed to react with chlorine to produce **2a–f**.[14] Of the halonitro compounds, the *p*-methoxy derivative, **2f**, proved to be unstable and decomposed on standing at room temperature with the evolution of a brown gas. Although the spectral data for this compound (see Experimental Section) substantiated its structure, the rapid decomposition precluded elemental analysis and solvolysis studies. Compounds **2a–d** are oils which were purified by elution chromatog-



a, X = CH_3 **d**, X = Br
b, X = H **e**, X = NO_2
c, X = Cl **f**, X = CH_3O

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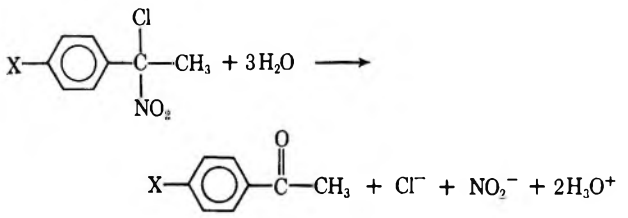
(13) F. G. Bordwell and A. C. Knipe, *ibid.*, **35**, 2959 (1970).
(14) The syntheses of the nitro compounds utilized in this study have recently been reported by F. G. Bordwell, W. J. Boyle, Jr., and K. C. Yee [*J. Amer. Chem. Soc.*, **92**, 5926 (1970)]. They have also been synthesized by an alternative route: M. Fukuyama, P. W. K. Flanagan, F. T. Williams, L. Frainier, S. A. Miller, and H. Shechter, *ibid.*, **92**, 4689 (1970).

raphy using Florisil, and **2e** is a solid that was purified by recrystallization from aqueous ethanol

The stoichiometry of the hydrolysis of **2a–e** is given in the equation. In aqueous ethanol solutions the hydrolyses were followed by an ultraviolet spectrophotometric



technique based on the absorbance changes resulting from the production of the substituted acetophenones. The reactions were usually followed to approximately 60% completion, and good, first-order kinetics were observed in all cases. The calculated infinity readings generally agreed quite closely with those observed after several half-lives, which indicated that the ketones were produced quantitatively. Spectrophotometric analysis of the reaction of **2e** was precluded by its strong absorption at 257 nm (ϵ 11,500) which masked the developing absorption of *p*-nitroacetophenone at 263 nm (ϵ 12,600). This hydrolysis was therefore followed by a titrimetric method for chloride ion. All runs in 90% formic acid were analyzed by the titrimetric method because of the intensity of the end absorption of the formic acid contained in the diluted samples. Spectrophotometric examination of a reaction mixture of **2a** after 16 half-lives revealed that in 90% formic acid *p*-methylacetophenone was produced quantitatively, but the analysis involved measurements on the steep part of the end-absorption curve, such that the spectrophotometric method appeared to be less desirable than the titrimetric method for kinetic measurements. The equivalency of the methods was demonstrated by titrimetric runs using compound **2a** in 50% ethanol at 50.0°. The rate constants obtained by both methods (see Table I) agreed within 12%.

The rate of hydrolysis of 1-chloro-1-nitro-1-(*p*-nitrophenyl)ethane (**2e**) in 80% ethanol was so slow that it was inconvenient to measure. The rate constant in this solvent was calculated from the rates in 50 and 40% ethanol using the Winstein–Grunwald equation.[15] Several attempts were made to measure the rate of hydrolysis of the unstable 1-chloro-1-nitro-1-(*p*-anisyl)-ethane (**2f**). Hydrolysis in 50% ethanol at 30° produced *p*-methoxyacetophenone but did not show good first-order kinetics.

The rate constants determined in the various solvents and at different temperatures are collected in Table I. A comparison of the general magnitude of those rate constants to those of the corresponding benzyl chlorides shows about the same relationship as revealed by comparison of the rate constant for hydrolysis of chlorodiphenylnitromethane (α-nitrobenzhydryl chloride) (**3**) with that of benzhydryl chloride. Specifically, the relative rate of solvolysis in 80% ethanol at 25° for α-nitrobenzhydryl chloride[7] compared to benzhydryl chloride[16] is 4.88×10^{-4}, whereas at 50° the relative rate for 1-chloro-1-nitro-1-phenylethane compared to α-phenylethyl chloride[17] is 2.74×10^{-4}. This suggests that the α-nitro group produces in both the benzhydryl and benzyl systems the same change in degree of carbonium ion character in the transition state leading to solvolysis.

(15) S. Winstein and E. Grunwald, *J. Amer. Chem. Soc.*, **70**, 846 (1948).
(16) A. M. Ward, *J. Chem. Soc.*, 2285 (1927).

TABLE I

SOLVOLYSIS OF 1-CHLORO-1-NITRO-1-(*p*-X-PHENYL)ETHANES

X	Solvent[a]	Temp, °C	k_1, sec^{-1}	n[b]	% devn[c]
CH_3	50% ethanol	80.0	2.49×10^{-4}	5	2.9
		65.0	5.55×10^{-5}	3	2.9
		50.0[d]	1.03×10^{-5}	3	0.9
		50.0[e]	0.91×10^{-5}	2	2.8
	80% ethanol	80.0	1.76×10^{-4}	2	0.5
	90% formic acid	50.0	4.32×10^{-4}	2	0.0
		40.0	1.46×10^{-4}	2	1.2
H	50% ethanol	80.0	1.19×10^{-5}	5	4.7
		65.0	2.21×10^{-6}	3	1.7
		50.0	2.91×10^{-7}	5	3.7
	80% ethanol	80.0	1.84×10^{-6}	2	1.5
	90% formic acid	80.0	6.12×10^{-4}	2	4.6
Cl	50% ethanol	80.0	8.53×10^{-6}	3	0.8
		65.0	1.36×10^{-6}	3	3.0
		50.0	1.96×10^{-7}	3	3.6
	80% ethanol	80.0	1.46×10^{-6}	2	0.9
Br	50% ethanol	80.0	6.04×10^{-6}	4	7.0
		65.0	1.14×10^{-6}	3	1.4
		50.0	1.52×10^{-7}	3	0.8
	80% ethanol	80.0	9.42×10^{-7}	2	7.5
	90% formic acid	80.0	3.44×10^{-4}	2	1.8
NO_2	40% ethanol	80.0	1.41×10^{-6}	1	
	50% ethanol	80.0	7.35×10^{-7}	3	3.4
	80% ethanol	80.0	8.99×10^{-8}	...[f]	
	90% formic acid	80.0	6.35×10^{-7}	2	2.7

[a] Volume per cent. All runs in aqueous ethanol contained 0.05 mol/l. of $NaClO_4$, and those in formic acid contained 0.065 mol/l. of $NaClO_4$. [b] Number of runs. [c] Standard deviation expressed in per cent. [d] Determined spectrophotometrically. [e] Determined titrimetrically. [f] This value was obtained by application of the Winstein–Grunwald equation using the values obtained in 40 and 50% ethanol.

Substitutuent Effects.—The substituents employed represent a reasonable range of electronic character from the strongly electron-withdrawing nitro group ($\sigma^+ = +0.79$) to the electron-donating methyl group ($\sigma^+ = -0.31$).[18] In both 50 and 80% ethanol the *p*-methyl derivative hydrolyzed much faster than would be expected from its σ^+ value and the ρ value obtained for the other substituents. The rates for compounds **2b–e** are well-correlated in both solvents, however, with $\rho = -1.52$ ($r = -0.9976$) in 50% ethanol, and $\rho = -1.62$ ($r = -0.9959$) in 80% ethanol. A σ^+ value of -0.87 in 50% ethanol and of -1.16 in 80% ethanol would be required to place the *p*-methyl derivative on the least square lines. The use of σ or σ^- values provides an even less satisfactory correlation, and, in keeping with the analogous deviation of compounds containing electron-donating substituents in various other solvolyses of benzylic systems (*vide infra*), it is apparent from the overall direction of substituent effects on the rates of the present solvolyses that the transition state involves the accumulation of electron deficiency at the reaction center.

(17) A. M. Ward, *ibid.*, 445 (1927).
(18) The various types of substituent constants and their applications have been briefly summarized by C. D. Ritchie and W. F. Sager in "Progress in Physical Organic Chemistry," Vol. 2, S. G. Cohen, A. Streitwieser, Jr., and R. W. Taft, Ed., Interscience, New York, N. Y., 1964, pp 323–400.

Activation Parameters.—Table II shows the activation parameters derived from the temperature dependence of the hydrolysis rates in 50% aqueous ethanol. Also included are the calculated rate constants at 25.0°, and the activation parameters for the *p*-methyl derivative, **2a**, in 90% formic acid. Because it was not possible to measure the rates for the *p*-nitro derivative, **2e**, as a function of temperature, data are not available for this substance. The entropies of activation are of particular interest, since they seem to offer evidence that solvent is involved nucleophilically in the transition state. Schalegar and Long have examined the entropies of activation for 23 hydrolysis reactions and have found apparently good correlation between the magnitude of $\Delta S^{\pm}$ and whether or not a water molecule is involved in the transition state.[19] In SN1 and A1 reactions, in which no solvent is thought to be directly involved, the entropies of activation fall in the range of 0 to +10 eu. In SN2 and A2 reactions, in which a water molecule is involved as a nucleophile, the magnitude of $\Delta S^{\pm}$ is from 0 to −30 eu. These ranges seemed to be valid for reactions in aqueous acetone, aqueous ethanol, aqueous dioxane, and water. Additionally, Bordwell and Knipe have shown that for the hydrolysis of α-bromophenylacetate ions, in which the carboxylate anion participates in electrostatic interaction with the reaction center, the magnitude of $\Delta S^{\pm}$ is from +11 to +22 eu.[12] The entropies of activation for the present α-chloronitro systems, which range from −3.0 to −8.6 eu, thus seem to accord best with those of reactions involving a nucleophilic push from solvent. Why the $\Delta S^{\pm}$ for the *p*-methyl derivative, **2a**, is more negative than that of any other derivative, and why this compound has the same $\Delta S^{\pm}$ in both 50% aqueous ethanol and 90% formic acid, are temporary perplexities.

TABLE II

ACTIVATION PARAMETERS FOR THE HYDROLYSIS OF 1-CHLORO-1-NITRO-1-(*p*-X-PHENYL)ETHANES[a]

X	E_a, kcal/mol	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, eu	k, sec^{-1} (25°)
CH_3	24.2	23.6	−8.6	4.371×10^{-7}
H	28.1	27.5	−3.5	7.649×10^{-9}
Cl	28.5	27.9	−3.0	4.697×10^{-9}
Br	27.9	27.3	−5.4	4.078×10^{-9}
CH_3[b]	21.8	21.2	−8.6	2.535×10^{-6}

[a] Hydrolysis in 50% aqueous ethanol containing [$NaClO_4$] of 0.05 mol/l. Rate constants at 25° were obtained by extrapolation using the Arrhenius equation. Activation parameters were calculated at 25°. [b] Hydrolysis in 90% formic acid containing [$NaClO_4$] of 0.065 mol/l.

Reaction Mechanism.—Because of the unexpected facility of these hydrolyses, worthwhile consideration can be given to several mechanistic possibilities. Although free-radical processes appear unlikely, based on previous work with the α-nitrobenzhydryl system,[7] a pathway involving nucleophilic attack on chlorine to give hypochlorous acid and nitronate anion seems plausible at first sight. The reduction of α-halonitro compounds to nitro compounds provides ample precedent for such a reaction course.[20] However, such a scheme is in conflict with the direction of the substituent effects found for the compounds under investigation. Bordwell, Boyle, and Yee have recently shown by measuring the "kinetic acidities" of a series of substituted 1-nitro-1-(X-phenyl)ethanes that substituent effects result in a ρ value of +1.44.[14] In the transition state for this reaction, a proton is being transferred to a hydroxide ion and nitronate anion is being formed. In the present solvolyses, if nucleophilic attack were on chlorine the transition state should resemble electronically that in which a proton is being transferred, and substituent effects in both reactions should be parallel. Since this is not the case, a "positive halogen" type mechanism seems improbable.

An alternative process which involves the initial loss of nitrite ion or nitrous acid to form a chlorocarbonium ion should be considered. Two observations from other systems tend to support the possibility of such a scheme. First, in the α-phenylethyl system, the presence of an α-chloro atom labilizes a leaving group toward ionization by a factor of 32,[21] which suggests that it might be easier to lose the nitro group in these systems than in other nitro compounds. Second, an acid-catalyzed reaction of α-halonitro compounds has recently been reported that clearly involves the loss of nitrous acid to form halocarbonium ion.[22] The reactions reported were carried out either at room temperature with concentrated sulfuric acid or by heating the α-halonitro compound with trichloroacetic acid. The solvolyses reported here are probably mechanistically different from these reactions, based on the apparent lack of influence of acid concentration in the present reactions. During the course of the present runs, the hydronium ion concentration increased because no effort was made to maintain it at a constant value. For example, in one particular run that was followed titrimetrically in 50% ethanol, the pH of the solution went from approximately 7 to less than 2 as the reaction was followed to about 70% completion. No systematic drift was observed in the rate constants calculated from the individual points. On this basis, it seems likely that these solvolyses involve a breaking of the carbon–chlorine bond as the initial process. Although this conclusion seems reasonably well justified for the solvolyses in aqueous ethanol, it may not be valid for the reactions in 90% formic acid.

The lack of a linear correlation for the whole range of substituents in this reaction is reminiscent of the nonlinear Hammett plots obtained for the reactions of a variety of benzylic systems. Such plots are found for the reaction of benzyl chlorides with triethylamine in benzene, of benzyl bromides with pyridine in acetone, of benzyl tosylates in aqueous acetone, aqueous dioxane, and acetic acid, and of α-bromophenylacetate ions in water. Although Hammond and coworkers felt that the nonlinearity reflected a systematic variation of a

(19) L. L. Schaleger and F. A. Long in "Advances in Physical Organic Chemistry," Vol. 1, V. Gold, Ed., Academic Press, New York, N. Y., 1963, pp 1–31.

(20) (a) M. O. Forster, *J. Chem. Soc.*, **75**, 1141 (1899); (b) M. O. Forster, *ibid.*, **77**, 254 (1900); (c) 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) W. G. Kofron, F. B. Kirby, and C. R. Hauser, *J. Org. Chem.*, **28**, 873 (1963); (e) C. R. Hauser, W. G. Kofron, W. R. Dunnavant, and W. F. Owen, *ibid.*, **26**, 2627 (1961).

(21) J. F. Arens and D. A. van Dorp, *Recl. Trav. Chim. Pays-Bas*, **67**, 973 (1948).

(22) F. Wassmundt, K. B. Galleo, and J. A. Christiano, *Tetrahedron Lett.*, 4311 (1969).

single mechanism,[23] Streitwieser and his coworkers report an abrupt change in mechanism in going from compounds containing activating substituents to those containing deactivating substituents.[24] In support of Streitwieser's interpretation are the results of Gassman and Fentiman.[25] These authors found a linear Hammett correlation over a wide range of substituents for the hydrolysis in 70:30 dioxane–water of 7-aryl-7-norbornyl *p*-nitrobenzoates. With *syn*-7-aryl-*anti*-7-norbornenyl *p*-nitrobenzoates under the same conditions, a sharp break appears in the plot at the point for the *p*-methoxy derivative, and this was interpreted in terms of cessation of neighboring-group participation of the π-electron pair. Here again, the two different ρ values within the series of compounds were interpreted as reflecting two different mechanisms.

It seems likely that the nonlinearity of the Hammett plot for the present data for aqueous ethanol solutions also results from the operation of two mechanism. It should be noted, however, that the limited number of compounds employed in this study precludes stipulation of precisely where the change of slope occurs in the plot. Although it cannot be stated with certainty that the parent compound, for instance, is correctly grouped with the *p*-nitro derivative rather than with the *p*-methyl derivative, visual inspection of the plot suggests that **2b–e** follow one mechanism while **2a** follows another. Speculation concerning the detailed differences between the two is unfortunately premature at this point. It can be observed, however, that the entropies of activation recorded in Table II argue in favor of mechanisms involving the same molecularity. Within the limitations of validity of this argument, a gradation of mechanism, rather than an abrupt change, should perhaps be considered. Because of the paucity of detail afforded by the data, it is assumed for the purpose of discussion that compounds **2b–e** hydrolyze by a mechanism involving a transition state with a lesser degree of carbonium ion character than that for the hydrolysis of **2a**. Further distinction will not be attempted.

Such a mechanistic dichotomy could be attributed to either of two possible phenomena. If compounds **2b–e** require nucleophilic assistance at the reaction center in attaining the transition state, it could be provided either by nitro group participation or by solvent molecules from the solvation sphere. On the basis of very similar findings with respect to ρ values, Bordwell and Knipe,[12] as well as Kemp and Metzger,[11] have argued in favor of carboxylate ion participation in the hydrolysis of α-bromophenylacetate ions substituted with electron-withdrawing substituents. However, the results obtained in 90% formic acid do not substantiate this kind of interpretation for the hydrolysis of the α-halonitro compounds employed in the present investigation. A reasonably good, linear Hammett correlation ($\rho = -3.73$; $r = -0.9951$) is obtained for the hydrolysis of compounds **2a**, **2b**, **2d**, and **2e** (**2c** was not run) in 90% formic acid. It has been pointed out by several authors that ρ is roughly dependent upon the solvent ionizing power, Y. Hammond observed a decrease in ρ (to more negative values) for the solvolysis of benzyl tosylates on increasing the water content of aqueous acetone.[23] Bordwell and Knipe have recently made a similar finding for the solvolysis of α-bromo-β-arylpropionates and α,β-dibromo-β-arylpropionates in aqueous ethanol.[13] Data for the hydrolysis of 1-chloro-1-nitro-(*p*-X-phenyl)ethanes also indicate this, as seen by the large decrease in ρ in going from ethanol-water mixtures to 90% formic acid; ρ values are collected in Table III.

TABLE III

VARIATION OF ρ WITH SOLVENT IONIZING POWER IN HYDROLYSIS OF 1-CHLORO-1-NITRO-1-(*p*-X-PHENYL)ETHANES AT 80°

Solvent	Y	ρ	r
80% Ethanol	0.000	−1.62[a]	−0.9959
50% Ethanol	1.655	−1.52[a]	−0.9976
90% Formic acid	2.222	−3.73[b]	−0.9951

[a] Does not include *p*-methyl derivative. [b] Includes *p*-methyl derivative.

It is interesting to scrutinize the change in ρ in the two solvent mixtures for a possible indication of nitro group participation. Winstein and Heck have suggested that neighboring group participation in solvolysis reactions increases in going to less nucleophilic and more ionizing solvents.[26] If the nitro group is functioning as an internal nucleophile in the hydrolysis of the 1-chloro-1-(*p*-X-phenyl)ethanes, the effect should be more pronounced in 90% formic acid than in the more nucleophilic ethanol–water solvents. The large negative ρ value (−3.73) in 90% formic acid indicates that the incipient benzylic cation in this reaction is very sensitive to substituent effects. If the nitro group is imparting stability to the developing carbonium ion by nucleophilic interaction, a more positive ρ value (less sensitivity to substituent effects) would perhaps be expected.

It is also expected that if nitro group participation is important the extent of such participation should increase as the stability of the incipient benzylic carbonium ion decreases. On this basis the participation should be most important in the *p*-nitro derivative, and consequently the rate should be faster than would be expected from its σ^+ value. The fact that a good correlation exists between log k and σ^+ for all the substituents studied indicates that nucleophilic participation by the nitro group is insignificant in the rate-determining step for the hydrolysis of 1-phenyl-1-nitro-1-chloroethanes.

A more plausible interpretation of the finding is as follows. In the more nucleophilic solvents, 50 and 80% ethanol, there is a greater contribution of the direct displacement reaction by solvent for the compounds containing deactivating substituents. In the more ionizing but less nucleophilic solvent, 90% formic acid, a single mechanism with a high degree of carbonium ion character prevails even for the case of the *p*-nitro compound. The slow hydrolysis rate for the *p*-nitro derivative (0.00104, relative to H) in formic acid is indicative of the inability of this substituent to stabilize a positive charge. However, the same mechanism apparently predominates throughout this series of compounds in 90% formic acid and consequently a good correlation with σ^+ obtains. It would perhaps be informative to compare the results of this system with the solvolysis of benzyl tosylates and α-bromophenylacetates in 90% for-

(23) G. S. Hammond, C. E. Reeder, F. T. Fang, and J. K. Kochi, *J. Amer. Chem. Soc.*, **80**, 568 (1958).

(24) A. Streitwieser, H. A. Hammond, R. H. Jagow, R. M. Williams, R. G. Jesaitis, C. J. Chang, and R. Wolf, *ibid.*, **92**, 5141 (1970).

(25) P. G. Gassman and A. F. Fentiman, Jr., *ibid.*, **92**, 2549 (1970).

(26) S. Winstein and R. Heck, *ibid.*, **78**, 480 (1956).

mic acid. Unfortunately, neither system would be amenable to study in such a solvent.

The possibility of a more dramatic change in mechanism in going to 90% formic acid cannot be ruled out. It is conceivable that in this solvent protonation of the nitro group could occur and loss of nitrous acid to give a chlorocarbonium ion might be the rate-controlling step.

Experimental Section

Melting points were determined on a Büchi melting point apparatus (capillary method) and are uncorrected. Infrared spectra were determined with a Beckman Model IR-8 or a Perkin-Elmer Model 621 grating infrared spectrophotometer. Nuclear magnetic resonance (nmr) spectra were obtained using a Varian Model HA-60 spectrometer with tetramethylsilane as internal reference. Chemical shifts are reported in parts per million (δ) and signals are described as s (singlet), d (doublet), or m (complex multiplet). Ultraviolet and visible spectra were determined using a Cary Model 14 recording spectrophotometer. Elemental analysis was done by M-H-W Laboratories, Garden City, Mich., or by Galbraith Laboratories, Knoxville, Tenn.

1-Nitro-1-(*p*-X-phenyl)ethanes (1a–f).—These compounds were prepared by the method of Bordwell, Boyle, and Yee.[14] Chromatography through 60–100 mesh Florisil using 10:1 petroleum ether[27]–ether eluent, followed by evaporation of solvent, produced these compounds in sufficient purity for elemental analysis. The infrared and nuclear magnetic resonance spectra also accorded with expectation based on the model spectra described.[14]

1-Chloro-1-nitro-1-(*p*-X-phenyl)ethanes (2a–f).—These substances were prepared by the following general procedure.

1-Chloro-1-nitro-1-phenylethane (2b).—Into a 500-ml erlenmeyer flask was placed a solution of 6.83 g (0.045 mol) of 1-phenyl-1-nitroethane in 150 ml of 5% aqueous potassium hydroxide. The flask was cooled to 0° in an ice bath and chlorine was bubbled through the stirred solution for 2 hr. The mixture was extracted twice with 200-ml portions of ether, which were combined, washed with 50 ml of 2 *N* hydrochloric acid and three times with 50-ml portions of water, and dried over magnesium sulfate. Evaporation of the solvent left 7.51 g of a light yellow oil, which was chromatographed on an 18-in. column packed with 60–100 mesh Florisil using petroleum ether (bp 39–60°) as the eluent to give 5.40 g (0.029 mol, 65%) of 1-chloro-1-nitro-1-phenylethane as a light yellow oil: ir (neat) 1560, 1345 (NO_2), 2885, 1460 (CH), 3070, 700 cm^{-1} (ArH); nmr (CCl_4) δ 2.37 (s, 3, CH_3), 7.14–7.60 (m, 5, ArH).

Anal. Calcd for $C_8H_8ClNO_2$: C, 51.72; H, 4.35; N, 7.55; Cl, 19.10. Found: C, 51.64; H, 4.39; N, 7.38; Cl, 19.24.

1-Chloro-1-nitro-1-(*p*-tolyl)ethane (2a).—This substance was obtained in 74% yield, bp 60° (2×10^{-4} Torr). Its spectral properties are as follows: ir (neat) 1560, 1330 (NO_2), 3000, 845, 785, 725 (ArH), 2875 cm^{-1} (CH_3); nmr (CCl_4) δ 2.37 (s, 3, CH_3), 2.30 (s, 3, $ArCH_3$, broadened), 6.95–7.44 (2 distorted d, 4, ArH).

Anal. Calcd for $C_8H_{10}ClNO_2$: C, 54.17; H, 5.05; N, 7.02. Found: C, 54.31; H, 5.03; N, 6.83.

1-Chloro-1-nitro-1-(*p*-chlorophenyl)ethane (2c).—This material was prepared in 67% yield. It is a colorless oil: ir (neat) 1559, 1334 (NO_2), 2876, 1383, 1491 (CH_3), 3000, 1596, 751, 825, 848 cm^{-1} (ArH); nmr (CCl_4) δ 2.40 (s, 3, CH_3), 7.12–7.54 (m, 4, ArH).

Anal. Calcd for $C_8H_7NO_2Cl_2$: C, 43.82; H, 3.20; N, 6.35. Found: C, 43.77; H, 3.11; N, 6.12.

1-Chloro-1-nitro-1-(*p*-bromophenyl)ethane (2d).—This compound was produced in 74% yield as a colorless oil: ir (neat) 1563, 1335 (NO_2), 748, 825, 850, 3000 (ArH), 2875, 1383 cm^{-1} (CH_3); nmr (CCl_4) δ 2.42 (s, 3, CH_3), 7.14–7.54 (m, 4, ArH).

Anal. Calcd for $C_8H_7NO_2ClBr$: C, 36.33; H, 2.67; N, 5.30; Br, 30.21; Cl, 13.40. Found: C, 36.58; H, 2.65; N, 5.08; Br, 30.18; Cl, 13.39.

1-Chloro-1-nitro-(*p*-nitrophenyl)ethane (2e).—Crystallization of the crude reaction product from 90% ethanol gave this substance in 46% yield: mp 45°; ir (KBr) 1345, 1560 (NO_2), 690, 720, 860 cm^{-1} (ArH); nmr (CCl_4) δ 2.48 (s, 3, CH_3), 7.64–8.22 (m, 4, ArH).

Anal. Calcd for $C_8H_7N_2O_4Cl$: C, 41.67; H, 3.06; N, 12.15; Cl, 15.37. Found: C, 41.47; H, 3.03; N, 11.96; Cl, 15.60.

(27) Bp 30–60°.

1-Chloro-1-nitro-1-(*p*-anisyl)ethane (2f).—This was obtained in 35% yield as a clear, viscous oil: ir (neat) 1560, 1332 (NO_2), 3000, 760, 800, 842, 875 (ArH), 1480, 1390, 2935 cm^{-1} (CH_3). A shift of the nitro group asymmetrical absorption band from 1550 to 1560 cm^{-1}, and in the symmetrical band from 1360 to 1332 cm^{-1}, is evidence of chlorination α to a nitro group. The compound decomposed over a period of hours with the evolution of nitrogen dioxide.

Solutions.—To assure uniformity of solvent composition in all the kinetic runs, stock solutions of the different solvent mixtures were prepared. Aqueous ethanol mixtures of 80, 50, and 40% v/v were prepared by mixing at room temperature the appropriate amounts of commercial 95% ethanol with distilled water. A stock solution of 90% v/v formic acid was similarly prepared by diluting 97% formic acid (Aldrich Chemical Co.) with distilled water. For approximately 1 l. of solution, 927.8 ml of 97% formic acid was mixed with 72.2 ml of distilled water. The formic acid solution for the kinetic runs was made 0.065 *M* in sodium perchlorate by placing 7.959 g (0.065 mol) of anhydrous reagent sodium perchlorate (G. Frederick Smith Chemical Co.) in a 1-l. volumetric flask and diluting to the mark with 90% formic acid. Sodium chloride solutions were prepared by accurately weighing predetermined amounts of the reagent grade material into volumetric flasks and diluting to the mark with the appropriate solvent.

A standard solution of silver nitrate (Baker) was prepared by addition of an accurately weighed amount of silver nitrate (dried at 110° for 1 hr) to a volumetric flask and diluting to the mark with distilled water. Aqueous potassium thiocyanate solutions were prepared by dissolving a preweighed amount of potassium thiocyanate (Fisher White Label) in water and standardizing with standard silver nitrate using a nitric acid solution of ferric ammonium sulfate as the indicator.

Kinetic Measurements.—Kinetics were run in a well-insulated, well-stirred constant-temperature water or mineral oil bath. Temperature control of $\pm 0.05°$ was accomplished by using a Sargent Model ST Thermonitor. Temperatures were recorded with a thermometer graduated every 0.1°. Elapsed time was recorded using a Precision Scientific Co. clock with a digital read-out in minutes.

Hydrolysis of α-Nitrobenzhydryl Chloride in Aqueous Ethanol.—The kinetics of the solvolysis of α-nitrobenzhydryl chloride were determined by measuring the optical density of the benzophenone produced as a function of time. Freshly sublimed samples of α-nitrobenzhydryl chloride were accurately weighed into 50-ml volumetric flasks and diluted to the mark with stock 80% aqueous ethanol. The final concentrations ranged from 4.138×10^{-4} to 7.234×10^{-4} mol/l. After vigorous shaking to completely dissolve the α-nitrobenzhydryl chloride, the flasks were immersed in the water bath at the appropriate temperature; 1-ml aliquots were removed at various time intervals and diluted to 10 ml with 95% ethanol. The resulting optical densities were recorded at 252 nm against an ethanol blank. For those runs containing added chloride ion, appropriate quantities of a sodium chloride solution were introduced into the reaction flasks.

To determine the exact initial concentration of α-nitrobenzhydryl chloride, the reactions were allowed to proceed for several half-lives until a constant infinity absorption value was obtained.

Hydrolyris of 1-Chloro-1-nitro-1-(*p*-X-phenyl)ethanes in Aqueous Ethanol.—The extent of solvolysis in aqueous ethanol mixtures of the 1-chloro-1-nitro-1-(*p*-X-phenyl)ethanes, where X = H, Br, Cl, and CH_3, was determined by measuring the optical density of the corresponding acetophenone end products as a function of time. To determine the exact wavelength at which measurements were to be made, commercial samples of the acetophenones were carefully purified and the ultraviolet spectra were recorded in 95% ethanol. Table IV lists the wavelengths

TABLE IV

WAVELENGTHS AND MOLAR ABSORPTIVITIES FOR PARA-SUBSTITUTED ACETOPHENONES

X	λ_{max}, nm	$\epsilon \times 10^{-4}$
H	242	1.52
Br	255	1.71
Cl	252	1.56
CH_3	253	1.47
OCH_3	272	1.59

of maximum absorption and the average molar absorptivities for the acetophenones which were determined from several scans at different concentrations.

The 1-chloro-1-nitro-1-(*p*-X-phenyl)ethanes were accurately weighed into 50-ml volumetric flasks and diluted to the mark with the appropriate stock solution of aqueous ethanol. Aliquots of these solutions were transferred to 25-ml volumetric flasks and diluted with the appropriate solvent for the kinetic runs. Runs were made in triplicate and the amount of substrate used was that amount calculated to give a final infinity absorption value between 1.00 and 2.00 OD units. For the runs containing sodium perchlorate or sodium chloride, the desired concentrations were obtained by pipetting aliquots of these salt solutions into the, reaction flasks. The flasks were vigorously shaken, stoppered, and placed in the oil or water bath at the desired temperature; 1-ml aliquots were removed with a pipet and diluted to 10 ml with 95% ethanol. The optical densities of these solutions were determined at the appropriate wavelength in matched 1.000 cm cells using 95% ethanol as the blank.

The infinity absorption values were obtained by allowing the reaction to proceed through several half-lives until a constant OD reading was obtained. Calculations were made from the integrated first-order rate expression

$$kt = 2.303 \log [(OD_\infty - OD_0)/(OD_\infty - OD_t)]$$

where k = first-order rate constant, t = time in seconds, OD_∞ = optical density at infinity time, OD_0 = optical density at zero time, and OD_t = optical density at time t. A plot of log $(OD_\infty - OD_t)$ *vs.* t gives a straight line with slope equal to $-k/2.303$. The slopes were calculated from a least-squares computer program.

Hydrolysis of 1-Chloro-1-nitro-1-(*p*-X-phenyl)ethanes in 90% Formic Acid.—Kinetics for these runs could not be followed spectrophotometrically because of solvent cut-off in the range of interest due to the high concentration of formic acid. The rates were followed instead by measuring the amount of chloride ion released by the reaction as a function of time. The Volhard titrimetric procedure was employed.[28]

Samples of the 1-chloro-1-nitro-1-(*p*-X-phenyl)ethanes sufficient to give a final concentration of approximately 3.0×10^{-2} mol/l. were accurately weighed into 25-ml volumetric flasks and diluted to the mark with stock 90% formic acid containing 0.065 mol/l. of sodium perchlorate. The flasks were shaken until dissolution of the substrate was complete and were then immersed in an oil or water bath at the desired temperature; 2-ml aliquots were removed at various time intervals and pipetted into 5 ml of water contained in a 50-ml erlenmeyer flask.

A known excess of standard silver nitrate solution was added to the flask, followed by 2 ml of dilute nitric acid, 1 ml of a saturated solution of ferric ammonium sulfate in dilute nitric acid, and 1 ml of nitrobenzene. The mixture was vigorously agitated with a magnetic stirrer and the excess silver nitrate was back titrated to the rusty-red end point with standard potassium thiocyanate.

Calculations were made from the integrated first-order rate expression

$$k = (2.303/t) \log [a/(a - x)]$$

where k = first-order rate constant, t = time in seconds, a = initial quantity of substrate in given volume, x = amount of substrate reacting in time t, and $a - x$ = amount of substrate remaining at time t. A plot of log $[a/(a - x)]$ *vs.* t gives a straight line with slope equal to $k/2.303$.

Activation Parameters.—Activation parameters were calculated by least-squares programs utilizing the Arrhenius and absolute rate equations.

Registry No.—**2a**, 31659-47-9; **2b**, 31657-66-6; **2c**, 31657-67-7; **2d**, 31657-68-8; **2e**, 31657-69-9; **2f**, 31657-70-2.

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Chlorination of Alkenes with Trichloramine[1]

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Trichloramine in nonpolar solvent gave excellent yields of vicinal dichlorides with certain types of olefins. Nitrogen was generated almost quantitatively, along with the by-products, ammonium chloride and basic material. With 1-hexene, 1-octene, cyclopentene, cyclohexene, 3-chloropropene, and 1,1-dichloroethylene as substrates, yields of the corresponding *vic*-dichlorides ranged from 89 to 97%. The *meso*:*dl* ratios for chlorination of the isomeric 2-butenes were similar to those obtained from molecular chlorine under radical conditions. Additional evidence for a radical mechanism was derived from relative reactivities, catalysis, formation of some *cis*-1,2-dichlorocyclohexane from cyclocyclohexene, and participation of an alkane additive. The high addition:substitution ratios suggest that free chlorine atoms are generated in no more than minor amounts. The detailed aspects of the radical pathway are discussed.

The most pertinent prior reference describes the formation of 1,2-dichlorocyclohexane in 77% yield from cyclohexene and trichloramine.[3] However, there has been no follow-up of this work since it appeared more than 40 years ago.

The bulk of the previous investigations involving the interaction of *N*-chloramines with olefins involves the chloramination reaction. Only a brief summary will be presented since a review of the subject is available elsewhere.[4] Coleman and coworkers revealed that trichloramine underwent addition to various olefins, *e.g.*, ethylene, isobutylene, cyclohexene, and styrene.[5-7] *N*,*N*-Dichloro-β-chloroalkylamines were postulated as the initial adducts which were converted to β-chloroalkylamines, <20%, after work-up with concentrated hydrochloric acid. Unspecified amounts of dichloride, along with nitrogen and ammonium chloride, were also obtained. Unsymmetrical olefins formed β-chloroalkylamines in which chlorine was affixed to the least substituted olefinic carbon atom. Under photolytic or thermal conditions chloramine gave low yields of *vic*-dichlorides with simple olefins.[8,9] *N*-Halo-1,2,4-

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(2) From the Ph.D. Thesis of K. W. F., Case Western Reserve University, 1970; the research was carried out at the University of Wisconsin—Milwaukee.

(3) N. Stoll, *Bull. Soc. Chim. Belg.*, **38**, 71 (1929).

(4) P. Kovacic, M. K. Lowery, and K. W. Field, *Chem. Rev.*, **70**, 639 (1970).

(5) G. H. Coleman, G. M. Mullins, and E. Pickering, *J. Amer. Chem. Soc.*, **50**, 2739 (1928).

(6) G. H. Coleman and H. P. Howells, *ibid.*, **45**, 3084 (1923).

(7) G. H. Coleman and A. W. Campbell, *ibid.*, **50**, 2754 (1928).

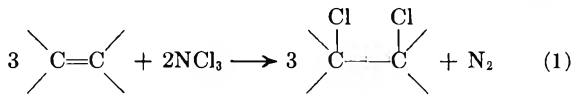
(8) Y. Ogata, Y. Izawa, and H. Tomioka, *Tetrahedron*, **23**, 1509 (1967).

(9) H. Prakash and H. H. Sisler, *J. Org. Chem.*, **35**, 3111 (1970).

triazoles have also been investigated as halogen donors in this type of reaction.[10] This paper describes a detailed investigation of the synthetic merits of the trichloramine–alkene reaction, along with a treatment of the mechanistic aspects.

Results and Discussion

We found that a solution of trichloramine in methylene chloride functions as a halogenating agent for various types of olefins (eq 1). Excellent yields, 81–97%,



(1)

of *vic*-dichlorides were obtained from substrates (Table I) of the type CH_2=CHR, RCH=CHR, and CH_2=CX_2 (R = alkyl; X = halogen). Nitrogen was generated almost quantitatively (~90% yield) with certain olefins, along with the by-products, ammonium chloride and basic material. These substances were also reported by Coleman and coworkers.[5-7] Due to the nature of the by-products and the specificity of addition *vs.* substitution, simple purification methods sufficed to provide pure, >98%, *vic*-dichloride.

TABLE I

CHLORINATION OF OLEFINS WITH TRICHLORAMINE

Olefin[a]	Temp, °C	Product	Yield, %
1-Butene[b]	−15 ± 3	1,2-Dichlorobutane	81
Isobutylene[b]	−15 ± 3	3-Chloro-2-methylpropene	50
		1,2-Dichloro-2-methylpropane	25
1-Hexene[c]	0 ± 2	1,2-Dichlorohexane	97
1-Hexene[c,d]	0 ± 2	1,2-Dichlorohexane	90
1-Hexene[c,e]	0 ± 2	1,2-Dichlorohexane	94
1-Octene[c]	0 ± 2	1,2-Dichlorooctane	93
Cyclopentene[c]	0 ± 2	*trans*-1,2-Dichlorocyclopentane	89
Cyclohexene[b]	0 ± 2	*trans*-1,2-Dichlorocyclohexane	92
Cyclohexene[c]	0 ± 2	*trans*-1,2-Dichlorocyclohexane	91
		cis-1,2-Dichlorocyclohexane	~3
3-Chloropropene[b]	2 ± 2	1,2,3-Trichloropropane	92
cis-1,2-Dichloroethylene[f,g]	25 ± 2	1,1,2,2-Tetrachloroethane	82
cis-1,2-Dichloroethylene[f,h]	25 ± 2	1,1,2,2-Tetrachloroethane	56
1,1-Dichloroethylene[b]	25 ± 1	1,1,1,2-Tetrachloroethane	89
Trichloroethylene[b,i]	23 ± 1	Pentachloroethane	32
Trichloroethylene[b,j]	23 ± 1	Pentachloroethane	41

[a] Molar ratio, NCl_3:olefin = 0.04:0.09. [b] Trichloramine solution was added dropwise to the olefin in methylene chloride. [c] Olefin in methylene chloride was added dropwise to trichloramine solution. [d] Fourfold scale. [e] Molar ratio, NCl_3:olefin = 0.04:0.075. [f] Trichloramine solution and olefin combined in one portion. [g] The mixture of olefin and trichloramine was purged with nitrogen and illuminated for 4 hr with a 275-W sun lamp. [h] Complete reaction after 1 week. [i] 24 hr at 23°; a slightly yellow color still remained. [j] Benzoyl peroxide, 0.1 g, was added to the olefin solution prior to trichloramine addition.

Several studies were undertaken to determine optimum reaction conditions. The molar ratio of trichloramine:olefin was usually 0.04:0.09; however, as shown with 1-hexene only a slight decrease in yield was observed when a molar ratio of 0.04:0.075 was used. It should be noted that 0.04 mol of trichloramine is theoretically capable of producing 0.06 mol of the corresponding dichloride. In the presence of a 25% excess of the olefin, excellent yields can be obtained. With cyclohexene, the mode of addition, olefin to trichloramine or vice versa, did not affect the yield of dichloride or the amount of side products. The effect of temperature on the chlorination of cyclohexene in methylene chloride solvent was investigated. Below −40° nitrogen was not evolved; however, upon warming to −30 ± 5° the reaction proceeded. Best yields were realized in the −30–0° range. At 38° the yield decreased, accompanied by a corresponding increase in side products. The use of other nonpolar organic solvents for chlorination of cyclohexene at 0 ± 2° did not alter the yield of dichloride in most cases. The low yield figure obtained with carbon disulfide is attributed to a slow reaction of trichloramine with solvent, as evidenced by gas evolution from a mixture of the two.

When compared to other chlorinating agents (Table II), the merits of trichloramine become evident. Although not widely recognized, it is well established that the formation of *vic*-dichlorides from molecular chlorine and olefins has limited synthetic utility due to the occurrence of side reactions.[11-14] The situation is improved in the presence of oxygen.[15] Certain olefinic substrates with sulfuryl chloride also give undesirable by-products.[16] Phosphorus pentachloride has been investigated only to a relatively small extent, as is also the case for tetrabutylammonium iodotetrachloride[17] and iodobenzene dichloride.[15] It should be noted that the trichloramine solutions are easy to prepare and safe to handle with simple precautions.[18]

TABLE II

YIELDS OF *vic*-DICHLORIDES FROM VARIOUS METHODS

Halogenating agent	*vic*-Dichloride, %, from 1-Hexene	1-Octene	Cyclohexene	3-Chloropropene
NCl_3	97	93	91	92
SO_2Cl_2	79[a]	63[a]	89[b]	80–90[b]
PCl_5[c]		83	87	
Cl_2[d]			70	

[a] Reference 16. [b] M. S. Kharasch and H. C. Brown, *J. Amer. Chem. Soc.*, **61**, 3432 (1939). [c] D. P. Wyman, J. Y. C. Wang and W. R. Freeman, *J. Org. Chem.*, **28**, 3173 (1963). [d] H. Böhme and R. Schmitz, *Chem. Ber.*, **88**, 357 (1955).

Recent studies involving the reaction between chlorine and certain types of olefins, *e.g.*, CH_2=CHR and RCH=CHR, in the absence of initiators and inhibitors revealed that the mechanism was predominantly radi-

(10) H. G. O. Becker, *et al.*, *Z. Chem.*, **9**, 325 (1969).

(11) P. B. D. de la Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems," Elsevier, New York, N. Y., 1966, p 105.
(12) M. L. Poutsma, *J. Amer. Chem. Soc.*, **87**, 2161 (1965).
(13) M. L. Poutsma, *ibid.*, **87**, 2172 (1965).
(14) M. L. Poutsma, *ibid.*, **87**, 4285 (1965).
(15) M. L. Poutsma, "Methods in Free-Radical Chemistry," E. S. Huyser, Ed., Vol. 1, Marcel Dekker, New York, N. Y., 1969, Chapter 3, section VI.
(16) M. S. Kharasch and A. F. Zavist, *J. Amer. Chem. Soc.*, **73**, 964 (1951).
(17) R. E. Buckles and D. F. Knaack, *J. Org. Chem.*, **25**, 20 (1960).
(18) P. Kovacic and S. S. Chaudhary, *Org. Syn.*, **48**, 4 (1968).

cal.[12,13] In the presence of oxygen as inhibitor, the pathway was diverted almost completely in the polar direction. These significant reports by Poutsma clarified conflicting mechanistic interpretations in previous investigations.

Polar addition of chlorine to the 2-butene isomers gave 97–98% addition products, stereospecifically trans. Under radical conditions there was a loss of stereospecificity, accompanied by a greater percentage of substitution products (15–20%).[13] Chlorination of the isomeric 2-butenes with trichloramine under nitrogen in the dark gave *meso*:*dl* ratios corresponding closely to those obtained for chlorine under radical conditions (Table III). The substitution products

TABLE III

meso:*dl* RATIOS FOR CHLORINATION OF 2-BUTENES

2-Butene	Chlorinating agent	1,2-Dichlorobutane, %[a] Meso	*dl*
Cis	Cl_2 (polar)[b]	0	100
	Cl_2 (radical)[b]	33	67
	NCl_3	28	72
Trans	Cl_2 (polar)[b]	100	0
	Cl_2 (radical)[b]	88	12
	NCl_3	86	14

[a] Per cent of the isomeric mixture. [b] Reference 13.

normally observed with chlorine were essentially absent in our case (less than 2% of unidentified material). A small amount of polar reaction may accompany the radical category with both halogenating agents.[13]

Fundamental similarities in the two chlorination systems are also apparent from a comparison of the *meso*:*dl* ratios for various mole fractions, N, of *cis*-2-butene in nonpolar solvent. Analysis of a trichloramine reaction in methylene chloride, $N = \sim 1$ to $N = 0.30$, gave a constant ratio of *ca.* 0.4. The ratios obtained for chlorine in 1,1,2-trichlorotrifluoroethane ranged from 0.49 for $N = 1$ to 0.43 for $N = 0.40$.[13] Trichloramine must be used in solution, whereas chlorine can be passed directly into the neat olefin.

Chlorination in the presence of several different solvents did not affect the *meso*:*dl* ratios from the 2-butene isomers (Table IV). In each case the isomeric

TABLE IV

EFFECT OF SOLVENT ON STEREOCHEMISTRY OF CHLORINATION

2-Butene	Solvent	1,2-Dichlorobutane, %[a] Meso	*dl*
Cis	CH_2Cl_2	28	72
	CCl_4	31	69
	o-$Cl_2C_6H_4$	30	70
	CS_2	28	72
Trans	CH_2Cl_2	86	14
	CCl_4	89	11

[a] Per cent of the isomeric mixture.

2,3-dichlorobutanes composed 98% of the reaction mixture. With *o*-dichlorobenzene and carbon disulfide as diluents, only traces of ammonium chloride were formed. It seems that the salt arises from the action on trichloramine of hydrogen chloride[19] which is most likely generated during hydrogen abstraction. The paucity of ammonium chloride suggests that these side reactions are essentially eliminated in certain solvents. A possible rationale is the formation of a complex from solvent and the abstracting entity,[12,15,20–22] thereby increasing the selectivity of the radical moiety.

Several other findings are in accord with a radical pathway. In the presence of cyclohexane, halogenation of *cis*-2-butene with trichloramine gave cyclohexyl chloride, 2–3%, in addition to the isomeric 2,3-dichlorobutanes. A similar finding was observed for the chlorine–cyclohexene–cyclohexane system.[12] According to the literature, the relative reactivity per hydrogen for abstraction by a chlorine atom is 0.6 for a primary allylic hydrogen in *cis*-2-butene *vs.* a secondary hydrogen in cyclohexane.[13] A radical mechanism is consistent with attack on the alkane.[12,15] Identification of the major side product, *cis*-1,2-dichlorocyclohexane, ~2–3%, from the chlorination of cyclohexene proved mechanistically informative. Ionic reaction of chlorine gave 99% of the adduct as *trans*-1,2,-dichlorocyclohexane; however, under radical conditions up to 4% cis addition was obtained.[12] Our observed order of reactivity, $CH_2{=}CCl_2$ > *cis*-ClCH=CHCl, is in accord with prior studies entailing addition of chlorine[22] and polymerization.[23] The difference in reactivity[15] appears to be substantially greater for trichloramine in comparison with chlorine. Factors affecting the relative rates in radical additions have been discussed.[22]

In an attempt to intercept the chain-propagating radicals, several inhibitors were added to the trichloramine–cyclohexene mixture. No inhibition was observed (Table V). In the presence of cumene, there

TABLE V

EFFECT OF INHIBITORS ON CHLORINATION

Olefin	Inhibitor	*vic*-Dichloride Yield, %[a]
Cyclohexene	2,6-Di-*tert*-butylphenol[b]	86
	Cumene[c]	87
	Oxygen	81
	d	87
		meso *dl*
cis-2-Butene	Oxygen	29 71
	d	28 72

[a] The *meso*:*dl* ratio is given for 2,3-dichlorobutane. [b] Molar ratio, NCl_3:C_6H_{10}:2,6-[$(CH_3)_3C]_2C_6H_3OH$ = 0.04:0.09:0.15. [c] Molar ratio, NCl_3:C_6H_{10}:$(CH_3)_2CHC_6H_5$ = 0.04:0.09:0.045; no dicumyl was detected by glpc analysis. [d] Under nitrogen.

was no formation of dicumyl. The decrease in yield with oxygen may be due to loss of trichloramine during oxygen sweep. With *cis*-2-butene, identical *meso*:*dl* ratios were obtained in the presence of oxygen or nitrogen.

A brief investigation was made of the effect of photolytic conditions. The product distribution was essentially unchanged with cyclohexene (very fast reaction in both cases). In the case of *cis*-1,2-dichloroethylene, the reaction rate was markedly increased, accompanied by a substantial increase in the yield of tetrachloroethane. We are uncertain whether photolysis favors the reaction which takes place under stan-

(19) W. A. Noyes, *J. Amer. Chem. Soc.*, **42**, 2173 (1920).

(20) G. A. Russell, *ibid.*, **80**, 4987 (1958).

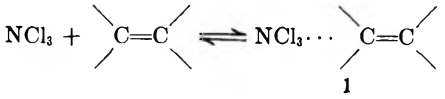
(21) C. Walling and M. F. Mayahi, *ibid.*, **81**, 1485 (1959).

(22) M. L. Poutsma and R. L. Hinman, *ibid.*, **86**, 3807 (1964).

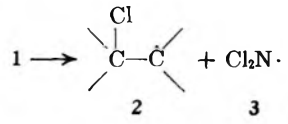
(23) F. W. Billmeyer, Jr., "Textbook of Polymer Science," Interscience, New York, N. Y., 1965, p 263.

dard conditions or dissociates the reagent to chlorine[24] which then participates.

The indicated mechanistic schemes seem relevant in view of the experimental data and literature analogy. Initiation could be of the molecule-induced type[12,25] (eq 2 and 3). Equation 2 appears plausible since this



(2)



(3)

type of complex is postulated for many "even" molecule reactions. Although trichloramine is not an "even" type, it has been classified as the most covalent molecule in the unsymmetrical category because the electronegativities of chlorine and nitrogen are essentially the same.[26] Initiation under certain conditions might also occur *via* initial homolysis of the N–Cl bond (47.7 kcal/mol)[27] (eq 4). A third possibility involves

$$NCl_3 \rightleftharpoons Cl\cdot + \mathbf{3} \quad (4)$$

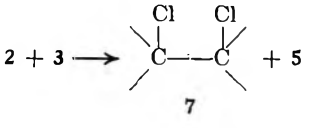
a molecule-induced reaction by traces of molecular chlorine.[13] Finally, **2** might arise by interaction of the olefin with a species generated subsequently, *e.g.*, **3**, **4**, or **6**.

Once formed, reactive **3** could subsequently participate in a number of processes (eq 5–8). Possible path-

$$\mathbf{2}\ \mathbf{3} \rightleftharpoons \underset{\mathbf{4}}{Cl_2NNCl_2} \quad (5)$$

$$\mathbf{2}\ \mathbf{3} \rightleftharpoons NCl_3 + \underset{\mathbf{5}}{NCl} \quad (6)$$

$$\mathbf{2}\ \mathbf{5} \longrightarrow \underset{\mathbf{6}}{ClNNCl} \quad (7)$$



(8)

ways for generation of *vic*-dichloride are illustrated (eq 8–11). Nitrogen might also be produced as described in eq 12. In relation to energetics, a favorable

$$\mathbf{2} + NCl_3 \longrightarrow \mathbf{7} + \mathbf{3} \quad (9)$$

$$\mathbf{2}\ \mathbf{2} + \mathbf{4} \longrightarrow \mathbf{2}\ \mathbf{7} + \mathbf{6} \quad (10)$$

$$\mathbf{2}\ \mathbf{2} + \mathbf{6} \longrightarrow \mathbf{2}\ \mathbf{7} + N_2 \quad (11)$$

$$\mathbf{5} + \mathbf{6} \longrightarrow NCl_3 + N_2 \quad (12)$$

driving force is associated with the ultimate formation of nitrogen.

Although tetrachlorohydrazine and dichlorodiazine have not been isolated, their fluorine analogs are well documented.[28–30] Based on analogy between trifluoramine, $\Delta H_f = -26 \pm 2$ kcal/mol, and trichloramine, $\Delta H_f = 55.4$ kcal/mol, **4** and **6** would most likely be very unstable.[31] In fact, failure was met in an attempt to prepare tetrachlorohydrazine from hydrazine dihydrochloride by a procedure similar to that for trichloramine.[18] Even at temperatures as low as −50°, nitrogen was generated quantitatively. Several other investigators have also postulated Cl_2N, ClN, and Cl_2N_2 as reaction intermediates.[24,32] In a related study,[33] chlorodifluoramine was found to react under photolytic conditions with ethylene to give 1,2-dichloroethane and tetrafluorohydrazine.

The trichloramine–cyclohexene reaction also produced ~4% yield of 7-azabicyclo[4.1.0]heptane. Since chloramination is known to proceed to a limited extent in this type of system,[5] the aziridine product is probably generated *via* 2-chloro-*N*,*N*-dichlorocyclohexylamine. Addition of chloronitrene (**5**) is deemed unlikely since several attempts to prepare the *N*-fluoro derivative of the aziridine from cyclohexene and fluoronitrene were unsuccessful.[34] Similarly, no adduct of **5** with cyclohexene resulted from the use of dichloramine–triethylamine.[35] The paucity of nitrogen adducts presumably reflects the relatively high activation energy needed for addition of nitrogen radicals to the double bond.[9] The figure for the addition of $F_2N\cdot$ to simple olefins is about 12–14 kcal/mol,[36] in contrast with a value ≤1.4 kcal/mol for chlorine atoms.[37] Since the activation energy for reaction of the 2-chloroethyl radical with chlorine is 0–1 kcal/mol,[38] the analogous interactions with **4** and **6** should also be near zero.

Unlike the chlorinations involving chlorine or sulfuryl chloride, the trichloramine procedure produces *vic*-dichlorides accompanied by very minor amounts of other organic materials. The greater selectivity with trichloramine for addition *vs.* substitution is taken as evidence for no more than quite minor involvement of free chlorine atoms.[12,15,22] One can account for the similar *meso*:*dl* ratios for the products from the 2-butenes and either chlorine or trichloramine on the basis of formation of the same crucial intermediate, **2**, in both cases. Lack of inhibition in chlorination with trichloramine suggests that carbon radical **2** reacts more readily with intermediates containing the N–Cl bond than with the inhibitors. The rapidity of reaction even at low temperatures reflects the very favorable energetics. In contrast, inhibition occurs with the chlorine–olefin system[12,13] (compare the bond dissociation energies for Cl–Cl, 58 kcal/mol,[27] and N–Cl, 47.7 kcal/mol; a number of the components containing the N–Cl bond in our reaction system should be considerably more labile).

With several substrates appreciable participation of ionic reactions seems likely.[13,14] Isobutylene gave 3-chloro-2-methylpropene (**10**), 50% yield, and 1,2-dichloro-2-methylpropane (**11**), 25% yield (Table I). A substantial amount of ammonium chloride, 66% yield, was also obtained. Photolytic conditions pro-

(24) A. G. Briggs and R. G. W. Norrish, *Proc. Roy. Soc., Ser. A*, **278**, 27 (1964).
(25) J. C. Martin and E. H. Drew, *J. Amer. Chem. Soc.*, **83**, 1232 (1961).
(26) L. Pauling, *ibid.*, **54**, 3570 (1932).
(27) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960, p 85.
(28) J. K. Ruff, *Chem. Rev.*, **67**, 665 (1967).
(29) S. F. Reed, Jr., *J. Org. Chem.*, **33**, 2634 (1968), and references cited therein.
(30) C. L. Bumgardner and M. Lustig, *Inorg. Chem.*, **2**, 662 (1963).
(31) T. Moeller, "Inorganic Chemistry," Wiley, New York, N. Y., 1957, p 589.
(32) D. E. Milligan, *J. Chem. Phys.*, **35**, 372 (1961).
(33) R. C. Petry, *J. Amer. Chem. Soc.*, **89**, 4600 (1967).
(34) D. L. Klopotek, Ph.D. Thesis, Utah State University, 1967.
(35) W. LeNoble, cited in ref 34.
(36) A. J. Dijkstra, J. A. Kerr, and A. F. Trotman-Dickenson, *J. Chem. Soc. A*, 582 (1966).
(37) E. W. R. Steacie, "Atomic and Free Radical Reactions," Vol. II, Reinhold, New York, N. Y., 1954, p 673.
(38) P. B. Ayscough, A. J. Cocker, F. S. Dainton, and S. Hirst, *Trans. Faraday Soc.*, **58**, 313 (1962).

duced no significant change in distribution of the organic products. Ionic reaction (eq 13–17) most likely

$$(CH_3)_2C{=}CH_2 + NCl_3 \longrightarrow \underset{8}{(CH_3)_2\overset{+}{C}CH_2Cl} + \underset{9}{NCl_2^-} \quad (13)$$

$$8 \xrightarrow{-H^+} \underset{10}{CH_2{=}\overset{CH_3}{\overset{|}{C}}CH_2Cl} \quad (14)$$

$$8 + 9 \longrightarrow \underset{11}{(CH_3)_2CClCH_2Cl} + 5 \quad (15)$$

$$9 \longrightarrow 5 + Cl^- \quad (16)$$

$$8 + Cl^- \longrightarrow 11 \quad (17)$$

involves positive chlorine in the initial step.[5] Precedence exists for the decomposition indicated in eq 16.[39]

Poutsma[13] found that molecular chlorine and isobutylene gave **10** and **11** in the ratio of 87:13. Evidence was presented to support the contention that a polar process was involved. For example, under photolytic conditions the ratio was unity or less. Comparison of these data with our own suggests that a combination of radical and ionic mechanisms may pertain in the trichloramine system. If **6** is generated according to eq 7, this intermediate might be responsible for radical addition. Alternatively, a purely ionic process may pertain; the difference in product distribution from chlorine and trichloramine may reflect a change in the gegenanion.

Styrene, 1-methylcyclohexene, and norbornene gave complex product mixtures with trichloramine. The major component in the case of norbornene was nortricyclyl chloride, the same product as obtained from use of chlorine in a process designated as ionic.[40] The reaction of chlorine with styrene is known to be in the ionic category when no external initiation is supplied.[13]

Experimental Section

Materials.—Oxygen (Airco USP) was passed through a sulfuric acid scrubber before use. Nitrogen (Linde, H. P. Dry) was passed through consecutive scrubbers containing Fieser's solution, lead acetate solution, sodium hydroxide pellets, and sulfuric acid.[41] Cyclohexene (Matheson Coleman and Bell) was distilled from sodium and methylene chloride (Fisher Chemical Co.) from calcium hydride. Carbon tetrachloride (Fisher Chemical Co.), *o*-dichlorobenzene (Eastman Organic Chemicals), and carbon disulfide (Matheson Coleman and Bell) were distilled from Drierite. The butene isomers, CP grade (99%), and chlorine CP grade (99.5%), were obtained from J. T. Baker Chemical Co. *trans*-2-Chlorocyclohexanol was obtained from K & K Laboratories, Inc. Most reagents were used as received after their purity had been checked by glpc analysis.

Analytical Procedures.—Infrared spectra were obtained with a Beckman IR-8 spectrophotometer on neat samples or as ~10% solutions in carbon disulfide. Nmr spectra were determined with a Varian HA-100 instrument on ~20% deuteriochloroform solutions with tetramethylsilane as an internal standard. Refractive indexes were recorded from a Bausch and Lomb refractometer. All spectra were taken on samples purified by glpc. Gas chromatography was carried out with an Aerograph Hi-Fi 1200 (column A, 200 ft by 0.01 in., stainless steel, SE-30, Perkin-Elmer wall-coated open tube) or with an Aerograph 1800 [column B, 15 ft by 0.25 in., Carbowax 20M (20%) on Chromosorb P (60–80 mesh), and column C, 4 ft by 0.25 in., molecular sieve (5A)]. Melting points, Thomas-Hoover capillary apparatus, and boiling points are uncorrected. Analysis for positive chlorine is described elsewhere.[18]

Preparation of Trichloramine Solution.—Trichloramine was prepared[18] in purified methylene chloride, carbon tetrachloride, *o*-dichlorobenzene, or carbon disulfide. Unless otherwise specified, chlorinations were performed with trichloramine in methylene chloride.

General Procedure. A. Chlorination of Olefins.—In a 250-ml three-necked flask fitted with a mechanical stirrer, condenser, and addition funnel was placed a solution (*ca.* 60 ml) of trichloramine (0.04 mol) in methylene chloride. A solution of the olefin (0.09 mol) in 32 ml (0.5 mol) of methylene chloride was added over a period of 1–1.5 hr at the desired temperature, after which a sample was removed for glpc analysis. The olefin need not be dissolved in methylene chloride; however, use of a dilute solution permits easier temperature regulation. The mixture was stirred for an additional 20–30 min at the same temperature and then poured into a solution of 10 ml of concentrated hydrochloric acid and 40 ml of water. After the resulting two-phase system was stirred magnetically for 30 min, the aqueous layer was separated. The organic phase was washed with two 50-ml portions of distilled water and dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure, followed by distillation of the residue through a short Vigreux column, afforded the *vic*-dichloride (Table I). Glpc analysis of the water-washed and unwashed organic portion gave similar product compositions.

The acidic water wash contained, in each case, a small amount of ammonium chloride, identified by the reaction with solutions of sodium hydroxide and silver nitrate and by the infrared spectrum. Nitrogen, which was evolved almost quantitatively during the addition of trichloramine, was characterized by glpc peak enhancement (column C at 25°, helium flow 12 ml/min).

Yields (distilled product) are based on trichloramine, three available chlorines. Product yields in several cyclohexene studies (temperature, solvent, and Table V) were determined by glpc analysis (column B) with bromobenzene as internal standard. Nitrogen evolution during chlorination was monitored with a Precision Scientific Co. wet test meter.

The indicated data were obtained in a temperature study with cyclohexene, °C (% yield of *trans*-1,2-dichlorocyclohexane): 38 ± 1 (80); 0 ± 2 (>91); −30 ± 5 (89).

B. Chlorination of *cis*- and *trans*-2-Butene.—The oven-dried apparatus consisted of a 250-ml, three-necked flask equipped with a Telfon stirring bar, constant pressure addition funnel, thermometer, and a Dry Ice reflux condenser. The butene isomers were introduced as gases and condensed; the amount was determined by volumetric calibration marks on the reaction vessel. The apparatus was flushed with nitrogen for 30 min prior to addition. The requisite amount of trichloramine solution (molar ratio, olefin:NCl_3 = 10) was placed in the addition funnel by means of a syringe. The trichloramine solution was added dropwise at −15 ± 3° (carbon tetrachloride–Dry Ice bath) over *ca.* 30 min in the dark with a slow nitrogen purge. After the mixture was swept with nitrogen for an additional 10 min at −15°, a sample was removed for anslysis. The remainder of the reaction mixture was washed with water, and the organic portion was dried over anhydrous sodium sulfate. Glpc analysis (column B) of the water-washed and unwashed organic phase gave identical *meso*:*dl* ratios (Table III). Less than 2% of unidentified side products was detected.

Chlorination Products. 1,2-Dichlorobutane, bp 123–124°, $n^{25}D$ 1.4432 (lit.[42a] bp 124°, $n^{15}D$ 1.4474), possessed an infrared spectrum identical with that published.[43a]

***meso*-2,3-Dichlorobutane.**—The major product from *trans*-2-butene, collected by glpc, possessed an infrared spectrum identical with that of authentic *meso*-2,3-dichlorobutane.

***dl*-2,3-Dichlorobutane.**—The principal product from *cis*-2-butene, isolated by preparative glpc, was shown to be *dl*-2,3-dichlorobutane on the basis of the infrared spectrum.

3-Chloro-2-methylpropene and 1,2-Dichloro-2-methylpropane.—Isobutylene afforded a mixture which was separated by distillation through a 24-in. spinning-band column: 3-chloro-2-methylpropene, bp 70–71° (lit.[13] bp 71°), infrared spectrum identical with the published spectrum;[43b] 1,2-dichloro-2-methyl-

(39) F. A. Johnson, *Inorg. Chem.*, **5**, 149 (1966).

(40) M. L. Poutsma, *J. Amer. Chem. Soc.*, **87**, 4293 (1965).

(41) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 393.

(42) R. C. Weast, Ed., "Handbook of Chemistry and Physics," 48th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1967–1968, (a) p C-218; (b) p C-490; (c) p C-308.

(43) "Sadtler Standard Spectra," The Sadtler Research Laboratories, Philadelphia, Pa., 1965, (a) Vol. 23, No. 23668; (b) Vol. 4, No. 4689; (c) Vol. 4, No. 4653; (d) Vol. 1A, No. 182.

propane, bp 102–104°, infrared spectrum identical with that of authentic material. Evaporation of the water wash gave ammonium chloride, 66% yield based on trichloramine. Illumination of an identical chlorination with a 275-W sun lamp did not change the ratio of 3-chloro-2-methylpropene to 1,2-dichloro-2-methylpropane.

1,2-Dichlorohexane: bp 66° (22 mm); n^{24}D 1.4483.

1,2-Dichlorooctane: bp 87–88° (13 mm); n^{25}D 1.4516.

trans-**1,2-Dichlorocyclopentane:** bp 53–55° (27 mm); n^{25}D 1.4781 [lit.[44] bp 53–53.5° (25 mm); n^{25}D 1.4781]; nmr δ 1.22 (4 H), 1.47 (2 H), and 2.40 (2 H).

trans-**1,2-Dichlorocyclohexane:** bp 32° (0.7 mm); $n^{24.5}$D 1.4889 [lit.[12] bp 66–67° (11 mm); n^{24}D 1.4891]. A sample, collected by glpc, was identical with authentic material (Aldrich Chemical Co.).

1,2,3-Trichloropropane: bp 156–158°; n^{25}D 1.4823 (lit.[42b] bp 156°; n^{20}D 1.4858). The infrared spectrum was in agreement with the published data.[43c]

1,1,2,2-Tetrachloroethane.—Modified general procedure A was used. A 500-ml flask equipped with a condenser topped with a drying tube was charged with trichloroamine, *cis*-1,2-dichloroethylene, and solvent. After 1 week under nitrogen, the yellow color had disappeared. Ammonium chloride was removed by filtration and the tetrachloride isolated by distillation, bp 144–145°, n^{26}D 1.4913 (lit.[42c] bp 146°, n^{20}D 1.4944). The infrared spectrum was in agreement with the published spectrum.[43d] A similar experiment went to completion in 4 hr (disappearance of yellow color) under illumination with a 275-W sun lamp (Table I).

1,1,1,2-Tetrachloroethane: bp 128–129°, n^{25}D 1.4805 (lit.[42c] bp 129–130°; n^{20}D 1.4821); ir (neat) 3050, 2975, 1420, 1280, 1197, 1052, 955, 810, 745, 714 cm^{-1}; nmr δ 4.28 (singlet).

Pentachloroethane: bp 160–164°; n^{24}D 1.5040 (lit.[42c] bp 162°; n^{15}D 1.5054). The infrared spectrum was identical with that of commercial material (Aldrich Chemical Co.).

Nortricyclyl Chloride.—This was the major product from norbornene by comparison of the infrared spectrum (glpc collection) with the published spectrum.[45]

Authentic Materials. *meso*-**2,3-Dichlorobutane.**[13]—The compound was prepared by passing chlorine gas through liquefied *trans*-2-butene under oxygen until a yellow color appeared. Distillation of the crude dichloride provided a major fraction, bp 112–113.5° (lit.[13] bp 112.5°); glpc analysis revealed that the product was 97% meso and 3% *dl*. Preparative glpc gave material of >99% purity, n^{25}D 1.4396 (lit.[13] n^{24}D 1.4392).

dl-**2,3-Dichlorobutane.**[13]—The procedure was identical with that described for the meso isomer except that *cis*-2-butene was used. Distillation of the crude dichloride gave a major fraction, bp 116–117.5° (lit.[13] bp 116.5°); glpc analysis provided the ratio, 96% *dl* and 4% meso. Pure *dl*, >90%, was isolated by preparative glpc, n^{25}D 1.4416 (lit.[13] n^{24}D 1.4413).

1,2-Dichloro-2-methylpropane.[13]—The material was prepared by photochlorination of *tert*-butyl chloride. A 100-ml flask was charged with 50 ml of *tert*-butyl chloride and exposed to a 275-W sun lamp for 45 min. During illumination, steady streams of chlorine and nitrogen were passed through the liquid *via* two dispersion tubes. After excess *tert*-butyl chloride was removed, distillation gave 10.7 g of the desired product: bp 102–104° (lit.[13] bp 103–104°); n^{25}D 1.4353; nmr δ 1.62 (6 H) and 3.64 (2 H).

1,2-Dichlorohexane.—A literature method was used.[16] To a solution of benzoyl peroxide (0.1 g) in 1-hexene (8.5 g, 0.1 mol) was added dropwise a solution of sulfuryl chloride (17.5 g, 0.13 mol) in 1-hexene (36 g, 0.43 mol) at 63–65°. After the solution had been stirred for an additional 2 hr at the same temperature, work-up afforded 1,2-dichlorohexane (83%): bp 66° (22 mm); n^{26}D 1.4471 [lit.[16] bp 59–65° (14 mm); n^{20}D 1.4500].

1,2-Dichlorooctane.—The procedure for 1,2-dichlorohexane was employed with 1-octene. 1,2-Dichlorooctane was isolated in 60% yield: bp 87° (9 mm); n^{27}D 1.4503 [lit.[16] bp 67–71° (4 mm); n^{20}D 1.4531].

cis-**1,2-Dichlorocyclohexane.**—Adherence to a published procedure[46] gave the desired product, bp 93.5° (29.5 mm) [lit.[12] bp 99–100° (30 mm)]. According to preparative glpc analysis the material was predominantly the cis isomer, n^{25}D 1.4934 (lit.[46] n^{25}D 1.4945).

Mechanistic Studies. A. Yield Effect of Solvent.—A constant molar ratio (NCl_3:C_6H_{10}:solvent = 0.04:0.09:0.5) was employed, solvent (% yield of *trans*-1,2-dichlorocyclohexane): CH_2Cl_2 (89); CCl_4 (84); *o*-$C_6H_4Cl_2$ (86); CS_2 (70).

B. Chlorination of *cis*-2-Butene in the Presence of Cyclohexane.—The method used is described in part B of the general procedure. A mixture of cyclohexane and *cis*-2-butene (molar ratio, C_6H_{12}:C_4H_6:NCl_3 = 0.23:0.23:0.023) was chlorinated at $-15 \pm 3°$. Glpc analysis (column B) revealed the presence of chlorocyclohexane, 2–3%, and a *meso*:*dl* ratio of 72:28 for the dichloride. The yield of chlorocyclohexane was not determined quantitatively but based on area ratios obtained from glpc.

C. Solvent Effect on Stereochemistry of Addition.—The 2-butene isomers were chlorinated as described for 2-butene in general prodedure B (Table IV). In a similar study, *cis*-2-butene was chlorinated; however, samples were removed periodically to determine the *meso*:*dl* ratio (glpc, column A) at various mole fractions, N, of olefin in methylene chloride.

D. Inhibitor Study.—Cyclohexene was chlorinated by a modified general procedure. A common inhibitor of radical reactions was added to the reaction mixture prior to trichloramine addition (Table V). Oxygen was introduced through a gas dispersion tube.

Registry No.—Trichloramine, 10025-85-1; 1-butene, 106-98-9; isobutylene, 115-11-7; 1-hexene, 592-41-6, 1-octene, 111-66-0; cyclopentene, 142-29-0; cyclohexene, 110-83-8; 3-chloropropene, 107-05-1; *cis*-1,2-dichloroethylene, 156-59-2; 1,1-dichloroethylene, 75-35-4; trichloroethylene, 79-01-6; 1,2-dichlorohexane, 2162-92-7; 1,2-dichlorooctane, 21948-46-9.

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Pyrolysis of 1,1,3,3-Tetrafluoroacetone

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The pyrolysis of 1,1,3,3-tetrafluoroacetone was studied in a flow system at 575–690°. The principal products of the pyrolysis are CO, CF_2H_2, CF_2HCF_2H, CF_2CFH, CF_3CHCF_2, $CF_2HCF_2CF_2H$, and HF (as SiF_4). Evidence has been obtained for the insertion of CF_2 into HF, elimination of HF from excited CF_2HCF_2H, and the intermediacy of difluoroketene.

The principal products of the pyrolysis of acetone in flow systems at about 600° are carbon monoxide, methane, ethane, and ketene.[1] Important steps in the mechanism are thought to be

$$CH_3COCH_3 \longrightarrow CH_3\cdot + \cdot COCH_3$$
$$\cdot COCH_3 \longrightarrow CH_3\cdot + CO$$
$$CH_3\cdot + CH_3COCH_3 \longrightarrow CH_4 + \cdot CH_2COCH_3$$
$$\cdot CH_2COCH_3 \longrightarrow CH_2CO + \cdot CH_3$$
$$2\cdot CH_3 \longrightarrow C_2H_6$$

One might therefore expect that the pyrolysis of 1,1,3,3-tetrafluoroacetone (TFA) would give difluoroketene, a compound which has not previously been isolated.[2] Although we did not obtain difluoroketene as a product of the pyrolysis of TFA in a flow system at 575–690°, we did find evidence that it was an intermediate. Furthermore, the pyrolysis of TFA revealed two elementary steps of importance: the elimination of hydrogen fluoride from excited difluoromethyl dimers and the insertion of difluoromethylene into hydrogen fluoride to form trifluoromethane.

$$CF_2HCF_2H^* \longrightarrow CF_2{=}CFH + HF$$
$$CF_2 + HF \longrightarrow CF_3H$$

TFA was completely pyrolyzed at 690° with a contact time of 3.3–4.5 sec. At 575° only 5% of the TFA was pyrolyzed. Semiquantitative analysis of condensable products of the 690° pyrolysis gave the following product distribution (mole %): CF_2H_2 (32), CF_2H-CF_2H (11), $CF_2HCF_2CF_2H$ (10), CF_3CHCF_2 (10), CF_2CFH (8), CF_3H (7) (less at lower temperatures), SiF_4 (4), CF_2HCF_3 (4), CFH_2CF_3 (4), $CF_2HCF_2CF_2CF_2H$ (2), CF_2HCOF (1) (more at lower temperatures), CF_2CH_2 (0.7), CF_2O (0.04), unidentified (6), CF_2CF_2 (trace) (significantly more at lower temperatures). Infrared and molecular weight data suggest that the major unidentified products are fluorobutanes and fluorobutenes. When CO analyses were performed, a semiquantitative agreement between CO production and TFA pyrolysis was found.

Steps analogous to the formation of methane and ethane in the pyrolysis of acetone account for the large amounts of CF_2HCF_2H and CF_2H_2. However, when difluoromethyl radicals combine, the excited dimer, in addition to undergoing collisional deactivation to stable CF_2HCF_2H, can also eliminate HF to form trifluoroethylene, a process also observed by Pritchard and Bryant in the photolysis of TFA.[3] These investigators argued on the basis of RRK unimolecular kinetics theory that the yield of CF_2CFH should increase with temperature, a prediction supported by our observations. The importance of this process is underscored by the formation of CF_3CFH_2 which can be explained by the addition of HF to CF_2CFH. The formation of CF_3CFH_2 lends support to the notion that symmetric fluoroethanes will be converted to asymmetric ones if a mechanistic pathway is provided. Although the thermodynamic functions for some of the tetrafluoroethanes have not been reported, data on trifluoroethanes [CF_3CH_3, $\Delta H_f°$ (298°) = −178.2 kcal/mol; CF_2HCFH_2, $\Delta H_f°$ (298°) = −158.9 kcal/mol][4] suggest that the asymmetric isomer is the more stable. An estimate of the enthalpies of formation of the tetrafluoroethanes using the group substitution methods[5] gives the supporting results: $\Delta H_f°$ (CF_3CFH_2) = −210 kcal/mol and $\Delta H_f°$ (CF_2HCF_2H) = −199 kcal/mol. A similar calculation on the trifluoroethanes gives $\Delta H_f°$ (CF_3CH_3) = −171 kcal/mol and $\Delta H_f°$ (CHF_2CH_2F) = −149 kcal/mol, in fair absolute and good relative agreement with the experimental values.[6]

Some higher molecular weight products result from difluoromethyl–olefin reactions

$$\cdot CF_2H + CF_2CF_2 \longrightarrow CF_2HCF_2CF_2\cdot$$
$$CF_2HCF_2CF_2\cdot + CF_2HCOCF_2H \longrightarrow CF_2HCF_2CF_2H + CF_2HCOCF_2\cdot$$
1
$$CF_2HCF_2CF_2\cdot + \cdot CF_2H \longrightarrow CF_2HCF_2CF_2CF_2H$$
2

A photolysis of a TFA–CF_2CF_2 mixture yielding **1** and **2** (as well as CF_2H_2 and CF_2HCF_2H) as major products was performed to check this mechanism. Extension of the chain by means of HF elimination and addition provides a reasonable explanation for higher molecular weight products. Trifluoroethylene–difluoromethyl-radical reactions are not needed to account for the identified products but may play a role in the formation of minor higher molecular weight products. Photolysis of a TFA–CF_2CFH mixture yielded mostly CF_2H_2 and CF_2HCF_2H with only trace amounts of unidentified higher molecular weight products.

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(6) From the enthalpy of formation of CF_2CF_2 at 25°, −157.6 kcal/mol (ref 4), and the enthalpy of hydrogenation of CF_2CF_2 at 120°, −42.26 kcal/mol (J. R. Lacher and J. D. Park, AF-AFOSR Report 810-67), the enthalpy of formation of CF_2HCF_2H at 25° is calculated to be −200.6 kcal/mol. The adjustment of the enthalpy of hydrogenation of CF_2CF_2 to 25° (−0.6 kcal/mol) was made using the heat capacities [CF_2CF_2 and H_2, JANAF Thermochemical Tables, 1965; CF_2HCF_2H, calculated by statistical thermodynamics from infrared data of P. Klaboe and J. R. Nielsen, *J. Chem. Phys.*, **32**, 899 (1960)]. Entropy differences between fluoroethane isomers are assumed to be essentially zero.

Although difluoroketene was not isolated, its role as an intermediate is indicated by the isolation of CF_2CF_2 (and its addition products), CF_3H, and CF_2HCOF. By analogy to the known chemistry of ketenes,[7] difluoroketene would be expected to decompose to CF_2 and CO. C_2F_4 arises from the well-known dimerization of CF_2. A secondary route for the formation of CF_2 could be the following reaction.[7]

$$CF_2 + CF_2CO \longrightarrow CF_2CF_2 + CO$$

CF_3H arises from the insertion of CF_2 into HF, a reaction previously unreported. The insertion of CF_2 into HCl has been reported.[8] We have observed that CF_3H is a product of the pyrolysis of a mixture of HF and difluorodiazirine (a thermal source of CF_2).[9] The formation of $CF_2HCF_2CF_2CF_2H$ cannot be attributed to the insertion of CF_2 into $CF_2HCF_2CF_2H$ as Mitsch has shown that CF_2, a species more discriminating and less reactive than methylene, does not insert into C–H bonds.[10] Insertion of CF_2 into C–F bonds is also ruled out as it has not been observed in simpler systems.[10] Reaction of CF_2 with CF_2H, for which $\Delta H = -53$ kcal/mol,[11] could be another route to CF_2HCF_2H and to $CF_2HCF_2CF_2H$. However, no products, such as $CF_2HCF{=}CF_2$, were isolated that would be characteristic of this mechanism. A hypothetical decomposition of CF_2HCOF, a product presumed to arise from addition of HF to CF_2CO, is not a likely alternative pathway to CF_3H (and CO). Although CF_2HCOF is a product of the pyrolysis of difluoroacetic anhydride, CF_3H is not. The isolation of CF_2HCOF is more direct evidence of the CF_2CO intermediate. A reaction of HF with CF_2CO parallels ketene chemistry; for example, HCl reacts with ketene to produce acetyl chloride.[12]

In their paper on the pyrolysis of hexafluoroacetone, Batey and Trenwith propose that the observed trifluoroacetyl fluoride results from the primary step in the decomposition[13]

$$CF_3COCF_3 \longrightarrow CF_3COF + CF_2$$

Such a route in the TFA pyrolysis would require the production of fluoromethylene (CFH) as an intermediate which could combine to form 1,2-difluoroethylene. Since neither 1,2-difluoroethylene nor its HF addition products were observed, this route for CF_2HCOF production seems unlikely. CF_2H_2 could be interpreted as an insertion product of CFH into HF, but the large excess of CF_2H_2 over CF_2HCOF and COF_2, a possible decomposition product, rules this out as as major mechanistic pathway. However, the ketene route, in which each mole of CF_2H_2 is accompanied by 1 mol of CF_2, following ketene decomposition, is supported within the accuracy of the semiquantitative data by the mass balance between CF_2H_2 and CF_2 derived products. At 690°, CF_2H_2 = 32 mol %; $2CF_2CF_2 + CF_2HCF_2CF_2H + 2CF_3CF_2H + CF_2CHCF_2 + CF_3H + CF_2HCOF + 2CF_2HCF_2CF_2CF_2H$ = 40 mol %. Finally, the Batey–Trenwith mechanism does not account for products which can easily be explained by the intermediacy of difluoroketene and its decomposition products.

When CF_2CFH itself is pyrolyzed between 500 and 700°, the principal products are CF_3CHCF_2 and $CF_3CH{=}CHCF_3$ with the butene being generally twice as large in amount.[14] Knunyants, German, and Rozhkov have explained these products with the mechanism

$$CF_2CFH \longrightarrow CF_3CH:$$
$$2CF_3CH: \longrightarrow (CF_3CH:)_2$$
$$CF_2CFH \longrightarrow CF_2: + CFH:$$
$$CF_2CFH + CF_2: \longrightarrow \underset{\diagdown\ \diagup}{CF_2{-}CFH} \longrightarrow CF_3CHCF_2$$
$$CF_2$$

Since studies of the pyrolysis of fluorocyclopropanes (*vide infra*) would seem to rule out pentafluorocyclopropane as an intermediate in the formation of CF_3CHCF_2, it seems likely that the CF_3CHCF_2 found in the pyrolysis of TFA results more directly from the reaction

$$CF_3CH: + CF_2: \longrightarrow CF_3CHCF_2$$

$CF_3CH{=}CHCF_3$ was not observed as a product in the TFA pyrolysis, suggesting that the proposed CF_3CH: was trapped by difluoroketene-originated CF_2: before dimerization could occur.

The instability of difluoroketene relative to ketene is probably due in part to the enhanced stability of difluoromethylene relative to methylene. Difluoromethylene is stable enough to allow determination of its microwave spectrum.[15] Furthermore, whereas activated perfluorocyclopropane eliminates CF_2,[16] cyclopropane isomerizes to propene without elimination.[17] The activation energy for the former process is 38.6 kcal, considerably less than the 65.5 kcal which is required for the latter. Other excited highly fluorinated molecules such as 1,1,2,2-tetrafluorocyclopropane[18] and perfluoroethylene oxide[19] also eliminate CF_2.

Although CF_2 is known to add to olefins to form cyclopropanes,[9,10] no evidence for fluorocyclopropanes was found in the pyrolysis products. This does not rule out the intermediacy of highly fluorinated cyclopropanes since these compounds have been shown to decompose readily at 300°,[16,18,20] a temperature considerably below the pyrolysis temperature. However, these references and the thermochemical estimates of O'Neal and Benson[21] show that highly fluorinated cyclopropanes do not isomerize to propylenes, ruling these compounds out as a route to higher olefins. In particular, pentafluorocyclopropane cannot be the source of $CF_3CH{=}CF_2$ for it decomposes to CF_2CFH and CF_2CF_2 at 250°.

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Experimental Section[22]

1,1,3,3-Tetrafluoroacetone.—TFA was prepared by reaction of 70 g of $CF_2ClCOCF_2Cl$ (Allied Chemical Co.) and H_2 on a palladium-on-charcoal catalyst in a monel flow system at 200°.[23] Fractionation of the crude product, followed by preparative vpc of the 57–61° cut on the DBP-FP column[22] at 75° gave material free of other acetones, 23 g (50%), but still containing some HCl and water. HCl was removed by passing the TFA as a gas over solid K_2CO_3, and water was removed by passage over P_4O_{10}: ir 3550 (w), 1785 (s), 1390 (m), 1345 (s), 1175 (s), 1115, 1100 (vs), 860 (m), 675 (m), 565 (m), 525 (m), 435 cm^{-1} (m). The wet TFA has additional gas phase bands at 3620, 3020, 1320, 980, and 780 cm^{-1}; pmr δ 6.1 (t with complex substructure, J_{HF} (gem) = 54 Hz).

Difluoroacetyl Fluoride.—CF_2HCOF was made by reaction of KHF_2 and difluoroacetic anhydride (DFAA), which was obtained by refluxing difluoroacetic acid (Columbia Chemical Co.) over P_4O_{10}.[24] DFAA (5.1 g) and KHF_2 (0.65 g) were stirred and heated at 130° for 2.5 hr while the product acid fluoride distilled into a trap held at −80°, yield 0.16 g. The identity of the acid fluoride, bp 2°, was established from its gas density and ir spectrum: mol wt 99 g/mol (calcd 98 g/mol); ir 2980 (s), 1895, 1880, 1870 (vs), 1365, 1360 (s), 1250 (s), 1145 (vs), 1110, 1100, 1090 (vs), 915 (s), 860 (s), 740 (m), 575 cm^{-1} (s); ir of DFAA 3000 (m), 1870, 1800 (s), 1350 (s), 1220 (s), 1140, 1110, 1070 (vs), 930 cm^{-1} (s).

1,1,2,2-Tetrafluoroethane and Pentafluoroethane.—CF_2HCF_2H and CF_3CF_2H were prepared by overnight photolysis with a medium-pressure mercury lamp of an equimolar gaseous mixture of TFA and hexafluoroacetone in a 3-l. Pyrex flask.[25] In addition to the desired ethanes the products included CF_2H_2, CF_3H, and CF_3CF_3. Pure CF_2HCF_2H and 95% pure CF_3CF_2H were isolated by repeated vpc on the DBP-FB column at 0°. Elution times: CF_3CF_3, 1.0; CF_3H, 1.6; CF_3CF_2H, 2.4; CF_2H_2, 3.9; and CF_2HCF_2H, 9.7.

1,1,1,2-Tetrafluoroethane.—CF_3CFH_2 was isolated from the TFA pyrolysis products by vpc at 0° on the DBP-FB column followed by the HC-FB column and identified by its ir spectrum.

1,1,2,2,3,3-Hexafluoropropane and 1,1,2,2,3,3,4,4-Octafluorobutane.—$CF_2HCF_2CF_2H$ was obtained from photolysis of a gaseous 100:16 Torr mixture of TFA and CF_2CF_2 (Peninsular ChemResearch Co.). This propane (29 mg) was isolated by vpc on the HC-FB column at 0°. The propane was identified by its gas density and its pmr[26] and ir spectra: mol wt 146 g/mol (calcd 152 g/mol); pmr δ 5.9 (t of t, J_{HF} = 53, 5.5 Hz); ir 3000 (m), 1415 (s), 1380 (s), 1345 (s), 1295 (s), 1270 (vs), 1215 (vs), 1185 (vs), 1120 (vs), 1085 (vs), 875 (s), 775 (m), 710 (s), 645 (m), 575 (m), 450 cm^{-1} (m).

A smaller fraction of moderate purity obtained from this photolysis was tentatively identified as $CF_2HCF_2CF_2CF_2H$ on the basis of its gas density (11-mg sample) and ir spectrum: mol wt 181 g/mol (calcd 202 g/mol); ir 3000 (m), 1395 (m), 1350, 1255, 1235 (s), 1150 (vs), 1120 (vs), 1065 (s), 840 (m), 790 (m), 700 (m), 565 cm^{-1} (m).

1,1,3,3,3-Pentafluoropropene-1 and 1,1,2,2,3,3-Heptafluoropropane.—A fluoroalkane and a fluoroalkene, separated from the products of pyrolysis of TFA by the HC-FB and DBP-FB columns at 0°, were identified as CF_3CHCF_2 and $CF_3CF_2CF_2H$ by their ir spectra.

Other Fluorocarbons.—Analytical samples of CF_2H_2, CF_3H, CF_2CF_2, CF_2CFH, and SiF_4 were obtained from commercial sources.

Pyrolysis of Difluorodiazirine with Hydrogen Fluoride.—A 60:240 Torr gaseous mixture of CF_2N_2[9] and HF (Matheson Co.) was heated for 4 hr at 155° in a monel cylinder. Products, in addition to nitrogen, were CF_3H (10%) and CO_2 (90%), based on available CF_2. The monel cylinder was not given a prior treatment to remove any oxide film from the interior, and water may have been present in the HF.

Pentafluorocyclopropane.—c-C_3F_5H was prepared by heating a mixture of CF_2N_2 and CF_2CFH.[27] c-C_3F_5H (0.8 mmol, 30% yield) was separated from the other condensable product, perfluorocyclopropane, by vpc: ir 3140 (m), 1530 (m), 1325, 1320 (s), 1270 (vs), 1250 (vs), 1225, 1215 (vs), 1180, 1175 (m), 970, 965 (s), 830 (s), 780 (s), 685, 675 (w), 600 (m), 530 (m), 430 cm^{-1} (m). c-C_3F_5H was heated in a Pyrex tube at 250° yielding CF_2CFH and CF_2CF_2 as principal products with some perfluorocyclopropane.

Pyrolysis of Tetrafluoroacetone.—TFA was pyrolyzed in a flow system, which was built onto a conventional vacuum system, with He as a carrier gas. Reaction took place in a 20 × 1.6 cm carbonized quartz tube. (Although TFA pyrolyzed readily at 650° in the quartz tube, no pyrolysis was observed in a monel tube even at 830°.) Helium, at atmospheric pressure, bubbling through TFA in a trap maintained at room temperature, picked up the acetone at a pressure of about 100 Torr. Products were collected in three traps. The trap next to the furnace was maintained at −30°, somewhat above the freezing point of TFA; the other two were at −195°. Noncondensable gases were continuously vented to the atmosphere. The flow rate of He ranged from 8.7 to 6.0 l./hr, giving a contact time of 3.3–4.5 sec. Temperature was measured with two thermocouples placed inside the furnace.

Condensable products were analyzed primarily by infrared spectrometry, using literature spectra for identification whenever possible.[28] The 10-cm gas cell was constructed with a monel body and 5-cm KBr windows sealed with O rings. During an analysis, involatile deposits, absorbing at 1120–1020, 730, and 475 cm^{-1}, built up on the cell windows, making frequent repolishing necessary. Products condensed in the two −195° traps were combined in a mixing flask, from which were obtained gaseous samples for representative spectra at various pressures. Generally, the overlap of useful, strong absorption bands, particularly in the 1400–1000-cm^{-1} region, was such that a second step was necessary to obtain an analysis. The entire −195° fraction was condensed in a bulb, and gaseous aliquots were taken in sequence for ir spectra by allowing the material to warm slowly from −195°. This procedure gave significantly simplified spectra of mixtures of products having similar boiling points. Analytical vpc, using HC-FB and DBP-FB columns at 0°, with ir analyses on various fractions was also used to complement the boil-off method. In the −30° trap, essentially only unreacted TFA was found.

CO, the only noncondensable product, was determined by diluting a portion of the gaseous He–CO mixture from each trap with a measured quantity of air and then analyzing by vpc. A 4 m × 1.0 cm activated charcoal column at room temperature was used. From the CO–N_2 ratio, the He (plus CO)–N_2 ratio, the flow rate of He, and the duration of the run, the amount of CO was calculated.

Registry No.—TFA, 360-52-1; CF_2HCOF, 2925-22-6; $CF_2HCF_2CF_2H$, 680-00-2; $CF_2HCF_2CF_2CF_2H$, 377-36-6; c-C_3F_5H, 872-58-2.

(22) Gas phase ir spectra were run on a Perkin-Elmer Model 621 spectrometer, and nmr spectra were run on a Varian A-60 spectrometer with TMS as an internal standard and $CFCl_3$ as a solvent. Preparative and analytical vpc was performed with 4 m × 1.0 cm columns packed with 20% dibutyl phthalate on either Fluoropak 80 (DBP-FP) or firebrick (DBP-FB) and halocarbon oil on firebrick (HC-FB).

(23) J. Gordon and C. Woolf, U. S. Patent 2,917,546 and General Chemical Division of Allied Chemical Co. product development data sheets.

(24) E. Sawicki, *J. Org. Chem.*, **21**, 376 (1956). Control of the purity of DFAA made by this method is difficult. The pyrolysis of DFAA is a possible source of CF_2CO in analogy to the pyrolysis of $(CH_3CO)_2O$ to give ketene; *cf.* M. Szwarc and J. Murawski, *Trans. Faraday Soc.*, **47**, 269 (1951). Pyrolysis of DFAA in a flow system in a monel tube at 400° gave HF, CO, and CF_2HCOF as principal products. Pyrolysis at 700° yielded CO_2, CF_2CF_2, and formyl fluoride. Neither CF_2CO nor CF_3H were obtained in temperature range 260–700°.

(25) G. O. Pritchard and J. T. Bryant, *J. Phys. Chem.*, **70**, 1441 (1966).

(26) D. D. Elleman, L. C. Brown, and D. Williams, *J. Mol. Spectrosc.*, **7**, 322 (1961), gave −0.68-ppm shift relative to an external 10% water in deuterium oxide reference and J_{HF} = 52.7, 8.5 Hz. The proton resonance was not fully resolved.

(27) R. A. Mitsch, *J. Heterocycl. Chem.*, **1**, 271 (1964).

(28) CF_3H, E. K. Plyler and W. S. Benedict, *J. Res. Nat. Bur. Stand.*, **47**, 202 (1951); CF_2H_2, *ibid.*, **47**, 202 (1951); CF_2CH_2, W. F. Edgell and C. J. Ultee, *J. Chem. Phys.*, **22**, 1983 (1954); CF_2CF_2, J. R. Nielsen, H. H. Claassen, and D. C. Smith, *ibid.*, **18**, 812 (1950); CF_3CFH, D. E. Mann, N. Acquista, and E. K. Plyler, *ibid.*, **22**, 1586 (1954); CF_3CF_2H, J. R. Nielsen, H. H. Claassen, and N. B. Moran, *ibid.*, **23**, 329 (1955); CF_3HCF_2H, P. Klaboe and J. R. Nielsen, *ibid.*, **32**, 899 (1960); CF_3CFH_2, W. F. Edgell, T. R. Riethoff, and C. Ward, *J. Mol. Spectrosc.*, **11**, 92 (1963); $CF_3CF_2CF_2H$, N. B. S. Spectra File, No. 363; CF_3CHCF_2, R. N. Haszeldine and B. R. Steele, *J. Chem. Soc.*, 923 (1954), and D. M. S. Spectra File, No. 77a; F_2CO, A. H. Nielsen, T. G. Burke, P. J. H. Woltz, and E. A. Jones, *J. Chem. Phys.*, **20**, 596 (1952). Grating quality gas phase reference spectra and absorption coefficients for principal bands are on file.

Acknowledgments.—G. Frederick Hatch made the initial studies of this system, and Eric A. Gislason prepared and characterized CF_2HCOF. We are indebted to Dr. R. A. Mitsch of the 3M Co. for the CF_2N_2 sample. C. D. J. and W. E. S. were supported by National Science Foundation Summer URP Grants.

Organic Oxalates. VI. Pyrolysis of Di(α-substituted benzyl) Oxalates[1]

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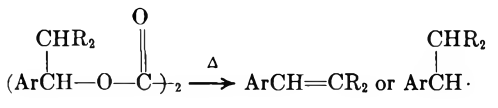
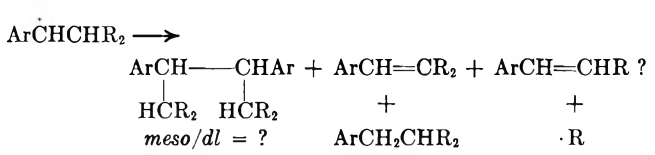
Products from the low-pressure gas phase pyrolysis of di(α-substituted benzyl) oxalates are reported. Di(α-substituted benzyl) oxalates which contain β hydrogen atoms undergo an elimination reaction in addition to homolytic decomposition to α-substituted benzyl radicals. Coupling of α-substituted benzyl radicals occurs only when the α substituent is a methyl or trifluoromethyl group. When the α substituent is a trichloromethyl, an ethyl, a pentafluoroethyl, or an isopropyl group, β scission is the chief reaction of the radicals. No evidence for disproportionation of the radicals is presented. The *meso/dl* ratios for the coupling products from the α-methylbenzyl and α-trifluoromethylbenzyl radicals are 52:48 and 42:58, respectively. Mechanistic implications of these results are discussed.

Recently we reported that pyrolysis of ring-substituted dibenzyl oxalates under vacuum gave exclusively bibenzyls resulting from coupling of benzyl radicals.[2] These oxalates did not contain β hydrogen atoms and consequently could not undergo elimination reactions such as those observed by Karabatsos and coworkers who pyrolyzed dialkyl oxalates that possessed β hydrogen atoms in the liquid phase.[3] In this paper we report the study of di(α-substituted benzyl) oxalates. One objective of this study was to determine if the pyrolysis of an oxalate that contains β hydrogen atoms under our conditions leads to an elimination reaction or benzyl radical formation. Another objective was to determine the fate of α-substituted benzyl radicals in cases where they are produced. Specifically, we wished to know whether



these radicals couple, disproportionate, or undergo β scission under our conditions, and the *meso/dl* ratio of the coupling products when coupling occurs.



Results

Glpc and nmr analyses of the pyrolysate of di-α-methylbenzyl oxalate at 570° showed that styrene was the main product and benzaldehyde and *meso*- and *dl*-2,3-diphenylbutanes were minor products obtained in comparable amounts. Pyrolyses carried out from 400 to 650° showed that the ratio of styrene to 2,3-diphenylbutanes ranged from 4.9 to 9.0. The large amount of styrene probably comes from a concerted cyclic elimination pathway, the usual pyrolytic route of esters,[4] since disproportionation of the α-methylbenzyl radical should lead to ethylbenzene in addition to styrene and only a negligible amount of ethylbenzene was detected. Thus di-α-methylbenzyl oxalate seems to decompose chiefly by the elimination route and the main reaction of the α-methylbenzyl radicals which are produced is coupling to form the 2,3-diphenylbutane diastereomers. The origin of benzaldehyde is not clear, and it may come from the mono-α-methylbenzyl oxalate which results from the elimination reaction.

The *meso/dl* ratio of the 2,3-diphenylbutanes produced at 480° was found to be 52/48. The meso isomer was passed through the oven heated to 480° with negligible isomerization to the *dl* isomer.

Pyrolysis of di-α-trifluoromethylbenzyl oxalate at 650° gave the two isomers of 2,3-diphenyl-1,1,1,4,4,4-hexafluorobutane (DPHFB) in 40% yield. These isomers were separated by glpc (SE-30 column) and their structures were confirmed by nmr, ir, and mass spectra and elemental analyses. The lower melting isomer, mp 73–75°, was assigned the *dl* structure and the other isomer, mp 156–158°, was assigned the meso structure since the symmetry of the unit cell of the higher melting isomer demands that the molecule has an inversion center. Only the meso isomer can have a center of symmetry. Weissenberg photographs of a single crystal of the high melting isomer showed the D_{2h} Laue symmetry appropriate for the orthorhombic crystal class. The cell constants, measured from Weissenberg photographs, are $a = 14.43 \pm 0.08$, $b = 7.41 \pm 0.01$, $c = 13.28 \pm 0.05$ Å.

(1) (a) Part V: W. S. Trahanovsky and P. W. Mullen, *Chem. Commun.*, 102 (1971). (b) This work was partially supported by Public Health Service Grant GM 13799 from the National Institute of General Medical Sciences and Grant 3219-A from the Petroleum Research Fund, administered by the American Chemical Society. The mass spectrometer was purchased with funds from the National Science Foundation (NSF) Grant GP 1715 and a grant from the Iowa State Alumni Research Fund. We thank these organizations for their support. (c) Based on work by C. C. O. in partial fulfillment of the requirements for the Ph.D. degree at Iowa State University. (d) Preliminary communication: Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, 33-P. (e) Alfred P. Sloan Research Fellow, 1970–1972. (f) NSF Undergraduate Research participant, summer 1970.

(2) W. S. Trahanovsky, C. C. Ong, and J. A. Lawson, *J. Amer. Chem. Soc.*, **90**, 2839 (1968).

(3) (a) G. J. Karabatsos, J. M. Corbett, and K. L. Krumel, *J. Org. Chem.*, **30**, 689 (1965); (b) G. J. Karabatsos and K. L. Krumel, *J. Amer. Chem. Soc.*, **91**, 3324 (1969).

(4) C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).

The systematic extinctions on $h0l$ (absent if $l = 2n + 1$), $0kl$ (absent if $k = 2n + 1$), and $hk0$ (absent if $h = 2n + 1$) uniquely determine the space group as $Pbca$ (D_{2h}^{15}). The density, determined by flotation in aqueous potassium iodide, is 1.42 g/cm³. This implies that there are four molecules per unit cell. The calculated density for $Z = 4$ is 1.49 g/cm³. Since space group $Pbca$ requires 8 molecules of the isomer if no molecular symmetry were used in the crystal, the two halves of the molecule must be related by the crystallographic inversion center. Thus, in the absence of disorder, the high melting dimer must be the meso and it must pack in the anti conformation which has an inversion center.

Our assignment of stereochemistry is consistent with the generalization that the more symmetrical isomer melts at a higher temperature than the less symmetrical isomer.[5] Moreover, the *dl* isomer is eluted before the meso isomer on an SE-30 column which is the same behavior exhibited by the 2,3-diphenylbutanes, but polarity differences of the two sets of isomers make their glpc behavior difficult to predict. The average *meso/dl* ratio of DPHFB obtained from seven runs of the pyrolysis of di-α-trifluoromethylbenzyl oxalate was 42.1/57.9 = 0.728 ± 0.024. The pyrolysis temperature of these runs ranged from 420 to 650°. No significant temperature variation of the *meso/dl* ratio was noted; however, at low pyrolysis temperatures where the yields of DPHFB became low, the glpc peak of an impurity which was eluted at the same rate as the *dl* isomer became important. Using a 17-ft 20% SE-30–3-ft 20% SE-95 column the peaks for the impurity and *dl* isomer were resolved. Using this column, a *meso/dl* ratio of 42.5/57.5 was obtained for a run carried out at 420°. In this run, only 7% of these products were obtained relative to recovered starting material.

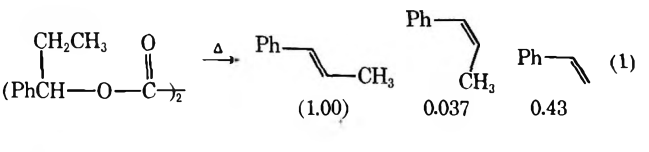
The *meso/dl* ratio was the same for runs that were made using a mixture of the meso and *dl* oxalates or one of the pure, crystalline isomers of the oxalate. The meso DPHFB was found not to isomerize significantly when passed through the furnace at 500°.

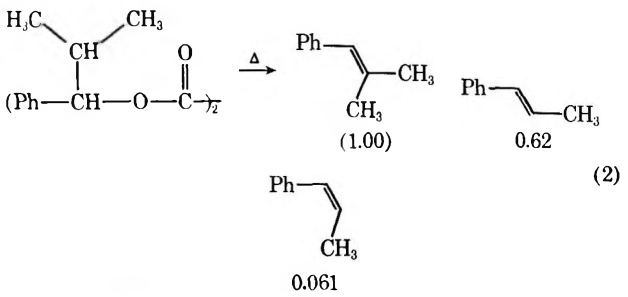
Unlike the di-α-trifluoromethylbenzyl oxalate, di-α-trichloromethylbenzyl oxalate gave rise to the elimination product, not the product from the coupling reaction. A 32% yield of β,β-dichlorostyrene was obtained from the pyrolysis of di-α-trichloromethylbenzyl oxalate at 500 and 680°.[6]

Pyrolysis at 570° of di-α-ethylbenzyl and di-α-isopropylbenzyl oxalates gave the olefins that result from elimination reactions of the oxalates and fragmentation reactions of the substituted benzyl radicals. Relative yields of these products are presented in eq 1 and 2 and in both cases the absolute yield of these products was >60%. No evidence for coupling products from the benzyl radicals was obtained.

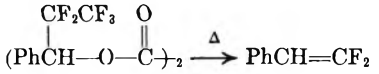
Attempts to prepare di-α-*tert*-butylbenzyl oxalate were unsuccessful.

Pyrolysis of di-α-pentafluoroethylbenzyl oxalate at 650° gave almost exclusively β,β-difluorostyrene. Nmr analysis of the pyrolysate showed that 1.36 mol of





β,β-difluorostyrene was formed per mol of oxalate pyrolyzed. Glpc analysis showed the presence of three high boiling components. Two of these components might by the coupling products of the inter-



mediate radical but their low yield prevented their identification. Undoubtedly the β,β-difluorostyrene was formed from β scission of the α-pentafluoroethylbenzyl radical.

Pyrolysis of di-α,α-dimethylbenzyl oxalate gave a quantitative yield of the elimination product, α-methylstyrene.

Discussion

We have reported previously that the major mode of thermal decomposition of ring-substituted dibenzyl oxalates in the gas phase is homolytic cleavage to form benzyl radicals which couple to form bibenzyls.[2] From the present study it is clear that di(α-substituted benzyl) oxalates which contain β hydrogen atoms undergo an elimination reaction in addition to homolytic decomposition to benzyl radicals. Indeed, the elimination reaction becomes the exclusive pathway of decomposition of di-α,α-dimethylbenzyl oxalate.

The most reasonable mechanism for the elimination reaction is that proposed for monoester pyrolyses, a concerted cyclic pathway.[4] An ion pair mechanism as proposed by Karabatsos and coworkers[3] for the thermal decomposition of oxalates in the liquid phase cannot be entirely ruled out but is less likely than the concerted cyclic process for a gas phase reaction.

Although the elimination reaction is the dominant one during the gas phase pyrolysis of di(α-alkyl-substituted benzyl) oxalates that contain β hydrogen atoms, formation of α-alkyl-substituted benzyl radicals does occur. Coupling of these radicals take place, however, only when the α substituent is a methyl group. When the α substituent is an ethyl or isopropyl group, β scission is the chief reaction of the radicals. No evidence for disproportion of the radicals was obtained in any case.

Replacement of the hydrogen atoms on the α substituent with fluorines prevents the elimination reaction but the α-perfluoroalkyl-substituted benzyl radicals

(5) K. Wiberg, "Laboratory Techniques in Organic Chemistry," McGraw-Hill, New York, N. Y., 1960, pp 77–79.

(6) This oxalate was pyrolyzed at lower pressures (10^{-4}–10^{-5} mm) than was used for the other oxalates since a different pyrolysis apparatus was used.

undergo reactions similar to the hydrocarbon radicals. It is interesting to note that the α-pentafluoroethylbenzyl radical undergoes β scission just like the α-ethylbenzyl radical to give a fair yield of β,β-difluorostyrene. The α-trichloromethylbenzyl radical, unlike the α-trifluoromethylbenzyl radical, undergoes β scission to give a fair yield of β,β-dichlorostyrene.

Fragmentation of alkyl radicals, especially α-alkylbenzyl radicals has not been extensively investigated. Only a few scattered examples are cited in the literature such as fragmentation of lower alkyl radicals,[7] bond scission of aryl-substituted alkyl radicals during high temperature cracking of alkylbenzene,[8] and reversibility of radical addition to olefins.[9,10] Recently, Bartlett and McBride[11] have reported that the 1-phenyl-1-methylisobutyl radical undergoes exclusively dimerization and disproportionation. The fact that we have obtained exclusively β scission products from similar radicals is undoubtedly due to the high temperature of our reactions.

Coupling of the α-methyl- and α-trifluoromethylbenzyl radicals leads to meso and *dl* products. Since we measured these *meso/dl* ratios from pyrolyses carried out under conditions that did not isomerize one of the pure isomers, our ratios should measure the rates of formation of these two isomers and not their thermodynamic stabilities. α-Methylbenzyl radicals have been generated from several sources and under a variety of conditions and the latest results indicate that statistically distributed α-methylbenzyl radicals couple to give approximately equal amounts of *meso*- and *dl*-2,3-diphenylbutanes.[12,13] Thus our results agree with those previously published and indicate that the activation energies for the formation of the *meso*- and *dl*-2,3-diphenylbutanes are equal which indicates that no great steric or polar differences exist in the two diasteromeric transition states.

In contrast to the *meso/dl* ratio found for the products from α-methylbenzyl radicals, the *meso/dl* ratio of the products from the coupling of the α-trifluoromethylbenzyl radicals was found to be 42/58. This difference in yields of meso and *dl* isomers from the coupling of the α-trifluoromethylbenzyl radicals suggests that there is a substantial polar effect which favors formation of one diastereomer over the other. However, it is difficult to understand the predominance of the *dl* isomer since the most favored transition state that leads to coupling would seem to be the one that has the two trifluoromethyl groups as far apart as possible so that their dipole moments cancel, and the two phenyl groups as far apart as possible in order to minimize steric interactions. This transition state would lead to the meso isomer. Thus, the greater yield of the *dl* isomer indicates that some other types of polar or steric factors must be important which causes the *dl* transition state to be more stable than the meso transition state.

The *meso/dl* ratios of products from other radicals that have been studied are usually close to 1.[12i,j,14] There are only a few cases which are reported to give unequal amounts of meso and *dl* coupling products, and, in these cases, usually the meso isomer was obtained in higher yield.[12h,14a,15]

The yield of the two 2,3-diphenyl-1,1,1,4,4,4-hexafluorobutanes was 40% from a pyrolysis at 650°. This reaction illustrates the synthetic utility of oxalate pyrolyses since we have not been able to synthesize these compounds by other routes. The Grignard coupling reaction is often used to produce bibenzyls[2] but α-fluoro Grignard and lithium reagents are quite unstable and difficult to work with.[16]

Experimental Section

Materials and Methods.—Most equipment, some materials, and methods have been previously described.[2,17]

In addition to using the previously described pyrolysis apparatus, a high-vacuum pyrolysis apparatus was also used. This apparatus was constructed as follows. The pyrolysis tube consisted of a 31 × 2.8 cm Vycor tube filled with short pieces (~6 mm) of 7-mm Vycor tubing. It was sealed on one end to an inner H.V.S., ground, Pyrex, ⅌ 40/35, o-ring joint with a silicone rubber o-ring (Scientific Glass Apparatus) for attachment to the sample holder; the other end was sealed to a 90° angle portion of Pyrex tubing and then an o-ring seal, 2.5-cm i.d., joint for attachment to the product trap. The sample was held in a small boat inside the constrictured outer portion of the ⅌ 40/35 joint and could be externally heated by an aluminum cylinder wrapped with heating tape and asbestos tape. The product trap joints were both 2.5-cm i.d., o-ring seal. The furnace was an 800-W Lindberg Hevi-Duty "Mini Mite," with input control and pyrometer. The temperature was measured only at the center of the tube. A two-stage oil diffusion pump (H. S. Martin and Son) was used and was monitored with a cold cathode gauge (H. S. Martin and Son). The stopcocks (Scientific Glass) to the roughing line and between the product trap and vacuum line were both Teflon sized 0–10 and 0–15 mm, respectively.

α-Methylbenzyl, α-ethylbenzyl, α-isopropylbenzyl, and α,α-dimethylbenzyl alcohols were obtained from Aldrich.

α-Trifluoromethylbenzyl alcohol was prepared by the lithium aluminum hydride reduction of trifluoroacetophenone (Pierce Chemical Co.): yield 80%; bp 70–74° (15 mm) [lit.[18] bp 64–65° (5 mm)]; nmr ($CDCl_3$) δ 7.32 (s, 5), 4.82 (q, 1, J = 7 Hz), and 3.33 (s, 1).

α-Pentafluoroethylbenzyl Alcohol.—Pentafluoroethyl phenyl ketone was prepared by the method of Simmons, Black, and Clark[19] by the Friedel–Crafts reaction of pentafluoropropionyl chloride (Pierce Chemical Co.) with benzene in the presence of aluminum trichloride, yield 30%, bp 159–160° (lit.[19] bp 161–

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TABLE I

YIELDS, MELTING AND BOILING POINTS, ELEMENTAL ANALYSES, NMR SIGNALS, AND IR ABSORPTION BANDS OF DI(α-SUBSTITUTED BENZYL) OXALATES (PhCHROCO$\rightarrow_2$

R	Registry no.	Yield, %	Mp or bp, (mm) °C	Found, % C	Found, % H	Calcd, % C	Calcd, % H	Chemical shifts, δ, ppm[a] Aromatic H	—CH—	Other	Ir frequency,[b] cm^{-1} >C=O
CH_3	24523-30-6	65	172–176 (1.5)	71.79	5.98[c]	72.45	6.09	7.3 (m)	5.96 (q)	1.57 (d, J = 7 Hz, CH_3)	1770 1740
CH_3CH_2	31164-21-3	56	170–172 (0.4)	73.67	6.92[d]	73.58	6.79	7.3 (m)	5.78 (t, J = 7 Hz)	1.83 (quintet, CH_2) 0.88 (t, J = 7 Hz, CH_3)	1775 1730
$(CH_3)_2CH$	31164-22-4	68	160–163 (0.2)	74.46	7.43[c]	74.53	7.40	7.3 (s)	5.61 (d, J = 7 Hz)	2.21 (m, CH) 1.0 (d, J = 7 Hz, CH_3) 0.82 (d, J = 7 Hz, CH_3)	1770 1740
			140–143 (0.3)								
CF_3	31164-23-5	45	63–87 97–99[e]	52.80	2.87[d]	53.18	2.98	7.3 (s)	6.2 (q, J = 7 Hz)		1795 1770
CF_3CF_2	31208-73-8	60[f]	...[g]	47.28	2.58[c]	47.42	2.39	7.3 (s)	6.3 (q, separations between peaks are 9, 6, and 9 Hz)		1790 1770
CCl_3	31164-24-6	66	102–117[h]	42.81	2.15[i]	42.81	2.39	7.5[j] (m)	6.4 (s)		1790[j] 1765

[a] Solvent was $CDCl_3$. [b] Solvent was $CHCl_3$. [c] Analyzed by Spang Microanalytical Laboratory, Ann Arbor, Mich. [d] Analyzed by MHW Laboratories, Garden City, Mich. [e] The distilled oxalate was presumably a mixture of the meso and *dl* isomers. One isomer (mp 97–99°) could be purified by recrystallization from 95% ethanol. [f] Estimated approximately from nmr spectrum. [g] No pure product was isolated. The analytical sample was purified by glpc. [h] Presumably this material was a mixture of the meso and *dl* isomers. [i] Analyzed by Chemalytics, Inc., Tempe, Ariz. [j] Solvent was CCl_4.

162°). The ketone was reduced to the alcohol with lithium aluminum hydride: 80% yield; bp 45–50° (2.8 mm) [lit.[18] bp 52° (3 mm)]; nmr ($CDCl_3$) δ 7.35 (s, 5), 5.03 (q, each peak separated by 8 Hz, 1) and 4.26 (s, 1).

α-Trichloromethylbenzyl Alcohol.—Phenyltrichloromethyl ketone was prepared according to the procedure of Cohen, Wolinski, and Scheuer[20] by chlorination (with excess Cl_2) of acetophenone first in glacial acetic acid at 50–60° and then at 95–100° in the presence of added sodium acetate: crude yield 95%, slightly colored viscous liquid; nmr (CCl_4) δ 8.2 (m, 2) and 7.5 (m, 3) with no evidence for mono- or dichloroacetophenone. The crude ketone (22.3 g) was reduced to the alcohol with aluminum isopropoxide according to the procedure of Bergkvist:[21] crude yield 94%; slightly colored viscous liquid; nmr (CCl_4) δ 7.4 (m, 5), 5.03 (d, 1, CHOH, J = 4.5 Hz), and 3.92 (d, 1, OH, J = 4.5 Hz).

Preparation of Di(α-substituted benzyl) Oxalates.—Methods I,[2] II,[2] and III[17] have been previously described. In Table I are presented pertinent data for each new di(α-substituted benzyl) oxalate. These oxalates were prepared by method III.

Di-α,α-dimethylbenzyl oxalate was prepared as described previously:[3a] yield 91%; mp 68–70° (from ethanol); ir ($CHCl_3$) 1772 and 1740 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.32 (s, 5) and 1.85 (s, 6).

Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.58; H, 6.80. Found: C, 73.12; H, 6.85.

meso- and *dl*-**2,3-diphenylbutanes** were prepared by the method of Barber, Slack, and Woolman[22] by a Grignard coupling reaction of α-chloroethylbenzene, prepared as described by Shirley.[23]

Procedure for pyrolysis of oxalates at high temperatures under vacuum has been illustrated by that of dibenzyl oxalate.[2]

Pyrolysis of Di-α-methylbenzyl Oxalate.—Glpc analysis of the pyrolysate of di-α-methylbenzyl oxalate run at 570° showed the presence of at least eight components. Nmr analysis showed that the components were styrene, benzaldehyde, *dl*- and *meso*-2,3-diphenylbutanes, possibly the formate of α-methylbenzyl alcohol, and other unknowns. The identity of 2,3-diphenylbutanes was confirmed also by glpc peak enhancement [8 ft × 0.25 in. 20% SE-30 column (column A) at 135°]. The ratio of styrene and 2,3-diphenylbutanes was based on nmr analysis. The relative ratio of the diastereomers was determined from the glpc peak areas with the assumption that their thermal conductivities were equal.[12i] *meso*-2,3-Diphenylbutane was passed through the pyrolysis apparatus with different furnace temperatures and the *meso*/*dl* ratios were obtained by nmr analysis. Less than 5% *dl* isomer was obrained when the furnace was heated to 500° or less and 15% *dl* isomer was obtained when the furnace was at 540°.

Pyrolysis of Di-α-ethylbenzyl Oxalate.—Di-α-ethylbenzyl oxalate was pyrolyzed at 570° with a head temperature of 135–140°. Nmr analysis of the pyrolysate showed the presence of 0.76 mol of *trans*-methylstyrene, 0.026 mol of *cis*-methylstyrene, 0.31 mol of styrene, and other unknown components using dimethyl oxalate as an internal standard. The identity and ratio of the components were also confirmed by glpc analysis (column A at 90°).

Pyrolysis of Di-α-isopropylbenzyl Oxalate.—Di-α-isopropylbenzyl oxalate was pyrolyzed at 570°. Glpc analysis of the pyrolysate indicated the presence of a small amount of styrene and an unknown and the three olefins given in eq 2 which were identified by glpc peak enhancement. Nmr analysis of the pyrolysate using dimethyl oxalate as an internal standard showed that 0.36 mol of *trans*-β-methylstyrene was formed per mol of oxalate pyrolyzed.

Pyrolysis of Di-α-trifluoromethylbenzyl Oxalate.—Di-α-trifluoromethylbenzyl oxalate was pyrolyzed at 420–650° with a head temperature of 130–135°. Glpc analysis of the pyrolysate showed the presence of six components. The two major components were collected by glpc [5 ft × 0.25 in. 20% SE-30 column (column B) at 190°]. Mass spectra of both components showed parent ion peak at *m/e* 318 corresponding to the assigned structure of 2,3-diphenyl-1,1,1,4,4,4-hexafluorobutane (DPHFB). The ir spectra of both components were similar with broad absorptions from 1350–1050 cm^{-1}. The product with the shorter

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retention time was assigned the *dl* structure (see Results): nmr ($CDCl_3$) δ 7.3–6.8 (m, 5) and 4.0 (m, 1);[24] mp 73–75°.

Anal. Calcd for $C_{16}H_{12}F_6$: C, 60.35; H, 3.82. Found: C, 60.49; H, 3.90.

The product with the longer retention time was assigned the meso structure (see Results): nmr ($CDCl_3$) δ 7.4 (s, 5) and 4.0 (m, 1);[24] mp 156–158°.

Anal. Calcd for $C_{16}H_{12}F_6$: C, 60.35; H, 3.82. Found: C, 60.42; H, 3.84.

In a large-scale run, the combined pyrolysate from 30 g of oxalate, pyrolyzed in 3-g portions at 650°, was dissolved in hot ethanol. Upon cooling, the impure meso isomer separated as white crystals, mp 160–162°, leaving the ethanol rich in the *dl* isomer. Recrystallization of these crystals from ethanol gave 5 g of the meso isomer, mp 161–162°. Evaporation of the initial mother liquor gave a residue which, when recrystallized from petroleum ether (bp 30–60°), gave 3 g of white crystals, mp 65–70°. This low-melting material was further purified by chromatography on alumina using petroleum ether as the eluent giving white crystals of the *dl* isomer, mp 72–74°.

Single crystals of the high-melting isomer suitable for X-ray diffraction were grown by slow evaporation of a petroleum ether (bp 30–60°) solution. These crystals melted at 161–162°. A crystal of approximate dimension 0.2 mm on an edge was chosen and mounted along the *a* axis. Weissenberg photographs were taken with Ni-filtered Cu K_α radiation (1.5418 Å) of the 0*kl* and 1*kl* zones. A second crystal was mounted and the *h*0*l* and *h*1*l* zones were recorded.

The ratio of the two DPHFB isomers obtained from a pyrolysis at 500° was based on glpc analysis. The thermal conductivities of the two isomers were found to be identical. The absolute yield of the DPHFB isomers was obtained from the pyrolysate based on nmr analysis using bibenzyl as an internal standard. Less than 5% *dl*-DPHFB was obtained when *meso*-DPHFB was passed through the pyrolysis apparatus with the furnace heated to 500°.

Pyrolysis of Di-α-pentafluoroethylbenzyl Oxalate.—Pyrolysis of di-α-perfluoroethylbenzyl oxalate took place at 650° with a head temperature of 135–140°. The characteristic nmr spectrum of the β,β-difluorostyrene was the main feature of the nmr spectrum of the pyrolysate.[25] The yield of β,β-difluorostyrene was determined by nmr analysis using bibenzyl as an internal standard. Glpc analysis of the pyrolysate showed the presence of at least three high-boiling components in small amounts (column A).

Pyrolysis of di-α-trichloromethyl oxalate was carried out at 500 and 680° at 10^{-4}–10^{-5} mm with a head temperature of 135°.[6] The nmr spectrum (CCl_4) of the pyrolysate showed essentially a single product, β,β-dichlorostyrene, present in 32% yield relative to an internal standard, 1,1,2,2-tetrachloroethane (δ 6.00): nmr (CCl_4) δ 7.37 (m, 5, C_6H_5) and 6.78 (s, 1, $CH=CCl_2$) [lit.[26] nmr ($CDCl_3$) δ 7.25 (m, 5) and 6.72 (s, 1)]. Glpc analysis of the product mixture (column B) showed one main peak and several smaller peaks, the smaller peaks accounting for less than 5% of the crude mixture assuming equal thermal conductivities. A mass spectrum of the crude mixture gave a parent ion peak at *m/e* 172.

Pyrolysis of Di-α,α-dimethylbenzyl Oxalate.—The nmr spectrum of the pyrolysate run at 340° showed exclusively the characteristic spectrum of α-methylstyrene. Nmr analysis using bibenzyl as an internal standard showed that a quantitative yield of the styrene was obtained. The identity of the product was further confirmed by glpc analysis (column B).

Registry No.—Di-α,α-dimethylbenzyl oxalate, 31164-25-7; *dl*-DPHFB, 31208-74-9; *meso*-DPHFB, 31164-26-8.

(24) The appearance of the nmr signal for the aromatic protons of DPHFB is highly solvent dependent (unpublished work by W. S. T., J. G. P., and F. L. W.).

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The Thermal Decomposition of β-Hydroxy Esters

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The products and kinetics of the thermal decomposition of several β-hydroxy esters have been studied. It has been shown that all of the β-hydroxy esters studied pyrolyze to form a mixture of the corresponding ester and aldehyde or ketone and that the decomposition follows first-order kinetics and appears to be homogenous and unimolecular. Based on these data a six-membered cyclic transition state is proposed for the reaction. The absence of large substituent effects indicates that little charge separation occurs during the breaking of the carbon–carbon double bond.

It has recently been shown[1] that ethyl 3-hydroxy-3-methylbutanoate decomposes thermally in xylene solution to a mixture of acetone and ethyl acetate (eq 1).

$$(CH_3)_2COHCH_2CO_2C_2H_5 \longrightarrow (CH_3)_2C{=}O + CH_3CO_2C_2H_5 \quad (1)$$

It was proposed that the reaction involves a cyclic six-membered transition state similar to that thought to be involved in other similar thermal decomposition reactions such as the thermolysis of β-hydroxy ketones,[2] β-hydroxy olefins,[3] β-hydroxy alkynes,[4] and esters.[5] The present paper reports the products and kinetics of the thermolysis in the gas phase of several other β-hydroxy esters.

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(3) G. G. Smith and B. L. Yates, *J. Chem. Soc.*, 7242 (1965).
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Results

The β-hydroxy esters listed in Table I were pyrolyzed in evacuated, sealed glass tubes. All of the β-hydroxy esters pyrolyzed to a mixture of the ester and aldehyde or ketone according to eq 2.

$$R_2COHCHRCO_2C_2H_5 \longrightarrow R_2CO + RCH_2CO_2C_2H_5 \quad (2)$$

The products of the reaction were identified by their glc retention times and by the formation of 2,4-dinitrophenylhydrazones of the aldehyde or ketone from the products of the reaction. No other major products of reaction were observed by glc, and quantitative glc measurements using *p*-xylene as an internal standard indicated that the above reaction occurred to at least 90% for all of the β-hydroxy esters studied. No peak due to water was observed indicating that under the conditions of reaction no dehydration occurred. Also in the case of the ethyl esters no peak due to ethylene was observed indicating that a possible side reaction, the pyrol-

TABLE I

RATE CONSTANTS AND ACTIVATION PARAMETERS FOR THE PYROLYSIS OF SOME β-HYDROXY KETONES

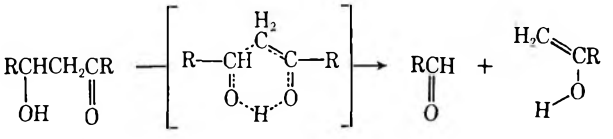
Compd	Registry no.	Temp, °C	10^4k, sec^{-1}	E_a, kcal/mol	$\log_{10} A$	$\Delta S^{\pm}$, eu
Ethyl 3-hydroxybutanoate	5405-41-4	340	6.98			
		330	4.13	39.7	10.98	−11.7
		320	2.32			
		310	1.32			
Ethyl 3-hydroxy-2-methyl-butanoate	27372-03-8	330	12.6			
		320	7.45	39.0	11.25	−10.4
		310	4.12			
		300	2.34			
Ethyl 3-hydroxy-3-methyl-butanoate	18267-36-2	320	10.2			
		310	5.73	38.5	11.20	−10.6
		300	3.30			
		290	1.78			
Methyl 3-hydroxy-3-methyl-butanoate	6149-45-7	320	9.10			
		310	5.12	39.1	11.34	−10.0
		300	2.80			
		290	1.55			
Ethyl 3-phenyl-3-hydroxy-propionate	5764-85-2	280	3.23			
		270	1:69	38.1	11.57	−9.0
		260	0.877			
		250	0.445			

ysis of the ester[5] involving the $-OC_2H_5$ group, takes place to a negligible degree at the temperature of the reaction.

The kinetics of the thermolysis were followed by glc using *p*-xylene as an internal standard. Visual observation of the hot capillary tubes confirmed that the sample was completely vaporized at the temperature of the reaction, except in the case of the ethyl 3-phenyl-3-hydroxypropionate. This compound pyrolyzed at too low a temperature to be vaporized and its rate of pyrolysis was determined in the liquid phase by sealing in the capillaries a sample of sufficient size so that all remained in the liquid state (see Experimental Section). Good first-order kinetics were observed for the thermolysis of all the β-hydroxy esters, the reaction being followed both by the rate of appearance of the products as by the rate of disappearance of the β-hydroxy ester. Identical rate constants were obtained, and in all cases plots of $\log_{10} C/C_0$ were found to be linear to at least 3 half-lives. The rate constants obtained are listed in Table I. They were found to be reproducible to within ±5%. No variation in rate constant was obtained by using different concentrations of the β-hydroxy ester in toluene (in the range of 1–10% of ester by volume) nor by sealing different sample sizes in the capillaries (as long as the sample size was sufficiently small that all was completely vaporized). The reaction was shown to be homogeneous by increasing the surface area of the reaction vessel. Thus, in the case of ethyl 3-hydroxy-3-methylbutanoate, a rate constant of 1.04×10^{-3} sec^{-1} was obtained at 320° in glass tubes packed with capillary tubing, which increased the surface area by a factor of five, compared to 1.02×10^{-3} in unpacked tubes. All Arrhenius plots showed excellent linearity. The calculated energies and entropies of activation are listed in Table I. They are estimated to be accurate to within ±1.2 kcal and ±1.8 eu, respectively.

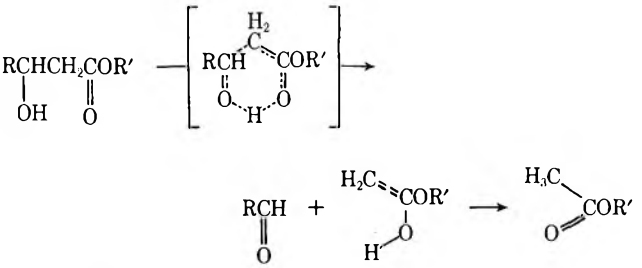
Discussion

It has previously been shown[2] that β-hydroxy ketones pyrolyze to mixtures of aldehydes and ketones and, based on the products and kinetics of the reaction, a cyclic transition state was proposed for the reaction.



This mechanism was further supported by the observation[6] that the bicyclic compound, 3,3-dimethyl-1-(1-hydroxy-1-methylethyl)bicyclo[2.2.1]heptanone, which cannot form a cyclic transition state without forming a double bond at the bridgehead is essentially stable to heat.

The results obtained in the present study suggest that the pyrolyses of β-hydroxy esters and β-hydroxy ketones are closely related. Thus β-hydroxy esters pyrolyze to mixtures of esters and aldehydes or ketones, these being products that would be expected if the reaction followed a mechanism similar to that proposed for the β-hydroxy ketone pyrolysis. Furthermore, the kinetics obtained for the pyrolysis of the β-hydroxy esters are very similar to those obtained for the pyrolysis of β-hydroxy ketones; both reactions appear to be homogeneous and monomolecular with negative entropies of activation in the range of −8.7 to −12.6 eu. These values are typical of unimolecular reactions that are thought to involve cyclic transition states.[7] On these bases it is proposed that β-hydroxy esters pyrolyze through a six-membered



(6) T. Mole, *Chem. Ind.* (*London*), 1164 (1960).

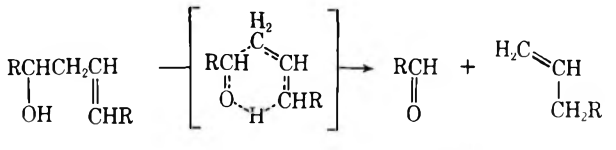
(7) S. W. Benson, "The Foundation of Chemical Kinetics," McGraw-Hill, New York, N. Y., 1960, p 257.

transition state similar to that previously proposed for the pyrolysis of β-hydroxy ketones.

It was previously observed that[3] in xylene solution at 200° the β-hydroxy ketone, 4-hydroxy-4-methyl-2-pentanone, pyrolyzes 360 times more rapidly than the analogously substituted β-hydroxy ester, ethyl 3-hydroxy-3-methylbutanoate. In the present study this behavior is confirmed; all of the β-hydroxy esters pyrolyze much more slowly than the correspondingly substituted β-hydroxy ketone. In particular, in the gas phase at 300° 4-hydroxy-4-methyl-2-pentanone pyrolyzes 630 times[7] as fast as ethyl 3-hydroxy-3-methylbutanoate. The mechanism proposed above is consistent with this greater ease of pyrolysis of the β-hydroxy ketones given the greater difficulty of formation of the enol form of esters than of ketones.[1,8]

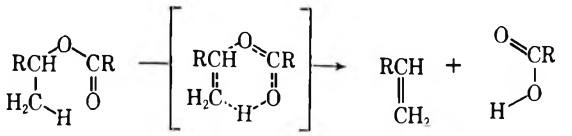
Furthermore, as would be expected[9] for an intramolecular unimolecular reaction, the effect of a nonpolar solvent on the velocity of pyrolysis of the β-hydroxy esters is small. Thus the energy and entropy of activation for pyrolysis of ethyl 3-hydroxy-3-methylbutanoate in xylene solution at 200° are 37.9 kcal and −10.7 eu and, for the same reaction in the gas phase at 300°, 38.5 kcal and −10.6 eu. These activation parameters give extrapolated rate constants for the reaction in solution and in the gas phase at 250° of 6.3×10^{-5} and 1.7×10^{-5} sec^{-1}. Similarly, the effect of solvent was found to be small in the pyrolysis of β-hydroxy ketones. For the pyrolysis of 4-hydroxy-4-methyl-2-pentanone at 200°, rate constants of 5.4 and 6.8×10^{-4} sec^{-1} were obtained for the reaction in the gas phase and in xylene solution, respectively.

On comparing the relative rates of pyrolysis of the β-hydroxy esters given in Table I, it can be seen that the effect of methyl groups on the ease of breaking of the carbon–carbon bond appears to be small. Thus the relative rates of pyrolysis at 300° of ethyl 3-hydroxy-3-methylbutanoate, ethyl 3-hydroxy-2-methylbutanoate, and ethyl 3-hydroxybutanoate are 4.6:3.2:1.0. These results are similar to those previously obtained in the pyrolysis of β-hydroxy ketones;[2] the relative rates of pyrolysis of 4-hydroxy-4-methyl-2-pentanone, 4-hydroxy-3-methyl-2-pentanone, and 4-hydroxy-2-pentanone are 2.9:1.9:1.0. Similar small effects of methyl groups on the breaking carbon–carbon bond are found in the pyrolysis of β-hydroxy olefins[3] and β-hydroxy alkynes,[4] both of which reactions are thought to involve similar cyclic transition states.



The relative rates of pyrolysis at 350° of the β-hydroxy olefins 3-buten-1-ol, 4-penten-2-ol, and 2-methyl-4-penten-2-ol are 1:2.9:5.5,[3] and of the β-hydroxy acetylenes 3-butyn-1-ol, 4-pentyn-2-ol, and 2-methyl-4-pentyn-2-ol are 1:2.0:2.5.

On the other band, in the pyrolysis of esters the effect of substitution on the breaking carbon–oxygen bond is much more marked.



The rates of pyrolysis of ethyl, isopropyl, and *tert*-butyl acetates are 1:19:1170.[5] Although part of this effect is statistical, there being more hydrogens available for reaction in the case of the more highly branched esters, the effect is too big to be accounted for solely on this basis, and it has been suggested[10] that some carbonium ion character is developed on the carbon atom during the breaking of the carbon–oxygen bond. The much smaller effect of methyl substitution in β-hydroxy ester pyrolysis would thus seem to indicate much less charge separation during the breaking of the carbon–carbon bond, which is reasonable when it is considered that in the breaking of the carbon–oxygen bond in ester pyrolysis two atoms of different electronegativity are involved.

The 3-phenyl group has a small accelerating effect on the rate of pyrolysis of the β-hydroxy esters. Thus the relative rates of pyrolysis at 300° of ethyl 3-phenyl-3-hydroxypropionate and ethyl 3-hydroxybutanoate are 15:1. Part of this accelerating effect is due to the fact that the pyrolysis of ethyl 3-phenyl-3-hydroxypropionate was carried out in the liquid phase. Nevertheless, this cannot account for all of the increased rate of pyrolysis of the phenyl compound. The extrapolated values for the rate of pyrolysis of ethyl 3-hydroxy-3-methylbutanoate in the gas phase and in xylene solution at 250° are 1.7×10^{-5} and 6.3×10^{-5}; that is, in the liquid phase the reaction is about three times as fast as in the gas phase. Furthermore, the rates of pyrolysis of ethyl 3-hydroxy-3-methylbutanoate and ethyl 3-phenyl-3-hydroxypropionate in xylene solution at 250° are 6.3×10^{-5} and 4.45×10^{-5} sec^{-1}, respectively. That is, a phenyl group joined to the carbinol carbon has about five times the accelerating effect on the rate of pyrolysis as a methyl group in a similar position and about the same effect as two methyl groups. A similar accelerating effect of a phenyl group has been noted in the case of β-hydroxy olefins and β-hydroxy acetylenes. Thus, 1-phenyl-3-buten-1-ol pyrolyzes 7.5 times as fast as 4-penten-2-ol and 1-phenyl-3-butyn-1-ol pyrolyzes 6.2 times as fast as 4-pentyn-2-ol. It is difficult to say whether this small accelerating effect of a phenyl group on β-hydroxy ester pyrolysis is due to stabilization of the transition state by conjugation with the forming carbonyl group or stabilization of a partial positive charge on the carbinol carbon. Nevertheless, it is notable that in ester pyrolysis in which the transition state would appear to be much more polarized, a similarly substituted phenyl group has a much greater effect, the relative rates of pyrolysis at 300° of 1-phenylethyl acetate and ethyl acetate being 58:1.[11]

Finally, as would be expected and as can be seen from Table I, little difference is observed between the rates of thermolysis of methyl and ethyl esters. Thus the rates of pyrolysis at 300° of ethyl 3-hydroxy-3-methylbutanoate and methyl 3-hydroxy-3-methylbutanoate are 3.30 and 2.80×10^{-4} sec^{-1}, respectively.

(8) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 60.

(9) See ref 7, p 506.

(10) G. G. Smith, F. D. Bagley, and R. Taylor, *J. Amer. Chem. Soc.*, **83**, 3047 (1961).

(11) R. Taylor, G. G. Smith, and W. H. Wetzel, *ibid.*, **84**, 4817 (1962).

The results of this study thus indicate that β-hydroxy esters pyrolyze to mixtures of the corresponding ester and aldehyde or ketone and that the reaction involves a cyclic transition state, which owing to the comparatively small substituent effects observed, most probably is concerted.

Experimental Section

β-Hydroxy Esters.—Ethyl 3-hydroxybutanoate was bought (Aldrich Chemical Co.); the other β-hydroxy esters were prepared by the Reformatsky reaction[12] between the appropriate aldehyde or ketone and α-bromo ester. All of the esters were distilled carefully before use and their purity checked by glc. The physical properties (boiling point and refractive index) of all the esters prepared agree closely with literature values.

Thermolysis of the β-Hydroxy Esters.—Thermolysis of the esters were carried out in carefully washed glass tubes, 2-mm i.d. and 40–50-mm length. The ester (20 μl) was placed in the tube, the contents were frozen in Dry Ice–acetone, and the tube was evacuated, flushed several times with nitrogen, and finally evacuated and sealed. The tubes were then placed in a heated aluminum block (see the kinetic measurements), and thermolyzed during 4 or 5 half-lives. At the end of the reaction, the tubes were cooled in Dry Ice–acetone, and a sample was withdrawn and analyzed by glc using a 5-ft SE-30 column. A further sample was withdrawn and added to a solution of 2,4-dinitrophenylhydrazine in phosphoric acid,[13] and the resulting 2,4-dinitrophenylhydrazone was filtered and crystallized and its melting point was determined.

Kinetic Procedures.—The kinetic methods used were those described previously.[4] ACS reagent grade toluene was used without further purification. *p*-Xylene (Aldrich Chemical Co.) was refluxed over sodium and then fractionated. Thermolyses were carried out in a heated aluminum block 14 in. long by 8 in. in diameter insulated by glass wool. The block was heated by a resistance coil and its temperature controlled to ±0.2° by a Fielden type TCB2 temperature controller. The absolute temperature was checked by a chromel–alumel thermocouple. Approximately 10–15 μl of a solution of the β-hydroxy ester (4% v/v) and *p*-xylene (2% v/v) in toluene was injected through a rubber septum into a nitrogen-filled capillary, 2-mm i.d. and 40–50-mm length. The capillary was then sealed. Five such capillaries were placed in holes drilled in the block, the holes being of such diameter that the tubes fitted precisely, and at determined intervals the tubes were withdrawn and the reaction was quenched by quickly plunging them into cold water. The contents of the tubes were analyzed by glc using a 5-ft SE-30 column at 180° for the phenyl ester and 100° for the other esters. Under these conditions retention times of 1–2 min were observed. The areas of the peaks due to the starting β-hydroxy ester and the standard *p*-xylene were compared using a Photovolt Model 49 integrator. In the case of ethyl 3-hydroxy-3-methyl butanoate, the reaction was also followed at various temperatures by comparing the areas of the peaks due to ethyl acetate and acetone (the products of the reaction) with that of the standard *p*-xylene. Identical rate constants were obtained as by the former method.

The validity of this method was established by a determination of the rates of pyrolysis of 2-methyl-4-penten-2-ol at 330 and 320°. Rates of 10.5 and 6.20 × 10^{-4} sec^{-1} were obtained compared to extrapolated literature values[3] of 11.1 and 6.31 × 10^{-4} sec^{-1}. In the case of ethyl 3-phenyl-3-hydroxypropionate, decalin (refluxed over sodium and fractionated) was used as an internal standard, the reaction was studied in the liquid phase. Sufficient solution (50–100 μl) of the ethyl 3-phenyl-3-hydroxypropionate in toluene was injected into the capillary so that the capillary was about half full. Under these conditions all of the sample remained in the liquid phase. A sample placed in the hot block showed no decrease in volume but rather an increase due to the thermal expansion of the sample.

Quantitative measurement of the yield of the products of reaction was carried out under the same conditions as for the kinetic measurements, but the reaction mixture was pyrolyzed during 4–5 half lives and then analyzed by glc using a 5-ft SE-30 column. The areas of the peaks obtained were compared to those obtained from a known mixture of the aldehyde or ketone, ester, and *p*-xylene in toluene using a Photovolt integrator Model 49 to compare the peak areas.

Acknowledgments.—The authors would like to thank the Fund for Overseas Grants and Education (FORGE) and the Comité de Investigaciones of the Universidad del Valle for support of this work.

(12) V. Hartmeann and H. Buenger, *Justus Liebigs Ann. Chem.*, **667**, 35 (1963); R. Shriner, *Org. React.*, **1**, 1 (1942).

(13) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 330.

Stable Carbocations. CXXII.[1] Diprotonation of Allophanates and Their Cleavage Reactions to Alkylcarbenium Ions and Diprotonated Allophanic Acid in Fluorosulfuric Acid–Antimony Pentafluoride ("Magic Acid"®) Solution

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The behavior of alkyl allophanates has been investigated in FSO_3H–SbF_5–SO_2 solution. Carbonyl oxygen diprotonation was observed in all cases by means of low-temperature pmr spectroscopy. With some of the diprotonated allophanates, cleavage occurred in the extremely strong acid system at higher temperatures to give stable alkylcarbenium ions and diprotonated allophanic acid. The elusive allophanic acid thus was directly observed for the first time in its stable diprotonated form.

Protonated amides and alkyl carbamates have been investigated in superacid solutions.[3–6] The protonation of allophanates, their cleavage reactions, and the possibility of the existence of allophanic acid in its diprotonated form have not as yet been investigated. It was felt of interest to extend our studies to the behavior of allophanates in FSO_3H–SbF_5–SO_2 solution and to investigate, over a range of temperature, their cleavage reactions.

Results and Discussion

Methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, and *tert*-butyl allophanates were studied in FSO_3H–

(1) Part CXXI: G. A. Olah and R. D. Porter, *J. Amer. Chem. Soc.*, in press.

(2) National Institutes of Health Predoctoral Research Investigator, 1967–1970.

(3) R. J. Gillespie and T. Birchall, *Can. J. Chem.*, **41**, 148, 2642 (1963).

(4) G. A. Olah and M. Calin, *J. Amer. Chem. Soc.*, **90**, 401 (1968).

(5) V. C. Armstrong, D. W. Farlow, and R. B. Moodie, *Chem. Commun.*, 1362 (1968).

(6) G. A. Olah, J. A. Olah, and R. H. Schlosberg, *J. Org. Chem.*, **35**, 328 (1970).

TABLE I

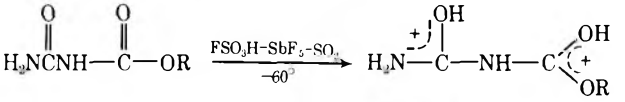
PMR CHEMICAL SHIFTS[a] AND COUPLING CONSTANTS[b] OF PROTONATED ALLOPHANATES IN FSO_3H–SbF_5–SO_2 SOLUTION

Compd	Registry no.	Temp, °C	—OH / —C—	NH	NH_2	H_1	H_2	H_3	H_4
$H_2NCONHCOCH_3$	761-89-7	−90	13.0	9.8	8.95	4.71			
	31585-11-2[c]		12.1		8.40	4.88			
$H_2NCONHCOCH_2CH_3$	626-36-8	−60	12.9	9.87	8.60	5.30	1.73		
	31585-12-3[c]		11.9		8.36	(q, 7.0)[b]	(t, 7.0)		
$H_2NCONHCOCH_2CH_2CH_3$	31598-83-1	−70	12.8	10.0	8.63	5.23	2.15	1.15	
	31585-13-4[c]		11.9		8.40	(t, 6.0)	(m)	(t, 6.0)	
$H_2NCONHCOCH_2CH_2CH_2CH_3$	3147-85-1	−80	13.0	10.1	8.78	5.36	2.16	1.77	1.20
	31585-14-5[c]		12.2		8.50		(m)	(m)	(t, 6.0)
$H_2NCONHCOH$	625-78-5	−80	13.4[d]	10.0	8.85				
	31585-15-6[c]		11.3		8.43				
			12.8						

[a] Chemical shifts are in δ, parts per million, referred to external TMS as standard. [b] Coupling constants, in hertz, are given in parentheses following the multiplicity of the peak. [c] Diprotonated derivative. [d] Observed only at temperatures below −90°.

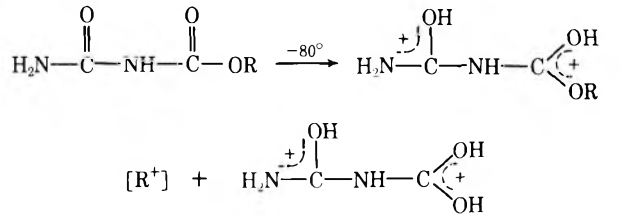
SbF_5–SO_2 solution at low temperature, generally at −78°.

In the superacid solvent system, FSO_3H–SbF_5–SO_2 solution, methyl, ethyl, *n*-propyl, and *n*-butyl allophanates are diprotonated on the carbonyl oxygen atoms as observed by pmr spectroscopy. The pmr chemical shifts and coupling constants are summarized in Table I. The protons on oxygen occur at lower

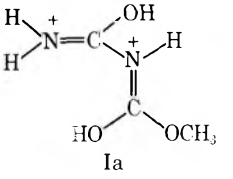


R = CH_3, CH_3CH_2, $CH_3CH_2CH_2$

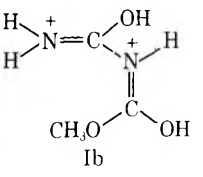
field than those in protonated amides and carbamates, but is more shielded than those in diprotonated ketocarboxylic acids.[7] Isopropyl, isobutyl, and *tert*-butyl allophanates studied under the same conditions undergo alkyl oxygen cleavage to give diprotonated allophanic acid and alkyl carbenium ions.



The pmr spectrum of methyl allophanate in FSO_3H–SbF_5 solution diluted with SO_2 at −90° consists of two methyl singlets at δ 4.88 and 4.71 with a relative area ratio of 3:2, two broad singlets for the NH_2 protons at δ 8.95 and 8.40, two singlets at δ 10.1 and 9.8 for the NH proton, and two OH resonances at δ 12.1 and 13.0 with the same peak area ratios (3:2). This indicates that methyl allophanate is diprotonated on the carbonyl oxygens, and two isomeric species (Ia and Ib) are observed due to restricted rotation at low temperatures around the C=N bonds.



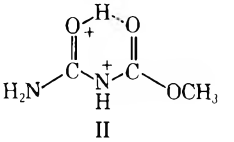
Ia



Ib

On raising the temperature to −40°, because of the low barrier of rotation around the C–N bond, the nmr spectrum showed only one singlet at δ 4.79 for the methyl group, a singlet for NH at δ 9.80, and a broad peak at δ 8.40 for the NH_2 protons. The OH protons are not observed at this temperature owing to fast proton exchange with the acid solvent system.

After keeping the sample at room temperature for about 1 hr and then cooling it back to −90°, the pmr spectrum showed only a singlet for the CH_3 group at δ 4.50 (0.38 ppm higher field than what is observed before heating the sample) and three resonances for the protons on nitrogen at δ 7.98, 7.80, and 9.90 with a relative area ratio of 1:1:2 and no absorptions in the OH region. The appearance of higher field chemical shifts for the CH_3 and NH_2 protons than those in ions Ia and Ib can probably be attributed to the nitrogen-protonated species II. The OH resonance is not observed due to rapid equilibration between the carbonyl oxygen atoms and rapid proton exchange with the acid–solvent system.

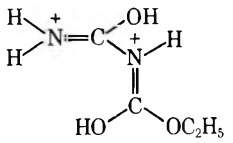


II

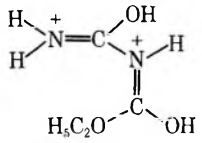
Ethyl allophanate in FSO_3H–SbF_5 diluted with SO_2 at −60° showed the NH proton at δ 9.87, the NH_2 protons

(7) G. A. Olah, A. T. Ku, and J. Sommer, *J. Org. Chem.*, **35**, 2159 (1970).

at δ 8.60 and 8.36, the CH_2 quartet at δ 5.30, the CH_3 triplet at δ 1.73, and an OH resonance at δ 12.9. On lowering the temperature to $-90°$, a new broad OH resonance at δ 11.9 and new resonances in the NH region are also observed, indicating that at this low temperature two protonated forms (IIIa and IIIb) are



IIIa



IIIb

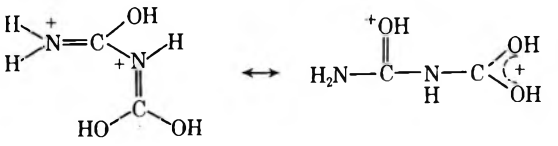
observed. On warming the solution, ion III decomposed to, so far, unidentified products.

***n*-Propyl allophanate,** again in FSO_3H–SbF_5–SO_2 solution, is diprotonated. At $-70°$, the nmr spectrum showed the NH singlet at δ 10.1, NH_2 singlets at δ 8.63 and 8.40, the α-CH_2 at δ 5.32 (t, 6.0), β-CH_2 at δ 2.15, and methyl triplet at δ 1.15. As the temperature was lowered to $-90°$, two broad peaks at δ 12.8 and 11.9 appeared which are assigned to protons on oxygen. Obviously only one isomer of diprotonated *n*-propyl allophanate was observed. As, however, no coupling was observed, no structural assignment could be made. On raising the temperature to $-20°$, alkyl–oxygen cleavage occurred to give diprotonated allophanic acid and *tert*-hexyl cations.

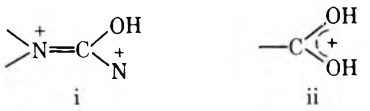
***n*-Butyl allophanate** in FSO_3H–SbF_5 is also diprotonated on the carbonyl oxygens. The derived chemical shifts are shown in Table I. Even at $-90°$, the nmr spectrum also showed a small singlet at δ 4.0 which is assigned to the *tert*-butyl cation and is probably due to cleavage because of local overheating during sample preparation. The intensity of this peak did not increase with time at $-80°$. At $-60°$, the δ 4.0 singlet increased with time, indicating that alkyl–oxygen cleavage occurred to give *tert*-butyl cation and diprotonated allophanic acid. At $-20°$, the cleavage was completed within a few minutes.

Protonated **isopropyl, isobutyl,** and ***tert*-butyl allophanates** could not be observed. Cleavage reactions occurred even at a temperature as low as $-90°$, to give diprotonated allophanic acid and the corresponding stable alkyl carbenium ions (*tert*-butyl and *tert*-hexyl cations).

Diprotonated allophanic acid was thus generated with ease by cleavage of isopropyl, isobutyl, and *tert*-butyl allophanates in FSO_3H–SbF_5 solution containing an equal volume of SO_2 as diluent. The nmr spectrum at $-80°$ showed OH absorptions at δ 11.3 and 12.8, NH at δ 10.0, and NH_2 at δ 8.85 and δ 8.43. At $-90°$, the nmr spectrum showed another broad peak in the OH region at δ 13.4. This indicates that allophanic acid is diprotonated. The resonance at δ 13.4 is



assigned to the OH proton in i; the two OH resonances at higher field are assigned to the OH protons of ii.



i ii

These resonances are broadened, but no resolvable coupling was observable. Hence no differentiation or assignment could be made between the two OH protons. The nmr spectrum also showed a singlet at δ 9.40 which is not understood at the present time.

Experimental Section

Materials.—Methyl, ethyl, and isopropyl allophanates were prepared by the method of Dains and Wertheim[8] by the reaction of urea and the corresponding alkyl chloroformates. *n*-Propyl and *n*-butyl allophanates were prepared by the reaction of the corresponding alcohols in glacial acetic acid with potassium cyanate.[9] Isobutyl allophanate was prepared by treating isobutyl alcohol with cyanic acid generated from cyanuric acid.[10] Fluorosulfuric acid and antimony pentafluoride were distilled prior to their use.

Preparation of Solutions.—Samples of protonated allophanates were prepared by dissolving approximately 2 ml of FSO_3H–SbF_5 in an equal volume of SO_2 and cooling to $-78°$, Dry Ice–acetone temperature. The allophanate ($\sim$0.5 g) was slowly added to the acid solution with vigorous agitation. The acid was always in large excess as indicated by the large acid peak at δ 10.4–11.0.

Nmr Spectra.—A Varian Associates Model A-56/60A nmr spectrometer equipped with low-temperature probe was used for all spectra. Chemical shifts are reported in parts per million (δ) from external (capillary) tetramethylsilane.

Registry No.—Isobutyl allophanate, 31598-85-3; *tert*-butyl allophanate, 31598-86-4; isopropyl allophanate, 763-58-6.

Acknowledgment.—Support of this work by a grant from the National Institutes of Health is gratefully acknowledged.

(8) F. B. Dains and E. Wertheim, *J. Amer. Chem. Soc.*, **42**, 2303 (1920).
(9) E. S. Lane, *J. Chem. Soc.*, 2764 (1951).
(10) F. A. P. Remfry, *ibid.*, **99**, 610 (1911).

Stable Carbocations. CXXIII.[1] Relating to the Reported N Protonation of *N,N*-(Diisopropyl)carbamates. Evidence for O Protonation Followed by Rearrangement

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Alkyl carbamates in FSO_3H–SO_2ClF solutions at low temperature (−80°) are exclusively O protonated. O-Protonated methyl and ethyl *N,N*-(diisopropyl)carbamates are shown to slowly rearrange upon raising the temperature to the thermodynamically more stable N-protonated species. It is suggested that the previous observation by Moodie of N protonation of ethyl *N,N*-(diisopropyl)carbamate was due to $=\overset{+}{O}H \rightarrow \overset{+}{N}H$ rearrangement following usual O protonation of the carbamate.

Protonated amides[4] and carbamates[5] have been observed in superacid solutions. The position of protonation has always been shown to be on the carbonyl oxygen atom. Armstrong, Farlow, and Moodie[6] found that ethyl *N,N*-(diisopropyl)carbamate, when dissolved in 90–98% sulfuric acid, or fluorosulfuric acid, gave an nmr spectrum at temperatures below 0° indicating N protonation through the presence of one nitrogen-bound proton. They, however, also found[6] that *N,N*-diisopropylacetamide and *N,N*-diisopropylbenzamide in 98% sulfuric acid gave no nmr peaks attributable to a nitrogen-bound proton. In both cases[6] separate methyl resonances for the two isopropyl groups were observed which were thought to be due to restricted rotation about the carbonyl carbon–nitrogen bond owing to protonation on oxygen. In both cases, however, no proton on oxygen was observed under the experimental conditions.

It was suggested by Moodie that the interesting and unexpected N protonation of ethyl *N,N*-(diisopropyl)-carbamate was due to steric reasons, the bulky substituents interfering with O protonation.

Due to our continuing study of protonation of heteroorganic compounds, we felt it of interest to reexamine the protonation of alkyl carbamates with bulky substituents on the nitrogen atom (such as isopropyl, *tert*-butyl) in the strong acid systems, FSO_3H–SO_2 and FSO_3H–SO_2ClF. It was also hoped that the increased acidity of the system would result in sufficiently slowing down proton exchange with the solvent at obtainable low temperatures to allow direct observation of protons (if any) on oxygen as well as on nitrogen atoms by pmr spectroscopy. The use of SO_2ClF as solvent in the FSO_3H acid system allows the temperatures of the solution to be lowered to as low as −120°. At this low temperature we found that protonation of methyl and ethyl *N,N*-(diisopropyl)carbamates takes place on the carbonyl oxygen atom. Upon slowly raising the temperature to −30°, rearrangement to the nitrogen-protonated carbamate takes place. For comparison, we have also studied ethyl *N*-(isopropyl)carbamate and ethyl *N*-(*tert*-butyl)carbamate.

(1) Part CXXII: G. A. Olah, A. T. Ku, and J. A. Olah, *J. Org. Chem.*, **36**, 3582 (1971).

(2) National Institute of Health Postdoctoral Research Investigator, 1968–1969.

(3) National Institute of Health Predoctoral Research Investigator, 1967–1970.

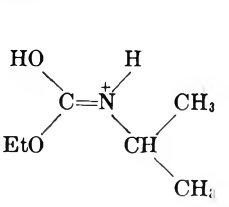
(4) R. J. Gillespie and T. Birchall, *Can. J. Chem.*, **41**, 1481, 2642 (1963).

(5) G. A. Olah and M. Calin, *J. Amer. Chem. Soc.*, **90**, 401 (1968).

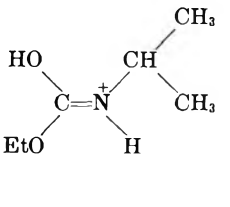
(6) V. C. Armstrong, D. W. Farlow, and R. B. Moodie, *Chem. Commun.*, 1362 (1968).

Results and Discussion

Ethyl *N*-(isopropyl)carbamate in FSO_3H–SO_2 at −80° gave an pmr spectrum showing an OH singlet at δ 9.73 indicating oxygen protonation. The N–H proton appeared as two sets of doublets at δ 6.90 and 6.60. This indicates two isomers (**1a** and **1b**) of the O-protonated



1a



1b

species to be present due to restricted rotation about the carbon–nitrogen bond. The pmr spectrum showed no changes even then solutions were heated up to −20° No indication for N protonation was obtained.

Methyl *N,N*-(diisopropyl)carbamate in FSO_3H–SO_2 at −80° gave a pmr spectrum (Figure 1) indicating about 50% oxygen protonation and 50% nitrogen protonation. Both the OH and NH protons are observed (OH at δ 9.25, NH at δ 7.30) at this temperature. The pmr spectrum also showed a singlet at δ 4.26 for the CH_3O protons and multiplets at δ 4.23 for the methine proton and two doublets for the isopropyl methyls in the nitrogen- and oxygen-protonated species respectively at δ 1.50 and 1.40. At −50°, the CH_3O peaks are shown to be two singlets, one each, for nitrogen- and oxygen-protonated species. At this temperature the oxygen-protonated species gradually rearranges to the nitrogen-protonated species. This is evident by the increase of the peak areas of the nitrogen-protonated species at δ 4.20 and 1.46 and the decrease of the peak intensity of the oxygen-protonated species at δ 4.25 and 1.36 (Figure 2). At −30°, the rearrangement goes to completion showing only the N-protonated species.

Ethyl *N,N*-(diisopropyl)carbamate, when dissolved in FSO_3H–SO_2 solution at −80°, gave an nmr spectrum (Figure 3 A) showing an OH proton at δ 9.20 and giving no indication for a nitrogen-bounded proton at this temperature. At −100°, the proton exchange is slow and the OH resonance sharpens. At −60°, the oxygen-protonated species, however, slowly rearranges to the nitrogen-protonated species. This process goes faster and even to completion at higher temperature, such as −30°. At −30°, the methylene quartet appears at δ 4.66, the methine multiplet at δ 4.10, the methyl triplet at δ 1.46, and the methyl doublet of the isopropyl

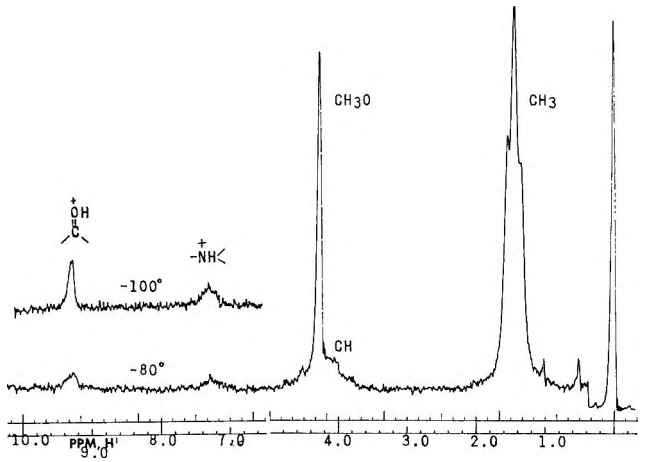


Figure 1.—Protonation of methyl *N,N*-(diisopropyl)carbamate in FSO_3H–SO_2 at −80°.

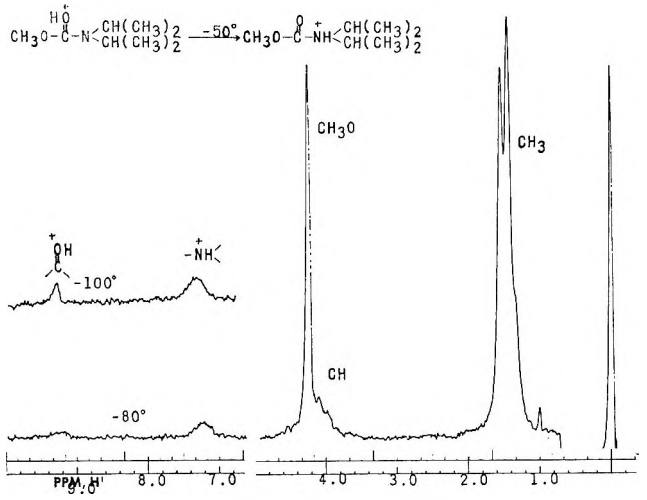


Figure 2.—Heating the solution shown in Figure 1 to −50° and recording the spectra by cooling to −80 and −100°, respectively, showed isomerization of O-protonated species to the more stable N-protonated carbamate.

group at δ 1.46. The proton on nitrogen is observed at this temperature. However, on cooling the solution back to −80° or below, the nmr spectrum (Figure 3 B) showed a broad N–H singlet at δ 7.20, and no OH absorption could be observed, indicating the oxygen-protonated species went completely to the N-protonated species and the process is not reversible.

Protonated ethyl *N*-(*tert*-butyl)carbamate in FSO_3H–SO_2 solution could not be observed. Cleavage reaction occurs even at temperatures as low as −80° to give the *tert*-butyl cation and protonated ethyl carbamate (which had previously been reported).[5] In FSO_3H–SbF_5 solution, the formed *tert*-butyl cation reacts slowly with the system to give unidentified products. In 1:1 *M* FSO_3H–SbF_5–SO_2 solution, the *tert*-butyl cation formed is stable and the nmr spectrum gave resonances for the carbonyl oxygen of the protonated ethyl carbamate and the *tert*-butyl cation.

Conclusion

In strong acid solutions at low temperature, carbonyl oxygen atoms of carbamic acid esters are kinetically first protonated. However, carbamates with two isopropyl groups substituted on nitrogen, such as methyl *N,N*-(diisopropyl)carbamate and ethyl *N,N*-(diisopropyl)carbamate, rearrange slowly to the N-protonated species, upon raising the temperature. It is evident that in protonated carbamic acid esters with bulky substituents on nitrogen the stabilization due to the contribution of I is very small. Hence they rearrange to the thermodynamically more stable N-protonated species.

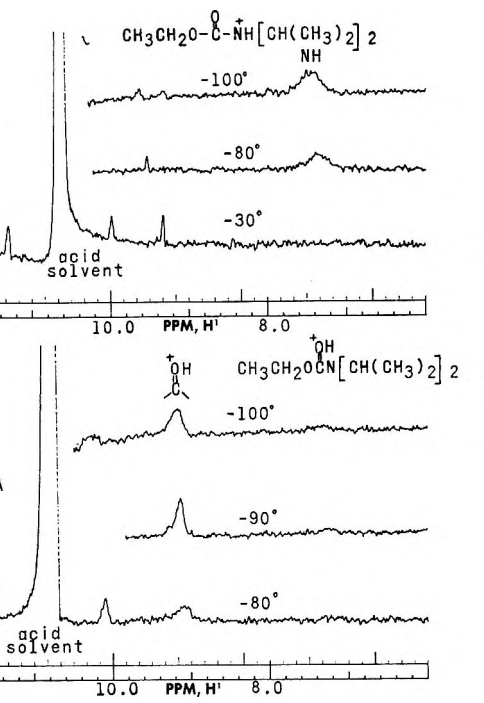
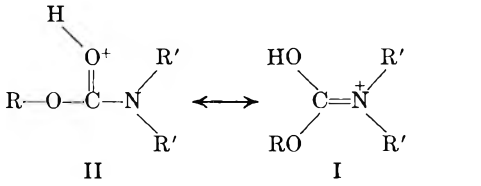


Figure 3.—(A) The OH and NH absorptions of the pmr spectrum of protonated ethyl *N,N*-(diisopropyl)carbamate at −80 to −100° showing O protonation. (B) The OH and NH absorptions of the pmr spectrum of protonated ethyl *N,N*-(diisopropyl)-carbamate after the sample has been treated to −30° indicating $=\overset{+}{O}H \rightarrow -\overset{+}{N}H<$ isomerization.



R′ = isopropyl

We are presently studying the question of O *vs.* N protonation of amides in solvents of varying acid strength and will report our results separately.

Experimental Section

Materials.—All the carbamates used in this study were prepared[7] by reacting the related alkyl chloroformates with amines.

Nmr Spectra.—Varian Associates Model A-56/60A spectrometer with a variable-temperature probe was used for all spectra.

Preparation of Solutions.—Samples of protonated carbamates were prepared by dissolving approximately 1.5 ml of HSO_3F in an equal volume of SO_2 (or SO_2ClF) and cooling to −78°. The carbamate (approximately 0.2 ml) was dissolved in 1 ml of SO_2

(7) R. H. McKee, *Amer. Chem. J.*, **42**, 22 (1909).

(SO_2ClF) cooled to −78° and with vigorous agitation was slowly added to the acid solution. The acid was always in large excess as indicated by the large acid peak at δ 10.6–10.9.

Registry No.—Methyl *N,N*-(diisopropyl)carbamate, 31603-49-3, 31585-09-8 (protonated derivative); ethyl *N,N*-(diisopropyl)carbamate, 20652-39-5, 31585-10-1 (protonated derivative).

Acknowledgment.—Support of this work by a grant from the National Institutes of Health is gratefully acknowledged.

A Kinetic Study of the Nitrogen-15 Exchange of Para-Substituted Benzamides with Ammonia[1a]

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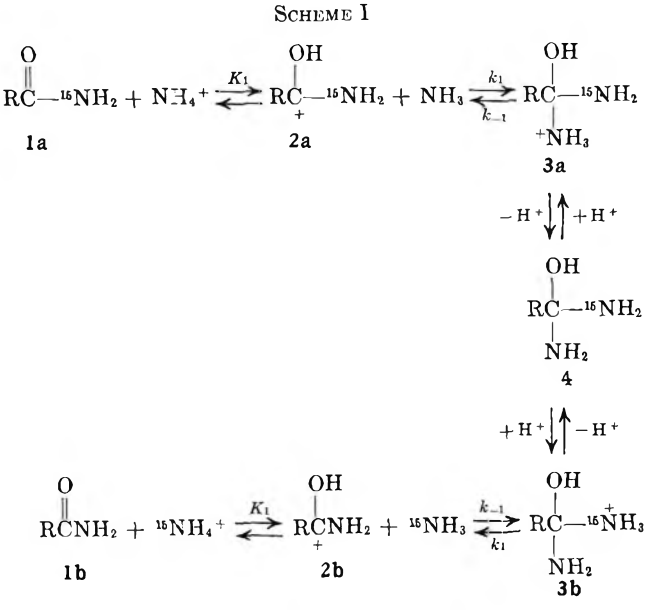
A kinetic study has been carried out on the nitrogen-15 exchange of para-substituted benzamides-^{15}N with liquid ammonia as a function of temperature and catalyst concentration. Neither a neutral nor a base-catalyzed exchange pathway is detectable under the conditions employed. The relative rates for the acid-catalyzed (ammonium chloride catalyzed) exchange of the para-substituted benzamides at 40° in the presence of 3 *M* ammonium chloride are NO_2:Cl:H:CH_3:CH_3O = 8.78:2.13:1.00:0.55:0.44. Hammett plots are linear with $\rho = +1.25$. The kinetic data indicate a first-order dependence of the exchange rate on the ammonium ion concentration. All of the reactions exhibit pseudo-first-order kinetics. The trends in the kinetic data are what would be expected for an exchange mechanism involving a rapid preequilibrium protonation of the amide followed by a slow rate-determining addition of ammonia to form a tetrahedral intermediate, which can revert to reactants or decompose to products depending upon which nitrogen is lost.

Nitrogen-15 labeled benzamide and other amides are known[2-4] to undergo isotopic exchange with ammonia in liquid ammonia solution catalyzed by ammonium ion. No exchange is observed in the absence of a catalyst except at very high temperatures.[2,3] At 20° in the presence of 3.33 molar ammonium chloride, Heyns, Brockmann, and Roggenbuck[2] observed that *p*-nitrobenzamide, benzamide, and *p*-methoxybenzamide underwent 29.7 ± 2.0, 4.2 ± 2.0, and 1.8 ± 2.0% exchange, respectively, after 7 days. They determined the rate constant for exchange of *p*-nitrobenzamide at 20° in the presence of 3.33 *M* ammonium chloride as 1.27×10^{-8} sec^{-1}. In a related study Heyns, Grutzmacher, and Roggenbuck[3] determined the activation energy for the liquid ammonia ammonolysis of *p*-nitrobenzamide to be 17.0 ± 0.5 kcal/mol.[5] They also noted a continual increase in exchange rate with increased ammonium chloride concentration up to about 12 mol/l.

Brodskii and coworkers[4] have also made a study of the nitrogen exchange between ammonia enriched with nitrogen-15 and various compounds dissolved in the ammonia. The exchange proceeds (at 180°)[6] in −C(=X)-NH_2 (X = O, S, NH), amino acids, and urea. According to these workers, the relative rates of exchange in a series of amides are proportional to the electrophilicites of the carbon atoms to which the nitrogen is attached. Electron donor groups in meta and para positions in aromatic amides hinder the exchange, while electron acceptor groups accelerate it.

Information about nitrogen exchange reactions of aromatic amides is, at best, qualitative and incomplete. We now wish to present the results of a kinetic study of the effect of para substituents on the rate of the acid- and base-catalyzed isotopic exchange between benzamides-^{15}N and liquid ammonia. If the aminolysis of benzamides with an acid catalyst is analogous to the acidic hydrolysis of amides, as suggested by Heyns and coworkers,[2,3] then a similar mechanism may be postulated involving attack by an ammonia molecule on the conjugate acid of the amide as the rate-determining step, shown in Scheme I. The tetrahedral intermediate

SCHEME I



(1) (a) Supported by U. S. Atomic Energy Commission Contract AT-(40-1)-3234; from the Ph.D. Dissertation of C. R. E., University of Arkansas, Fayetteville, Ark., 1970; presented in part at the Combined Southeast-Southwest Regional Meeting of the American Chemical Society, New Orleans, La., Dec 1970. (b) NSF Trainee, 1966–1969.

(2) K. Heyns, R. Brockmann, and A. Roggenbuck, *Justus Liebigs Ann. Chem.*, **614**, 97 (1958).

(3) K. Heyns, H. F. Grutzmacher, and A. Roggenbuck, *Chem. Ber.*, **93**, 1488 (1960).

(4) A. I. Brodskii, N. A. Vysotskaya, I. I. Kukhtenko, G. P. Miklukhin, L. L. Strizhak, and L. V. Sulima, *Izotopy Izluch. Khim., Tr. Vses. Nauch. Tekh. Konf. Primen. Radioaktiv. Stabil. Izotop. Izluch. Nar. Khoz. Nauke, 2nd*, 20 (1957); L. L. Gordienko and A. I. Brodskii, *Dokl. Akad. Nauk SSSR*, **134**, 595 (1960); L. L. Strizhak, S. G. Demidenko, and A. I. Brodskii, *ibid.*, **124**, 1089 (1959).

(5) Instead of determining the extents of exchange at a series of times and calculating the rate constants from the best straight lines, they calculated rate constants from the amount of exchange only at 120 hr for each temperature or catalyst concentration studied.

(6) Ammonia has a critical temperature of 132°; hence reactions above 132° are not liquid ammonia ammonolyses but vapor phase reactions.

TABLE I

PSEUDO-FIRST-ORDER RATE CONSTANTS AND ACTIVATION PARAMETERS FOR THE AMMONIUM CHLORIDE CATALYZED NITROGEN-15 EXCHANGE OF PARA-SUBSTITUTED BENZAMIDES, p-$XC_6H_4CO^{15}NH_2$, WITH AMMONIA (NH_4Cl) = 3.00 M

X	Registry no.	$k_{32} \times 10^7$ sec^{-1} [a]	$k_{36} \times 10^7$ sec^{-1} [a]	$k_{40} \times 10^7$ sec^{-1} [a]	$\Delta H^{\pm}$, ±2.0 kcal	$\Delta S^{\pm}$, ±6.0 eu	$\Delta G^{\pm}$, ±0.1 kcal
NO_2	31656-60-7	11.77	16.41	24.42	16.7	−31.2	26.3
Cl	31656-61-8	2.52	3.51	5.93	16.9	−33.4	27.2
H	31656-62-9	1.37	1.89	2.78	14.0	−44.1	27.6
CH_3	31656-63-0	0.77	1.15	1.52	13.7	−46.0	27.9
CH_3O	31656-64-1	0.53	0.75	1.21	16.4	−38.0	28.1

[a] The rate constants are reproducible to ±4%.

4 can decompose to reactants or products depending upon which amino group is lost.

Results and Discussion

The main findings of this research are summarized in Tables I and II. No exchange is noted in the absence of a catalyst at temperatures as high as 40.0°. In the acid-catalyzed exchange reactions of these para-substituted benzamides, electron-withdrawing groups accelerate the exchange and electron-donating groups retard the exchange relative to the unsubstituted compound. The relative rates of exchange at 40° in the presence of 3 M ammonium chloride as a function of the para substituent are NO_2:Cl:H:CH_3:CH_3O = 8.78:2.13:1.00:0.55:0.44. The kinetic data (Table II) indicate a first-order dependence of the exchange rate on the ammonium ion concentration. All of the reactions exhibit excellent pseudo-first-order kinetics. Hammett plots of of log k/k_0 *vs* σ for the data at 32, 36, and 40° give good straight lines, with $\rho = +1.25$.

TABLE II

RATE CONSTANTS AS A FUNCTION OF ACIDITY (AMMONIUM CHLORIDE CONCENTRATION) AT 36.0°

Benzamide	NH_4Cl, M	$k \times 10^7$ sec^{-1} [a]
p-$NO_2C_6H_4CO^{15}NH_2$	0.75	3.58
	1.50	7.30
	3.00	16.41
	4.30	25.03
	5.00	33.39
	6.00	42.75
$C_6H_4CO^{15}NH_2$	0.75	0.35
	1.50	0.83
	3.00	1.89

[a] The rate constants are reproducible to ±4%.

The large errors associated with the enthalpy and entropy of activation shown in Table I arise from the fact that the kinetics were determined at points separated by only 8°. This small temperature range was made necessary by the slowness of the exchange reactions at low temperatures and the high vapor pressure of liquid ammonia at higher temperatures.

Acid-Catalyzed Nitrogen Exchange.—The trends in the kinetic data are what would be expected for an exchange mechanism (Scheme I) involving a rapid preequilibrium protonation of **1a** followed by a slow, rate-determining addition of ammonia to form, after rapid proton transfer, a tetrahedral intermediate **4**. This mechanism is similar to that proposed for the hydrolysis of amides.[7] The proposed mechanism[8] gives rise to the kinetic expression, $k_{obsd} = {}^1/_2k_1K_1 \cdot (NH_4^+)$, if it is assumed that (a) the rate-determining step is the formation of the tetrahedral intermediate, (b) the proton transfer steps are not kinetically significant, and (c) any isotope effects involved are included in the rate and equilibrium constants. This rate expression predicts first-order dependence of the exchange rate on the ammonium ion concentration. It can be seen from the data in Table II that the exchange rate approximately doubles when the NH_4^+ concentration is doubled, indicating a first-order dependence of rate on NH_4^+ ion concentration within the limits to be expected for data taken at such high acid concentrations.

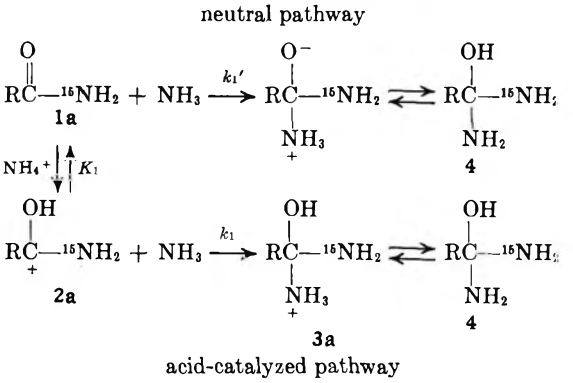
Para substituents on the ring would be expected to have opposing electronic effects on the rate constant and equilibrium constant in the above expression. Electron-withdrawing groups should decrease the basicity of the carbonyl oxygen, decreasing the equilibrium constant K_1. At the same time, electron-withdrawing groups should increase the electrophilicity around the carbonyl carbon, facilitating the formation of the tetrahedral intermediate and increasing the rate constant k_1. The reverse would be expected for electron-donating groups.

In the case of the analogous acidic hydrolysis of aromatic amides in dilute acid solution, these ambiguous polar requirements have been cited[9] as the cause of the almost complete insensitivity to polar effects which that reaction demonstrates. This same behavior was noted by Menon[10] for the acid-catalyzed oxygen exchange between para-substituted benzophenones and water. He found the rate constants for exchange to vary by only a factor of two in the series p-methoxy to p-nitro. In the present study the rate of isotopic exchange in the presence of 3.00 M ammonium chloride at 36.0° varies by a factor of 22 as one proceeds from the strongly electron-donating p-methoxy substituent to the strongly electron-withdrawing p-nitro substituent. This is not a particularly large variation and could easily arise from a combination of opposing electrical factors on K_1 and k_1 with those on k_1 predominating. If the isotopic exchange reaction were to be studied at higher ammonium ion concentrations where all of the para-substituted benzamides would be converted substantially completely to their conjugate acids, a somewhat larger vari-

(7) V. K. Krieble and K. A. Holst, *J. Amer. Chem. Soc.*, **60**, 2976 (1938).
(8) C. R. Everly, Ph.D. Dissertation, The University of Arkansas, Fayetteville, Ark., 1970.
(9) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 786.
(10) B. C. Menon, Ph.D. Dissertation, University of Arkansas, Fayetteville, Ark., 1964.

ation of rate with substituent would be expected. This type of behavior was observed by Leisten[11] in his study of the effects of substituents as a function of acid concentration in the hydrolysis of benzamides in perchloric acid at 95°.

Neutral Nitrogen Exchange.—The existence of an equilibrium between the benzamide and its conjugate acid (**1a** and **2a**) shown in Scheme I infers that the exchange might proceed partly through a neutral pathway. This would involve a nucleophilic attack by ammonia on the benzamide leading to the tetrahedral intermediate **4**. If a neutral exchange were



occurring, it should be possible to increase the proportion of molecules undergoing exchange by this pathway by lowering the acid concentration, since this would shift the equilibrium in favor of the amide. The neutral exchange pathway would be expected to be facilitated by electron-withdrawing groups. Hence the ratio of the rate constant for exchange of benzamide to that for *p*-nitrobenzamide should decrease as the acid catalyst concentration is lowered (k_{NO_2} should decrease more slowly than k_H) if any exchange is taking place by the neutral mechanism. The nitrogen exchange of benzamide and *p*-nitrobenzamide was studied at 36.0° in the presence of decreasing amounts of ammonium chloride. The ratio k_H/k_{NO_2} is 0.11, 0.11, and 0.10 at 3.00, 1.50, and 0.75 *M* ammonium chloride concentration, respectively (see Table II). The constancy of this ratio, within experimental error, shows that para-substituted benzamides undergo exchange only by an acid-catalyzed mechanism even at the lowest acid concentration employed. Experiments at lower acid concentrations were not attempted because of the slow rate of exchange. It might be possible to demonstrate the existence of a neutral exchange employing lower acid concentrations at higher temperatures.

Base-Catalyzed Nitrogen Exchange.—A base-catalyzed pathway of exchange employing added amide ion was not detectable. Sodium and potassium amide concentrations ranging from 5×10^{-5} to 5.0 *M* with an organic amide concentration of 0.1 *M* were employed at 32.00° for as long as 18 days. In every case the recovered amide showed the same nitrogen-15 enrichment as did the starting material. Only in the cases of the most dilute base concentrations were the reaction solutions homogeneous, the precipitates probably being the metal salts of the benzamides, $RCONH^-M^+$. Even for that portion of the salt which is in solution, the exchange reaction would be expected to be very slow, since nucleophilic attack on an anion would be involved.

Other Possible Mechanisms.—Other mechanisms which have been discussed for the nitrogen exchange of amides with ammonia or for the acid-catalyzed hydrolysis of amides which might be extended to the present research can be ruled out on the basis of the present evidence. If the rate-determining step in the nitrogen exchange reaction were the protonation of benzamide,[12] the effect of an electron-withdrawing para substituent in the benzamide surely would be to decrease the rate by decreasing the stability of the carbonium ion formed. The opposite is observed to be true in the present research.

A mechanism involving a preequilibrium protonation[12] of the benzamide followed by a unimolecular rate-determining decomposition step to an ammonia molecule and an acyl carbonium ion can be eliminated for the present case by an analogous argument to that given in the last paragraph. Furthermore, the proposal by Long, Pritchard, and Stafford[13] that the entropy of activation be used as a criterion of the mechanism of acid-catalyzed hydrolysis reactions can be applied directly in the present case. These hydrolysis reactions are usually classified as involving a unimolecular rate-determining decomposition step or a bimolecular rate-determining step. It seems quite reasonable that the loss of translational and rotational freedom of a water molecule associated with the formation of a tetrahedral intermediate in the acid-catalyzed bimolecular process should lead to a lower entropy of activation than the unimolecular loss of water from one positive ion to form another positive ion case. This prediction is borne out by entropies of activation for acid-catalyzed hydrolyses, typical values of $\Delta S^{\pm}$ being 0 to 10 eu for unimolecular and −15 to −30 eu for bimolecular reactions.[14] The isotopic exchange reaction being studied here shows a large negative entropy of activation, indicating by this criterion[13,15] that the rate-determining step is bimolecular rather than being a unique molecular decomposition. It is interesting to note that the acid-catalyzed oxygen exchange in water of benzoic acids exhibits an entropy of activation of −30 eu.[16]

Other mechanisms involving variations in the timing of the protonation (and possibly even its position), nucleophilic attack, and leaving group release cannot be excluded on the basis of the present data. For instance, the present data are also consistent with concerted rate-determining protonation and nucleophilic attack to form a tetrahedral intermediate. Furthermore, the assumptions of rapid proton transfers among tetrahedral intermediates such as those proposed here may not be so reliable as they once seemed,[17] although, as pointed out above, the positive ρ value observed makes it clear that nucleophilic attack is the predominant factor in controlling the rate. Although it does not seem likely in view of the greater basicity of amide oxygen than nitrogen, the present data do not exclude mechanisms involving protonation on nitrogen, either

(11) J. A. Leisten, *J. Chem. Soc.*, 765 (1959).

(12) D. Rosenthal and T. I. Taylor, *J. Amer. Chem. Soc.*, **79**, 2684 (1957).

(13) F. A. Long, J. G. Pritchard, and F. E. Stafford, *ibid.*, **79**, 2362 (1957).

(14) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 24 (1963).

(15) R. Taft, *J. Amer. Chem. Soc.*, **74**, 5372 (1952).

(16) C. A. Bunton, D. James, and J. Senior, *J. Chem. Soc.*, 3364 (1960).

(17) For instance, see D. G. Oakenfull and W. P. Jencks, *J. Amer. Chem. Soc.*, **93**, 178 (1971), and earlier papers cited therein.

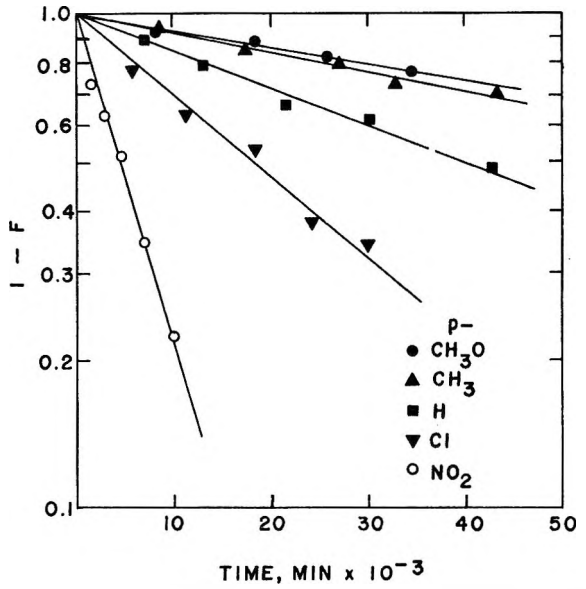


Figure 1.—The kinetics of the ammonium chloride catalyzed nitrogen-15 exchange of nitrogen-15 enriched para-substituted benzamides with liquid ammonia at 40.0° (NH_4Cl = 3.00 M).

concerted with or followed by nucleophilic attack on carbon and release of the leaving group.

Experimental Section

Preparation of Labeled Compounds.—For the preparation of the labeled amides, ammonia-^{15}N was generated from an aqueous solution of commercial ammonium-^{15}N nitrate or chloride by the dropwise addition of 40% sodium hydroxide. The ammonia-^{15}N was carried on a stream of dry nitrogen through a sodium hydroxide drying tube and bubbled through a solution of the appropriate para-substituted benzoyl chloride in dry benzene. The unreacted ammonia was trapped in two hydrochloric acid traps. As the ammonia–nitrogen mixture bubbled through the benzene solution, the forming amide precipitated. The precipitate was filtered, washed with benzene to remove excess acid chloride, washed with water to remove ammonium chloride, and then crystallized from water or methanol. In all cases the physical constants of the labeled benzamides agree with the literature values for the unlabeled compounds. In general, the amides were prepared with a nitrogen-15 content of approximately 6%, and they were then diluted with unlabeled material to the desired enrichment of about 1.5% excess nitrogen-15. Yields typically ranged from 62 to 88%.

Kinetics of Acid-Catalyzed Exchange.—The acid-catalyzed exchange reactions were carried out using 5-ml samples of liquid ammonia which were 0.1 M in para-substituted benzamide and which contained various concentrations of ammonium chloride. For one run usually six samples were prepared. Exchange flasks were made from 15-cm-long sections of 19-mm Pyrex tubing with smaller neck sections 10 cm long of 9-mm Pyrex tubing; the smaller neck made sealing easier when the tube was evacuated. After weighing appropriate quantities of the benzamides and ammonium chloride into the sample flasks, 5 ml of liquid ammonia was distilled into each flask with a system patterned after that of Blair.[18] The ammonia solution was frozen with a liquid air bath, the exchange tube was evacuated, and the reaction tube was sealed off. The exchange flasks were placed in steel bombs, which were then placed in an oil bath at 32, 36, or 40° ± 0.01°. When the contents of the flasks had reached temperature equilibrium, usually after 1 hr, the zero-time sample was removed. The remaining samples were taken out at convenient intervals. The exchange flasks were removed from the steel bombs and placed in an alcohol–Dry Ice bath to stop the reaction. The flasks were then opened and the ammonia was allowed to evaporate. The amide was crystallized from water and dried thoroughly in a vacuum desiccator overnight, and the melting point was taken. In every case the melting point was identical with that of the starting amide. The nitrogen-15 content of each sample was then determined. It should be pointed out that the nitrogen-15 enrichment of the zero-time samples agreed within experimental error with the determined enrichments of the starting materials. This showed that the ammonium chloride had been removed during the work-up.

Kinetics of Base-Catalyzed Exchange.—The attempted nitrogen exchange using commercial sodium amide as the catalyst followed the procedure described previously for the acid-catalyzed exchange except that sodium amide was used in place of ammonium chloride.

The nitrogen exchange reaction was also attempted using potassium amide as the catalyst. The potassium amide was generated by dissolving an appropriate amount of potassium metal in liquid ammonia along with approximately 25 mg of ferric nitrate hydrate to catalyze the formation of the potassium amide.[19] The solution was allowed to sit for 30 min to ensure complete formation of the potassium amide. During this time ammonia was added as necessary to maintain the desired volume.

The potassium amide–liquid ammonia solution was added to an exchange tube containing the organic amide by means of a pipette which had been cooled to liquid air temperature. The remainder of the kinetic run was then carried out as described in the acid-catalyzed section.

Isotopic Analysis.—The nitrogen in the organic samples was converted to nitrogen gas for isotopic analysis by the pyrolysis method of Rolle.[20] For each isotopic analysis a sample of the nitrogen-15 enriched compound of a size sufficient to produce approximately 2 ml of nitrogen upon complete pyrolysis was used. The sample, together with about 500 mg of copper oxide, about 200 mg of calcium oxide, and several small lengths of copper wire, was placed in a tube equipped with a break off seal. The tube was evacuated and sealed. The sample was then pyrolyzed at 500° for 8 hr. The purification of the nitrogen produced in the pyrolysis was carried out on a vacuum line by circulating the pyrolysis gases for 30 min over copper–copper oxide contained in a Vycor tube heated to approximately 700° by means of an automatic Toepler pump. During the circulation any carbon dioxide and water which had formed were condensed in a liquid air cold trap. The nitrogen was then pumped into a sample bulb for mass spectrometric analysis.

The 29/28 m/e ratios for the samples were determined with an isotope ratio mass spectrometer. In order to correct for any day-to-day instrumental variations, an analysis of standard nitrogen taken from a lecture bottle was made after each series of three analyses. The factor necessary to correct the standard to an arbitrary nitrogen-15 value, taken as the normal abundance figure of 0.359%, was determined, and all the analytical results taken for a given series were multiplied by this factor. Periodically, a background spectrum was determined. It was never necessary to make a background correction.

Calculations.—The nitrogen-15 content of the nitrogen gas was calculated from the mass spectra by standard means.[8]

An example of the kinetics obtained is shown in Figure 1, a semilogarithmic plot of $(1 - F)$, where F is the fraction of reaction, *vs.* time for the ammonium chloride catalyzed nitrogen-15 exchange of nitrogen-15 enriched para-substituted benzamides with liquid ammonia at 40°. Figure 1, as well as all of the others obtained, clearly shows a first-order dependence of the exchange rate with time. The rate constants shown in Tables I and II were calculated from the slopes of these lines using a least-squares program on an IBM 7040 computer. Several of the fastest exchange reactions have been followed for several half-lives and have proved to be first order over the entire range. Many of the reactions could not be followed through even 1 half-life due to the excessive time requirements.

In calculating the fraction of reaction from the analyzed nitrogen-15 content, the value of the nitrogen-15 content at infinite time was taken as 0.359%, the natural abundance, since ammonia is present in large excess compared to the amide. The ammonia used as the solvent for these exchange reactions gave this natural abundance figure within experimental error when analyzed for nitrogen-15.

Registry No.—Ammonia, 7664-41-7.

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(19) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 907.

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Kinetics and Mechanism of the Reaction of Phenylglyoxal Hydrate with Sodium Hydroxide to Give Sodium Mandelate[1a]

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The kinetics of the reaction of phenylglyoxal hydrate with sodium hydroxide to give sodium mandelate in aqueous solution at 35.1° have been studied spectrophotometrically. From the first ionization constant of the aldehyde hydrate, determined by potentiometric titration, and the dependence of the reaction rate on the sodium hydroxide concentration, it is concluded that the reaction proceeds *via* rate-controlling internal hydride ion transfers in the anions $PhCOCH(OH)O^-$ and $PhCOCH(O^-)_2$. Most of the reaction proceeds *via* the double-charged anion at sodium hydroxide concentrations above about 0.003 *M*.

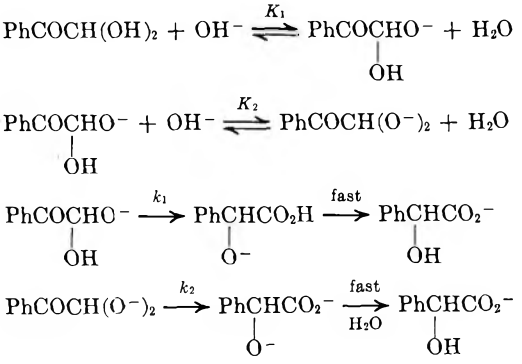
The mechanism of action of glyoxalase, an enzyme that catalyzes the transformation of methylglyoxal to lactate, is of interest in relation to the suggestion that a cancer cell is a cell that has lost its ability to bind its own glyoxalase.[2] For this and other reasons we became interested in the mechanism of the rearrangements of monosubstituted glyoxals to derivatives of α-hydroxy acids, which may be regarded as internal Cannizzaro reactions. Kinetic studies show that in intermolecular Cannizzaro reactions the active hydride ion donor is sometimes the dianion of the aldehyde hydrate **1** and sometimes the monoanion **2**.[3a] According to the con-

1 **2**

cept of "the acidity of transition states,"[3b] the tendency to react *via* the dianion should increase with increasing acidity of the aldehyde hydrate. Since the hydrates of glyoxal derivatives should be more acidic than most aldehyde hydrates, the reaction of a glyoxal derivative with hydroxide ions to give the anion of an α-hydroxy acid might be expected to proceed to a major extent *via* the dianion under conditions where such simple aldehydes as formaldehyde and furfural do. It is not surprising then that the transformation of glyoxal to glycolate by hydroxide ions in aqueous solution is first order in glyoxal and second order in hydroxide ions.[4] It is somewhat surprising, however, that the reaction of phenylglyoxal with hydroxide ion to give mandelate has been reported to be first order in phenylglyoxal and first order in base in 50% aqueous methanol.[5] This difference in behavior cannot be due to a fundamental change in the type of reaction occurring; labeling studies show that it is the hydrogen atom and not the phenyl group that migrates and that this migration is intramolecular[6] just as the corresponding migration of hydrogen in the reaction of glyoxal is.[4,7] In order to compare the phenylglyoxal reaction with Cannizzaro reactions without having to correct for complications arising from solvent effects, we have studied the kinetics of the reaction of phenylglyoxal with sodium hydroxide in water, where several Cannizzaro reactions have been studied.

Results

Crystalline phenylglyoxal hydrate was used in making the reaction solutions. Equilibrium constants for the formation of the dihydrate and each of the two possible monohydrates of phenylglyoxal were calculated from Bell's Taft-equation correlation of the hydration of carbonyl compounds in aqueous solution[8] (using, in some cases, estimated σ^* and E_s values). From the results it was concluded that more than 99% of the material was present as $PhCOCH(OH)_2$ and less than 0.1% as the free aldehyde. The kinetics were followed by uv absorbance measurements at 249.5 nm, where the reactant has an absorption maximum and where the extinction coefficient of the product, sodium mandelate, is less than 2% as large. The sodium hydroxide was present in at least 20-fold excess and linear first-order rate plots were obtained. The rate data were treated in terms of mechanism 1. If the fraction of



(1)

reactant present as the dianion is negligibly small compared with that present as the monoanion and the neutral molecule, and if the concentration of water is absorbed into the equilibrium constants (so that K_1 and K_2 have the dimensions M^{-1}), then the observed first-order rate constants may be expressed as shown

(1) (a) This investigation was supported in part by Public Health Service Research Grant AM 10378 from the National Institute of Arthritis and Metabolic Diseases and by Grant DA-ARO-D-31-124-G648 from the Army Research Office, Durham, N. C. (b) The Ohio State University. (c) Public Health Service Fellow under Award 6 FO2 CA39914-01A1 from the National Cancer Institute.

(2) A. Szent-Györgyi, *Science*, **161**, 988 (1968).

(3) (a) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, section 11-4a; (b) section 5-2e.

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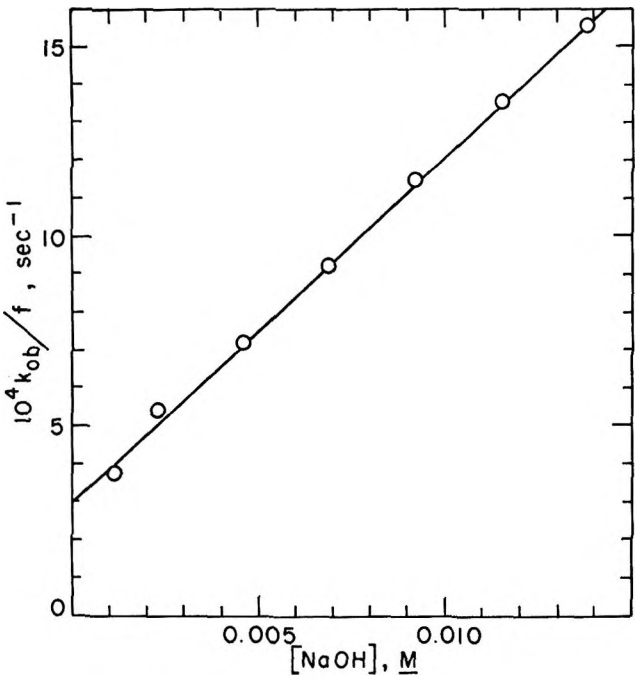

Figure 1.—Plot of k_{obsd} divided by the fraction of phenylglyoxal hydrate present as the monoanion *vs.* the sodium hydroxide concentration.

in eq 2, where f, the fraction of reactant present as the monoanion, may be expressed as in eq 3. The

$$k_{obsd} = f(k_1 + k_2K_2[OH^-]) \quad (2)$$

$$f = \frac{K_1[OH^-]}{1 + K_1[OH^-]} \quad (3)$$

value of K_1 was found to be 247 ± 17 in 0.10 M aqueous sodium chloride at 35° by potentiometric titration. From this result the value of f may be calculated at any given hydroxide ion concentration.

Using the observed first-order rate constants listed in Table I that were determined at ionic strength 0.1 M,

TABLE I
RATE CONSTANTS FOR THE REACTION OF PHENYLGLYOXAL HYDRATE WITH SODIUM HYDROXIDE IN WATER AT 35° [a]

10^3[NaOH], [b] M	A_B [c]	$10^5 k_{obsd}$, sec^{-1}
1.13	0.644	8.01
2.28	0.635	19.5
4.59	0.628	38.1
6.89	0.622	57.8
9.21	0.627	79.5
11.52	0.613	100.2
13.82	0.618	120.1
11.52[d]	0.614	109.0
11.52[e]	0.638	86.6

[a] Initial concentration of phenylglyoxal hydrate about 5.66×10^{-5} M in all runs. Sodium chloride added to bring the ionic strength to 0.10 M except where noted otherwise. [b] This is the average concentration present throughout the run allowing for that used by transformation to mandelate and by partial neutralization of aldehyde hydrate. In the worst case, the initial and final concentrations differ from this by 0.9%. [c] Absorbance extrapolated to zero time. [d] Ionic strength 0.20 M. [e] Ionic strength 0.05 M.

values of k_{obsd}/f were plotted against the hydroxide ion concentration, as shown in Figure 1. According to eq 2, the intercept in this plot, 2.95×10^{-4} sec^{-1}, is equal to k_1, and the slope, 9.14×10^{-2} M^{-1} sec^{-1}, is equal to k_2/K_2.

Comparison of the three runs made in the presence of 0.01152 M sodium hydroxide shows that there is a positive ionic strength effect, as would be expected for a reaction proceeding largely by a mechanism in which a double-charged transition state in the rate-controlling step is formed from two single-charged reactants.

Discussion

The kinetic results obtained are consistent with mechanism 1. An alternative in which the rate-controlling step for that part of the reaction involving two hydroxide ions is the formation, rather than the decomposition, of the dianion would give a kinetic equation with the same form as eq 2. However, calculations of the same type used in a study of the cleavage of phenylpropargylaldehyde[9] show that the formation of the dianion is almost undoubtedly millions of times as fast as that of the mandelate ion.

According to the values of k_1 and k_2K_2 that we have obtained, reaction *via* rearrangement of the dianion is the principal path for reaction at hydroxide ion concentrations above about 0.003 M. There are two important reasons why reaction *via* the dianion should be less important in 50% aqueous methanol, the solvent used by Alexander, than in water. The first is that equilibrium constants for the addition of methanol to carbonyl groups tend to be larger by about 20-fold than the equilibrium constants for addition of water to the same carbonyl groups.[10] Therefore, the reaction solution will contain much more of the methyl hemiacetal of phenylglyoxal, which can rearrange only *via* a monoanion, than of the hydrate, which can rearrange *via* either a monoanion or a dianion. Assuming equal acidities of the hydroxylic hydrogens of the hydrate and the hemiacetal and equal reactivities of the two different monoanions, this factor should increase the relative contribution of reaction *via* the monoanion by about fivefold on going from water to 50% methanol. The second reason for a decrease in the extent of reaction *via* the dianion is the fact that a poorer ion-solvating medium should destabilize a multiply charged transition state relative to a single-charged one. Although there is reason to believe that reaction *via* the dianion should be relatively less important in 50% methanol than in water, it is less clear what the facts are concerning the kinetics of the reaction in 50% methanol. The kinetic equation used was based on the implicit assumption that the fraction of reactant present in a monoanionic form was always negligible.[5] The concentrations of excess base used (as much as 0.03 M) would transform as much as 88% of the phenylglyoxal hydrate present to its conjugate base in aqueous solution. Since the methyl hemiacetal of phenylglyoxal should be about one-half as acidic as the hydrate, and methanol is about one-third as acidic as water, it seems possible that significant fractions of the reactant were present as monoanions in the study in 50% methanol. Ignorance of how much was present in this form makes it difficult to be sure whether any significant fraction of the reaction went through the dianion.

(9) J. Hine and G. F. Koser, *J. Org. Chem.*, **36**, 1348 (1971).
(10) *Cf.* E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 6154 (1968).

Many studies of the kinetics of Cannizzaro reactions have been made.[3a] In a number of these studies the form of the kinetic equation was *assumed*, or the concentrations of reactants were not varied greatly, or the acidity of the aldehyde hydrate was assumed to be negligible, or side reactions (especially prevalent in alcoholic solvents) were neglected, etc. For these reasons a detailed discussion of the factors that influence the relative contributions of reaction *via* the double-charged anion 1 and the single-charged anion 2 is not believed to be worth the space it would require. Hence we shall merely note that the reaction of phenylglyoxal with hydroxide ions is analogous to Cannizzaro reactions in that both the monoanion and dianion may contribute significantly to the reaction.

If the value of K_1 is independent of the ionic strength, as it should be according to the Debye–Hückel limiting law, and if it is the same at 25° as at 35°, then the pK_a of phenylglyoxal hydrate at zero ionic strength is 11.29 at 35° and 11.61 at 25°. According to a Taft-equation correlation of the acidities of aldehyde hydrates at 25°,[9] this is the value it should have if the σ^* constant for the benzoyl group is 1.47. Although Taft lists no value for benzoyl, the value for acetyl (1.65)[11] is not much different from this.

Experimental Section

Reagents.—Various procedures for the purification of phenylglyoxal hydrate gave products with varying melting points perhaps because of the removal of varying amounts of water during the purification. The procedure used for kinetic samples consisted of dissolving the material in ~80% methylene chloride–20% acetone, filtering, and adding hexane. Three such recrystallizations gave colorless needles. The extent of hydration of this material may be somewhat uncertain, but this will have no appreciable effect on the rate constants obtained since the sodium hydroxide was used in large excess.

Kinetic Runs.—In a typical run 3.00 ml of a standard solution of sodium hydroxide and sodium chloride was placed in both the sample and reference cells of a Cary spectrophotometer, Model 14. After thermal equilibrium had been reached at 35.1 ± 0.1°, 12 μl of 1.427×10^{-2} *M* aqueous phenylglyoxal hydrate was added at a recorded time to the sample cell, which was shaken and returned to the cell holder. During the approximately 30 sec that the cell was out of the thermostated cell holder its temperature dropped by about 0.6°, and it then took about 5 min to return to the 35.1 ± 0.1° range. Absorbance measurements at 249.5 nm were recorded from the time the cell was returned to its holder until the reaction was at least 47% and usually about 70% complete. The "infinity" absorbance measured after 10.7 half-lives was found to be 0.012. Rate constants were calculated by the method of least squares from the slope of the plot of log $(A - A_\infty)$ (where A is the absorbance) *vs.* time. The infinity absorbance calculated from the extinction coefficient of sodium mandelate is 0.010. In a duplicate experiment in which the reaction was run at the same concentrations on a 1-l. scale and the solution then evaporated to a smaller volume, the absorption maxima of the mandelate ion at 252, 257, and 263 nm could be seen.[12] The linearity of the plots was about the same as that obtained in the cleavage of phenylpropargylaldehyde.[9]

p*K* Determination.—Recorded potentiometric titrations of 25-ml samples about 0.008 *M* in phenylglyoxal hydrate and 0.100 *M* in sodium chloride were carried out, using a Radiometer automatic titrator (ABU1, PHM26c, SBR2c, and type C electrode), with 2.5 ml of 0.1165 *M* sodium hydroxide at 35.0 ± 0.2°. The total elapsed time was less than 100 sec, during which time less than 1% transformation to mandelate should occur. Analogous titrations were also made on 0.100 *M* sodium chloride reference solutions that contained no phenylglyoxal hydrate. Hydroxide ion concentrations were calculated from eq 4, where $[OH^-]_{ref}$ is

$$[OH^-] = [OH^-]_{ref}\, 10^{pH - pH_{ref}} \quad (4)$$

the hydroxide ion concentration and pH_{ref} the pH at the analogous point of the titration of the reference solution. Values of K_1 were then calculated from eq 5 where $[PhCOCH(OH)_2]_t$ is the total

$$K_1 = \frac{([H^+]/[OH^-]) + ([OH^-]_{ref}/[OH^-]) - 1}{[PhCOCH(OH)_2]_t + [OH^-] - [H^+] - [OH^-]_{ref}} \quad (5)$$

concentration of phenylglyoxal hydrate in all forms. Under the conditions of the titration the two terms containing $[H^+]$ may be neglected. From 11 points taken in each of four titrations the value 247 with a standard deviation of 17 and no clear trend was obtained for K_1.

Registry No.—Phenylglyoxal hydrate, 1075-06-5; sodium hydroxide, 1310-73-2; sodium mandelate, 31657-31-5.

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

(12) We are indebted to Mr. Carl D. Fischer, Jr., for carrying out this experiment.

Light- and γ-Ray-Induced Reactions of Purines and Purine Nucleosides with Alcohols

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Photochemical- and γ-ray-induced reactions of purines and purine nucleosides with alcohols are described. The reactions of 6-substituted and 2,6-disubstituted purines resulted in substitution of an alcohol moiety for the hydrogen atom at C-8, while with 2-aminopurine a primary attack took place at the C-6 position of the purine system. Yields of up to 80% were obtained. A free-radical mechanism is proposed for the reactions, and the following order of reactivity of the various sites in the purine system toward the alcohol-free radicals has been found: C-6 > C-8 > C-2.

The photochemical reactions of nucleic acids and their constituents have been the subject of an extensive investigation in recent years.[2] While the photoreactions of the pyrimidine bases and their products have been examined in detail, those of purine derivatives remain to be studied. The purines form part of the light-absorbing system in nucleic acids, but this apparently does not result in their photochemical alteration, and the absorbed light may well be transferred to other moieties in the molecule.[3]

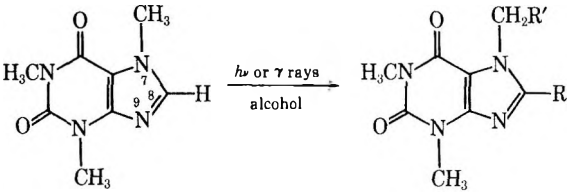
Substituents on the purine moiety are known to affect its reactivities in chemical reactions,[4] and apparently such effects are also observed in photochemical- and γ-ray-induced reactions of purine derivatives. Thus, while ultraviolet-light-induced reactions of purine itself and purine riboside with a variety of alcohols resulted in the addition of the alcohol across the 1,6 double bond,[5] similar reactions of substituted purines led to substitution at the C-8 position.[6]

The aim of the present study is to investigate the reactions of purines and purine nucleosides with various substrates under ultraviolet and γ radiation. These serve as model reactions for the investigation of the photochemical reactions of purine moieties in nucleic acids. The eventual development of a photochemical procedure which will lead to a purine modified DNA or RNA is also hoped for in the course of this project.[7] The present publication includes a full description of the photochemical- and γ-ray-induced reactions of some alcohols with a variety of purines, including those from nucleic acids.

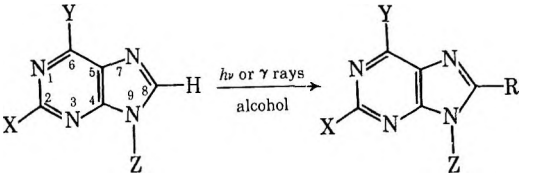
Results and Discussion

It has been found that purines and purine nucleosides, such as caffeine, adenine, 2-aminopurine, or guanosine, undergo photoreactions when irradiated in the appropriate alcohol with ultraviolet light or when exposed to γ radiation. In all purines and purine nucleosides studied the reactions resulted in substitution at the C-8 position, except for 2-aminopurine which underwent a primary attack at C-6. The resulting substituent depended on the alcohol employed and was usually the corresponding hydroxyalkyl group; however, in some reactions of caffeine and primary alcohols the newly introduced substituent at C-8 was an alkyl group. The reactions can be presented as shown in Scheme I.

SCHEME I



1, R = CH_3CHOH; R′ = H
2, R = $(CH_3)_2COH$; R′ = H
3, R = $CH_3CH_2CH(OH)CH_3$; R′ = H
4, R = CH_3CH_2; R′ = H
5, R = $CH_3CH_2CH_2$; R′ = H
6, R = R′ = $(CH_3)_2COH$



X = H; Y = NH_2; Z = H (adenine) — **7**, R = $(CH_3)_2COH$
X = H; Y = NH_2; Z = ribose (adenosine) — **8**, R = $(CH_3)_2COH$
9, R = $CHOHCH_3$
X = NH_2; Y = OH; Z = ribose (guanosine) — **10**, R = $(CH_3)_2COH$
X = NH_2; Y = OH; Z = 2′-deoxyribose — **11**, R = $(CH_3)_2COH$
X = H; Y = OH; Z = H (hypoxanthine) — **12**, R = $(CH_3)_2COH$
X = H; Y = EtO; Z = H — **13**, R = $(CH_3)_2COH$
14, R = X = $(CH_3)_2COH$
X = NH_2; Y = H; Z = H — **15**, R = H; Y = $(CH_3)_2COH$
16, R = Y = $(CH_3)_2COH$

The primary product of the reaction of 2-aminopurine and 2-propanol was the N-1,C-6 addition product (1,6-dihydropurine type),[5] as shown by the gradual disappearance of the maximum at 310 nm in the ultraviolet spectrum of the reaction mixture. This band reappeared upon exposure of the reaction mixture to air, and work-up led to the isolation of **15** which resulted from oxidation of the primary product. In the other purines and purine nucleosides the alcohol moiety substituted at C-8 leading to the N-7,C-8 addition products

(1) Stiftung-Volkswagenwerk Fellow, 1968–1970.

(2) For reviews, see (a) K. C. Smith, *Radiat. Res., Suppl.*, **6**, 54 (1966); (b) J. K. Setlow, *ibid.*, **6**, 141 (1966); (c) J. C. Burr, *Advan. Photochem.*, **6**, 193 (1968); (d) E. Fahr, *Angew. Chem., Int. Ed. Engl.*, **8**, 578 (1969).

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(6) D. Elad, I. Rosenthal, and H. Steinmaus, *Chem. Commun.*, 305 (1969); H. Steinmaus, I. Rosenthal, and D. Elad, *J. Amer. Chem. Soc.*, **91**, 4921 (1969).

(7) H. Steinmaus, D. Elad, and R. Ben-Ishai, *Biochem. Biophys. Res. Commun.*, **40**, 1021 (1970).

TABLE I

ULTRAVIOLET- AND γ-RADIATION-INDUCED REACTIONS OF PURINES AND PURINE NUCLEOSIDES WITH ALCOHOLS

Purine or purine nucleoside	Alcohol	Product (yield, %)[a]	Source of radiation	Radiation time, hr
Caffeine	Ethanol	**4** (11)	Uv[b]	72
		4 (17) **1** (14)	γ rays[c]	19
Caffeine	Ethanol[d]	**2** (35) **1** (41)	γ rays	24
Caffeine	1-Propanol	**5** (14)	Uv[b]	140
Caffeine	2-Propanol	**2** (35)	Uv[b]	72
		2 (37)	γ rays	25
Caffeine	2-Propanol[d]	**2** (78) **6** (10)	Uv[e]	24
		2 (67)	γ rays	30
Caffeine	2-Butanol	**3** (44)	Uv[b]	72
Adenine	2-Propanol	**7** (59)	Uv[b]	94
Adenine	2-Propanol[d]	**7** (69)	Uv[e]	14
		7 (81)	γ rays	19
Adenosine	2-Propanol	**8** (62)	Uv[b]	70
Adenosine	2-Propanol[d]	**8** (50)	Uv[e]	11
		8 (54)	γ rays	14
Adenosine	Ethanol	**9** (28)	Uv[b]	125
Guanosine	2-Propanol[d]	**10** (45)	Uv[e]	15
		10 (68)	γ rays	15
2′-Deoxyguanosine	2-Propanol[d]	**11** (25)	Uv[e]	18
		11 (41)	γ rays	14
Hypoxanthine	2-Propanol[d]	**12** (27)	Uv[e]	10
6-Ethoxypurine	2-Propanol[d]	**13** (41) **14** (25)	Uv[e]	17
		13 (47) **14** (19)	γ rays	30
2-Aminopurine	2-Propanol[d]	**15** (30) **16** (34)	Uv[e]	8

[a] Based on total amount of starting purine. [b] Hanovia 450-W high-pressure mercury vapor lamp (Corex filter). [c] ^{60}Co γ source, Gamma cell 220 (Atomic Energy of Canada Ltd., Ottawa, Canada). Dose rate = 1.27×10^{18} eV ml^{-1} min^{-1}. [d] With acetone as sensitizer; alcohol–acetone 1:1 (v/v). [e] Pyrex filter.

(C-8,N-9 addition products in caffeine), which were very sensitive to oxygen. These, upon work-up, gave the corresponding C-8 substituted purines. The addition of the alcohol to the 7,8 (or 8,9) double bond could be observed through the changes in the ultraviolet spectra of the appropriate reaction mixtures. The spectra were characterized by reduction in the intensity at the 260-nm maximum (reintensified upon exposure to air). These spectral changes could be observed only in properly degassed mixtures. When oxygen was not thoroughly removed, *e.g.*, while working on a preparative scale, these changes were not significant, since the absorption spectra of the final products are similar to those of the starting purines. The primary substitution at C-6 in 2-aminopurine was followed by one at C-8, while with 6-ethoxypurine the primary substitution at C-8 was followed by one at C-2. In both cases the secondary attacks were of a slower rate than the primary ones.

The ultraviolet-induced reactions of caffeine with ethanol and 1-propanol led to 8-ethylcaffeine (**4**) and 8-propylcaffeine (**5**), respectively, while the γ-ray-induced reaction of caffeine and ethanol led to 8α-hydroxyethylcaffeine (**1**) and **4** in a 1:1 ratio. **1** could be transformed to **4** when irradiated in methanol, ethanol, or 2-propanol but not in dioxane.

The use of acetone as a photosensitizer for the reactions of 2-propanol led to higher yields of the corresponding purine C-8 substituted products. Sensitization with acetone of the γ-ray-induced reaction of caffeine and ethanol led to the formation of **2** in addition to **1**. The reactions studied are summarized in Table I.

Products of the caffeine, 6-ethoxypurine, and 2-aminopurine reactions were isolated by column chromatography on silica gel, while the photoproducts of the other purines and purine nucleosides were isolated by preparative paper chromatography. The progress of the reactions was followed by thin layer chromatography. Characterization of the products was achieved by elemental analyses as well as by nmr and mass spectra. The caffeine photoproducts were compared with authentic samples. Longer irradiation periods of the acetone-sensitized caffeine–2-propanol reaction led to some substitution at the N-7-CH_3 group.

The structures of compounds **1**–**12** have been discussed previously[6] and were derived from elemental analyses, mass spectra, nmr data, and deuterium exchange experiments. The latter are based on the observation that H-8 in the purines studied exchanges for deuterium with D_2O at 105°.[8] The nmr spectrum of 6-ethoxypurine showed, among others, bands at τ (DMSO-d_6; DSS, internal) 1.6 and 1.48. The absorption at τ 1.6 was reduced by 50% after treatment with C_2H_5OD at 100° for 4 hr and thus belongs to the H-8

(8) M. P. Schweizer, S. I. Chan, G. K. Helmkamp, and P. O. P. Ts'O, *J. Amer. Chem. Soc.*, **86**, 696 (1964); J. M. Rice and G. O. Dudek, *ibid.*, **89**, 2719 (1967).

proton.[9] This band was absent in the spectrum of the 6-ethoxypurine–2-propanol photoadduct, indicating that substitution took place at C-8. The 2-aminopurine–2-propanol photoproduct has an exchangeable H-8 purine proton, as does 2-amino purine. Thus, the primary substitution in 2-aminopurine occurred at C-6.

It is noteworthy that the sugar moiety remained intact during these photochemical- and γ-ray-induced reactions,[10] as proved by mild acid hydrolysis of the appropriate nucleoside photoproducts which gave ribose or 2′-deoxyribose (tlc). However, the absorption bands in the nmr spectra of the sugar protons in the C-8 substituted nucleosides indicate some conformational differences in the molecule as compared to the starting purine nucleosides.[11]

The mass spectra of the photoadducts confirmed the proposed structures for these compounds. In the case of caffeine photoproducts all showed the appropriate molecular ion peaks. The adenine and the hypoxanthine–2-propanol photoproducts behaved similarly and showed the appropriate molecular ion peaks. The adenosine–ethanol and –2-propanol products exhibited the appropriate molecular peaks as well as the typical fragmentation pattern of ribose nucleosides, *i.e.*, peaks of B + H, B + 24, B + 30 and M − 89 (B presents the mass of the free base with the C-8 side chain minus one).[12] Thus, the mass spectra supply additional proof for the preservation of the ribose moiety in the photoproducts. The guanosine photoproduct did not show a molecular ion peak; however, the mass spectra of guanosine did not show a molecular ion peak either under the same conditions of recording.

The reported reactions could be induced by light of wavelength of λ >260 nm (Corex filter) or λ >290 nm (Pyrex filter) in the presence of acetone. In the former case light is absorbed exclusively by the purine, since the alcohols absorb at shorter wavelengths. The possible initiation of the reactions with peroxides at elevated temperature (see Experimental Section) as well as esr studies[13] suggest the existence of free-radical intermediates. The alcohol free radicals are formed probably through the abstraction of a hydrogen atom from the alcohol by the excited purine, due to the abstraction ability of a C=N group in the excited state, which might be compared to that of a carbonyl.[14,15] The subsequent step involves the attack of an alcohol free radical on the carbon end of a C=N group of a ground state purine molecule[16] leading to a radical[17] which by further hydrogen atom abstraction from the solvent yields the N-1,C-6 or N-7,C-8 adducts ("dihydro" type). These are oxidized during work-up to the appropriate substituted purines.

In the sensitized reactions acetone absorbs most of the incident light (λ >290 nm), as shown from spectral data. The excited acetone may transfer the excitation energy to the purine,[18] which initiates the reaction as described above. On the other hand, excited acetone may also abstract a hydrogen atom from the alcohol which serves as solvent. Hence, two routes for the generation of alcohol free radicals may operate in the sensitized reactions. In the γ-ray-induced reactions most of the radiation energy is absorbed by the alcohol, which serves as solvent, and the excited alcohol molecules then fragment to produce the corresponding free radicals.[19]

The reactivities of the various sites of the purine nucleus toward alcohol free radicals have been derived. The reactions involve two types of attack: (1) at C-6, and (2) at C-8. Purine itself,[5] 2-aminopurine, and purine-9-riboside[5] belong to the first group, while the 6-substituted and 2,6-disubstituted purines and purine nucleosides belong to the second. The preliminary substitution at C-6 in purine and 2-aminopurine indicates that this site is more reactive than C-8 or C-2, while the primary attack at C-8 in adenine and 6-ethoxypurine indicates that C-8 is more reactive than C-2. Thus, current results, which are based on product analysis, suggest the following order of reactivity toward alcohol free radicals in the purine systems studied: C-6 > C-8 > C-2.[20]

Experimental Section

Kieselgel (0.05–0.20 mm; Merck) was used for chromatography. Petroleum ether refers to the fraction bp 60–80°. Ascending tlc was performed with cellulose CE F (Riedel-de-Haen) except for the caffeine products where Kieselgel SI F (Riedel-de-Haen) was used. Mixtures of 1-butanol–water–concentrated ammonia (86:9:5 v/v) or 2-propanol–water–concentrated ammonia (68:14:1.5 c/c) (for the guanosine derivative) eluted the products from cellulose, while mixtures of 2-propanol and petroleum ether were used as eluents for the Kieselgel. Spots were detected with a Mineralight lamp. Preparative ascending paper chromatography was performed with Whatman No. 17 paper in mixtures similar to those used for tlc. The product zone was detected with a Mineralight lamp and cut; the strips were rolled and placed into a glass tube where they were washed with meth-

(9) 6-Ethoxypurine was the only 6-substituted purine studied by us which had the H-8 proton absorbing at higher field than H-2. *Cf.* W. C. Coburn, M. C. Thorpe, J. A. Montgomery, and K. Hewson, *J. Org. Chem.*, **30**, 1114 (1965), for a similar effect in 6-methoxypurine.

(10) *Cf.* K. Keck, *Z. Naturforsch., B*, **23**, 1034 (1968).

(11) The most pronounced changes in the nmr spectrum of the adenosine photoadduct are a strong downfield shift of the H-1′ proton (anomeric) and a weaker one of H-2′ in the same direction. Thus, while H-1′ in adenosine absorbs at τ 3.97, it appears at τ 3.77 in C-8 CH(OH)CH_3 and 3.04 in C-8 $C(CH_3)_2OH$. The differences in the shifts of the other C–H proton in the sugar moiety are relatively small as compared to those of the starting nucleoside. The pronounced downfield shift (0.93 ppm) in the absorption of the anomeric proton of the adenosine–2-propanol adduct indicates that it is probably forced into the plane of the purine ring and is being deshielded by the ring current. The two possible conformations, anti or syn [J. Donohue and K. N. Trueblood, *J. Mol. Biol.*, **2**, 363 (1960); A. E. V. Haschemeyer and A. Rich, *ibid.* **27**, 369 (1967)] of the relative orientation of the planar purine with respect to the sugar ring in the photoproduct cannot be distinguished using these data. Examination with models indicates that in the anti conformation there is a strong interaction between the ribose moiety and the side chain at C-8. On the other hand, this interaction does not exist in the syn conformation. We, therefore, assume that the adenosine–2-propanol photoproduct adapts the more favorable syn conformation, as opposed to adenosine for which an anti conformation has been proposed [F. Jordan and B. Pullman, *Theor. Chim. Acta.*, **9**, 242 (1968)]. A recent publication by D. W. Miles, L. B. Townsend, M. J. Robins, R. K. Robins, W. H. Inskeep, and H. Eyring, *J. Amer. Chem. Soc.*, **93**, 1600 (1971), confirms our proposal.

(12) K. Biemann and J. A. McCloskey, *ibid.*, **84**, 2005 (1962); S. Hanessian, D. C. DeJongh, and J. A. McCloskey, *Biochim. Biophys. Acta*, **117**, 480 (1966); S. H. Eggers, S. I. Biedron, and A. O. Hawtrey, *Tetrahedron Lett.*, 3271 (1966).

(13) C. Helene, R. Santus, and P. Douzou, *Photochem. Photobiol.*, **5**, 127 (1966).

(14) F. R. Stermitz, C. C. Wei, and C. M. O'Donnell, *J. Amer. Chem. Soc.*, **92**, 2745 (1970).

(15) Helene, *et al.*,[13] observed the formation of alcohol free radicals in irradiated frozen alcoholic solutions of adenosine or guanosine and proposed an energy transfer process involving a higher excited state, populated *via* a biphotonic absorption, for the generation of these radicals. We, however, consider the hydrogen atom abstraction process to be more plausible.

(16) E. C. Taylor, Y. Maki, and B. E. Evans, *J. Amer. Chem. Soc.*, **91**, 5181 (1969), and references cited therein.

(17) *Cf.* W. Gordy, *Ann. N. Y. Acad. Sci.*, **158**, 1, 100 (1969).

(18) *Cf.* A. A. Lamola, *Photochem. Photobiol.*, **7**, 619 (1968).

(19) J. W. T. Slinks and R. J. Woods, "An Introduction to Radiation Chemistry," Wiley, New York, N. Y., 1964, p 129.

(20) *Cf.* ref 4, pp 270–275.

anol to elute the product. Infrared spectra were obtained with a Perkin-Elmer Infracord Model 137. Ultraviolet spectra were recorded on a Cary 14 spectrophotometer. Nmr spectra were determined with a Varian A-60 instrument in the appropriate organic solvent using TMS as internal standard. Spectra were taken in D_2O or DMSO-d_6 employing 1% (w/w) DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate, Merck Sharp Dohme of Canada, Ltd., Montreal) as an internal reference. Absorptions are reported in τ values. Mass spectra were recorded with an MAT-Atlas CH4 instrument. ORD spectra were determined on a Jasco Model ORD/UV-5 instrument.

Experiments were carried out at room temperature in an immersion apparatus with Hanovia 450-W high-pressure mercury vapor lamps which were cooled internally with running water. Corex filters (λ <260 nm) were employed except for the reactions with acetone where Pyrex filters (λ >290 nm) were used. The reaction apparatus was flushed with nitrogen for 15 min before irradiation. Some typical experiments are described in detail. Other experiments were conducted under similar conditions and are summarized in the tables. Progress of the reactions was followed by tlc. The γ-ray-induced reactions were performed in glass tubes which were placed into the ^{60}Co γ source.

Reaction of Caffeine and 2-Propanol with Ultraviolet Light.—A mixture of caffeine (1.5 g), 2-propanol (145 ml), and water (55 ml) was irradiated for 62 hr. Excess reagents were removed under reduced pressure and the residue was chromatographed on silica gel. Acetone–petroleum ether (3:17) eluted **2** (0.69 g, 35%): mp 199–200° (from 2-propanol); ir 3350 cm^{-1} (OH); nmr ($CDCl_3$) τ 5.8 (s, 3 H, N-7-CH_3), 6.46 (s, 3 H, N-3-CH_3), 6.6 (s, 3 H, N-1-CH_3), 6.83 (broad s, 1 H, OH), and 8.3 [s, 6 H, $C(CH_3)_2OH$].

Anal. Calcd for $C_{11}H_{16}N_4O_3$: C, 52.37; H, 6.39; N, 22.21; mol wt, 252. Found: C, 52.55; H, 6.47; N, 22.40; mol wt, 252 (mass spectrum).

The product was found to be identical with an authentic sample prepared from 8-acetylcaffeine[21] and CH_3MgJ. Further elution with the same solvent mixture (1:4) gave unreacted caffeine.

Reaction of Caffeine, 2-Propanol, and Acetone with Ultraviolet Light.—A mixture of caffeine (1.5 g), 2-propanol (100 ml), and acetone (100 ml) was irradiated for 24 hr. The usual work-up as above and chromatography on silica gel led to **6** [0.23 g, 10%: eluted with 2-propanol–petroleum ether (1:19)]: mp 206–207° (from ethanol); nmr τ 5.1 (s, 2 H, N-7-CH_2), 6.45 (s, 3 H, N-3-CH_3), 6.63 (s, 3 H, N-1-CH_3), 8.33 [s, 6 H, $C(CH_3)_2OH$], and 8.7 [s, 6 H, N-7-$CH_2C(CH_3)_2OH$].

Anal. Calcd for $C_{14}H_{22}N_4O_4$: C, 53.83; H, 7.74; N, 17.94; mol wt, 310. Found: C, 54.06; H, 7.50; N, 17.88; mol wt, 310 (mass spectrum).

Further elution with the same solvent mixture (3:7) gave **2** (1.5 g, 77.5%) followed by unreacted caffeine (0.29 g). Longer irradiation periods led to higher yields of the 2:1 adduct **6**. For example, after 48 hr of irradiation 1.07 g (45%) of this product was obtained.

Reaction of Caffeine and 2-Propanol with γ Rays.—A solution of caffeine (1.5 g) in 2-propanol (200 ml) was exposed to γ rays for 25 hr. The usual work-up led to **2** (0.63 g, 37%).

The reaction in the presence of acetone was carried out with caffeine (1.5 g), 2-propanol (100 ml), and acetone (100 ml) and was exposed to γ rays for 30 hr. The usual work-up gave **2** (1.3 g, 67%) and traces of **6**. Other reactions of caffeine and alcohols were conduced under similar conditions and are summarized in Tables I and II.

Reaction of Adenosine, 2-Propanol, and Acetone with Ultraviolet Light.—A mixture of adenosine (0.75 g), water (50 ml), 2-propanol (80 ml), and acetone (80 ml) was irradiated at room temperature for 11 hr. Solvents were removed under reduced pressure and the residue was chromatographed on paper in a mixture of 1-butanol–water–concentrated ammonia (86:9:5 v/v) leading to **8** (0.50 g, 50%): mp 227–230° (from water); nmr (0.2 *M* solution in D_2O, DSS as internal reference); τ 1.9 (s, 1 H, C-2-H), 3.04 (d, $J_{1',2'}$ = 7.5 Hz, C-1′-H), 4.77 (dd, $J_{2',1'}$ = 7.5 Hz, $J_{2',3'}$ = 5.5 Hz, 1 H, C-2′-H), 6 (an apparent d, 2 H, C-5′-H_2), and 8.15 [s, 6 H, $C(CH_3)_2OH$].

Anal. Calcd for $C_{13}H_{19}N_5O_6 \cdot 2H_2O$: C, 43.21; H, 6.42; N, 19.38; mol wt, 361. Found: C, 42.83; H, 6.35; N, 19.8; mol wt, 325 (mass spectrum).

(21) G. Ehrhart and I. Hennig, *Arch. Pharm.* (*Weinheim*), **289**, 453 (1956).

TABLE II

PRODUCTS OF REACTIONS OF CAFFEINE WITH ALCOHOLS

Alcohol[a]	Product	Mp, °C	Elution mixture
Ethanol	4[b]	184–186	Acetone–petroleum ether (3:7)
Ethanol	1[c]	178	2-Propanol–petroleum ether (3:17)
1-Propanol	5[b]	111–112	Acetone–petroleum ether (3:17)
2-Butanol	3[d]	138–139	2-Propanol–petroleum ether (1:9)

[a] Reactions were carried out in 30% aqueous–alcoholic mixtures. [b] *Cf.* E. S. Golovchinskaya and E. S. Chaman, *Zh. Obshch. Khim.*, 22, 2220 (1952). [c] An authentic sample has been prepared through $NaBH_4$ reduction of 8-acetylcaffeine. *Cf.* ref 21. [d] Nmr ($CDCl_3$) τ 5.83 (s, 3 H, N-7-CH_3), 6.43 (s, 1 H OH), 6.5 (s, 3 H, N-3-CH_3), 6.65 (s, 3 H, N-1-CH_3), 8 (q, J = 7.5 Hz, 2 H, CH_2CH_3), 8.33 [s, 3 H, $C(CH_3)OH$], and 9.11 (t, J = 7.5 Hz, 3 H, CH_2CH_3). *Anal.* Calcd for $C_{12}H_{18}N_4O_3$: C, 54.12; H, 6.81; N, 21.04; mol wt, 266. Found: C, 54.08; H, 7.08; N, 21.05; mol wt, 266 (mass spectrum).

Reaction of Adenosine and Ethanol with Ultraviolet Light.—A mixture of adenosine (0.6 g), ethanol (120 ml), and water (30 ml) was irradiated for 125 hr. The usual work-up and preparative paper chromatography (twice) led to a heavy oil which was dissolved in water (8 ml), filtered, and left in the refrigerator to deposit a solid which was pure **9** (0.2 g, 28%): mp 150°; nmr (0.2 *M* solution in D_2O, DSS as internal standard) τ 2.18 (s, 1 H, C-2-H), 3.8 (d, $J_{1,2}$ = 7.5 Hz, 1 H, C-1′-H), 4.79 [q, J = 6.5 Hz, 1 H, $CH(OH)CH_3$], 5 (dd, $J_{2',1'}$ = 7.5 Hz, $J_{2',3'}$ = 5.5 Hz, 1 H, C-2′-H), 5.54 (dd, $J_{3',2'}$ = 5.5 Hz, $J_{3',4'}$ = 2.0 Hz, 1 H, C-3′-H), 5.7 (m, 1 H, C-4′-H), signal at 6.12 (2 H, C-5′-H_2), and 8.36 [d, J = 6.5 Hz, 3 H, $CH(OH)CH_3$].

Anal. Calcd for $C_{12}H_{17}N_5O_5$: C, 46.30; H, 5.50; N, 22.50; mol wt, 311. Found: C, 45.95; H, 6.10; N, 22.83; mol wt, 311 (mass spectrum).

Other reactions of purines and purine nucleosides with 2-propanol were conducted under similar conditions and are summarized in Tables I and III.

Reaction of 6-Ethoxypurine, 2-Propanol, and Acetone with Ultraviolet Light.—A mixture of 6-ethoxypurine (0.475 g), 2-propanol (80 ml), and acetone (80 ml) was irradiated 17 hr. The usual work-up and chromatography on kieselgel (100 g) led to the 2,8-disubstituted product **14** [0.205 g, 25%; eluted with acetone–petroleum ether (1:3)]: mp 200–201° (from acetone–petroleum ether); nmr (DMSO-d_6 + D_2O DSS as internal standard) τ 5.37 (q, J = 7 Hz, 2 H, $=OCH_2CH_3$), 8.39 [s, 6 H, $C(CH_3)_2OH$], 8.45 [s, 6 H, $C(CH_3)_2OH$], and 8.53 (t, J = 7 Hz, 3 H, OCH_2CH_3).

Anal. Calcd for $C_{13}H_{20}N_4O_3$: C, 55.70; H, 7.19; N, 19.99; mol wt, 280. Found: C, 55.72; H, 7.48; N, 20.10; mol wt, 280 (mass spectrum).

Further elution with acetone–petroleum ether (7:13) gave **13** (0.265 g, 41%): mp 201–202° (from acetone–petroleum ether); nmr (DMSO-d_6 + D_2O, DSS as internal standard) τ 1.5 (s, 1 H, C-2-H), 5.38 (q, J = 7 Hz, 2 H, OCH_2CH_3), 8.35 [2, 6 H, $C(CH_3)_2OH$], and 8.54 (t, J = 7 Hz, 3 H, OCH_2CH_3).

Anal. Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21; mol wt, 222. Found: C, 53.98; H, 6.41; N, 25.10; mol wt, 222 (mass spectrum).

While exposing the same mixture to γ rays for 30 hr, **13** and **14** were obtained in 47 and 19% yield, respectively.

Reaction of 2-Aminopurine and 2-Propanol with Ultraviolet Light.—A suspension of 2-aminopurine (0.4 g) in 2-propanol (90 ml) and acetone (80 ml) was irradiated until the solid dissolved (8 hr). The usual work-up and chromatography on kieselgel led to the 6,8-disubstituted product **16** [0.17 g, 30%; eluted with 2-propanol–petroleum ether (1:3)]: mp 245–246° dec (from 2-propanol); nmr (DMSO-d_6–D_2O, TMS external) τ 8.4 [s, 6 H, $C(CH_3)_2OH$], 8.44 [s, 6 H, $C(CH_3)_2OH$].

Anal. Calcd for $C_{11}H_{17}N_5O_2$: C, 52.57; H, 6.82; N, 27.87; mol wt, 251. Found: C, 52.35; H, 7.00; N, 27.80; mol wt, 251 (mass spectrum).

Further elution with 2-propanol–petroleum ether (1:2) gave **15** (0.25 g, 34%), which was recrystallized successively from acetone and water and showed mp 205°; nmr (DMSO-d_6–D_2O, TMS external) τ 1.8 (s, 1 H, H-8), 8.4 [s, 6 H, $C(CH_3)_2OH$].

TABLE III
PRODUCTS OF THE REACTIONS OF PURINES AND PURINE NUCLEOSIDES WITH 2-PROPANOL

Purine or purine nucleoside	Product formula[a]	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Adenine	$C_8H_{11}N_5O \cdot H_2O$	249–251	45.49	6.20	33.16	45.19	6.21	33.19
Hypoxanthine	$C_8H_{10}N_4O_2 \cdot CH_3OH$		47.78	6.24	24.77	47.46	6.19	24.46
Guanosine	$C_{13}H_{19}N_5O_6 \cdot CH_3OH$	211–213	45.03	6.21	18.76	45.35	6.10	19.04
2′-Deoxyguanosine	$C_{13}H_{19}N_5O_5 \cdot 2CH_3OH$		46.26	6.99	17.99	46.03	6.94	18.50

[a] In some experiments purification of the product presented some difficulties since the crystalline product contained solvent of crystallization. It was necessary, therefore, to employ a pure solvent in the final recrystallization.

TABLE IV
REACTIONS OF CAFFEINE AND ALCOHOLS INDUCED BY DI-*tert*-BUTYL PEROXIDE

Alcohol	Product (8-substituted caffeine)	Yield, %
Methanol	CH_2OH[a]	24
Ethanol	$CH(OH)CH_3$	15
1-Propanol	$CH(OH)CH_2CH_3$[b]	6.2
	CH_2CH_3	6.7

[a] H. Bredereck, E. Sugel, and B. Foehlisch, *Chem. Ber.*, 95, 403 (1962). [b] Mp 154–155°; nmr ($CDCl_3$) τ 5.3 [t, J = 7 Hz, 1 H, CH(OH)], 6.05 (s, 3 H, N-7-CH_3), signal at 6.48 (1 H, OH), 6.58 (s, 3 H, N-3-CH_3), 4.7 (s, 3 H, N-1-CH_3), 8.07 (quintet J = 7 Hz, 2 H, CH_2CH_3), 8.98 (t, J = 7 Hz, CH_2CH_3). *Anal.* Calcd for $C_{11}H_{16}N_4O_3$: C, 52.37; H, 6.39; N, 22.21; mol wt, 252. Found: C, 52.49; H, 6.58; N, 22.21; mol wt, 252 (mass spectrum).

Anal. Calcd for $C_8H_{11}N_5O \cdot H_2O$: C, 45.49; H, 6.20; N, 33.16; mol wt, 211. Found: C, 45.64; H, 6.38; N, 33.20; mol wt, 193 (without H_2O, mass spectrum).

Reaction of 2-Propanol and Caffeine Induced by Di-*tert*-Butyl-peroxide.—A mixture of caffeine (0.7 g), 2-propanol (100 ml), and di-*tert*-butyl peroxide (1.5 g) was heated in a sealed tube at 130–140° for 35 hr. The usual work-up led to **2** (0.2 g, 22%). The other reactions of caffeine and alcohols induced by di-*tert*-butyl peroxide are described in Table IV.

Registry No.—**2**, 22439-97-0; **3**, 31326-94-0; **6**, 31385-42-9; **7**, 23865-41-0; **8**, 23844-14-6; **9**, 31326-97-3; **10**·CH_3OH, 31428-81-6; **13**, 31326-98-4; **14**, 31326-99-5; **15**, 31327-00-1; **16**, 31327-01-2; caffeine 8 substitutent $CHOHCH_2CH_3$, 31327-02-3; caffeine, 58-08-2; adenine, 73-24-5; adenosine, 58-61-7; guanosine, 118-00-3; 2′-deoxyguanosine, 961-07-9; hypoxanthine, 68-94-0; 6-ethoxypurine, 17861-06-2; 2-aminopurine, 26730-59-6; ethanol, 64-17-5; 1-propanol, 71-23-8; 2-propanol, 67-63-0; 2-butanol, 78-92-2.

The Mechanism of Formation of Some Pentofuranosyl Halides

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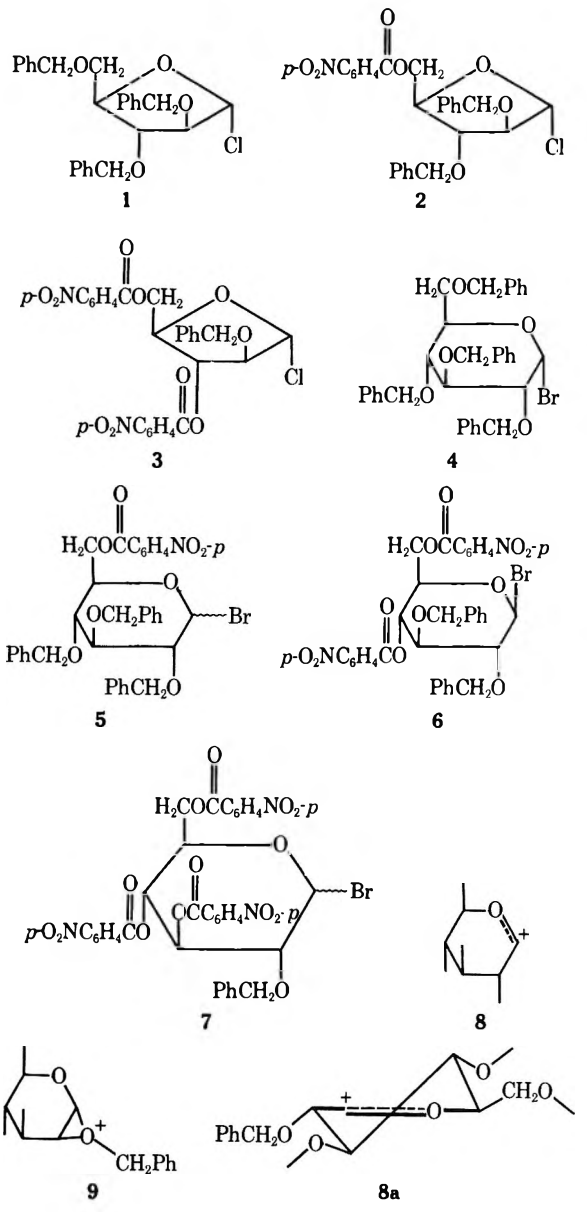
The behavior of the anomeric 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (**10** and **11**, Scheme I) with hydrogen chloride in dichloromethane solution has been studied. 2-*O*-Benzyl-1,3,5-tri-*O*-*p*-nitrobenzoyl-β-D-arabinofuranose (**15**, Scheme II) has been prepared through the action of silver *p*-nitrobenzoate on 2-*O*-benzyl-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl chloride (**3**, Chart I); the reaction of **15** and of its previously known anomer **14** with hydrogen bromide in dichloromethane solution has been examined. In the presence of added chloride ions, 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride (**1**) shows a levomutarotation in dichloromethane solution; the same phenomenon is shown by 2-*O*-nitro-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl bromide in the presence of bromide ions. All observations appear to be consistent with the view that the first step in the formation of the pentofuranosyl halides of the type studied is under kinetic control and leads to the α-D-arabinofuranosyl halide; partial anomerization to the corresponding β-D-arabinofuranosyl halides then follows but at a slower rate. A mechanism designed to rationalize these facts is discussed.

In 1965[1] we described studies of the methanolysis of 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride (**1**, Chart I), 2,3-di-*O*-benzyl-5-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl chloride (**2**), and 2-*O*-benzyl-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl chloride (**3**). Although the steric features of the methanolyses were virtually identical (methyl β-D-arabinofuranoside derivatives preponderating in each case), the rates of methanolysis contrasted sharply, standing in the order, respectively, of 106:13:1. Thus, replacement of the benzyl group at C-5 in **1** by a *p*-nitrobenzoyl group reduced the rate of methanolysis by a factor of 8 and the replacement of the benzyl group at C-3 by a second *p*-nitrobenzoyl group caused a further reduction in the methanolysis rate by a factor of 13. In order to see whether exchange of benzyl by *p*-nitrobenzoyl groups exerts a similar stabilizing effect on aldopyranosyl halides, a subsequent study[2] was directed to the methanolysis of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide (**4**), 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-D-glucopyranosyl bromide (**5**), 2,3-di-*O*-benzyl-4,6-di-*O*-*p*-nitrobenzoyl-β-D-glucopyranosyl bromide (**6**), and of the two anomeric forms of 2-*O*-benzyl-3,4,6-tri-*O*-*p*-nitrobenzoyl-D-glucopyranosyl bromide (**7**). Although the picture in the glucopyranose series is somewhat complicated by the anomeric effect, it was abundantly clear that this exchange of groups appeared to have a stabilizing effect on the C-1–halogen bond and that this effect is cumulative,

(1) C. P. J. Glaudemans and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.*, **87**, 4636 (1965).

(2) T. Ishikawa and H. G. Fletcher, Jr., *J. Org. Chem.*, **34**, 563 (1969).

CHART I



being roughly proportional to the number of *p*-nitrobenzoyl groups present.

In the studies referred to,[1,2] aldosyl halides were prepared according to Zorbach and Payne,[3] a 1-*O*-*p*-nitrobenzoyl group being displaced by halogen acid in dichloromethane solution. This process, in which the liberated *p*-nitrobenzoic acid is removed by filtration, is especially suited to the preparation of labile glycosyl halides,[4] and we have shown[5] that amorphous 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride (**1**, Chart I) of relatively high anomeric purity may be prepared in this manner from a mixture of the anomers of 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranose (**10** and **11**). 2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl chloride may also be prepared from 2,3,5-tri-*O*-benzyl-D-arabinofuranose through the action of hydrogen chloride in an inert solvent and in the presence of a solid desiccant; in this case, however, optical rotation and solvolysis studies showed[5] that the chloride contained appreciably more of the β anomer than when prepared from the mixture of **10** and **11**; we shall return to this point later. In the later solvolysis studies,[1] **1** was again prepared from a mixture of **10** and **11** and, this time, its anomeric configuration was confirmed through its nmr spectrum. Compounds **2** and **3**, on the other hand, were prepared from the corresponding D-arabinofuranose derivatives that were unsubstituted at C-1; nmr spectroscopy showed these two halides to be α anomers and, indeed, the latter was obtained in crystalline form.

In the D-glucopyranose series all of the glucosyl bromides needed for kinetic studies were made from the corresponding *p*-nitrobenzoates but in these cases a phenomenon which had not been observed in the preparation of the pentofuranosyl halides was seen; regardless of the anomeric configuration of the *p*-nitrobenzoate used, the initial product was the β bromide. Indeed, by suitably restricting the reaction time, **6** and the β anomers of **5** and **7** could be isolated in crystalline form. The presence of bromide ion, however, caused these reactive halides to isomerize to the more stable α anomers.

The initial formation of the more active (β) glucopyranosyl bromide from both of the anomeric *p*-nitrobenzoates seems to suggest that a single ionic species is produced and that a stereospecific attack on this by bromide ion gives the β-D-glucopyranosyl bromide. The glucosyl ion **8** may be presumed to assume a conformation such as **8a**, and it is possible that the benzyloxy group at C-2 provides sufficient steric hindrance to assure the initial formation of the β-D bromides. Neighboring-group participation as a means of steric control must also be considered. The benzyloxonium ion **9** would furnish such control but the benzyloxy group affords little if any anchimeric assistance when attached to a carbon atom immediately adjacent to that from which a group is departing.[6] However, at longer range, the benzyloxy group can function as an effective participator in displacements[7-12] and so it is possible that the benzyloxy group at C-4 is responsible for the formation of the β form of **5**. Even less steric strain would be involved in the participation of an acyloxy group at C-4 and so the *p*-nitrobenzoyl group at this position may provide steric control in the formation of **6**, β-**5**, and β-**7**. In passing, it should be noted that such transannular intermediates cannot be invoked to rationalize the methanolysis of these D-glucopyranosyl halides inasmuch as all of them afford preponderantly methyl α-D-glucopyranoside derivatives. Aside from being a reactant, the methanol used in the solvolysis serves also as the reaction milieu and so it is not surprising that the mechanism involved in the solvolysis of these halides appears

(3) W. W. Zorbach and T. A. Payne, *J. Amer. Chem. Soc.*, **80**, 5564 (1958).

(4) *p*-Phenylazobenzoic acid is also relatively insoluble in dichloromethane and, owing to their color, 1-*O*-*p*-phenylazobenzoylaldoses offer some advantages over the corresponding *p*-nitrobenzoates in the synthesis of aldosyl halides: J. D. Stevens, R. K. Ness, and H. G. Fletcher, Jr., *J. Org. Chem.*, **33**, 1806 (1968); M. Haga, R. K. Ness, and H. G. Fletcher, Jr., *ibid.*, **33**, 1810 (1968).

(5) C. P. J. Glaudemans and H. G. Fletcher, Jr., *ibid.*, **28**, 3004 (1963).

(6) K. J. Ryan, H. Arzoumanian, E. M. Acton, and L. Goodman, *J. Amer. Chem. Soc.*, **86**, 2497 (1964).

(7) G. R. Gray, F. C. Hartman, and R. Barker, *J. Org. Chem.*, **30**, 2020 (1965).

(8) J. S. Brimacombe and O. A. Ching, *Carbohyd. Res.*, **8**, 82 (1968).

(9) J. S. Brimacombe and O. A. Ching, *J. Chem. Soc. C*, 1642 (1968).

(10) J. S. Brimacombe and O. A. Ching, *ibid.*, 964 (1969).

(11) S. Dimitrijevich and N. F. Taylor, *Carbohyd. Res.*, **11**, 531 (1969).

(12) O. A. Ching Puente, *Bol. Soc. Quim. Peru*, **35**, 121 (1969); *ibid.*, **36**, 13 (1970).

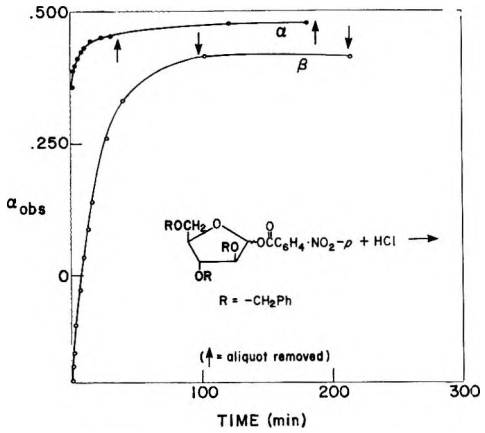


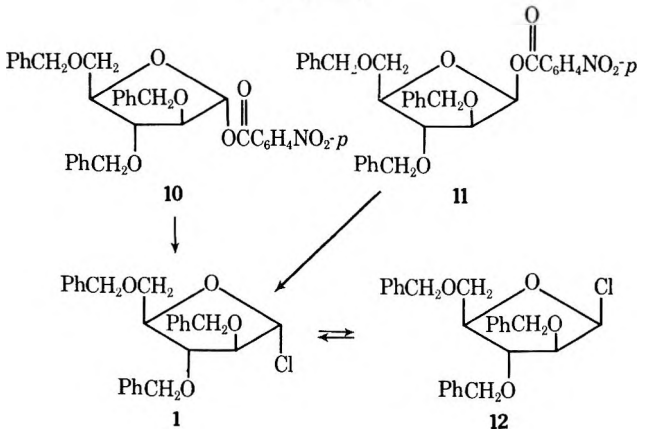
Figure 1.—Reaction of the anomeric 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (**10** and **11**) with hydrogen chloride in dichloromethane solution at 20°.

to have little in common with that of their formation.[13]

The unexpected features found in the formation of the D-glucopyranosyl bromides have led us to a reexamination of the formation of arabinofuranosyl halides that have a benzyl group at C-2. This work will now be described.

Each of the anomeric 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (**10** and **11**) was treated in dichloromethane solution with an excess of hydrogen chloride, and the resulting solution was observed polarimetrically, precipitated *p*-nitrobenzoic acid being removed by filtration as necessary (Scheme I). The

SCHEME I



plot of optical rotation *vs.* time is shown in Figure 1. Pseudo-first-order rate constants calculated for these two reactions were found to be quite similar: $\sim 1.5 \times 10^{-1}$ (min^{-1}) for **10** and $\sim 5 \times 10^{-2}$ for **11**. Actually, each series of observations passed through a maximum which is not evident on the time scale of Figure 1. All prior work in this laboratory[2,5] in which aldosyl halides having a benzyl group at C-2 have been treated with sodium methoxide has yielded results which are consistent with the view that the reaction has a high degree of SN2 character, aldosyl halides yielding methyl glycosides with inversion of configuration at C-1. We have, therefore, tentatively assumed that this reaction can serve as a basis for the analysis of anomeric mixtures of such halides.[5] Aliquots of the reaction mixture prepared from **10** and **11** with hydrogen chloride were withdrawn at intervals and treated with an excess of sodium methoxide. Glc of the resulting mixture of methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranosides afforded the data shown in Table I. Bearing in mind the assumption that the α-D glycoside represents β-D glycosyl halide in the reaction mixture (and vice versa), it will be seen that the reaction mixtures from the two anomeric esters were virtually identical and that the α halide **1** formed initially slowly anomerized to the β halide **12**, although the former preponderated after even a relatively prolonged reaction period. It appears, therefore, that kinetic control is followed by thermodynamic equilibration although the magnitude of the effect is considerably less dramatic than with the D-glucopyranose derivatives examined earlier.[2] Further study of the phenomenon in the D-arabinofuranose series is made difficult by the relative inaccessibility of suitable substrates. We have, however, been able to pursue this topic by experiments in two directions. In the earlier investigation,[1] we found that 2-*O*-benzyl 1,3,5-tri-*O*-*p*-nitrobenzoyl-α-D-arabinofuranose (**14**, Scheme II) could be prepared through the *p*-nitrobenzoylation of 2-*O*-benzyl-3,5-di-*O*-*p*-nitrobenzoyl-D-arabinofuranose (**13**) with *p*-nitrobenzoyl chloride in a mixture of dichloromethane and pyridine. However, while the anomeric ester **15** appeared to be isolable from the mother liquor, attempts to obtain it in chromatographically homogeneous form were unsuccessful. It has now been found that condensation of 2-*O*-benzyl-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl chloride (**3**) with silver *p*-nitrobenzoate affords a mixture from which, by repeated chromatography, both anomeric

TABLE I

REACTION OF 2,3,5-TRI-*O*-BENZYL-1-*O*-*p*-NITROBENZOYL-D-ARABINOFURANOSES (**10** AND **11**) WITH HCl IN DICHLOROMETHANE SOLUTION

Reaction time	Proportions of methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranosides found on glc of methanolyzed samples[a] α	β
	α Anomer **10**	
37 min	16	84
184 min	19	81
13 days	25	75
	β Anomer **11**	
85 min	17	83
137 min	21	79
13 days	31	69

[a] The trend of these values with time was confirmed by replicate experiments but the individual values are not readily reproducible; we deem it likely that the observed variations between experiments arose through the presence of traces of moisture.

(13) In earlier communications[1,2] reference has been made to a long-range effect of the *p*-nitrobenzoyl group in decreasing the reactivity of glycosyl halides. It is well to bear in mind the fact that this effect is based entirely on comparisons between the *p*-nitrobenzoyloxy group and the benzyloxy group. We have considered the possibility that the interpretation is reversed and that the effect arises from the greater anchimeric assistance afforded by benzyloxy groups suitably distant from C-1. However, at least one case seems to speak against this latter view. As already noted, replacement of the benzyloxy group at C-3 in **2** with a *p*-nitrobenzoyl group (to give **3**) diminishes the activity of the halide by a factor of 13. However, the greater activity of **2** can hardly be attributed to anchimeric assistance from the benzyloxy group at C-3 for this group is not favorably situated for back-side approach to C-1 and, even if it were, the resulting benzyloxonium ion would have a four-membered ring. As of this writing, we see no acceptable alternative to the view that *p*-nitrobenzoyl groups may exert a long-range stabilizing effect in glycosyl halides, possibly operating, as suggested earlier,[1] through the ring oxygen.

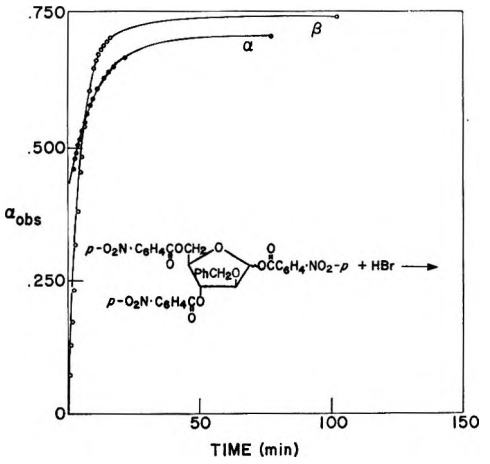
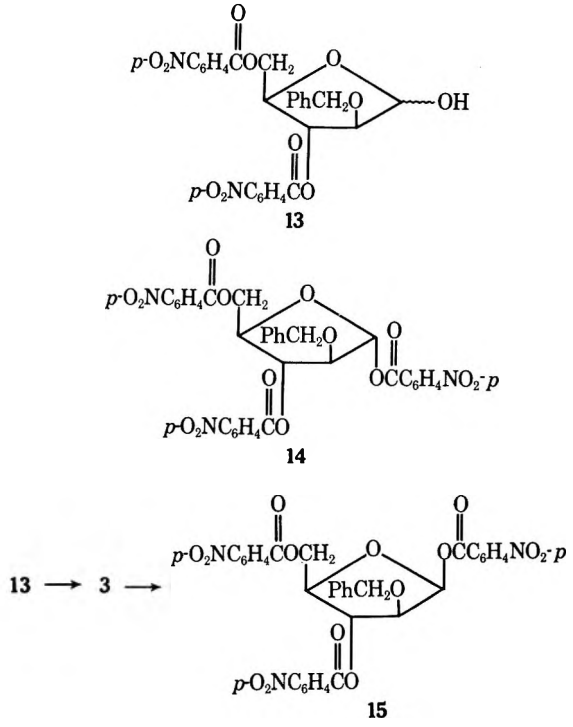


Figure 2.—Reaction of the anomeric 2-*O*-benzyl-1,3,5-tri-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (**14** and **15**) with hydrogen bromide in dichloromethane solution at 20°.

SCHEME II



2-*O*-benzyl-1,3,5-tri-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (**14** and **15**) can be obtained in pure crystalline form. Owing, presumably, to the deactivating influence of the *p*-nitrobenzoyl groups at C-3 and C-5, compounds **14** and **15** were found to react with hydrogen chloride at a rate which was impractically slow for the purpose at hand. With hydrogen bromide, however, these esters reacted promptly as is shown in the plot of observed rotation *vs.* time (Figure 2).[14] The subsequent rotational changes were in a levo direction. The reaction mixture from the β anomer **15** showed 0.744° at 162 min and 0.685° after 98 hr; the mixture from the α anomer **14** showed 0.706° after 77 min and 0.667° after 98 hr. At 14.5 min, a sample of the reaction mixture from **15** was treated with an excess of sodium methoxide and the resulting mixture of methyl 2-*O*-benzyl-D-arabinofuranosides was analyzed by glc after tri-

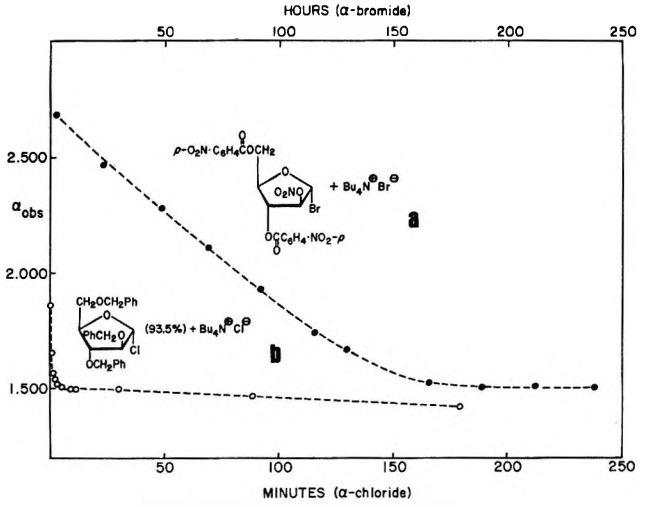


Figure 3.—Behavior of two α-D-arabinofuranosyl halides in the presence of the corresponding tetrabutylammonium halides in dichloromethane solution at 20°. Registry no. (a) 4153-32-6, (b) 4060-34-8.

methylsilylation. The mixture was found to consist of 8% of the α-D glycoside and 92% of the β-D glycoside, indicating (on the basis of the aforementioned assumption) that the 2-*O*-benzyl-3,5-di-*O*-*p*-nitrobenzoyl-D-arabinofuranosyl bromide was 92% α anomer and 8% β anomer. A similar analysis of the reaction mixture from **14** at 18 min showed the halide to be 83% α and 17% β anomer. In summary, the picture presented here is consistent with that found for the reaction of **10** and **11** with hydrogen chloride.

It should be borne in mind that the mode of analysis employed in this work effectively ignores all reaction species other than the D-arabinofuranosyl halides. One cannot wholly exclude the possibility that the inflections in observed rotations and the slow increase of **12** at the expense of **1** in the reaction mixture may be due to preferential conversion of the α-D halides into components of as yet unknown character. For this reason, we investigated the behavior of two α-D-arabinofuranosyl halides under conditions quite far removed from those used in their preparation, conditions deliberately designed to favor anomerization. 2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl chloride which was relatively rich in the α anomer **1** was dissolved in dichloromethane containing tetrabutylammonium chloride and the optical rotation of the resulting solution was observed. As may be seen from Figure 3, a rapid levomutarotation resulted. A parallel experiment was performed with 2-*O*-nitro-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl bromide[15] and tetrabutylammonium bromide; here again, a marked levomutarotation was observed (Figure 3). An estimate of the relative rates of the two reactions may be made by comparison of the two scales in Figure 3. While one would normally expect bromides to be more effectively isomerized by bromide ions, than chlorides by chloride ions, the stabilizing effect of the three strongly electronegative substituents on the bromide completely overrides the difference between chloride and bromide. While not conclusive, the data shown in Figure 3 are consistent with the view that an appreciable proportion of β anomer is

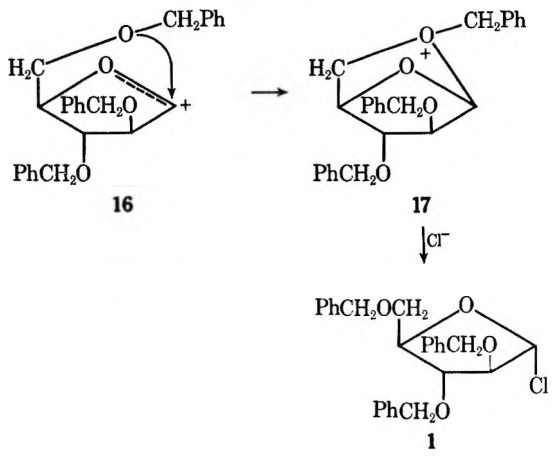
(14) The first-order rates were ~1 × 10^{-1} and ~3 × 10^{-1} (min^{-1}) for **14** and **15**, respectively.

(15) C. P. J. Glaudemans and H. G. Fletcher, Jr., *J. Org. Chem.*, **29**, 3286 (1964).

formed when a D-arabinofuranosyl halide is permitted to attain anomeric equilibrium.

Let us now turn briefly to a consideration of the mechanism of the formation of 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride (**1**) from the corresponding *p*-nitrobenzoates **10** and **11**. At the outset, the *p*-nitrobenzoate is rapidly removed; the difference in the rates of reaction of the two anomers may or may not be significant but, in any case, it is comparatively small. That the two anomers lead to a common ion, perhaps **16** (Scheme III) or some variant thereof, seems indicated by the fact that the steric make-up of the product from each ester is identical. What, then, steers the entering chloride ion to the "α side"? As with the D-glucopyranosyl ion **8a** mentioned earlier, one can invoke the steric effect of the benzyloxy group at C-2 and, indeed, this view is more attractive with the relatively planar five-membered ring. On the other hand, turning to neighboring-group considerations, the carbonium ion **16** might be stabilized through participation of the benzyloxy group at C-5 to give ion **17**. Some recent work of Brimacombe and Ching[10] lends credence to this view. These authors showed that the solvolysis of benzyl 5-*O*-*p*-bromophenylsulfonyl-2,3-*O*-isopropylidene-β-D-ribofuranoside takes place with migration of the benzyl group from C-1 to C-5. Since a benzyloxy group at C-1 can thus participate in a displacement at C-5, there should be no difficulty in accepting the participation of a benzyl group at C-5 in displacements at C-1. Attack on ion **17** by chloride ion could, of course, give only the α chloride **1**.[16] A somewhat related transannular participation may be operative in the formation of **3** from **14** and **15** as both of these have a *p*-nitrobenzoyl group at C-5.

SCHEME III



Attractive as these speculations may be, we feel that if a *single* mechanistic feature lies behind the kinetic control observed in the formation of these glycosyl halides, we are inclined at the present to favor that involving the steric hindrance of the benzyloxy group in the glycosyl ions as this view is consistent with the observed facts in the two types of cases investigated.

One apparent anomaly in the formation of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride remains to be discussed. When made[5] from the *p*-nitrobenzoates **10** and **11** by the Zorbach–Payne procedure, the halide is obtained as an amorphous product of $[\alpha]^{20}D$ +91.1 to +96° (*c* 1.25, CH_2Cl_2). Reaction of a typical sample with sodium methoxide, followed by glc, showed the formation of 98.3% β-D-arabinofuranoside and 1.7% of the α anomer. When 2,3,5-tri-*O*-benzyl-D-arabinofuranose is treated in dichloromethane solution (and in the presence of anhydrous magnesium sulfate) with hydrogen chloride, 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride of $[\alpha]^{20}D$ +73° (CH_2Cl_2) is obtained. When benzene is used as the reaction medium, the product has $[\alpha]^{20}D$ +72.5° (*c* 1.25, CH_2Cl_2); methanolysis gave 15.6% of methyl 2,3,5-tri-*O*-benzyl-α-D-arabinofuranoside and 84.4% of the β anomer. The optical rotation of the mixture of the methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranosides was in close agreement with the results of the glc analysis. Thus it appears that the preparation from 2,3,5-tri-*O*-benzyl-D-arabinofuranose is appreciably and consistently richer in 2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl chloride than is that from the Zorbach–Payne procedure. In view of the research described here, a possible explanation of this apparent anomaly can now be proposed. In the relatively anhydrous conditions of the Zorbach–Payne procedure, chloride ion concentration (and thus, anomerization of the α glycosyl chloride **1**) is at a minimum. With 2,3,5-tri-*O*-benzyl-D-arabinofuranose as a starting material, on the other hand, water is produced and, prior to the absorption of this water by the solid desiccant, it must increase the concentration of chloride ion and thus facilitate the partial anomerization of the **1** which is formed.

Experimental Section

Melting points are equivalent to corrected values. Qualitative tlc was conducted on silica gel G of E. Merck, Darmstadt, with the components being detected by heating after spraying with 10% sulfuric acid. Column chromatography was done with silica gel no. 7734 (0.05–0.2 mm) of the same manufacturer. Preparative tlc was done on plates (20 × 20 cm) of silica gel GF, 2 mm thick, from Analtech, Inc. For glc, a Hewlett-Packard chromatograph, Model No. 5750, equipped with a flame ionization detector, was used.

Anomeric 2,3,5-Tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (10 and 11).—A crystalline mixture of **10** and **11** which showed $[\alpha]^{20}D$ +6° (CH_2Cl_2) was made through the *p*-nitrobenzoylation of 2,3,5-tri-*O*-benzyl-D-arabinofuranose as was described for the enantiomorphic series.[17] The anomers were separated by successive recrystallizations from ether–hexane, some mechanical separation of the crystalline materials being used as well. Prepared thus, the α anomer **10** had mp 92–94° and $[\alpha]^{20}D$ +57° (*c* 1.22, CH_2Cl_2); the enantiomorph was reported[17] with mp 96–97° and $[\alpha]^{20}D$ −59° (*c* 2.0, CH_2Cl_2). The β-D anomer **11** had mp 76–77° and $[\alpha]^{20}D$ −44° (*c* 1.26, CH_2Cl_2), values which may be compared with the previously recorded[17] values for the β-L anomer, mp 77–78° and $[\alpha]^{20}D$ +43.9° (*c* 5.4, CH_2Cl_2).

Reaction of 10 and 11 with Hydrogen Chloride in Dichloromethane Solution.—Pure 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-α-D-arabinofuranose (**10**, 25.1 mg) was placed in a 1-dm polarimeter tube and 4 ml of dichloromethane, 0.162 *N* in HCl, was added (14.7 mol of HCl/mol of **10**). The observed optical rotation of the resulting solution at 20° is plotted as a function of time in Figure 1. After 97 min, precipitated *p*-nitrobenzoic acid was removed by filtration and the solution was returned to the polarimeter tube. At intervals, 3-drop aliquots were removed, neutralized with an excess of sodium methoxide, and chromatographed on a column (10 ft × 0.25 in. o.d.) of 3% SE-30 on

(16) Attack on **17** at C-5 is not excluded but the very great difference between C-1 and C-5 should give the benzyloxonium ion (**17**) a highly asymmetric character in regard to electronegativity.

(17) R. Barker and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 4605 (1961).

Chromosorb W[18] at 275°. The relative proportions of the anomeric methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranosides were estimated by means of peak areas and the data obtained are presented in Table I.

The β anomer 11 (25.5 mg) was treated in precisely the same manner, the precipitated *p*-nitrobenzoic acid being removed by filtration after 45 min. The approximate pseudo-first-order rate constants cited in the text were derived from the equation, $k = 1/t \ln (\alpha_0 - \alpha_\infty)/(\alpha_t - \alpha_\infty)$.

Anomeric 2-*O*-Benzyl-1,3,5-tri-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (14 and 15).—2-*O*-Benzyl-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl chloride[1] (**3**, mp 110–113°, $[\alpha]^{20}D$ +71° in CH_2Cl_2, 1.5 g) was dissolved in dry benzene (40 ml) and silver *p*-nitrobenzoate (6 g) was added to the solution. The mixture was stirred in the dark for 1 day; more silver *p*-nitrobenzoate (3 g) and benzene (20 ml) were added and stirring was continued for a second day. Tlc (5:1 benzene–ether) then showed the presence of the β-D ester **15** as the major component; a substantial amount of **13** and some of the α-D ester **14** were also detected. The mixture was filtered and the residue was washed with benzene. The combined filtrate and washings were concentrated, and the residue was stirred with a suspension of silver *p*-nitrobenzoate (6 g) in dichloromethane (70 ml). After removal of the solid material by filtration, the solution was concentrated to a syrup which was subjected to preparative tlc with 5:1 benzene–ether. After two passes of the solvent front, the slower moving component, 2-*O*-benzyl-1,3,5-tri-*O*-*p*-nitrobenzoyl-β-D-arabinofuranose (**15**), was obtained in pure form: 230 mg (12.4%); mp 177–181°; $[\alpha]^{20}D$ −28.1° (c 1.3, CH_2Cl_2). The nmr spectrum of the substance (in $CDCl_3$ at 60 MHz) included a doublet ($J_{1,2}$ = 2 Hz) centered at τ 3.35.

Anal. Calcd for $C_{33}H_{25}N_3O_{14}$ (687.58): C, 57.64; H, 3.66; N, 6.11. Found: C, 57.83; H, 3.87; N, 6.11.

After extraction from the silica gel, the faster moving component (290 mg) was rechromatographed on a column of silica gel with 5:1 benzene–ether. A solution of the chromatographically homogeneous product in dichloromethane was decolorized with carbon and the material was then recrystallized from 1:1 dichloromethane–ether: 160 mg (8.1%); mp 186–189°; $[\alpha]^{20}D$ +52.8° (*c* 0.5, CH_2Cl_2). The preparation was chromatographically indistinguishable from the 2-*O*-benzyl-1,3,5-tri-*O*-*p*-nitrobenzoyl-α-D-arabinofuranose (**14**) made earlier.[1] As reported previously,[1] the older preparation had mp 152° and $[\alpha]^{22}D$ +54° (CH_2Cl_2); however, on recrystallization from dichloromethane–ether and seeding with the higher melting form, the older preparation was found to have mp 185–189°. It seems likely that a case of dimorphism was involved here.

Behavior of the Anomeric 2-*O*-Benzyl-1,3,5-tri-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (14 and 15) with Hydrogen Chloride.—A sample (15.1 mg) of **15** was treated with 20 ml of dichloromethane which was 0.17 *N* in HCl. The reaction mixture was stored at 20° and aliquots were withdrawn from time to time. The compounds in these aliquots were separated by tlc in 10:1 benzene–ether; after the chromatograms had been sprayed with 10% sulfuric acid and heated, they were examined with a Joyce "Chromoscan." A series of curves, obtained thus at different sampling times, is shown in Figure 4; from these it is evident that the half-life of the reaction approaches 95 hr. The anomer **14** was examined in similar fashion and also found to react with hydrogen chloride at a very slow rate.

Reaction of the Anomeric 2-*O*-Benzyl-1,3,5-tri-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (14 and 15) with Hydrogen Bromide.—A sample (30.6 mg) of **14** was placed in a 1-dm polarimeter tube and dissolved in dichloromethane (4.0 ml) that was 0.162 *N* in HBr (14.6 mol of HBr/mol of **14**). The optical rotation of the reaction mixture was observed at 20° and the data thus obtained are plotted against time in Figure 2. *p*-Nitrobenzoic acid crystallized from the reaction mixture after 18 min and a 3-drop aliquot of the solution was withdrawn at that time. An excess of sodium methoxide was added to the aliquot and the resulting solution was stored for 5 days at +5°. One drop of glacial acetic acid was added and the solution was evaporated to dryness. The residue was extracted with warm ethyl acetate and the filtered extract was evaporated, the residue thus obtained being treated with Tri-Sil Z.[19] Samples of the trimethylsilylated derivative were subjected to glc on a column (6 ft × 0.25 in. o.d.) of 1% SE-30 on Gas-Chrom P[18] at 150°. A parallel run was carried out with the β anomer **15** (30.7 mg). In this case, crystallization of *p*-nitrobenzoic acid occurred after 14.5 min and an aliquot was withdrawn at that time and treated as already described. The rotational changes shown by **15** under these circumstances are plotted against time in Figure 2 while the analytical results obtained by glc are cited in the introductory part of this paper.

(18) Applied Science Laboratories, Inc., State College, Pa.
(19) Pierce Chemical Co., Rockford, Ill.

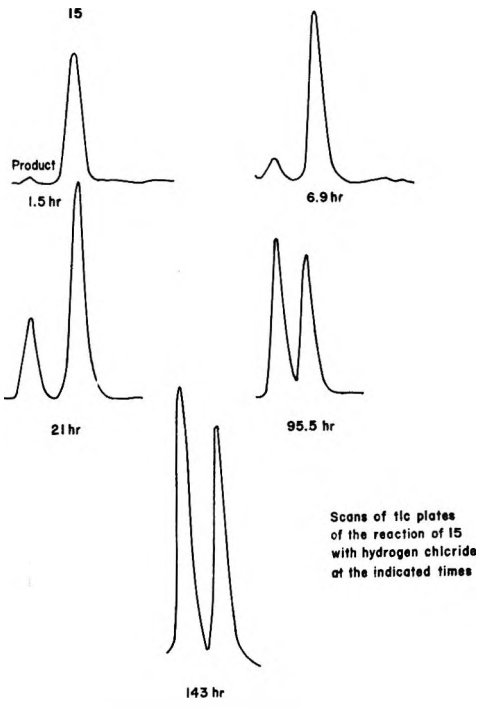


Figure 4.—Scans of thin layer chromatograms of aliquots taken at the indicated times from the reaction of **15** with hydrogen chloride in dichloromethane solution at 20°.

Anomeric Equilibration of 2,3,5-Tri-*O*-benzyl-α-D-arabinofuranosyl Chloride (3) and of 2-*O*-Nitro-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl Bromide under Neutral Conditions.—A sample of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride was prepared from a mixture of **10** and **11** as described in an earlier paper.[5] The syrupy material showed $[\alpha]^{20}D$ +89° (*c* 2.66, CH_2Cl_2) and analysis by treatment with sodium methoxide and subsequent glc as described earlier in this paper indicated that it contained 93.5% of the α anomer **1**. Of this material, 106.5 mg was dissolved in dichloromethane (4 ml) and 3 ml of the resulting solution was diluted with a 1 *N* anhydrous solution (1 ml) of tetrabutylammonium chloride in dichloromethane. The resulting ratio of chloride ion to **1** was 5.5. The optical rotation of the reaction mixture is plotted as a function of time in Figure 3. After 17 min an aliquot was treated with excess of sodium methoxide and then analyzed by glc as described earlier; the data obtained indicated that the original reaction mixture contained 84% of the α anomer **1**. Subsequent analyses over a period of 20 hr showed no further change.

Crystalline 2-*O*-nitro-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl bromide[15] (84.6 mg) was dissolved in dichloromethane to a volume of 5.0 ml. To this solution was added 1.0 ml of anhydrous dichloromethane that was 0.72 *N* in tetrabutylammonium bromide, making the molar ratio of the salt to the glycosyl bromide 4.7. The optical rotation of the solution was observed in a 2-dm tube and data thus obtained were plotted against time as shown in Figure 3.

Registry No.—**10**, 31598-79-5; **11**, 31598-80-8; **14**, 4060-30-4; **15**, 31662-30-3; hydrogen chloride, 7647-01-0; hydrogen bromide, 10035-10-6.

Acknowledgment.—We are indebted to the staff of the Section on Microanalytical Services and Instrumentation of this institute for elemental analyses and nmr spectra.

Mechanism of the Hydrogenation of Butadiene with Cobalt Hydrocarbonyl

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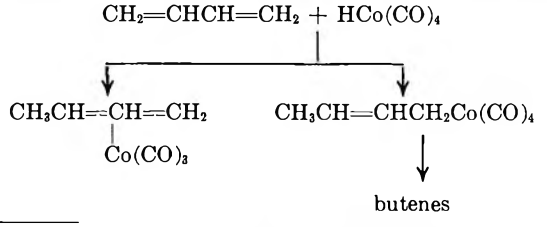
The isomeric *syn*- and *anti*-1-methyl-π-allylcobalt tricarbonyl complexes 1 and 2, respectively, are readily prepared from butadiene and $HCo(CO)_4$. Both of these isolable complexes react with $HCo(CO)_4$ to give, from 1, principally *trans*-2-butene and, from 2, 1-butene and *cis*-2-butene. However, the distribution of butenes obtained directly from butadiene and $HCo(CO)_4$ cannot be rationalized on the basis of exclusive intermediacy of these complexes. It is proposed that a σ-allyl complex also is an intermediate in the hydrogenation and that it is converted to 1-butene by hydride attack.

Since the time nearly 30 years ago when the hydroformylation reaction was first discovered[1] and recognized as a commercially important process until the present time when more than five billion pounds of oxo products are produced worldwide annually, much effort has been devoted to the possibility of using butadiene as a substrate. The introduction of carbonyl functions at both double bonds by this reaction is of great interest as an inexpensive route to adipic acid and its derivatives. To date the dihydroformylation of butadiene, using the cobalt catalyst system, has not been achieved, although substantial yields can be realized with a rhodium catalyst.[2] The difficulty is that under oxo conditions the diene is hydrogenated to butenes, which then undergo further reaction in a normal hydroformylation to the C-5 products which characterize the reaction. The present paper deals with the mechanism of the reaction between butadiene and stoichiometric quantities of $HCo(CO)_4$, the catalytic intermediate in the conventional high-pressure oxo synthesis.[3]

The stoichiometric reaction between conjugated diolefins and $HCo(CO)_4$ has been studied previously by several groups of workers.[4-12] These studies have been concerned primarily with the formation, isolation, and characterization of the resulting π-methallyl complexes. Only recently has attention been directed to the hydrogenation of butadiene to butenes and a mechanism proposed.[13] It was suggested that the butenes arise from a σ complex derived from 1,4 addition of



$HCo(CO)_4$ to C_4H_6 and that the π-methallyl complex was a by-product rather than an intermediate. Our work shows that the cis σ complex is probably the principal intermediate to 1-butene but also that the π-methallyl complexes are indeed precursors to 1-butene and other butenes as well.

Experimental Section

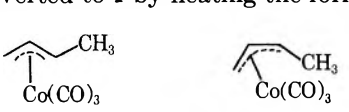
The vapor-phase reactions between C_4H_6 and $HCo(CO)_4$ were carried out at 24–25° in a 2.27-l. reactor and by a technique described elsewhere.[14] The reaction was very rapid and was accompanied by the formation of a brownish liquid on the walls of the reactor. This liquid disappeared during the course of the reaction and is apparently an intermediate. Its structure was not investigated. In liquid-phase reactions a 50-ml flask fitted with a magnetic stirrer and a serum stopper and side arm was first evacuated and 5 ml of decane was introduced by syringe. After introducing carbon monoxide to 1 atm, the flask was cooled, and the desired quantities of 1-pentene, liquid butadiene, and $HCo(CO)_4$ in pentane were introduced. Samples were taken either directly from the gas phase or in an alternate procedure, the volatile material was separated first and then vaporized and sampled for analysis. The reactions of $HCo(CO)_4$ with the π-methallyl complexes were carried out in essentially the same way as described for the liquid-phase hydrogenation of butadiene.

Pure (95%) *syn*-1-methyl-π-allylcobalt tricarbonyl was prepared by treating $Co_2(CO)_8$ with butadiene under oxo conditions at 120°.[15] After several distillations, the purified material was analyzed by nmr and stored at Dry Ice temperature. Yields of 20–30% based on $Co_2(CO)_8$ were obtained.

The preparation of a mixture of *anti*- and *syn*-1-methyl-π-allylcobalt tricarbonyl was achieved by introducing a cold pentane solution of $HCo(CO)_4$ (~9 g) into a cold (Dry Ice) autoclave. A 10 molar excess of liquid C_4H_6 was then added and the autoclave was pressured to 600 psi with carbon monoxide. After standing at room temperature overnight, the gases were vented through a cold trap. Analysis (vpc) showed recovered C_4H_6 and mixed butenes. On cooling the autoclave contents, 6 g of $Co_2(CO)_8$ was precipitated. Vacuum distillation of the mother liquor at room temperature gave about 2.5 g of π complex consisting of 30–35% of 1 and 65–70% of 2. The mixed complexes were stored at Dry Ice temperature. Yields of 20–30% of π complex based on $HCo(CO)_4$ were obtained.

Results and Discussion

The reaction of $HCo(CO)_4$ with C_4H_6 is reported[6] to lead to a mixture of two 1-methyl-π-allyl complexes, 1 and 2. The syn (when CH_3 and H on carbons 1 and 2, respectively, are in the cis configuration) isomer 1 is much more thermally stable than the anti isomer 2; indeed 2 is converted to 1 by heating the former at 120°.[6]



1 2

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TABLE I[a]

REACTIONS OF π-METHALLYL COMPLEXES WITH $HCo(CO)_4$ IN THE PRESENCE OF 1-PENTENE[a]

π-Allyl complex	Increment of $HCo(CO)_4$, mmol	Composition of butenes, % 1-	*cis*-2-	*trans*-2-	Recovered pentenes, % 1-	2-
Syn 1 (95%)	0.58	9.3	8.7	82.0	99	
	0.29	9.7	7.1	83.2	98	2
	0.29	9.8	8.2	82.1	94	6
1 (31%) + 2 (69%)	0.58	25.0	47.2	27.8	99	
	0.29	23.4	47.7	28.9	99	
	0.29	23.5	45.3	31.2	97	3

[a] Reaction conditions: 5 ml of decane, 1.9 mmol of complex, 0.58 mmol of $HCo(CO)_4$ per ml of solution, 2 mmol of 1-pentene, temperature 24–25°, 1 atm of CO.

TABLE II

HYDROGENATION OF BUTADIENE WITH $HCo(CO)_4$ IN THE PRESENCE OF 1-PENTENE

Partial pressure, CO, mm	Temp, °C	Composition of butenes, % 1-	*cis*-2-	*trans*-2-	Recovered pentenes, % 1-	2-
0[a]	25	44.7	29.7	25.6	95.5	4.5
150[a]	25	49.5	24.3	26.2	99+	
300[a]	25	48.2	21.0	30.8	99+	
300[a]	25	49.7	22.1	28.1	99+	
740[b]	−10	43.4	39.1	17.5	99+	
740[b]	0	44.1	35.5	20.6	99+	

[a] Reaction conditions: 2 mmol of $HCo(CO)_4$ in pentane (0.83 mmol per ml); 5 mmol of C_4H_6; 1.6 mmol of 1-pentene. [b] Reaction conditions: 2.5 mmol of $HCo(CO)_4$ in 10 ml of decane, 5 mmol of C_4H_6, 2 mmol of 1-pentene.

The two isomers can be identified readily by their nmr spectra[6,11] and the composition of mixtures of them can be determined from such spectra. In our work, the reaction of $HCo(CO)_4$ with C_4H_6 led to a mixture, which after purification to remove traces of paramagnetic species was analyzed by nmr. The spectrum showed that the mixture consisted of about 30–35% of 1 and 65–70% of 2. When butadiene is treated with $Co_2(CO)_8$ under oxo conditions, analysis (nmr) of the π-methallyl complexes shows that almost pure (95% or more) syn isomer is present.

The hydrogenolysis of the complexes 1 and 2 with $HCo(CO)_4$ was investigated. It is well known that $HCo(CO)_4$ readily isomerizes 1 olefins to 2 olefins.[16] One must therefore exercise extreme caution when deducing initial butene distribution from analysis of the final product. In order to minimize isomerization, it is desirable to have excess butadiene present at all times. In addition, the simultaneous presence of a monitoring olefin such as 1-pentene permits evaluation of the extent of isomerization caused by free $HCo(CO)_4$.

The reaction of pure (95%) syn isomer 1 with C_4H_6 was carried out by adding a total of 1.16 mmol of $HCo(CO)_4$ in pentane in three portions to 1.9 mmol of 1 in 5 ml of decane in the presence of 1-pentene (2.0 mmol) and 1 atm of carbon monoxide. The reaction mixture was sampled from the gas phase after the reaction with each incremental portion of $HCo(CO)_4$ was complete. The results of these experiments and analogous experiments with a mixture of 1 (31%) and 2 (69%) are shown in Table I. In order to make certain that no error was introduced by sampling from the gas phase, in one experiment, the total liquid product was subjected to distillation. The distillate was vaporized, collected, and analyzed (vpc). This analysis of the butene fraction showed a composition essentially identical with that from the vapor-phase sample.

Because of the very rapid reaction between the π complexes and $HCo(CO)_4$ to give butenes, the standard procedures reported for the preparation of such complexes should also produce butenes. As a matter of fact, the yield of complexes is generally low. In order to demonstrate that conditions that usually are employed for the formation of the π-allyl complexes also produce butenes, 14 g of $Co_2(CO)_8$ was transformed to $HCo(CO)_4$ by the standard procedure[17] and treated with 30 g of C_4H_6 as described in the Experimental Section. In addition to recovered C_4H_6, substantial quantities of butenes were found. The mixed butenes consisted of 41.2% 1-butene, 31.0% *cis*-2-butene, and 27.8% *trans*-2-butene. Approximately 6 g of $Co_2(CO)_8$ and 2.5 g of mixed 1-methyl-π-allyl complexes were formed.

Since we know the isomer distribution obtained from treating pure (95%) 1 with $HCo(CO)_4$ and the isomer distribution resulting from similar treatment of mixed 1 and 2 of known composition, we may estimate the isomer distribution expected from pure 2

$$1 \longrightarrow \begin{array}{ll} \text{trans} & C{-}C{=}C{-}C\ 86\% \\ \text{cis} & C{-}C{=}C{-}C\ 6\% \\ & C{=}C{-}C{-}C\ 8\% \end{array}$$

$$2 \xrightarrow{\text{(calcd)}} \begin{array}{ll} \text{cis} & C{-}C{=}C{-}C\ 65\% \\ & C{=}C{-}C{-}C\ 35\% \end{array}$$

With the knowledge of the behavior of 1-methyl-π-allyl complexes toward $HCo(CO)_4$, the hydrogenation of C_4H_6 with $HCo(CO)_4$ was now carried out. The results of the gas-phase studies are shown in Table II. The principal advantage of the gas-phase technique is control of the partial pressure of carbon monoxide and elimination of solvation effects. The data in Table II show that the carbon monoxide partial pressure has relatively little effect on product distribution. The liquid-phase reaction gave somewhat similar results (last two lines of Table II).

The hydrogenation of butadiene with $HCo(CO)_4$ in the gas phase and in the presence of carbon monoxide yields a mixture of butenes consisting of approximately

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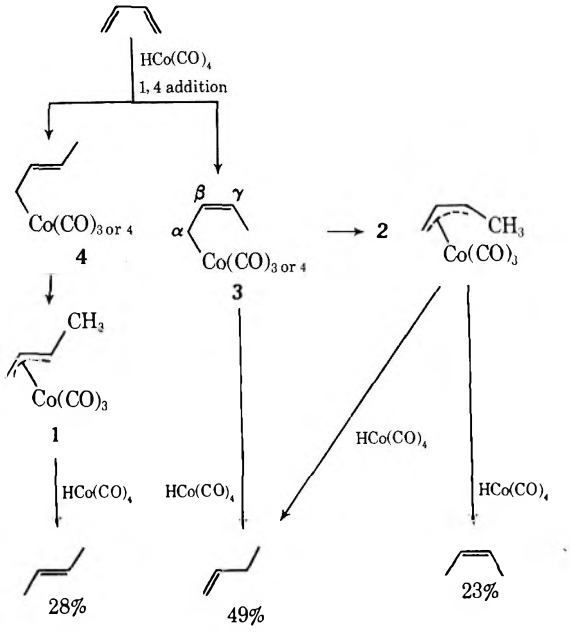
CHART I

A SCHEME FOR THE HYDROGENATION OF BUTADIENE WITH $HCo(CO)_4$



49% 1-butene, 23% *cis*-2-butene, and 28% *trans*-2-butene. Although we have shown that the π-allyl complexes 1 and 2 are both directly converted to butenes, the distribution of products from the butadiene reaction cannot be explained by the intermediacy of only these two complexes; another complex leading directly to 1-butene is required. This may very well be the σ complex **3** (Chart I), a precursor to **2**. The various reactions of importance which best explain the results are shown in Chart I. We believe that hydride attack at the γ carbon atom of intermediate **3**, accompanied by bond migration and elimination of cobalt, produces 1-butene almost exclusively. An analogous reaction with the complex **4** probably is repressed by steric factors, and hence **4** is rapidly converted to **1**, which yields *trans*-2-butene almost exclusively. Because attack of $HCo(CO)_4$ on **1** provides little 1-butene, it is also reasonable to assume that such attack on **4** is similarly ineffective in giving 1-butene while **3** is much more exposed to a γ attack. Analogous explanations have been used to explain product distribution from butadiene in the $[Co(CN)_5H]^{3-}$ system.[18] A σ complex arising from 1,2 Markovnikov addition is also a possible intermediate leading to 1-butene.

Although Chart I outlines what we consider to be the principal reactions, it must be kept in mind that equilibria probably exist between many of the species and that the number of coordinated carbon monoxides is variable.

Registry No.—**1**, 31627-44-8; **2**, 31627-45-9; butadiene, 106-99-0; cobalt hydrocarbonyl, 17186-02-6; 1-pentene, 109-67-1.

Acknowledgment.—The authors are grateful to the donors to the Petroleum Research Fund administered by the American Chemical Society for the support which made this work possible.

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Peroxyacetic Acid Oxidation of 4-Methylphenols and Their Methyl Ethers[1]

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Received March 1, 1971

The peroxyacetic acid oxidations of 4-methylpyrocatechol, 4-methylveratrole, *p*-cresol, *p*-methylanisole, 2-methoxy-*p*-cresol, and 4-methyl-*o*-benzoquinone were investigated in aqueous acetic acid at 25°. In all cases, *cis,trans*-β-methylmuconic acid and the related lactones γ-carboxymethyl-β-methyl-$\Delta^{\alpha,\beta}$-butyrolactone and γ-carboxymethyl-γ-methyl-$\Delta^{\alpha,\beta}$-butyrolactone were produced. With the exception of 4-methyl-*o*-benzoquinone, the substrates all produced γ-carboxymethyl-γ-hydroxy-β-methyl-$\Delta^{\alpha,\beta}$-butyrolactone. This product was suggested to arise from electrophilic hydroxylation ortho to the methyl substituent and para to an oxygen-bearing substituent followed by aromatic ring cleavage and lactonization. Similar hydroxylation was evident in the formation of 4-hydroxy-4-methyl-2,5-cyclohexadienone from *p*-eresol and *p*-methylanisole. 4-Methylveratrole and *p*-methylanisole each gave 2-methoxy-5-methyl-*p*-benzoquinone as a major product. This product was slowly oxidized in the presence of excess peroxyacetic acid. Although the combined yields of identified products were low, stoichiometry data on oxidant and substrate consumption for the unmethylated compounds agreed with that predicted on the basis of the products formed. Higher than predicted ratios of oxidant consumed/substrate consumed were found for the methylated substrates. The results can be accounted for on the basis of competitive pathways involving hydroxylation at activated ring positions, demethoxylation, ortho and para quinone formation, and aromatic ring cleavage.

Hydroxylation appears to be an important result of reactions between peroxy acids and many aromatic compounds. Thus, oxidation of *m*-xylene by trifluoroperoxyacetic acid gave 2,4- and 2,6-xylenol along with the corresponding *p*-quinone.[2] Oxidation of phenol by peroxyacetic acid is known to produce *p*-benzoquinone and muconic acid;[3-5] apparently, initial para and ortho hydroxylation are followed by further oxidation to the para quinone and the muconic acid, respectively. Peroxyacetic acid was reported to convert *p*-cresol to *cis,trans*-β-methylmuconic acid and a related lactone.[3,6] The muconic acid derivatives have also been reported

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TABLE I
PRODUCT YIELDS

Substrate	Reaction, %	Reaction time, hr	Product yield, % of theoretical: Muconic acids[a]	γ-Hydroxy lactone	p-Quinone	Dienone	2-Hydroxy-p-methylanisole	Total[a]
I	100	2–40	42 (56)	5				47 (61)
II	84	30	9 (13)	1	17			27 (31)
III	72	60	23 (32)	4		12		39 (48)
IV	25	40	8 (12)	2		22	6	38 (42)
IV	45	72	8 (15)	2	16	16	2	44 (51)
V	85	24	11 (20)	13				24 (33)
XI	100	0.1	70 (70)					70 (70)
XI	100	26	41 (55)					41 (55)

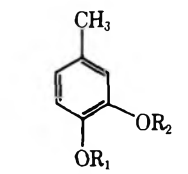
[a] The yield given in parentheses includes the identified acids and unidentified components believed to be isomeric acids; their amounts were approximated by the glc analysis.

as products from similar oxidations of pyrocatechol and 4-methylpyrocatechol.[4,6,7]

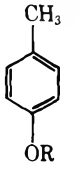
Somewhat similar findings have been reported for phenyl ethers. *p*-Quinones have been observed as products, although yields were low and water-soluble reaction products were not investigated.[8,9] Oxidation of 4-methylveratrole with peroxyacetic acid has been shown to give 2-methoxy-5-methyl-*p*-benzoquinone, which clearly involves demethylation.[9] Few well-defined examples of ring cleavage (muconic acid formation) induced by peroxy acid oxidation of phenyl ethers exist. Peroxybenzoic acid oxidized veratrole to dimethyl muconate[8] in 1% yield; naphthyl and phenanthryl methyl ethers underwent cleavage of the oxygenated ring,[10,11] producing carboxylic acids.

From investigations of peroxy acid oxidations of phenolic systems which have been carried out thus far, it is clear that these reactions are complex. *p*-Quinone and muconic acid formation have been observed, but the yields have generally been low. A clearer understanding of the course of such oxidations should ultimately lead to a better understanding of a much more complex situation, namely, oxidative delignification of wood. Peroxyacetic acid is known[12–16] to react with and solubilize the lignin (which contains phenolic and phenyl ether moieties) of certain wood species. It is clear that the oxidation can be quite selective in that very little carbohydrate material is oxidized; this is in marked contrast to conventional sulfur-based pulping procedures where dissolution of comparable amounts of lignin and carbohydrate occur. Evidence has been found that ring cleavage and demethylation do occur in peroxyacetic acid delignification.[17–20]

This study focused primarily on identification of reaction products, estimation of their amounts, and reaction stoichiometry in the peroxyacetic acid oxidations of 4-methylpyrocatechol (I), 4-methylveratrole (II), *p*-cresol (III), and *p*-methylanisole (IV). In addition, it was possible to obtain evidence for the existence of certain intermediates. All oxidations were carried out with a 3:1 mole ratio of oxidant to substrate in 10% peroxyacetic acid in aqueous acetic acid (17% by water weight) at room temperature. Reaction times depended on substrate reactivity and ranged from a few minutes to several days.



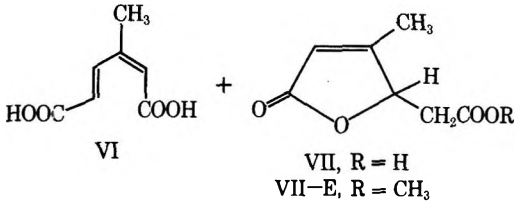
I, $R_1 = R_2 = H$
II, $R_1 = R_2 = CH_3$
V, $R_1 = H$; $R_2 = CH_3$
XIV, $R_1 = CH_3$; $R_2 = H$



III, R = H
IV, R = CH_3

Results and Discussion

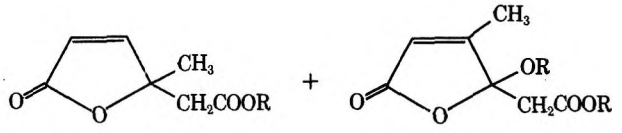
Table I includes the oxidation products formed and their yields. The common feature of all of the oxidations studied is the finding of "muconic acids." This term includes *cis,trans*-β-methylmuconic acid (VI) and the two five-membered-ring lactones (VII and VIII) isomeric with VI. Aromatic ring cleavage, therefore, is an important mode of reaction regardless of whether there is initially one oxygen on the ring or two. Methoxyl groups clearly do not prevent ring cleavage,



VI

VII, R = H
VII–E, R = CH_3

I →



VIII, R = H
VIII–E, R = CH_3

IX, R = H
IX–E, R = CH_3

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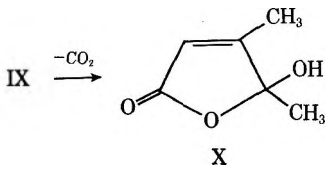
although *p*-quinone formation is competitive in these cases.

In the oxidation of 4-methylpyrocatechol, the dominant result is ring cleavage giving VI, along with related lactones γ-carboxymethyl-β-methyl-$\Delta^{\alpha,\beta}$-butyrolactone (VII) and γ-carboxymethyl-γ-methyl-$\Delta^{\alpha,\beta}$-butyrolactone (VIII).

Formation of VIII cannot result from VI because of the latter's cis,trans stereochemistry. Undoubtedly, the relatively unstable[6] *cis,cis*-β-methylmuconic acid is formed initially and is isomerized partly to the cis,trans acid and partly to VIII as well as other isomers (see Table I, footnote *a*). Earlier work[6] has shown both VI and VII to be formed, but the γ-methyl lactone (VIII) was not previously reported. The structural assignment is strongly supported by nmr and mass spectral data of the monomethyl ester (VIII-E). The doublets (J = 5.5 Hz) at δ 6.03 and 7.65 support cis vinyl protons, since known $\Delta^{\alpha,\beta}$-butyrolactone gives virtually the same chemical shifts for its vinyl protons. The $-CH_2-$ group appears as an AB pattern in contrast to the ABX pattern so clearly revealed in VII-E; the δ values are 2.70 and 2.92 for VIII-E and 2.63 and 2.84 for VII-E. The mass spectrum verified the molecular weight of VIII-E and also showed the fragmentation expected from such a structure. The base peak at *m/e* 97 must arise from loss of $-CH_2COOCH_3$ from the parent ion (*m/e* 170). A similar loss of the side chain was observed in the mass spectrum of VII-E and, indeed, this is common for lactones.[21,22]

The other product of 4-methylpyrocatechol oxidation found in this study was γ-carboxymethyl-γ-hydroxy-β-methyl-$\Delta^{\alpha,\beta}$-butyrolactone (IX). This product gave a dimethyl derivative IX-E, which gave nmr and mass spectra strongly supporting the assigned structure. The β-methyl group and the α-vinyl proton showed, as expected, signals very similar to the corresponding β-methyl lactone (VII-E) signals. The $-CH_2-$ group appeared as an AB pattern rather than an ABX as in VII-E. Again, the base peak at *m/e* 127 in the mass spectrum of IX-E was indicative of loss of a $-CH_2COOCH_3$ side chain from the parent ion (*m/e* 200). Loss of $-OCH_3$ was also suggested by a peak at *m/e* 169. It was discovered that IX readily decarboxylates on the gas chromatograph giving β,γ-dimethyl-γ-hydroxy-$\Delta^{\alpha,\beta}$-butyrolactone (X). The nmr spectrum strongly supports this structure assignment.



X

The stoichiometry (moles of peroxy acid consumed/moles of substrate consumed) results are shown in Table II. Also shown are predicted stoichometries which were derived on the basis of the structures and amounts of the products formed. The agreement between predicted and experimental stoichiometries in the 4-methylpyrocatechol oxidation was excellent. Since the γ-hydroxy lactone (IX) required 3 mol of oxidant per 1 mol of the catechol (I), a slight excess consumption of oxidant above 2.0 was expected.

TABLE II

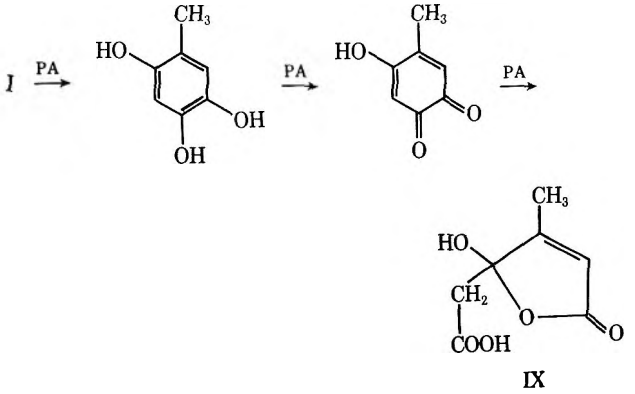
OXIDATION STOICHIOMETRY

Substrate	Reaction, %	Stoichiometry[a] Exptl	Stoichiometry[a] Predicted
I	100	2.1	2.1
II	18	2.2	
II	80	2.9	2.0
III	40	2.8	
III	60	2.8	2.6
IV	8	1.7	
IV	45	3.0	2.3
V	85	3.0	2.4
XI	100	1.0	1.0

[a] Moles of oxidant consumed/moles of substrate consumed.

Further insight into the course of the oxidation of I was sought through an oxidation of 4-methyl-*o*-benzoquinone (XI). Since *o*-quinones have been implicated by others[4,23-27] as precursors to muconic acids in a variety of systems, it seemed reasonable that XI was an intermediate here in the formation of β-methylmuconic acid (VI) and the isomeric lactones (VII, VIII). This view was supported by the fact that peroxyacetic acid oxidation of XI gave VI, VII, and VIII in essentially the same distribution observed in the oxidation of I. In addition, at least three unknown acids are also formed in the same relative amounts from both I and XI. It is also noteworthy that the γ-hydroxy lactone (IX) was not produced from the *o*-quinone (XI).

From the above, it would appear that there are two competitive oxidation pathways involved in the 4-methylpyrocatechol oxidation: (1) conversion to the *o*-quinone XI followed by oxidation to the muconic acid products (VI, VII, and VIII); and (2) hydroxylation (effectively electrophilic attack of OH^+ donated by PA)[28] at the 5 position of 4-methylpyrocatechol followed by ring cleavage and lactonization to IX as shown below. It can further be argued that such ring hydrox-



IX

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(28) Evidence that peroxy acid hydroxylation is the result of electrophilic attack by OH^+ (although OH^+ is probably not a discreet intermediate) and not the hydroxyl radical has been summarized by Norman and Smith.[27] We found no evidence for a free-radical process in experiments where methyl methacrylate was added to the oxidation system.

ylation should be more competitive if *o*-quinone formation is hampered by the need for prior demethylation. A test case was 2-methoxy-*p*-cresol (V). Here, indeed, the yield (Table I) of the γ-hydroxy lactone was more than twice that found in the catechol oxidation. Demethylation did occur, and the usual distribution of muconic acids (VI, VII, VIII) was observed.

In agreement with earlier work[9] 4-methylveratrole (II) was found to give 2-methoxy-5-methyl-*p*-benzoquinone (XII) as a major product of peroxyacetic acid oxidation. However, the present work has further shown that ring cleavage to muconic acids also occurs and that a small amount (1%) of the γ-hydroxy lactone (IX) is produced. The overall yield of products (Table I) was quite low, and this was reflected in the observed stoichiometry (Table II), which showed a substantially higher oxidant consumption than was predicted. The stoichiometry was found to increase as the reaction of 4-methylveratrole proceeded. This finding prompted a study of the stability of the known reaction products to further oxidation. Neither the muconic acid (VI) nor the β-methyl lactone (VII) consumed any significant amount of peroxyacetic acid in control experiments. The *p*-quinone (XII) was shown to be slowly oxidized, consuming 1.0 mol of oxidant per 1 mol of XII; product analysis was unsuccessful. It is doubtful that the increasing stoichiometry in the oxidation of 4-methylveratrole can be entirely accounted for by further oxidation of the *p*-quinone because the rate of that secondary oxidation would appear to be too slow.

The results of the 4-methylveratrole study show considerable similarity to the other dioxygenated substrates (I, XI, V). The following scheme emphasizes the previously discussed competitive pathways involving *o*-quinone formation and C-5 hydroxylation of the ring.

TABLE III

RELATIVE REACTIVITY OF SUBSTRATES[a]

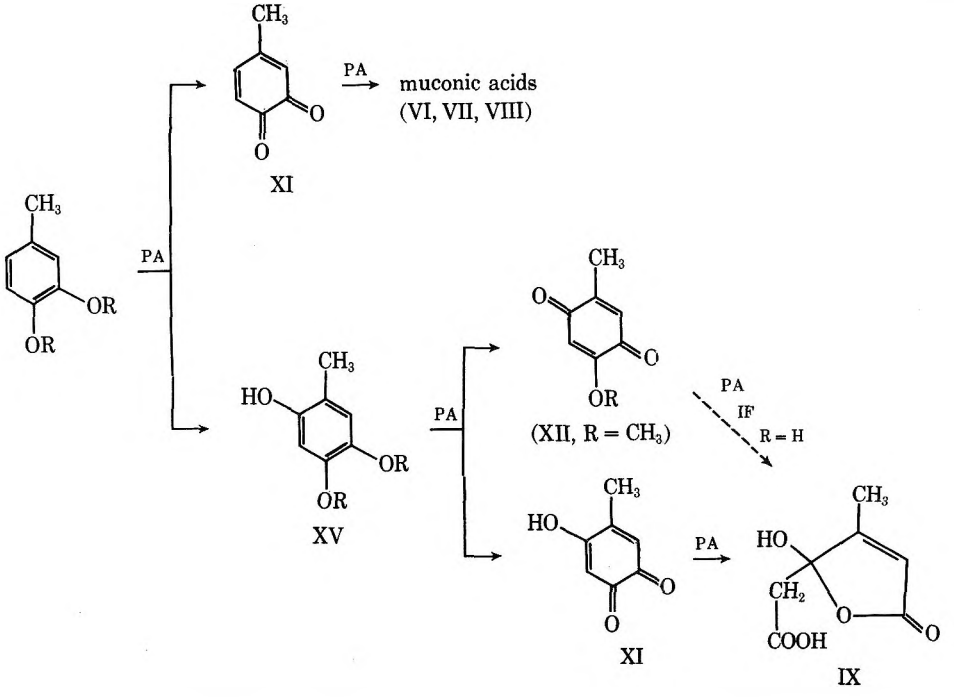
Substrate	Half-life, hr[b]	Substrate	Half-life, hr[b]
4-Methyl-*O*-benzoquinone (XI)	0.01	4-Methylveratrole (II)	5
4-Methylpyrocatechol (I)	0.2	*p*-Cresol (III)	25
2-Methoxy-*p*-cresol (V)	4.0	*p*-Methylanisole (IV)	100

[a] Conditions: 10% peroxyacetic acid, 3:1 mole ratio favoring oxidant, 25°. [b] Time required for disappearance of 50% of substrate.

pear to substantially alter the reaction pathways involved, they do retard the oxidation rate considerably (Table III). 4-Methylpyrocatechol is consumed about 20 times faster than either 4-methylveratrole (II) or 2-methoxy-*p*-cresol (V).

The above proposed reaction pathways place considerable emphasis on hydroxylation of the initial reactant to give an intermediate (XV). This proposed intermediate has not been studied independently or isolated during the reaction (it is probably too reactive); it is inferred as a reasonable hypothesis on the basis of the products. Further support that ring hydroxylation can occur in the oxidant system was obtained by showing that mesitylene (1,3,5-trimethylbenzene) was oxidized to hydroxymesitylene along with other products. More directly, evidence was obtained that 2-hydroxy-*p*-methylanisole (XIV) was an intermediate in the oxidation of *p*-methylanisole (IV) (discussed in greater detail below).

The oxidations of *p*-cresol (III) and *p*-methylanisole (IV) are very similar to the oxidations described above in the sense that ring cleavage to muconic acids is important (Table I). The *p*-quinone (XII) results from IV as it did from II. Hydroxylation ortho to the oxygen-containing substituent can provide a precursor for *o*-quinone formation and, ultimately, muconic acid systems. In the case of IV, this was clearly seen by our ability to detect 2-hydroxy-*p*-methylanisole (XIV) as a

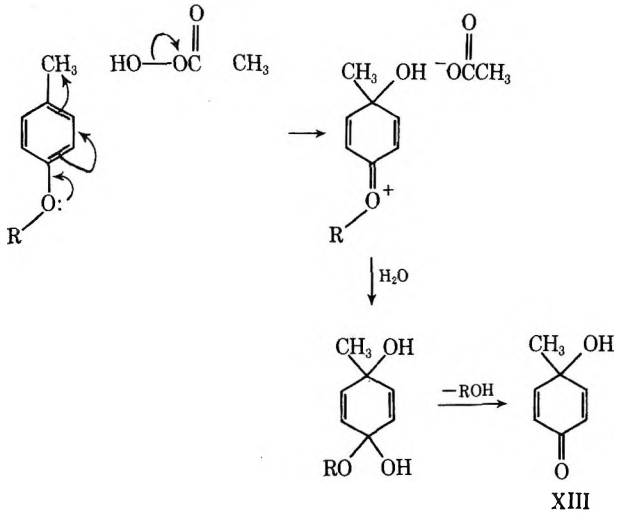


This latter pathway can lead either to the *p*-quinone (XII) or to the γ-hydroxy lactone (IX) depending on the retention of the C-1 methoxyl group. The mechanism of demethylation is not known, but may well involve displacement of methoxy by hydroxyl *via* a hemiacetal intermediate. Although methoxyl groups do not ap-

product. In numerous experiments, its yield was always lower (2 *vs.* 6%) at 45–55% reaction (of IV) than at 25% reaction. Thus, it is considered as a probable intermediate in the formation of muconic acids, *p*-quinone (XII), and γ-hydroxy lactone (IX). Similarly, 4-methylpyrocatechol (I) may well be one of the intermediates in the oxidation of *p*-cresol (III) although its reaction rate would be much too great to permit identification. This idea is supported by the finding that catechol is a probable intermediate in the peroxyacetic acid oxidation of phenol.[27]

Along with ortho hydroxylation in these substrates bearing a single oxygen, it is also clear that para hydroxylation occurs. Both III and IV gave 4-hydroxy-4-methyl-2,5-cyclohexadienone (XIII) in relatively large amounts. This compound has been previously reported as a product of aqueous hydrogen peroxide oxidation of *p*-cresol.[29] (It is not believed that hydrogen peroxide is an active oxidant under the conditions of this study because its concentration was kept below 0.3%.) The assignment of structure XIII was supported by ir, nmr, and mass spectra. The infrared spectrum agrees very well with spectra previously reported for cyclohexadienones.[30] The plane of symmetry in the molecule is clearly evident from the pair of doublets (J = 10 Hz) for the vinyl protons at δ 6.13 and δ 6.95 which each contain *two* identical protons; in addition, the methyl group appears as a singlet at δ 1.48. The mass spectrum gives a base peak (*m/e* 109) corresponding to loss of $-CH_3$. The peaks at *m/e* 81 and 96 may both arise by loss of carbon monoxide from the *m/e* 109 ion and the parent ion (*m/e* 124), respectively. In the latter case, the molecular ion probably undergoes ring opening with methyl migration to the adjacent carbon (a fairly common event in similar systems)[31] prior to elimination of CO.

The dienone can be visualized to form from either *p*-cresol or *p*-methylanisole as shown (where R = H or CH_3). The peroxyacetic acid acts as a donor of OH^+



XIII

to an aromatic nucleus activated for electrophilic attack. Subsequent reaction of the intermediate with water can then lead to demethoxylation of *p*-methylanisole.

The stoichiometry results from *p*-cresol oxidation are in reasonable agreement with the results predicted. This is not the case for *p*-methylanisole. In fact, all three methylated substrates (II, IV, and V) brought about higher oxidant consumption than could be predicted on the basis of identified products. Time dependence of stoichiometry was observed for the methylated substrates II and IV, but it was not observed for the unmethylated reactants (I and III). In view of the low yields of identified products, it is difficult to explain this difference. Further oxidation of the *p*-quinone (XII) which is formed only from II and IV, may be partly responsible, but, as was pointed out above, the rate of oxidation of XII does not appear great enough to account entirely for the experimental stoichiometries. Thus, some other unknown oxidative process probably contributes with the methylated systems. In the case of unmethylated systems where experimental stoichiometries agree with calculated values, the products unaccounted for may well arise from side reactions of intermediates and reaction products with each other. Some possibilities would include Diels–Alder reactions of quinones and possibly a reaction of the intermediate *o*-quinone with 4-methylpyrocatechol in a manner somewhat analogous to reaction of catechol with *o*-benzoquinone.[27]

Control experiments showed that 80–85% of the β-methyl lactone (VII) could be recovered after being subjected to the entire work-up procedure. However, only 47% of *cis,trans*-β-methylmuconic acid could be recovered (in the form of β-methyl lactone VII) when subjected to the work-up procedure.

Experimental Section

Analytical Methods.—Infrared spectra were determined using either a Perkin-Elmer Model 21 (prism) or a Model 621 grating spectrophotometer. A beam condenser was used for microsamples. A Varian Associates A-60A spectrometer equipped with a spin decoupler was used for the nmr spectra; tetramethylsilane and sodium 2,2-dimethyl-2-silapentane-5-sulfonate were used as internal standards in deuteriochloroform or deuterium oxide, respectively. Small quantities were analyzed using a semimicro sample tube (125 μl). Complex signals such as ABX patterns were analyzed by the procedure described by Garbisch.[32] Mass spectra were determined by Morgan–Schaffer Corp., Montreal, Canada using a Hitachi RMU-6D mass spectrometer. Low voltage spectra allowed confirmation of suspected parent ion peaks. Intensities were approximated by measuring peak heights.

A Varian Aerograph Moduline 202-C dual column gas chromatograph with a linear temperature programmer and thermal conductivity detector was used for glc. The following glc columns were employed: column A was a 5 ft × 0.25 in. o.d. stainless steel tube, packed with 15% Carbowax 20M on 60/80 mesh Chromosorb W (DMCS treated, acid washed); column B was a 5 ft × 0.25 in. o.d. stainless steel tube packed with 20% SE-30 on 60/80 Chromosorb W (DMCS treated, acid washed); column C was a 6 ft × 0.375 in. o.d. stainless steel tube packed with 15% Carbowax 20M on Chromosorb W (DMCS treated, acid washed).

Column A was used for separation of reactants, volatile reaction products, and methyl ester derivatives of carboxylic acids. Column B was used for analysis of 2-methoxy-5-methyl-*p*-benzoquinone (125°, 75 ml/min He) and all silylated carboxylic acids (165°, 75 ml/min). Column C was used for collecting oxidation products. Internal standards were selected for quantitative analyses, and response factors were measured; peak areas were determined by a Technicon Model AAG integrator/calculator.

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Chemicals.—Most of the compounds were purchased including *p*-methylanisole, *p*-cresol, 4-methylpyrocatechol, 4-methylveratrole (all from K & K Laboratories, Inc.), mesitylene (Aldrich Chemical Co.), and 2-methoxy-*p*-cresol (Eastman Organic Chemicals). These were all checked for purity by glc and were used without further purification.

4-Methyl-*o*-benzoquinone was prepared by oxidation of 4-methylpyrocatechol with tetrachloro-*o*-benzoquinone.[33] The product was washed with dry ether and stored over phosphorus pentoxide. The structure was confirmed by infrared and nmr analysis.

γ-Carboxymethyl-β-methyl-$\Delta^{\alpha,\beta}$-butyrolactone (VII) was prepared by reaction of concentrated sulfuric acid with 2-nitro-*p*-cresol.[34] The extracted product was recrystallized twice from water and once from ethanol–benzene (1:3) giving colorless crystals: mp 126.2–128.0° corrected (lit.[34] mp 130°); ir (KBr) 2580 (broad, carboxyl OH), 1730 (vs), 1687 (vs, C=O), 1640 cm^{-1} (m, C=C); nmr (D_2O) δ 2.04 (doublet of doublets, 3 H, J = 1.5, 0.8 Hz, β-CH_3), 2.68 (doublet of doublets, 1 H, J = 16.5, 8.4 HCH in an ABX pattern), 3.13 (doublet of doublets, 1 H, J = 16.5, 3.6 Hz, HCH in an ABX pattern), 5.43 (multiplet, 1 H, J = 8.4, 3.6, 0.8 Hz, γ H in an ABX pattern), and 6.00 ppm (quintet, 1 H, J = 1.5 Hz, α-vinyl H).

Methylation of the acid with 5% methanolic HCl followed by preparative glc on column C gave the methyl ester of γ-carboxymethyl-β-methyl-$\Delta^{\alpha,\beta}$-butyrolactone (VII-E) as an oil: ir (neat) 1760 (vs), 1740 (vs, broad, C=O), 1642 cm^{-1} (m, C=C); nmr ($CDCl_3$) δ 2.10 (multiplet, 3 H, β-CH_3), 2.63 (doublet of doublets, 1 H, J = 16.5, 7.7 Hz, HCH in an ABX pattern), 2.84 (doublet of doublets, 1 H, J = 16.5, 4.3 Hz, HCH in an ABX pattern), 3.77 (s, 3 H, ester CH_3), 5.25 (m, 1 H, γ H in an ABX pattern), and 5.86 ppm (m, 1 H, α-vinyl H); mass spectrum (70 eV) *m/e* (rel intensity) parent ion 170 (20), 139 (14), 111 (30), 110 (78), 97 (93), 69 (100), 68 (38).

Peroxyacetic acid was prepared by the hydrogen peroxide oxidation of acetic acid with sulfuric acid catalyst.[35] The reaction mixture was distilled giving a final solution containing approximately 35% peroxyacetic acid, 0.1% hydrogen peroxide, 5% acetic acid, and 60% water. This solution was stored at 5°. All glassware that came in contact with peroxyacetic acid was first passivated by soaking with detergent, sodium hydroxide, nitric acid, and hydrogen peroxide with distilled water rinses between each soaking treatment.[35]

General Procedure for Oxidations.—The stock solution of peroxyacetic acid (~35%) was diluted to 10% weight concentration by glacial acetic acid. The substrate (12 mmol) was dissolved in 25 ml (27 g) of 10% peroxyacetic acid (36 mmol), and the oxidation was allowed to proceed in a constant-temperature bath at 25°. The oxidations were run in the dark, but oxygen was not excluded. Use of freshly prepared peroxyacetic acid kept the hydrogen peroxide concentration below 0.3%. Aliquots (1.0 ml) were removed for stoichiometry determinations, and the unreacted peroxyacetic acid and hydrogen peroxide were analyzed by an iodimetric procedure;[36] unreacted substrate was measured by glc using an internal standard. Control runs without substrate allowed estimation of the decomposition of peroxyacetic acid so that the appropriate correction could be made in stoichiometry calculations; this correction only amounted to 10% of the initial oxidant concentration after 48 hr.

The oxidations were stopped at various times by addition of acetaldehyde (15 ml) to reduce the remaining oxidant. The reaction mixture was then neutralized, under a stream of nitrogen, to pH 8 (sodium carbonate), and the neutral products were removed by extraction (ether). The remaining alkaline layer was acidified (pH 2, HCl) and concentrated *in vacuo* at 50° to dryness; water was added; and the concentration was repeated to remove as much acetic acid as possible. The resulting product mixture was dissolved in a minimum of distilled water and extracted by ether in a continuous extractor for 24 hr to obtain an ether solution of the acidic products.

The dried ($MgSO_4$) ether extract containing the neutral products was then concentrated to about 10 ml and analyzed directly by glc with column A at 120 ml/min He and temperature programming from 100 to 160° at 2 deg/min. The ether extract containing the acidic products was dried ($MgSO_4$) and concentrated, and the resulting yellow syrup was silylated[37] with bis(trimethylsilyl)trifluoroacetamide (Regisil, Regis Chemical Co.). Glc analysis was performed with column B (165°, 75 ml/min He) using the TMS derivative of adipic acid as the internal standard. The acidic products were methylated (5% HCl in methanol) to permit collection of the pure methyl esters from column C.

4-Methylpyrocatechol Oxidation.—4-Methylpyrocatechol (I) was oxidized by the general procedure described above except that the reaction solution was initially cooled due to the exothermic nature of the oxidation. The reaction was complete within 1 hr. A precipitate which was formed during the reaction was identified as *cis,trans*-β-methylmuconic acid (VI, 2%): mp 179–182° (lit. mp 178–179°[4], 179°[6]); ir (KBr) 2680 (m), 2590 (m) (broad, carboxyl OH), 1685 (vs, C=O), 1623 (ms), 1594 cm^{-1} (ms, C=C); nmr (dimethyl-d_6 sulfoxide) δ 2.04 (d, 3 H, J = 1.5 Hz, β-CH_3), 6.00 (m, 1 H, J = 1 Hz, α-vinyl H), 6.18 (doublet of doublets, 1 H, J = 16, 1 Hz, α′-vinyl H), 8.48 (doublet of doublets, 1 H, J = 16, 1 Hz, β′-vinyl H), and *ca.* 12.1 ppm (very broad, -COOH).

The other products found were all carboxylic acids, and they were isolated by preparative gas chromatography of their methyl esters. Yields reported are average values, and were determined by glc analysis of the trimethylsilyl derivatives. The major product was γ-carboxymethyl-β-methyl-$\Delta^{\alpha,\beta}$-butyrolactone (VII, 36%); its identity was established by comparison of the infrared and nmr spectra of its methyl ester derivative with the corresponding spectra of the methyl ester of the authentic lactone acid. The methyl ester of γ-carboxymethyl-γ-methyl-$\Delta^{\alpha,\beta}$-butyrolactone (VIII-E, 4%) was also collected by glc and was identified by spectral data: ir (neat) 1755 (s, C=O), 1610 (w, C=C), 820 cm^{-1} (m, *cis*-HC=CHC=O); nmr ($CDCl_3$) δ 1.57 (s, 3 H, γ-CH_3), 2.70 (d, 1 H, J = 15.5 Hz, HCH in an AB pattern), 2.92 (d, 1 H, J = 15.5 Hz, HCH in an AB pattern), 3.68 (s, 3 H, ester CH_3), 6.03 (d, 1 H, J = 5.5 Hz, α-vinyl H), 7.65 ppm (d, 1 H, J = 5.5 Hz, β-vinyl H); mass spectrum (70 eV) *m/e* (rel intensity) parent ion 170 (4), 155 (4), 139 (4), 113 (20), 111 (5), 110 (6), 98 (9), 97 (100), 69 (32), 59 (14), 43 (49).

The dimethyl derivative of γ-carboxymethyl-γ-hydroxy-β-methyl-$\Delta^{\alpha,\beta}$-butyrolactone (IX-E, 5%) was also isolated after methylation of a product mixture followed by glc. Its structure was assigned primarily on the basis of spectral evidence: ir (neat) 1770 (vs), 1740 (vs, C=O), 1660 cm^{-1} (m, C=C); nmr ($CDCl_3$) δ 2.04 (d, 3 H, J = 1.5 Hz, β-CH_3), 2.88 (d, 1 H, J = 15 Hz, HCH in an AB pattern), 3.08 (d, 1 H, J = 15 Hz, HCH in an AB pattern), 3.17 (s, 3 H, γ-OCH_3), 3.63 (s, 3 H, ester CH_3), and 5.96 ppm (quartet, 1 H, J = 1.5 Hz, α-vinyl H); mass spectrum (70 eV) *m/e* (rel intensity) parent ion 200 (1.6), 169 (15), 127 (100), 99 (31), 68 (28), 59 (34). This oxidation product (IX) was observed to decarboxylate on the gas chromatograph to give β,γ-dimethyl-γ-hydroxy-$\Delta^{\alpha,\beta}$-butyrolactone (X): ir (neat) 3270 (s, OH), 1735 (vs, C=O), 1657 cm^{-1} (m, C=C); nmr ($CDCl_3$) 1.64 (s, 3 H, γ-CH_3), 2.08 (d, 3 H, J = 1.5 Hz, β-CH_3), 4.08 (broad, 1 H, disappears after addition of D_2O, OH), 5.73 ppm (quartet, 1 H, J = 1.5 Hz, α-vinyl H). The presence of the γ-hydroxylactone (IX) could not be demonstrated by silylation of the product mixture since it is apparently unstable to these conditions. Thus, the reported yield is based on quantitative glc analysis of the methyl ester (IX-E).

4-Methyl-*o*-benzoquinone (XI) Oxidation.—The oxidation was carried out by the general procedure, and the reaction was instantaneous. No significant amounts of volatile oxidation products were found. The acidic products were estimated as their trimethylsilyl derivatives and included *cis,trans*-β-methylmuconic acid (VI, 19%), β-methyl lactone (VII, 44%) and γ-methyl lactone (VIII, 8%). Identification was assured by comparison of retention times of the methylated and the silylated derivatives with those of authentic samples. Analysis of a product mixture after a 26-hr reaction period showed lower yields of VI (4%), VII (33%), and VIII (4%) and revealed at least three other unknown acids which were not detectable at the shorter reaction time.

4-Methylveratrole Oxidation.—The oxidation of 4-methylveratrole (II) was performed as described in the general pro-

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(37) J. F. Klebe, H. Finkbeiner, and D. M. White, *J. Amer. Chem. Soc.*, **88**, 3390 (1966).

cedure. After a 30-hr reaction period, approximately 85% of the substrate had been oxidized. Dilution of the product mixture with water precipitated a yellow solid. Recrystallization from methanol gave thin yellow platelets of 2-methoxy-5-methyl-*p*-benzoquinone (XII, 17%): mp 174–176° (lit. mp 175–176° [9]); ir (KBr) identical with Sadtler spectrum no. 22030,[38] 1675 (s), 1653 (s), 1605 cm^{-1} (vs, C=CC=O); nmr ($CDCl_3$) 2.07 (d, 3 H, J = 1.5 Hz, CH_3), 3.83 (s, 3 H, OCH_3), 5.96 (s, 1 H, C-3 H), 6.57 ppm (quartet, J = 1.5 Hz, C-6 H). Methylation or silylation followed by glc confirmed the presence of the β-methyl lactone (VII, 7%), γ-methyl lactone (VIII, 1%), and the γ-hydroxy lactone (IX, 1%) as well as traces of unidentified products. The three lactones were verified as products by comparison of their glc retention times and their infrared spectra with those of authentic materials.

p-Cresol Oxidation.—The general procedure was employed for this oxidation. Product analysis revealed that only 70% of the *p*-cresol (III) had been oxidized after 55 hr. The acidic products included *cis,trans*-β-methylmuconic acid (VI, 0.5%), β-methyl lactone (VII, 19%), γ-methyl lactone (VIII, 3%), and γ-hydroxy lactone (IX, 4%). These products were identified by comparison of their ir spectra and glc retention times (of the methyl and trimethylsilyl derivatives) with those of authentic materials.

The original ether extract of the reaction mixture (after sodium carbonate addition) yielded a neutral component, 4-hydroxy-4-methyl-2,5-cyclohexadienone (XIII, 12%): ir (neat) 3400 (ms, OH), 1660 (vs, C=O), 1630 (ms), 1617 (ms, C=C), 855 cm^{-1} (s, *cis*-CH=CH); nmr ($CDCl_3$) δ 1.48 (s, 3 H, CH_3), 3.07 (broad, 1 H, disappears on D_2O addition, OH), 6.13 (d, 2 H, J = 10 Hz, vinyl Hs α to carbonyl), 6.95 ppm (d, 2 H, J = 10 Hz, vinyl Hs β to carbonyl); mass spectrum (70 eV) *m/e* (rel intensity) parent ion 124 (33), 109 (100), 96 (46), 81 (58), 55 (23), 43 (36), and 27 (28). This compound has been reported to form during hydrogen peroxide oxidation of *p*-cresol.[29]

It was discovered that the acetaldehyde used to reduce the residual peroxyacetic acid diverted some of the dienone product to an acetal adduct. On the basis of infrared, nmr, decoupling experiments, and mass spectral analysis the probable structure is 6,8-dimethyl-3-keto-$\Delta^{4,5}$-7,9-dioxabicyclo[4.3.0]nonane. Since this adduct was unambiguously shown to result from reaction of dienone XIII with acetaldehyde, the yield of dienone was corrected according to the amount of acetal adduct observed.

p-Methylanisole Oxidation.—*p*-Methylanisole (IV) was oxidized according to the general procedure, and only 45% of it was consumed by peroxyacetic acid in 72 hr. Dilution with water gave a yellow precipitate of 2-methoxy-5-methyl-*p*-benzoquinone (XII, 16%) which gave an ir spectrum identical with that of an authentic sample. Analysis of the neutral products from the initial ether extract showed that 4-hydroxy-4-methyl-2,5-cyclohexadienone (XIII, 16%) was formed as shown by glc retention time and ir spectral comparisons with the authentic product obtained from *p*-cresol oxidation. Another neutral product was collected at the exit of the gas chromatograph and found to be 2-hydroxy-*p*-methylanisole (XIV, 2%); the compound's infrared spectrum was identical with the spectrum of an authentic sample.[39] Glc retention times and infrared spectra of the methyl esters of the carboxylic acid products showed that they were the ester derivatives of *cis,trans*-β-methylmuconic acid (VI, 0.2%), β-methyl lactone (VII, 7%), γ-methyl lactone (VIII, 1%), and γ-hydroxy lactone (IX, 2%).

A similar reaction in which the oxidation was quenched at an earlier time (30 hr, 25% of the substrate had reacted) gave the same reaction products except that 2-hydroxy-*p*-methylanisole was formed in higher yield (6%).

2-Methoxy-*p*-cresol Oxidation.—The general procedure was used for the oxidation of 2-methoxy-*p*-cresol (V). No products were found in the initial ether extract when the reaction had consumed 85% of the substrate (24 hr). The acidic products included *cis,trans*-β-methylmuconic acid (VI, 0.4%), β-methyl lactone (VII, 9%), γ-methyl lactone (VIII, 2%) and the γ-hydroxy lactone (IX, 13%); these were identified on the basis of glc retention times of their methyl and trimethylsilyl esters.

Mesitylene Oxidation.—Oxidation of mesitylene by the general procedure gave hydroxymesitylene which was collected by preparative glc; its infrared spectrum was identical with the infrared spectrum of an authentic sample. Other products were also formed but were not identified.

Product Stability.—When 2-methoxy-5-methyl-*p*-benzoquinone (XII, 0.43 g, 2.8 mmol) was mixed with 25 ml of 7% peroxyacetic acid (1.76 g, 23 mmol), 36% of the substrate reacted in 50 hr consuming approximately an equimolar amount of oxidant. Product analysis efforts were unsuccessful.

Separate control reactions were carried out with *cis,trans*-β-methylmuconic acid (VI), β-methyl lactone (VII), and its methyl ester using 5–8% solutions of peroxyacetic acid for extended periods of time (24–72 hr). Peroxyacetic acid was not consumed by these substrates. Good recoveries (80–85%) were obtained of β-methyl lactone (VII) after the entire work-up procedure. On the other hand, *cis,trans*-β-methylmuconic acid was recovered in only 47% yield (as β-methyl lactone).

Effect of Methyl Methacrylate.—An oxidation of *p*-cresol (III) was carried out in the usual manner except that methyl methacrylate (3.3% by weight) was added to the reaction. The rate of peroxyacetic acid consumption was the same in this reaction as with an oxidation carried out without methyl methacrylate. Product analysis showed no significant differences which could be ascribed to the presence of the monomer.

Registry No.—I, 452-86-8; II, 494-99-5; III, 106-44-5; IV, 104-93-8; V, 93-51-6; VI, 31659-59-3; VII, 6307-98-8; VII-E, 31656-70-9; VIII-E, 31656-71-0; IX-E, 31656-72-1; X, 14300-89-1; XI, 3131-54-2; XII, 614-13-1; XIII, 23438-23-5; peroxyacetic acid, 79-21-0.

Acknowledgments.—The authors are grateful to Drs. J. W. Green and N. S. Thompson for their comments and suggestions. The assistance of L. O. Sell in obtaining infrared and nmr spectra is also appreciated.

(38) C. Viel, J. M. Arnaud, R. Dorme, A. Cheutin, and P. Rumpf, *Bull. Soc. Chim. Fr.*, 431 (1967).

(39) W. Beckering and W. W. Fowkes, U. S. Bureau of Mines Report of Investigations, No. 5505, U. S. Bureau of Mines, Washington, D. C., 1959.

Stereoisomers of Trimethyl Methanetri(α-bromoacetate)

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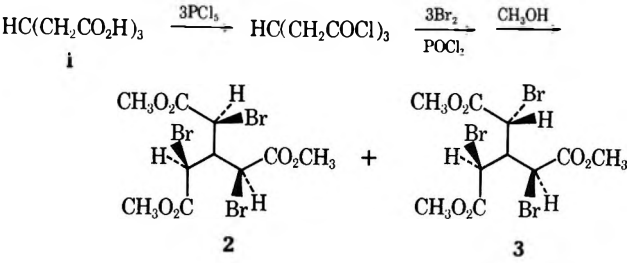
Received May 7, 1971

We have prepared two esters derived from methanetriacetic acid (1) which exhibit a novel diastereoisomerism as revealed by nmr spectroscopy. Vigorous bromination of the acid chloride of **1** in phosphorus oxychloride followed by quenching in methanol gave a mixture of esters. Separation into the components, mp 97 and 113°, could readily be effected by crystallization from methylcyclohexane. Both substances possessed the same composition ($C_{10}H_{13}Br_3O_6$) and had similar spectroscopic properties, indicating that they had the same general structure. We propose that they are the tribromides **2** and **3**, respectively.



The nmr spectra of the two esters demonstrated that they were indeed stereoisomeric. In deuteriochloroform both compounds exhibit only one methoxyl resonance at δ 3.82 ppm (intensity 9 H). The lower melting tribromide possessed a sharp doublet at δ 5.02 ppm (J = 4.8 Hz, intensity 3 H), corresponding to the three bromomethinyl protons adjacent to the carbomethoxy functions. The only other nmr absorption, a quartet at δ 3.64 ppm (J = 4.8 Hz, intensity 1 H), could be assigned to the remaining methinyl proton, which should be equivalently coupled to the three bromomethinyl protons in **2**. In contrast to **2**, the other tribromide **3** possessed complex absorption near δ 5 ppm. In the region where bromomethinyl resonances occur, six sharp irregularly spaced peaks of equal intensity were observed (total intensity 3 H). By examination of the spectrum at different field strengths this was interpreted as three doublets arising from *nonequivalent* bromomethinyl protons: δ 4.88 (J = 7.8 Hz), 4.94 (J = 4.2 Hz), and 5.07 ppm (J = 4.2 Hz). Such a pattern should arise from **3**, in which each of these protons would be coupled to the central proton (δ ~3.78 ppm, multiplet) but should otherwise differ with respect to the time-averaged magnetic environment, since no rotational processes can occur to bring about exchange between these three environments.[1] Therefore, the two structures may be identified as trimethyl *rac,rac*-methanetri(α-bromoacetate) (**2**) and trimethyl *meso,rac*-methanetri(α-bromoacetate) (**3**).

Some time ago Beesley and Thorpe[2] reported a triester related to **2** and **3** (from bromination of 1,1,1-ethanetriacetic acid) as an intermediate in some synthetic studies of unlikely veracity.[3] While the latter[2] workers' preparations have been claimed not to be reproducible,[4] the conditions of our synthesis of **2** and **3** are quite similar to those in the original report. Consequently, Thorpe's work[2] perhaps ought not to be discounted in its entirety. However, in contrast with his alleged findings our triester gave uncharacterizable tars with even mildly basic reagents (sodium azide or pyridine).

Experimental Section

Bromination of Methanetriacetic Acid Chloride.—A mixture of 10.0 g (0.053 mol) of methanetriacetic acid[5] (**1**) and 31 g of phosphorus pentachloride was heated until a homogeneous solution was obtained and gaseous hydrogen chloride evolution had ceased. To the resulting solution 30 g of bromine was added and heating was continued as hydrogen bromide was evolved. After 42 hr on a steam bath, excess bromine and phosphorus oxychloride were removed under aspirator pressure with heating. The residue was poured into 150 ml of methanol. After several hours the solution was concentrated under vacuum until a quantity of solid had separated, whereupon the mixture was chilled to 0° and the precipitate was collected and washed with a little cold methanol. The material thus obtained weighed 14.4 g and was a crude mixture of approximately equal amounts of **2** and **3**. Upon recrystallization from methylcyclohexane, **3** was observed characteristically to form clones of prisms adhering to the walls of the flask, whereas **2** formed rosettes of needles, more easily dispersed through the solvent; seed crystals could thereby be obtained; and the following separation procedure was devised. The solid mixture of isomers was dissolved in 200 ml of hot methylcyclohexane. The solution was filtered and allowed to cool to 50–60°, a seed of **3** was added, and the solution was allowed to cool to room temperature and stand undisturbed for 2 hr. The solution was then decanted from the mass of prismatic crystals coating the walls of the container and boiled down to a volume of 100 ml. The solution was cooled as before and seeded with **2**. Upon standing at room temperature, rosettes of needles grew. The solution was again decanted, boiled down to a volume of 50 ml, cooled and seeded with **3**, and allowed to crystallize. After decanting, the solution was concentrated to a volume of 25 ml and seeded with **2**. After the crystals had formed, the mother liquor was discarded.

The second and fourth fractions from the separation procedure were combined and recrystallized from 50 ml of methylcyclohexane to give 4.8 g (19.3% from **1**) of trimethyl *rac,rac*-methanetri(α-bromoacetate) (**2**): mp 97–98°; ir ν_{max}^{KBr} 1755, 1740 cm^{-1}; nmr (10% $CDCl_3$) see text.

Anal. Calcd for $C_{10}H_{13}Br_3O_6$: C, 25.61; H, 2.79; Br, 51.12. Found: C, 25.78; H, 2.79; Br, 50.94.

The first and third fractions from the separation procedure were combined and recrystallized from 50 ml of methylcyclohexane to give 7.5 g (30.5% from **1**) of trimethyl *meso,rac*-methanetri(α-

(1) K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, New York, N. Y., 1966. See also J. McKenna, J. M. McKenna, and B. A. Wesby, *Chem. Commun.*, 867 (1970).

(2) R. M. Beesley and J. F. Thorpe, *Proc. Chem. Soc.*, **29**, 346 (1913); *J. Chem. Soc.*, **117**, 591 (1920).

(3) It was reported[2] that strong base coverted the tribromide to methyltricyclobutanetricarboxylic acid, the properties of which were not consistent with what is currently known of this ring system: P. B. Shevlin and A. P. Wolf, *J. Amer. Chem. Soc.*, **92**, 406, 3523, 5291 (1970).

(4) H. O. Larson and R. B. Woodward, *Chem. Ind. (London)*, 193 (1959).

(5) D. D. Philips, M. A. Acitelli, and J. Meinwald, *J. Amer. Chem Soc.*, **79**, 3517 (1957); E. Stetter and H. Stark, *Chem. Ber.*, **92**, 732 (1959).

bromoacetate) (**3**): mp 113–114°; ir ν_{max}^{KBr} 1740 cm^{-1}; nmr (10% $CDCl_3$) see text.

Anal. Calcd for $C_{10}H_{13}Br_3O_6$: C, 25.61; H, 2.79; Br, 51.12. Found: C, 25.54; H, 2.83; Br, 50.96.

Registry No.—**2**, 31446-54-5; **3**, 31446-55-6.

Protonation and Alkylation of Dianions Derived from 1,4-Diphenyl-1,4-di(1-naphthyl)butatriene, 2,5-Diphenyl-2,3,4-hexatriene, 1,1,4-Triphenyl-1,2,3-pentatriene, and 1,1-Diphenyl-4-methyl-1,2,3-pentatriene

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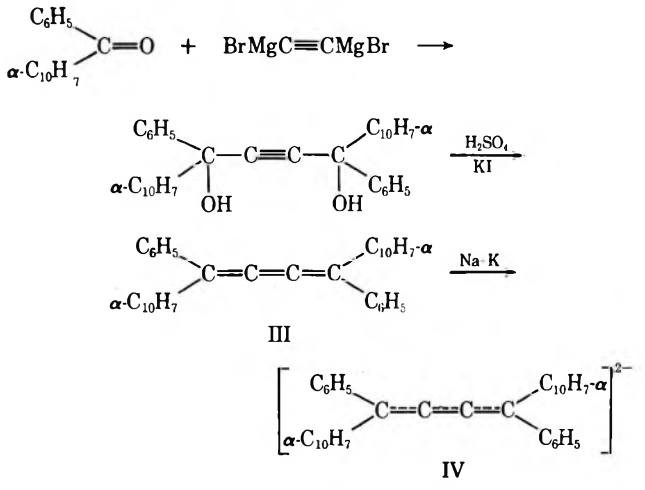
Received February 18, 1971

We have recently reported some of the reactions of dianions derived from 1,1,4,4-tetraphenylbutatriene[1] (I) and 1,4-bisbiphenylenebutatriene[2] (II). Both of these trienes are symmetrically substituted and their dianions are stabilized by considerable resonance energy. It was thought that a comparison of some reactions of dianions from less symmetrical butatrienes with reactions of the dianions derived from I and II would be of interest.

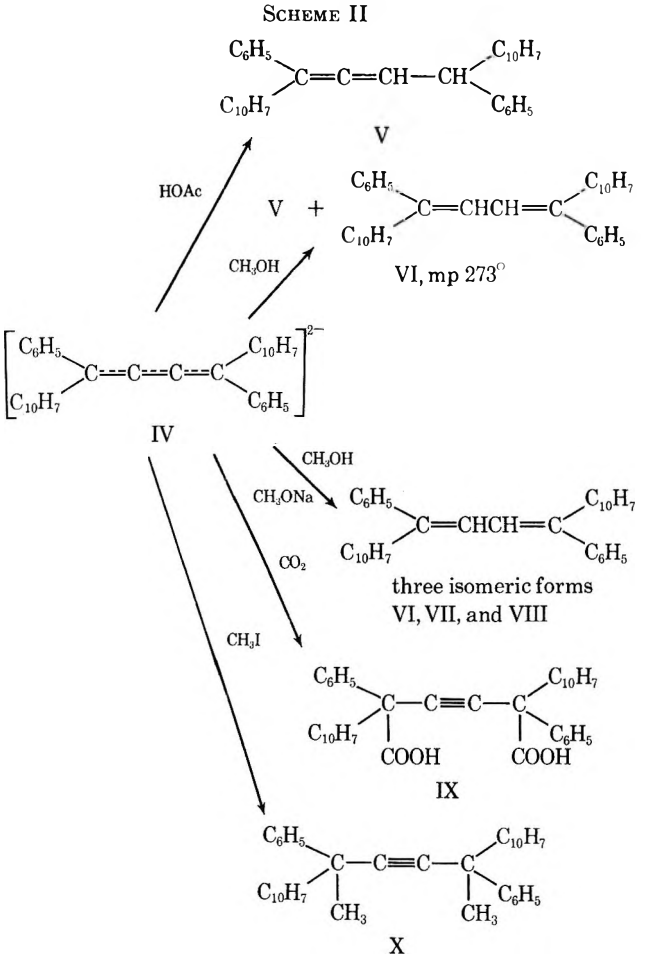
The first dianion which was studied was prepared according to the outline in Scheme I. 1,4-Diphenyl-

SCHEME I

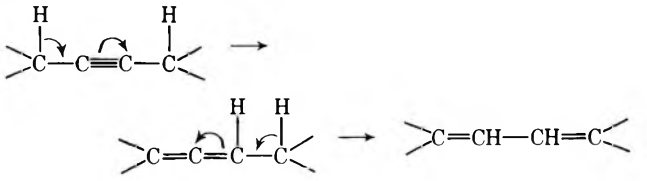


1,4-di(1-naphthyl)butatriene (III) theoretically may exist in cis and trans forms. Attempts to chromatographically separate the isomers failed.[3] Our attempts to separate isomers also failed. From an examination of models, it would appear that steric interference would make the cis form less probable. The reactions of the dianion from III are shown in Scheme II. We believe that all of these additions involve the same initial step, namely, 1,4 addition. In the case of protonation, the 1,4-dihydro compound, which is kinetically favored, rearranges to the thermodynamically

SCHEME II



more stable 1,2-diene and finally to the even more stable conjugated diene. In the other cases, *i.e.*, carbonation and methylation, the required hydrogen for the prototropic changes is not present.



1,4-Diphenyl-1,4-di(1-naphthyl)-1,2-butadiene (V) possessed a characteristic[4] infrared absorption at 1950 cm^{-1}. The nmr spectrum consisted of an aromatic multiplet at δ 7.24, an olefinic doublet at δ 6.2 (1, J_{AB} = 6 Hz), and a tertiary proton doublet at δ 5.6 (1, J_{AB} = 6 Hz). The tertiary proton has been shifted downfield owing to deshielding by the aromatic rings.

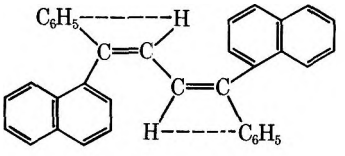
The 1,2-diene was also prepared by the reduction of the triene III with aluminum amalgam.[5] The diene prepared by this method was identical in every way with the sample obtained from the protonation of the dianion IV. A small amount of the conjugated diene, 1,4-diphenyl-1,4-di(1-naphthyl)-1,3-butadiene (VI), mp 273°, was also isolated. VI showed no allenic absorption at 1950 cm^{-1} and showed the usual conjugated absorption in the uv at 293 and 344 mμ. It was subse-

(1) S. F. Sisenwine and A. R. Day, *J. Org. Chem.*, **32**, 1770 (1967).
(2) J. M. Edinger and A. R. Day, *ibid.*, **36**, 240 (1971).
(3) R. Kuhn and J. Jahn, *Chem. Ber.*, **86**, 759 (1953).
(4) J. H. Wotiz and D. E. Mancuso [*J. Org. Chem.*, **22**, 207, (1957)] examined 58 allenic compounds and concluded that the infrared band at 1950 cm^{-1} was characteristic of allene bonds.
(5) R. Kuhn and H. Fischer, *Chem. Ber.*, **94**, 3060 (1961).

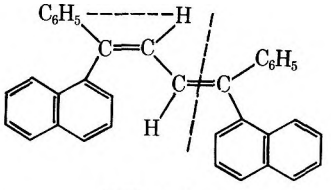
quently shown that V is easily rearranged to the 1,3-dienes by bases.

In an effort to prepare the conjugated diene in better yields, 1,4-diphenyl-1,4-di(1-naphthyl)butatriene (III) was reduced with zinc amalgam. Brand had previously reported that tetraphenylbutatriene, when reduced with zinc amalgam in amyl alcohol–acetic acid medium, gave the corresponding 1,3-diene.[6]

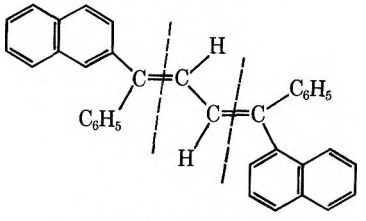
Reduction of III by this method gave two products melting at 259° (VII) and 194° (VIII) in contrast to the aluminum amalgam reduction which yielded a product melting at 273° (VI). None of these products showed an absorption at 1950 cm^{-1}, and the ultraviolet spectra were identical. Analyses and molecular weights for VI, VII, and VIII confirmed the belief that the three are geometric isomers. There should exist three forms, namely, *cis–cis*, *trans–trans*, and *cis–trans*. While all three forms have been isolated in pure form, we are reasonably certain only of the identity of the isomer melting at 194° (VIII).



VI or VII, cis-cis



VIII, cis-trans



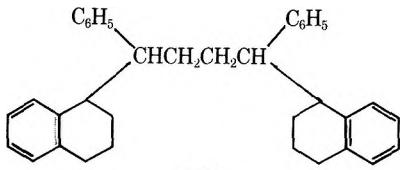
VI or VII, trans-trans

The nmr spectrum of VIII exhibited an aromatic multiplet at δ 7.7 (24) and an olefinic doublet at δ 6.1 (1, J_{AB} = 11 Hz). At first this spectrum appeared anomalous. However, on inspection of models it can be seen that the olefinic protons in VIII are not equivalent. The two protons split one another giving rise to an AB pattern one-half of which is visible in the spectrum. The other AB doublet presumably has merged with the aromatic multiplet and thus cannot be seen. These data best fit the cis–trans form. The isomer melting at 273° showed an aromatic multiplet at δ 7.35 (24) and an olefinic singlet at δ 6.6 (2), while the isomer melting at 259° showed an aromatic multiplet at δ 7.5 (24) and an olefinic singlet at δ 6.9 (2).

A mixture of the isomeric dienes VI, VII, and VIII was obtained when 1,4-diphenyl-1,4-di(1-naphthyl)-butatriene (III) was hydrogenated over Lindlar catalyst (lead-poisoned palladium). All three dienes as well as the triene were hydrogenated over 10% Pd/C to give 1,4-diphenyl-1,4-(1-naphthyl)butane (XI).

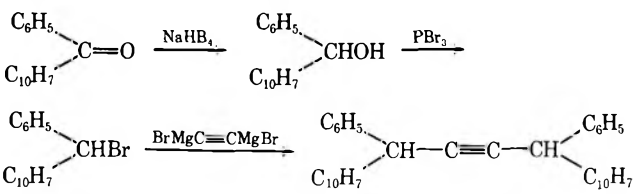
(6) K. Brand, *Chem. Ber.*, **54B**, 1987 (1921).

The characteristic absorptions for a conjugated diene were missing in the uv spectrum for XI, and its nmr spectrum displayed an aromatic multiplet at δ 8.75 (24), a tertiary proton multiplet at δ 4.6 (2), and an unsymmetrical methylene proton triplet at δ 2.2 (4). The latter is probably a complex which is the result of splitting with the methine and aromatic protons. A small amount of a side product was isolated from the 10% Pd/C hydrogenation which was identified as 1,4-diphenyl-1,4-di[1-(1,2,3,4-tetrahydronaphthyl)]butane (XII).



XII

As a final check against confusing one of the dienes with 1,4-diphenyl-1,4-di(1-naphthyl)-2-butyne (XIII), another possible protonation product, the unknown 2-butyne, was synthesized by a procedure published by Wieland and Kloss.[7] The product (XIII) was actually



XIII

a mixture (presumably of racemic and meso forms). This was not further studied since we were interested in absorption spectra only, and all fractions had the same spectra. For example, the nmr spectra displayed an aromatic multiplet at δ 7.5 (24) and a tertiary proton singlet at δ 5.5 (2). Hydrogenation of XIII over palladium gave the corresponding butane (XI).

Methylation of the dianion IV gave 2,5-diphenyl-2,5-di(1-naphthyl)-3-hexyne (XIV). Two isomers were obtained, mp 225° (75%) and mp 187–189° (3%). Presumably the higher melting isomer was the racemic form and the other the meso form. They had identical uv spectra and the nmr spectra were very similar.

Some work was also carried out on the protonation of the dianion from 1,4-diphenyl-1,4-di(1-naphthyl)-1,2-butadiene (V) and 1,4-diphenyl-1,4-di(1-naphthyl)-1,3-butadiene (VI). Both sources of the dianion gave the same end product. Protonation with acetic acid gave 1,4-diphenyl-1,4-di(1-naphthyl)-2-butene (XV). The ir spectrum showed a band at 975 cm^{-1} indicating a trans form. The nmr spectrum showed an aromatic multiplet at δ 7.45 (24), an olefin proton doublet at δ 5.85 (2, J = 4 Hz) and a tertiary proton doublet at δ 5.4 (2, J = 4 Hz).

The only significant difference noted between the reactions of the dianion IV from 1,4-diphenyl-1,4-di-(1-naphthyl)butatriene and the dianion derived from 1,4-bisbiphenylenebutatriene[2] was the difference in the protonation results with acetic acid. Dianion IV yielded only the 1,2-butadiene (X), whereas the dianion from 1,4-bisbiphenylenebutatriene gave only the corresponding 1,3-diene as the major product and the corresponding 2-butyne. There does not appear to be a satis-

(7) H. Wieland and H. Kloss, *Justus Liebigs Ann. Chem.*, **470**, 201 (1929).

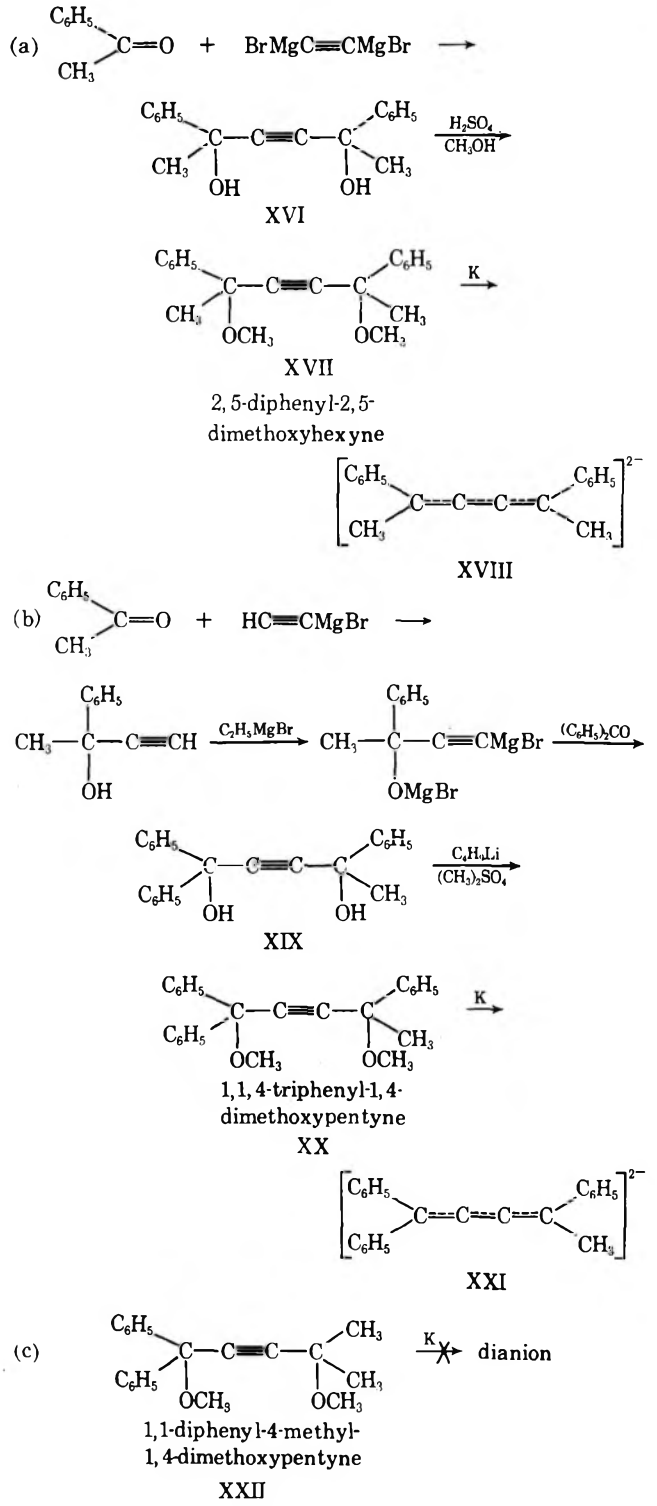
factory explanation for this difference at the present time. The fact that the 1,4-bisbiphenylenebutatriene dianion is more highly stabilized by resonance gives only a partial answer.

The fact that the least stabilized dianion permitted the ready isolation of the 1,2-diene prompted us to study the dianions of even less stabilized systems. For this purpose attempts were made to prepare the dianions of three tetrasubstituted butatrienes where one or two of the groups were methyl groups (Scheme III). 1,1-Diphenyl-4-methyl-1,4-dimethoxy-2-pentyne (XXII) was prepared by a method similar to that used for 1,1,4-triphenyl-1,4-dimethoxy-3-pentyne except that acetone was used as the starting materials. The dimethoxy compounds were used as the precursors of the dianions because of the relative instabilities of the corresponding butatrienes. Compound XXII apparently stopped with formation of the free-radical anion when treated with potassium.

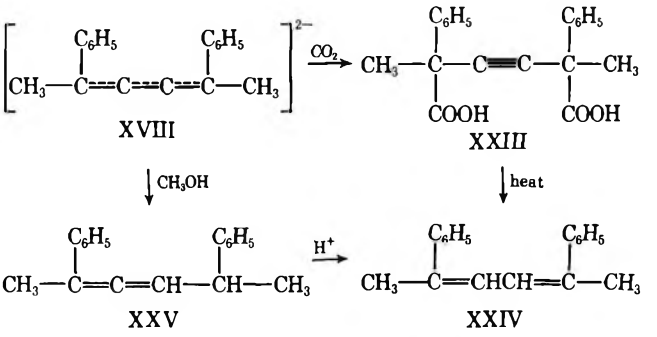
The reactions of the dianion XVIII are shown in Scheme IV. The ir spectrum for XXIII showed a strong carbonyl absorption at 1700 cm^{-1} and no absorption for allene bonds which would indicate 1,2 carbonation. Protonation of XVIII gave only the allene, 2,5-diphenyl-2,3-hexadiene (XXV). The diene gave a strong absorption at 1950 cm^{-1}. It was not isomerized by bases $(OCH_3)^-$ to the conjugated diene XXIV. 1,1,4,4-Tetraphenyl-1,2-butadiene was rapidly isomerized to the conjugated diene under similar circumstances.[1] However, the latter 1,2-diene $[(C_6H_5)_2C{=}C{=}CHCH(C_6H_5)_2]$ contains a benzhydryl hydrogen which is readily abstracted by the base to initiate the rearrangment to the more stable 1,1,4,4-tetraphenyl-1,3-butatriene. There is no benzhydryl hydrogen in XXV. The isomerization of XXV proceeded readily under acid conditions. The nature of the intermediate carbonium ion favors elimination of the C_1 hydrogen and the formation of the conjugated diene XXIV (Scheme V).

Anion XXI reacted very much like anion XVIII (Scheme VI). Compound XXVI showed a strong

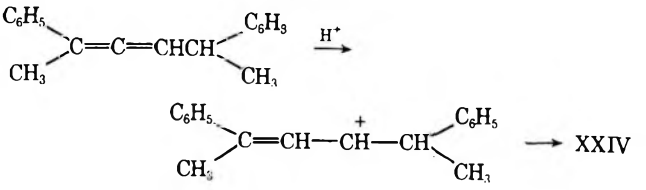
Scheme III



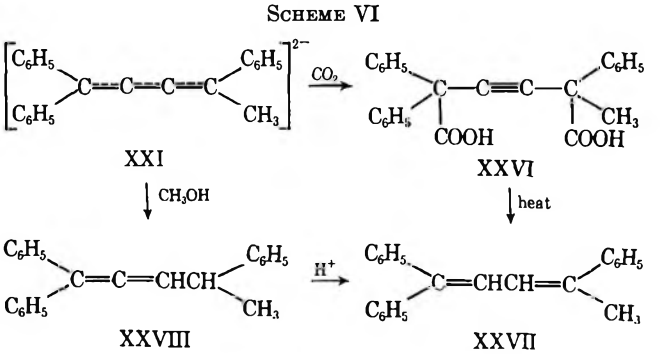
Scheme IV



Scheme V



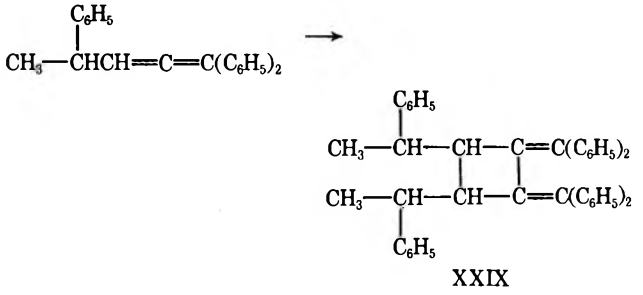
Scheme VI



carboxyl absorption at 1700 cm^{-1} and no peak at 1950 cm^{-1}. The ir spectrum for XXVII showed no band at 1950 cm^{-1}, and its uv spectrum showed a characteristic absorption at 335 mμ (ϵ_{max} 32,000). The nmr spectrum showed an aromatic multiplet at δ 7.3 (15), an olefinic singlet at δ 7.0 (1, J = 1 cps), and an olefinic doublet at δ 2.2 (3, J = 1 cps). The ir spectrum of XXVIII showed a strong allene absorption at 1948 cm^{-1}. The nmr spectrum showed an aromatic multiplet at δ 7.0 (15), an allenic proton doublet at δ 5.79–5.69 (1), an aliphatic proton quintet at δ 3.53 (1), and a methyl proton doublet at δ 1.43–1.33. The fact that XXVIII is not isomerized to XXVII by bases (OCH_3^-) is strong evidence for the absence of the isomeric allene [$(C_6H_5)_2$-$CHCH{=}C{=}C(C_6H_5)CH_3$], since the latter contains a benzhydryl hydrogen which would make it susceptible to base isomerization. XXVIII is readily isomerized to XXVII by acids.

Although 2,5-diphenyl-2,3-hexadiene (XXV) was relatively stable at 150°, 1,1,4-triphenyl-1,2-pentadiene (XXVIII) dimerized at this temperature to what appears to be 1,2-bis(diphenylmethylene)-3,4-bis(1-phenylethyl)cyclobutane (XXIX) (Scheme VII). This dimer

SCHEME VII

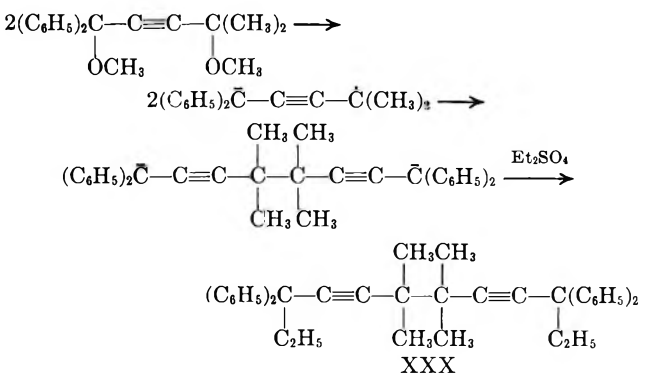


XXIX

had a uv absorption at 370 mμ (ϵ_{max} 15,000), and the nmr spectrum showed an aromatic multiplet at δ 6.81 (15), a cyclobutane proton singlet at δ 3.0 (1), an aliphatic proton multiplet at δ 2.47 (1), and a methyl proton doublet at δ 1.09–0.99 (3). The singlet at δ 3.0 is due to the cyclobutane proton which is at a 90° angle to the aliphatic proton. The multiplet at δ 2.73 should have been a quartet but the aliphatic proton is probably interacting with neighboring protons. The doublet at δ 1.09–0.99 is due to the methyl protons which are split by the aliphatic proton.

To this point the dianions prepared had at least one phenyl group attached to each of the terminal carbon atoms of the original butatriene. The dianion corresponding to 1,1-diphenyl-4-methyl-1,2,3-pentatriene has only methyl groups attached to the one carbon atom. Because of the absence of stabilizing phenyl groups at this position, it was of interest to see if a stable dianion could be prepared. The corresponding dimethoxy compound 1,1-diphenyl-4-methyl-1,4-dimethoxypentyne (XXII) was treated with excess potassium in the usual way. Diethyl sulfate was then added at a low temperature. Only one product could be isolated from the reaction mixture. Analytical and spectral data have shown this compound to be 3,3,-10,10-tetraphenyl-6,6,7,7-tetramethyl-4,8-dodecadiyne (XXX) (Scheme VIII). The ir spectrum of XXX showed absorptions for phenyl, methyl, and ethyl groups but no other characteristic absorptions. This

SCHEME VIII



XXX

ruled out the possibility of allenic structures and other olefinic structures that absorb in the ir. The nmr spectrum showed an aromatic multiplet at δ 7.6–7.2 (10), a methylene proton quartet at δ 2.3–2.2 (2), a methyl proton singlet at δ 1.4 (6), and a methyl proton triplet at δ 0.90 (3). The anion radical, in this case, is much more reactive than the ones made in our previous studies and dimerizes rapidly to form the stable dianion of the dimer which is then ethylated. The anion radical is thus similar in reactivity to the anion radical of 1,1-diphenylethylene.[8]

Experimental Section

All melting points were determined with a Thomas-Hoover capillary melting point apparatus. The ir spectra were measured on a Perkin-Elmer 521 recording spectrophotometer using KBr disks, Nujol mull, or thin films on NaCl disks. The uv spectra were determined on a Cary 14 spectrophotometer using 1-cm quartz cells. Nmr spectra were measured at 60 Hz on a Varian Associates Model A-60A spectrophotometer with the tetramethylsilane as an internal standard. Esr spectra were measured on a Varian E-3 spectrophotometer.

1,4-Diphenyl-1,4-di(1-naphthyl)butatriene (III).—1,2-Diphenyl-1,4-di(1-naphthyl)-1,4-butynediol[3] was converted to the butatriene III by the sulfuric acid–iodide method,[9] yield 67%, mp 236–237°.

1,4-Diphenyl-1,4-di(1-naphthyl)-1,4-dimethoxy-2-butyne.—This dimethyl ether was prepared in poor yield from the diol[3] by treatment with methanol and sulfuric acid, yield 11%, mp 189–190° (from ethanol). The low yield was probably due to rearrangement.

Anal. Calcd for $C_{38}H_{30}O_2$: C, 87.99; H, 5.83. Found: C, 87.87; H, 5.94.

Dianion from 1,4-Diphenyl-1,4-di(1-naphthyl)butatriene (III).—This dianion was prepared by the method published previously.[2] The solution was stirred for 12 hr during which time the color of the solution changed from a red color to a deep green and the esr signal had disappeared. The solution was stirred for an additional 2–3 hr.

1,4-Diphenyl-1,4-di(1-naphthyl)-2-butyne-1,4-dicarboxylic Acid (IX).—The dianion solution prepared from 2.739 g (0.006 mol) of III was poured over Dry Ice. The mixture was allowed to come to room temperature and the solvent was evaporated. The reddish solid was shaken with water and ether, and after the layers had separated (12 hr) the water layer was removed and acidified with hydrochloric acid. The tan precipitate was extracted with ether and the extract dried ($MgSO_4$). The ether was evaporated and the resulting solid was extracted with hot carbon tetrachloride. The insoluble residue was washed with carbon tetrachloride and then with water leaving a colorless solid: yield 12%; mp 314° (with evolution of CO_2); ir (KBr) 3060–2800 (broad), 1685 (s), 1270 (s), 800 (s), 775 (s), 700 cm^{-1} (s).

(8) W. Schlenk and E. Bergmann, *Justus Liebigs Ann. Chem.*, **463**, 1 (1928).

(9) J. Wolinski, *Rocz. Chem.*, **29**, 23 (1955).

Anal. Calcd for $C_{38}H_{26}O_4$: C, 83.50; H, 4.80; O, 11.70. Found: C, 83.32; H, 4.96; O, 11.80 (by actual analysis).

Protonation of Dianion IV with Acetic Acid. Preparation of 1,4-Diphenyl-1,4-di(1-naphthyl)-1,2-butadiene (V).—The dianion solution from 3.2 g (0.007 mol) of III was cooled in Dry Ice–acetone and 10 ml of acetic was added. Instant decolorization occurred. The solution was stirred for 0.5 hr and allowed to come to room temperature. The solvent was removed under reduced pressure and the residual brown oil was crystallized from methanol. The product was recrystallized from acetone, colorless crystals, yield 77%, mp 180–181°.

Anal. Calcd for $C_{36}H_{26}$: C, 94.28; H, 5.72; mol wt, 458. Found: C, 94.14; H, 5.74; mol wt, 442 (Rast method).

The solid that did not dissolve in the hot acetone proved to be pure 1,4-diphenyl-1,4-di(1-naphthyl)-1,3-butadiene (VI), yield 3%, mp 273°.

Anal. Calcd for $C_{36}H_{26}$: C, 94.28; H, 5.72. Found: C, 94.17, H, 5.78.

Zinc-Amalgam Reduction of 1,4-Diphenyl-1,4-di(1-naphthyl)-butatriene (III). Preparation of 1,4-Diphenyl-1,4-di(1-naphthyl)-1,3-butadiene (VII, Mp 259°) and 1,4-Diphenyl-1,4-di(1-naphthyl)-1,3-butadiene (VIII, Mp 194°).—The zinc-amalgam reduction method reported by Brand[6] for the reduction of tetraphenylbutatriene was used for the reduction of III. After the required refluxing, the mixture was filtered. The solid was extracted with carbon disulfide and water, and the carbon disulfide layer was washed with water and dried ($CaCl_2$). The solvent was removed under reduced pressure and the residual colored solid was washed with a little cold methanol followed by a small amount of cold acetone. The product was recrystallized from acetone: yield 50%; mp 259°; nmr, aromatic multiplet at δ 8.0–7.0 (24), olefinic singlet at δ 6.9 (2).

Anal. Calcd for $C_{36}H_{26}$: C, 94.28; H, 5.72; mol wt, 458. Found: C, 94.12; H, 5.92; mol wt, 455 (Rast method).

The original filtrate from the zinc-amalgam reduction, on further evaporation under reduced pressure, gave another colorless, crystalline 1,3-diene IX. It was dissolved in hot acetone and filtered while hot to remove a small amount of isomer VII. On cooling, isomer VIII crystallized, yield 34%, mp 194°.

Anal. Calcd for $C_{36}H_{26}$: C, 94.28; H, 5.72; mol wt, 458. Found: C, 94.37; H, 5.61; mol wt, 451 (Rast method).

The nmr spectrum was practically identical with that of VIII.

Catalytic Reduction of 1,4-Diphenyl-1,4-(1-naphthyl)butatriene (III) with Lindlar Catalyst.—Compound III (2.02 g, 0.0044 mol) and 4.7 g of Lindlar catalyst[10] in 150 ml of tetrahydrofuran were hydrogenated at 45 psi for 7 hr. The mixture was filtered and the solvent removed *in vacuo*. The solid was refluxed with acetone and filtered. The insoluble residue proved to be the conjugated diene, mp 259° (VII), yield 15.2%. Fractional evaporation of the acetone filtrate gave isomers VI (9%) and VIII (15.4%). Extended fractionation would increase the yields. The overall crude yield was nearly 100°.

Catalytic Hydrogenation of III with 10% Pd on Carbon. Preparation of 1,4-Diphenyl-1,4-di(1-naphthyl)butane (XI).—The hydrogenation was carried out at 45 psi for 28 hr in ethanol solution. At the end of 7 and 14 hr a small amount of fresh catalyst was added. The mixture was cooled and filtered, and the solvent was evaporated under reduced pressure to yield a negligible amount of an oil. The original precipitate was extracted with hot ethanol and the alcohol evaporated to give colorless crystals which were crystallized from ethanol, yield 47%, mp 160°.

Anal. Calcd for $C_{36}H_{30}$: C, 93.46; H, 6.54. Found: C, 93.42; H, 6.54.

Protonation of the Dianion IV from III with Methanol.—The procedure was the same as with the protonation with acetic acid. Decolorization of the dianion solution occurred more slowly. The 1,2-butadiene (V) was the main product. However, when V was recrystallized from acetone, a small residue proved to be the isomeric diene VI, mp 273°.

Preparation of 1,4-Diphenyl-1,4-di(1-naphthyl)-2-butyne (XIII).—Phenyl-1-naphthylcarbinyl bromide[11] (34.2 g, 0.115 mol) in 75 ml of benzene was added slowly to an ether solution of acetylene-dimagnesium bromide (0.225 mol). After the addition, the solution was refluxed for 4 hr and then cooled and poured into 500 ml of 2*N* hydrochloric acid and ice. The mixture was extracted with ether and the ether extract dried ($MgSO_4$). The ether was evaporated and the residual oil taken up in a minimum amount of petroleum ether (bp 60–110°). On standing at 3°, white crystals separated which were recrystallized from petroleum ether: yield 38%; mp 148–160°; nmr, aromatic multiplet at δ 8.0–7.0 (24) and a tertiary proton singlet at δ 5.65 (2). This product was probably a mixture of meso and racemic forms.

Anal. Calcd for $C_{36}H_{26}$: C, 94.28; H, 5.72. Found: C, 94.17; H, 5.83;

A small amount of one of the isomers was obtained by repeated recrystallization from acetone, mp 178–179.5°.

Anal. Found: C, 94.22; H, 5.67.

Catalytic Hydrogenation of 1,4-Diphenyl-1,4-di(1-naphthyl)-2-butyne (XIII) over 10% Pd on Carbon.—Catalytic hydrogenation (45 psi) in acetic acid gave both 1,4-diphenyl-1,4-di(1-naphthyl)-butane (XI) and 1,4-diphenyl-1,4-di[1-(1,2,3,4-tetrahydronaphthyl)]butane (XII). Their identities were established by analyses, melting points, and spectral studies.

Methylation of Dianion IV from III. Preparation of 2,5-Diphenyl-2,5-di(1-naphthyl)-3-hexyne (XIV).—Methyl iodide (10 ml) was added to the dianion solution prepared from 3.2 g (0.007 mol) of III at Dry Ice–acetone temperature. The mixture was stirred for 30 min and filtered, and the solvent was evaporated under reduced pressure. The resulting crystals were washed with a small amount of hot ethanol and dried, yield 74%, mp 225°.

Anal. Calcd for $C_{38}H_{30}$: C, 93.79; H, 6.21. Found: C, 93.72; H, 6.23.

An isomer was isolated in small amounts from the ethanol extract by evaporation, mp 187–189°.

Anal. Calcd for $C_{38}H_{30}$: C, 93.79; H, 6.21. Found: C, 93.79; H, 6.19.

Protonation of the Dianion from 1,4-Diphenyl-1,4-di(1-naphthyl)-1,2-butadiene (V). Preparation of 1,4-Diphenyl-1,4-di(1-naphthyl)-2-butene (XV).—The dianion was prepared in the usual manner from 2.1096 g of V and 0.4736 g of Na–K. Acetic acid (10 ml) was added to the solution cooled in Dry Ice–acetone. The mixture was stirred for 15 min, allowed to come to room temperature, and filtered. The solvent was evaporated under reduced pressure, leaving an oil which was taken up in ether. The ether extract was washed with water and dried ($MgSO_4$). The ether was evaporated and the resulting solid was extracted with ethanol. The residue was dried, yield 62%, mp 211–214°.

Anal. Calcd for $C_{36}H_{28}$: C, 93.87; H, 6.13. Found: C, 93.77; H, 6.31.

2,5-Diphenyl-3-hexyne-2,5-diol (XVI).[12]—Both the α and β forms were obtained in almost equal yields, 28–35% (70–75% overall): α form, mp 163°; β form, mp 125–126°.

2,5-Diphenyl-2,5-dimethoxy-3-hexyne (XVII).—Both diols gave good yields of the same dimethyl ether. The diol XVI was dissolved in 250 ml of warm methanol and to this solution was added 2 g of concentrated sulfuric acid in 20 ml of methanol. After 24 hr, the crystals were removed and washed with methanol, ammonium hydroxide, and again with methanol. The product was recrystallized from methanol, yield 85%, mp 76°; the ir spectrum showed no hydroxyl absorption.

Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.63; H, 7.48. Found: C, 81.60; H, 7.60.

1,1,4-Triphenyl-2-pentyne-1,4-diol (XIX).—The published synthesis of this compound[13] gave a yield of 64%. The product was recrystallized from benzene–cyclohexane, mp 124°.

1,1,4-Triphenyl-1,4-dimethoxy-2-pentyne (XX).—Over a period of 45 min a solution of 32.8 g (0.01 mol) of XIX in 250 ml of dry ether was added, under nitrogen, to 133 ml (0.2 mol) of a 15% butyllithium solution in hexane. The temperature was kept at 20°. At the end of the addition, the blue color had disappeared and the lithium salt had precipitated. Dimethyl sulfate (26 g, 0.22 mol) in 100 ml of dry ether was gradually added to the mixture at 5–10° and the mixture was stirred for 24 hr. A 0.5 *M* solution of sodium methoxide in methanol (100 ml) was added to destroy an excess dimethyl sulfate. The solution was washed with water and the ethane–hexane layer was dried ($MgSO_4$). The solvent was removed under reduced pressure and the residual oil was crystallized from methanol. The product was recrystallized from methanol, yield 69%, mp 54°. The ir spectrum had the characteristic methoxy absorption at 2825 cm^{-1} but no hydroxyl absorption.

(10) H. Lindlar and R. Dubuis, *Org. Syn.*, **46**, 89 (1966).

(11) P. Miquel, *Bull. Soc. Chim. Fr.*, **26**, 4 (1876); W. Bachmann, *J. Amer. Chem. Soc.*, **55**, 2136 (1933).

(12) G. Dupont, *C. R. Acad. Sci.*, **150** (1910).

(13) Y. S. Zalkind and A. P. Ivanov, *J. Gen. Chem. USSR*, **11**, 803 (1947).

Anal. Calcd for $C_{25}H_{24}O_2$: C, 84.27; H, 6.74. Found: C, 84.15; H, 6.60.

1,1-Diphenyl-4-methyl-2-pentyne-1,4-diol.—This diol was prepared by the method of Babayan,[14] yield 76%, mp 115°.

1,1-Diphenyl-4-methyl-1,4-dimethoxy-2-pentyne (XXII).—XXII was prepared by the procedure used for XX. Instead of crystallizing the residual oil from methanol, it was distilled *in vacuo*, yield 64%, bp 138–142° (0.55 mm), $n^{22}D$ 1.5495; the ir spectrum showed the methoxy absorption at 2825 cm^{-1}.

Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.63; H, 7.48. Found: C, 81.55; H, 7.41.

2,5-Diphenyl-3-hexyne-2,5-dicarboxylic Acid (XXIII).—2,5-Diphenyl-2,5-dimethoxy-3-hexyne (XVII) (5.88 g, 0.02 mol) was added to 200 ml of dry tetrahydrofuran, and 3.2 g (0.082 g-atom) of potassium was added under nitrogen. After stirring for 24 hr the dark solution was poured onto Dry Ice. The Dry Ice was allowed to evaporate and *tert*-butyl alcohol was added to destroy the excess potassium. The mixture was poured into water and the solution acidified with hydrochloric acid. The solution was extracted with ether and the extract was dried ($MgSO_4$). After removing the ether, the residue was recrystallized from carbon tetrachloride, yield 69%, mp 224° dec.

Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.53; H, 5.59. Found: C, 74.34; H, 5.68.

Decarboxylation of XXIII to 2,5-Diphenyl-2,4-hexadiene (XXIV).—Compound XXIII (1.61 g) was heated at 225° until the evolution of carbon dioxide had ceased. The residue was recrystallized from 95% ethyl alcohol, yield 68%, mp 138°; uv ($CHCl_3$) 317 mμ (ε 34,100). These values agreed with literature values.[15]

Protonation of the Dianion XVIII Corresponding to 2,5-Diphenyl-2,3,4-hexatriene. Preparation of 2,5-Diphenyl-2,3-hexadiene (XXV).—To a dianion solution prepared from 5.88 g (0.02 mol) of 2,5-diphenyl-2,5-dimethoxyhexyne-3 (XVII) and 3.2 g (0.082 g-atom) of potassium in 200 ml of tetrahydrofuran was added an excess of methanol at −20°. The solution was poured into water, and the resulting oil was separated, taken up in ether, and dried ($MgSO_4$). After removing the ether, the viscous oil was transferred to an alumina column with the aid of a little petroleum ether (bp 70–110°). The column was eluted with 500 ml of petroleum ether. The movement of the allene band was followed by the yellow color of the band and its fluorescence when irradiated with a uv lamp. Evaporation of the solvent gave the pure allene as a yellow oil, yield 48%; the uv spectrum showed the absence of any conjugated diene.

Anal. Calcd for $C_{18}H_{18}$: C, 92.30; H, 7.70; mol wt, 234. Found: C, 92.12; H, 7.82; mol wt, 242 (Rast method).

Isomerization of 2,5-Diphenyl-2,3-hexadiene (XXV) to 2,5-Diphenyl-2,4-hexadiene (XXIV).—XXV (1 g) was refluxed with 50 g of methanol containing 1 g of concentrated sulfuric acid for 2 hr. The solution was partially evaporated and cooled. The resulting product was recrystallized from ethanol, yield 60%, mp 138°, uv ($CHCl_3$) 320 mμ (ε 34,100).

1,1,4-Triphenyl-2-pentyne-1,4-dicarboxylic acid (XXVI).—A dianion solution prepared from 7.12 g (0.02 mol) of 1,1,4-triphenyl-1,4-dimethoxy-2-pentyne (XX) and 3.2 g (0.082 g-atom) of potassium, in 200 ml of tetrahydrofuran, was poured onto Dry Ice. The resulting solution was worked up as in the preparation of the diacid XXIII. The product was recrystallized from chloroform–cyclohexane, yield 64%, mp 194° dec.

Anal. Calcd for $C_{25}H_{20}O_4$: C, 76.71; H, 5.39. Found: C, 76.90; H, 5.49.

Decarboxylation of XXVI to 1,1,4-Triphenyl-1,3-pentadiene (XXVII).—Compound XXVI (1.92 g) was heated at 200° until the evolution of carbon dioxide had ceased. The residue was recrystallized from ethanol–water, yield 42%, mp 121–122°.

Anal. Calcd for $C_{23}H_{20}$: C, 93.24; H, 6.76. Found: C, 93.05; H, 6.87.

Protonation of Dianion XXI. Preparation of 1,1,4-Triphenyl-1,2-pentadiene (XXVIII).—To an anion solution prepared from 1,1,4-triphenyl-1,4-dimethoxy-2-pentyne (XX), prepared in the usual manner, was added an excess of methanol at −20°. The reaction mixture was worked up by the procedure used for XXV. A yellow oil was obtained after column chromatography, yield 55%.

Anal. Calcd for $C_{23}H_{20}$: C, 93.24; H, 6.76. Found: C, 93.11; H, 6.87.

Dimerization of 1,1,4-Triphenyl-1,2-pentadiene (XXVIII) to 1,2-Bis(diphenylmethylene)-3,4-bis(1-phenylethyl)cyclobutane (XXIX).—One gram of the allene XXVIII was heated at 150° for 2 hr. The residue was dissolved in acetone and precipitated by the addition of ethanol. The product was recrystallized from chloroform–methanol, yellow crystals, yield 39%, mp 197°.

Anal. Calcd for $C_{46}H_{40}$: C, 93.24; H, 6.76; mol wt, 592. Found: C, 93.41; H, 6.92; mol wt, 576 (Rast method).

Isomerization of 1,1,4-Triphenyl-1,2-pentadiene (XXVIII) to 1,1,4-Triphenyl-1,3-pentadiene (XXVI).—XXVII (1 g) was refluxed in 50 ml of ethanol containing 5 ml of concentrated sulfuric acid for 3 hr. On cooling, an oil separated which was crystallized from methanol–water and recrystallized from methanol–water, yield 34%, mp 121–122°.

Attempted Preparation of a Dianion Corresponding to 1,1-Diphenyl-4-methyl-1,2,3-pentatriene. Ethylation of the Resulting Solution to Form 3,3,10,10-Tetraphenyl-6,6,7,7-tetramethyl-4,8-dodecadiyne (XXX).—To a solution prepared from 5.88 g (0.02 mol) of 1,1-diphenyl-4-methyl-1,4-dimethoxy-2-pentyne (XXII) and 3.2 g (0.082 g-atom) of potassium was added 15.4 g (0.1 mol) of diethyl sulfate at 0°. After 30 min, methanol was gradually added to destroy the excess potassium, and the mixture was then poured into water. The oil which separated was taken up in ether, washed with water, and dried ($MgSO_4$). After the ether was removed, the residue was recrystallized from methanol, yield 50%, mp 154°.

Anal. Calcd for $C_{40}H_{42}$: C, 91.95; H, 8.05; mol wt, 522. Found: C, 91.76; H, 8.18; mol wt, 501 (Rast method).

Registry No.—III, 31382-35-1; IV, 12537-75-6; V, 31382-36-2; VI, 31382-37-3; VII, 31382-38-4; VIII, 31382-39-5; IX, 31382-40-8; XI, 31382-41-9; *rac*-XIII, 31382-42-0; *meso*-XIII, 31382-43-1; *rac*-XIV, 31382-44-2; *meso*-XIV, 31382-45-3; XV, 31382-46-4; XVI, 6289-26-5; XVII, 31382-48-6; XVIII, 12537-72-3; XIX, 2979-97-7; XX, 31382-49-7; XXI, 12537-74-5; XXII, 31382-50-0; XXIII, 31428-89-4; XXIV, 16819-47-9; XXV, 31382-52-2; XXVI, 31382-53-3; XXVII, 31382-54-4; XXVIII, 31382-55-5; XXIX, 31382-56-6; XXX, 31382-57-7; 1,1-diphenyl-4-methyl-1,2,3-pentatriene dianion, 12537-73-4; 1,4-diphenyl-1,4-di(1-naphthyl)-1,4-dimethoxy-2-butyne, 31382-58-8.

(14) J. Salkind and V. Teterin, *Chem. Ber.*, **60B**, 32 (1927); A. T. Babayan, *J. Gen. Chem. USSR*, **10**, 1177 (1940).

(15) M. Kolobielski and H. Pines, *J. Amer. Chem. Soc.*, **79**, 5820 (1957).

Isomerization of Fluorenone Anil *N*-Oxide to *N*-Phenylphenanthridone by Photochemical and Mass Spectral Pathways

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In an earlier note[2] it was suggested that in the isomerization of 2-phenylisatogen to 2-phenyl-4*H*-3,1-benzoxazin-4-one there was similar behavior in both the photolytic and the mass spectral pathways. The nitrone–amide rearrangement has been discussed in terms of a photochemical–mass spectral analogy.[3] A common oxaziridine intermediate was proposed for both 2-phenylisatogen and 2-phenyl-4*H*-3,1-benzoxazin-4-one in their mass spectral fragmentations.[2]

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(2) D. R. Eckroth, *Chem. Commun.*, 465 (1970).

(3) R. G. Cooks, *Org. Mass Spectrom.*, **2**, 481 (1969).

TABLE I

MASS SPECTRAL DATA

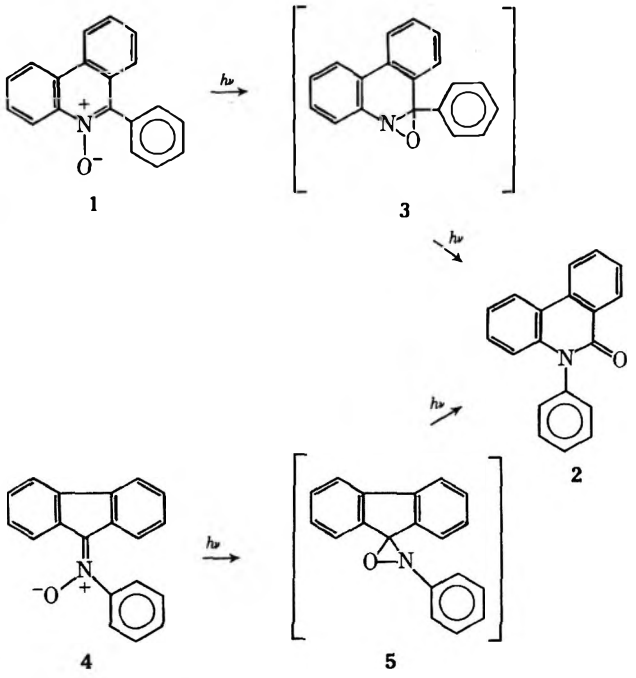
m/e in 1, 2, and 4	Rel intensity 1, 70 eV	Rel intensity 2, 70 eV	Rel intensity 4, 20 eV	Rel intensity 4, 70 eV	m/e in 4*[a]	Rel intensity 4*, 20 eV	Rel intensity 4*, 70 eV
272	17.3	21.7	21.0	20.0	^{13}C M$^+$	100.0	71.2
271 M$^+$	90.2	100.0	100.0	100.0	^{13}C M − H	97.5	100.0
270 M − H	100.0	33.9	34.5	75.0		27.0	46.1
256	7.8	0.7	2.2	2.8	^{13}C M − O	4.0	9.8
255 M − O	41.0	3.2	7.5	12.5	^{13}C M − OH	14.0	17.2
254 M − OH	89.6	7.4	2.0	15.8		13.5	14.5
244				1.5	^{13}C M − CO		3.5
243 M − CO	7.1	14.0	3.5	6.0	^{13}C M − ^{13}CO or ^{13}C M − CHO	8.0	10.5
242 M − CHO	21.2	9.5	3.2	19.2	^{13}C M − ^{13}CHO or ^{13}C M − NO	17.0	10.5
241 M − (CHO + H) or M − NO	14.7	10.2	0.5	4.8	^{13}C M − (^{13}CHO + H) or ^{13}C M − NOH	9.0	6.5
240 M − (CHO + 2H) or M − NOH	5.4	3.3		2.2			4.0
181			1.2	5.0	^{13}C M − C_6H_5N	18.0	21.8
180 M − C_6H_5N			7.1	32.5		11.0	18.8
179				2.1	^{13}C M − (C_6H_5 + O)		7.0
178 M − (C_6H_5 + O)	2.8	2.5		8.0			10.0
169	1.4	8.4		1.1		5.0	5.0
168 M − C_6H_5CN	9.2	54.2		7.0		4.0	5.0
164 M − (C_6H_5 + NO)				5.8			11.0
163 M − (C_6H_5 + NOH)				10.5			8.8
153				2.2			4.0
152 M − (C_6H_5N + CO)	2.3	0.8		2.1			16.5
151 M − (C_6H_5N + CHO)	5.3	2.3		13.1			14.0
139 M − (C_6H_5CN + CHO)	7.2	36.6		1.9			3.5
105	6.2	23.5					
91			13.1	84.0			85.0
77	5.0	10.6		5.3			6.5

[a] 4* contains 52.6:47.4 ^{13}C–^{12}C at C-9 calculated at 20 eV.

Taylor, *et al.*,[4] have described the photoisomerization of 10-phenylphenanthridine *N*-oxide (1) to *N*-phenylphenanthridone (2) for which they proposed the intermediate oxaziridine **3**.[5] The mass spectra[6] of **1** and **2** at 70 eV show similar fragmentation patterns; they appear to undergo skeletal rearrangement involving the oxaziridine intermediate **3**.

Fluorenone anil *N*-oxide (**4**) can be photoisomerized to **2** by irradiation for 3 hr in cyclohexane or absolute ethanol solutions of 10^{-3} or 10^{-4} *M* with Rayonet 2537-Å lamps. Johnson[7] irradiated 4.15×10^{-2} *M* **4** in acetonitrile with no observable reaction. We find irradiation of 10^{-2} *M* **4** in cyclohexane or absolute ethanol with a 450-W medium-pressure lamp exhibits no isomerization. A reaction dependence upon concentration is implied.[8] The oxaziridine **5** is proposed as an intermediate in the photoisomerization.

Earlier studies of mass spectral fragmentations of α-phenylnitrones have shown the oxaziridine intermediate to be unimportant in the metastable loss of CO.[9] In order to determine whether **5** is taking part in the fragmentation pattern of **4**, ^{13}C-labeled fluorenone anil *N*-oxide (**4***) was studied. That **5** is operative in the skeletal rearrangement of **4** is obvious since 80% of the CO lost in the spectrum of **4*** contained ^{13}C, while only approximately 20% of the fragmentation of **4*** to give CO involves loss of a carbon from one of the fused benzene rings. The metastable OH loss occurs by a H abstraction mechanism. All rearrangement processes are of the general type $[ABC]^+ \rightarrow [AC]^+ + B$.



(4) E. C. Taylor and G. G. Spence, *Chem. Commun.*, 767 (1966); 1037 (1968).

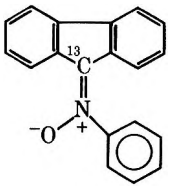
(5) G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, **70**, 231 (1970).

(6) Mass spectra were determined by Mrs. Willa Jones with an Atlas CH-4 mass spectrometer at 20 and 70 eV using a direct probe with source temperature of 175–225°.

(7) A. W. Johnson, *J. Org. Chem.*, **28**, 252 (1963).

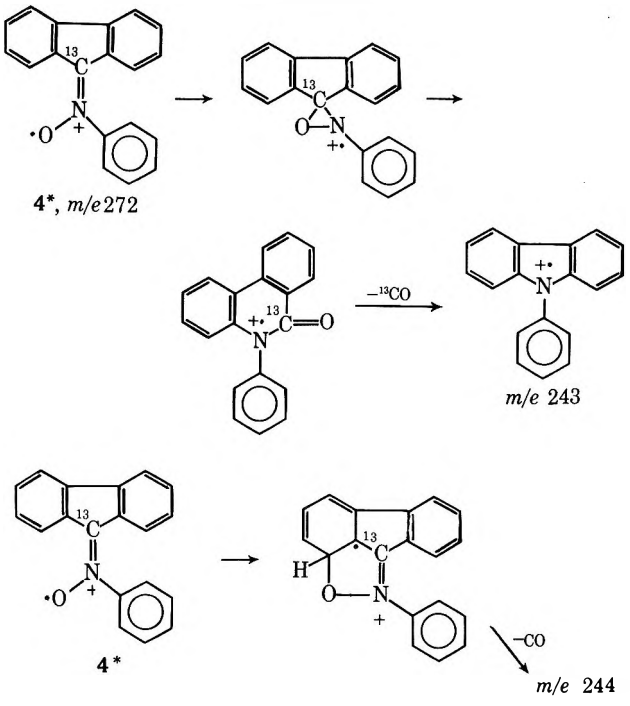
(8) Concentration dependence of photoisomerization has been observed before; see D. R. Eckroth and R. H. Squire, *ibid.*, **36**, 224 (1971).

(9) T. H. Kinstle and J. G. Stam, *Chem. Commun.*, 185 (1968).



4*

While the mass spectra of **1** and **4** are quite normal and in accord with results reported in an earlier study,[2] the mass spectral fragmentation of **2** is remarkably similar to that of **1** but significantly unlike that of **4** (see Table I).



Experimental Section

Fluorenone anil was prepared according to the procedure described by Reddelien.[10]

Fluorenone Anil *N*-Oxide (4).—To a solution of 5.0 g of fluorenone anil in 200 ml of chloroform was added 7.2 g of *m*-chloroperoxybenzoic acid (85% pure). The yellow solution, which turned pale yellow after 45 min, was kept at room temperature for 3 days. The solution was poured through a column of neutral alumina and then evaporated on the Rotovac. The resulting material was crystallized from 95% ethanol affording yellowish needles of **4**, 3.4 g (64%), mp 189–190° (lit.[7] mp 191–193°).

***N*-Phenylphenanthridone (2).** **A.**—A 4×10^{-3} *M* solution of **4** (500 ml) in cyclohexane was irradiated for 8 hr in a water-cooled chamber with a 450-W medium-pressure total immersion lamp (quartz filter). After irradiation, examination of the solution by thin layer chromatography gave evidence that most of the starting material had been unaffected by the irradiation. Evaporation of solvent gave an oil which was passed through a column of silica gel with chloroform. The first eluted fraction, after removal of solvent, was an oil which had an infrared spectrum similar to that of an authentic sample of *N*-phenylphenanthridone.

B.—A 10^{-4} *M* solution of **4** (500 ml) in 95% ethanol was irradiated for 3 hr in a Rayonet reaction chamber with 2537-Å lamps and then the solvent was evaporated. The solid residue (8.5 mg, mp 218°) was recrystallized from 95% ethanol to give colorless crystals of **2**, 2.8 mg (21%), mp 227° (lit.[11] mp 225°). The infrared spectrum, identical with that of an authentic sample of **2**, exhibited characteristic peaks at 2920, 1650, 1450, 1370, and 745 cm^{-1}.

(10) G. Reddelien, *Ber.*, **43**, 2476 (1910).
(11) D. H. Hey and T. M. Moynehan, *J. Chem. Soc.*, 1563 (1959).

Biphenyl-2-carboxylic Acid-α-^{13}C.—2-Iodobiphenyl was converted to the Grignard reagent which was carbonated using the vacuum line technique at −20° with 100 ml of $^{13}CO_2$[12] (54% enrichment, Bio-Rad Laboratories). Crystallization yielded 574.3 mg of colorless crystals (81.2% based on CO_2), mp 113.5–114°. The infrared spectrum exhibited a carbonyl peak at 1680 cm^{-1}; nmr (in CCl_4) showed peaks at δ 11.6 (s, H of acid) and 7.2–8.0 (m, 9 H).

Fluorenone-9-^{13}C.—Ring closure was carried out with 574.3 mg (2.92 mmol) of biphenyl-2-carboxylic acid-α-^{13}C dissolved in 2.6 ml of 80% sulfuric acid.[13] The mixture was heated at 85° for 0.5 hr and poured onto crushed ice. The greenish-yellow product was extracted with ether and the ether extract was washed with 3 *N* sodium hydroxide. Ether was removed and crystallization from water yielded 419.9 mg (2.32 mmol, 79.5%) of yellow-green product, mp 82° (lit.[13] 84–86°). Ir and nmr spectra were identical with those of unlabeled fluorenone.

9-Fluorenone hydrazone-α-^{13}C was prepared according to the procedure described by Wieland and Roseau.[14]

9-Diazofluorene-α-^{13}C was prepared by following the procedure of Closs, *et al.*[15]

Fluorenone anil *N*-oxide-α-^{13}C (4*) was prepared according to the procedure for the synthesis of **4** as described by Johnson.[16] A slurry of 383.2 mg of 9-diazofluorene-α-^{13}C (1.98 mmol) and 212 mg (1.98 mmol) of nitrosobenzene in 10 ml of dry ether was stirred for 1 hr. The mixture was filtered and the yellow crystals were recrystallized from 95% ethanol, mp 198–199° (lit.[16] mp 200°). Ir (CCl_4) exhibited a peak at 1270 cm^{-1} (N→O). The mass spectrum at 20 eV showed 52.6% excess ^{13}C.

Registry No.—**1**, 15263-58-8; **2**, 13355-65-2; **4**, 4535-09-5; biphenyl-2-carboxylic acid-α-^{13}C, 31504-46-8.

Acknowledgment.—We are grateful to Professor Edward C. Taylor for generous supplies of compounds **1** and **2**.

(12) A. Murray and D. H. Williams, "Organic Synthesis with Isotopes," Interscience, New York, N. Y., 1958, p 78.
(13) C. Heidelberger and H. Reike, *Cancer Res.*, **11**, 640 (1951).
(14) H. Wieland and A. Roseau, *Justus Liebigs Ann. Chem.*, **381**, 231 (1911).
(15) G. L. Closs and R. A. Moss, *J. Amer. Chem. Soc.*, **86**, 4042 (1964).
(16) A. W. Johnson, *J. Org. Chem.*, **28**, 2153 (1963).

Nitration of Antibiotic X-537A and Facile Conversion to 6-Hydroxy-2,7-dimethyl-5-nitroquinoline

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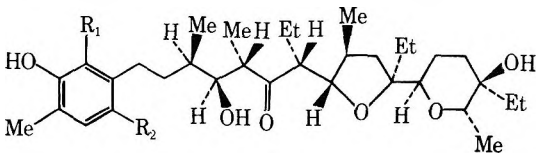
The structure[1] and biosynthesis[2] of antibiotic X-537A (**1a**) have been reported recently. As part of a chemical study on this antibiotic, we have investigated the nitration of **1a** in glacial acetic acid. Treatment with 5 molar equiv of concentrated nitric acid gave the expected 5-nitro derivative **1b**. However, the major product was shown by base degradation to be dinitrophenol **1c**. This result was consistent with the observation[3] that nitration of highly substituted benzene

(1) (a) J. W. Westley, R. H. Evans, Jr., T. Williams, and A. Stempel, *Chem. Commun.*, 71 (1970); (b) S. M. Johnson, J. Herrin, S. J. Liu, and I. C. Paul, *ibid.*, 72 (1970).
(2) J. W. Westley, R. H. Evans, Jr., D. L. Pruess, and A. Stempel, *ibid.*, 1467 (1970).
(3) H. Barbier, *Helv. Chim. Acta*, **11**, 157 (1928).

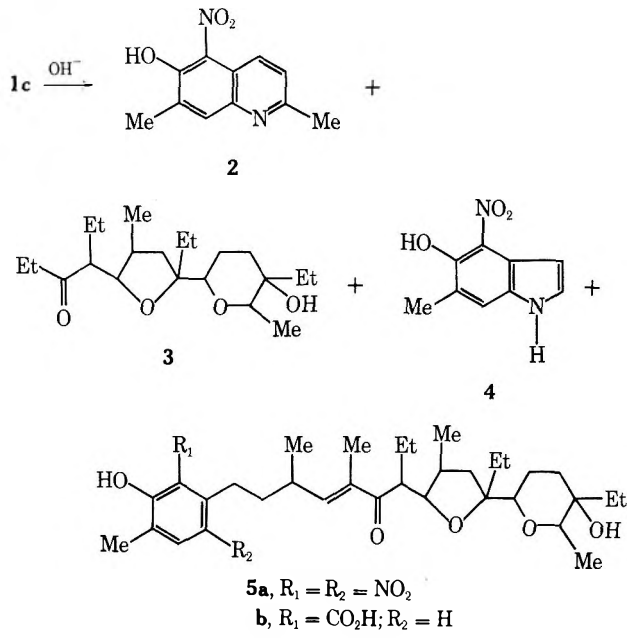
derivatives often results in the displacement of substituents meta to the entering group by additional nitro groups. In addition, salicylic acid is known to readily decarboxylate probably *via* a β-keto acid tautomer.



1a, $R_1 = CO_2H$; $R_2 = H$
b, $R_1 = CO_2H$; $R_2 = NO_2$
c, $R_1 = R_2 = NO_2$

To confirm the structure of **1c**, the derivative was treated under conditions known to cause retroaldol cleavage[1a] of the antibiotic. Four compounds were isolated from the reaction (Scheme I).

SCHEME I

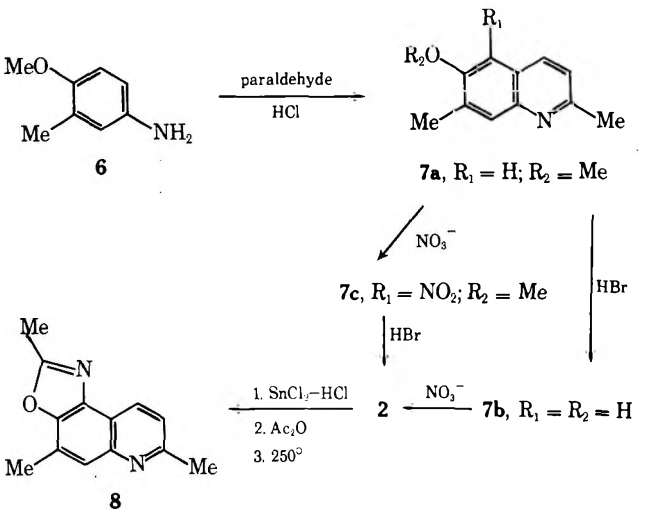


One product was identical with the ketone **3** previously isolated[1a] from **1a** under identical conditions. The other major cleavage product was tentatively identified by microanalysis and spectroscopic methods as 6-hydroxy-2,7-dimethyl-5-nitroquinoline (**2**). A third compound isolated in very low yield was identified as 5-hydroxy-6-methyl-4-nitroindole (**4**) by comparison with material prepared by nitration of 5-hydroxy-6-methylindole.[4]

The structure of the three cleavage products was consistent with the dinitrophenol structure **1c**, proposed for the major nitration product of antibiotic X-537A. The fourth compound isolated was the α,β-unsaturated ketone **5a**, which arose from dehydration of the β-ketol system in **1c**. The analogous compound **5b** has been isolated[5] from base treatment of the antibiotic.

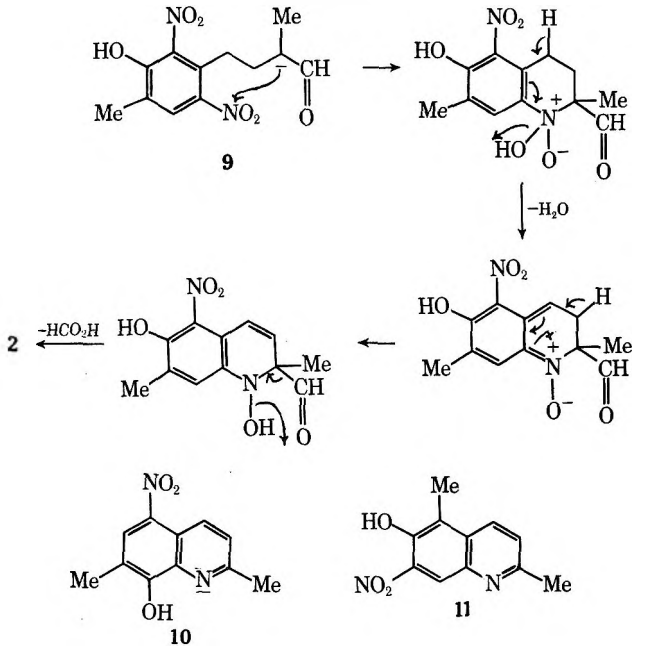
Confirmation of structure **2** was provided by an alternative synthesis (Scheme II). Conversion of **2** in three steps[6] to the oxazoquinoline **8** was further evidence of an *o*-nitrophenol structure for **2**.

SCHEME II



Compound **2** probably arose in the base degradation reaction *via* cyclization of the carbanion **9** followed by dehydration, tantomerization, and elimination of formic acid (Scheme III).

SCHEME III



It should be noted that, whereas cyclization of **9** could have given the 8-hydroxy isomer **10**, the other possible isomer from the Doebner–Miller reaction on 3-methyl-4-methoxyaniline[7] (**6**, Scheme II) would have led to the 2,5-dimethyl isomer **11**. Therefore, only **2** could have arisen from *both* syntheses.

The base-catalyzed cyclization of **9** to **2** is a novel type of quinoline synthesis. However, the aromatic substituents necessary to cause the base-catalyzed cyclization of *o*-nitrophenylbutyraldehyde to quinoline have not been determined.

(4) F. Troxler, G. Bormann, and F. Seemann, *Helv. Chim. Acta.*, **51**, 1203 (1968).
(5) J. W. Westley and R. H. Evans, Jr., unpublished results.
(6) R. C. Elderfield, "Heterocyclic Compounds," Vol. 5, Wiley, New York, N. Y., 1957, p 420.
(7) M. Heidelberger and W. A. Jacobs, *J. Amer. Chem. Soc.*, **41**, 1450 (1919).

Experimental Section[8]

Conversion of Antibiotic X-537A (1a) into the 5-Nitro Derivative of X-537A (1b) and 2-Methyl-4,6-dinitro-5-(7-ethyl-4-hydroxy-3,5-dimethyl-6-oxo-7-[5-ethyl-3-methyl-5-(5-ethyl-5-hydroxy-6-methyl-2-tetrahydropyranyl)-2-tetrahydrofuryl]heptyl)phenol (1c).—To a stirred solution of 2.0 g (3.39 mmol) of **1a** in 75 ml of glacial acetic acid was added 1 ml of concentrated nitric acid at room temperature. After 0.5 hr, 75 ml of water was added and the mixture was extracted with two 100-ml portions of ether. The combined extracts were washed with three 100-ml portions of saturated aqueous sodium carbonate solution, dried (Na_2SO_4), and evaporated to give 2.4 g of a yellow solid. Treatment with methylene chloride gave 840 mg (47%) of **1c** as the sodium salt which, on recrystallization from benzene, gave yellow needles: mp 165–170°; $[\alpha]_D$ +19.6° (c 1, DMSO); ir (KBr) 1710 and 1605 cm^{-1}; uv max (2-propanol) 413 mμ (ε 19,600); nmr (DMSO-d_6) δ 1.92 (s, 3, aromatic CH_3), 3.81 (s, 1, OH), 4.02 (d, 1, CHO, J = 6 Hz), 7.86 (s, 1, aromatic). *Anal.* Calcd for $C_{33}H_{51}N_2O_{10}Na$: C, 60.16; H, 7.80; N, 4.25. Found: C, 59.79; H, 8.07; N, 4.20.

The methylene chloride filtrate was concentrated under reduced pressure and chromatographed on 20 g of silica using methylene chloride–methanol (1%) as the eluent. The first fraction eluted gave 660 mg (37%) of **1b** sodium salt, which, on recrystallization from methylene chloride–hexane, gave pale yellow plates: mp 214–215°; $[\alpha]_D$ −98° (c 1, DMSO); ir ($CHCl_3$) 1710, 1605 cm^{-1}; uv max (2-propanol) 262 mμ (ε 5800) and 317 (5400); nmr (DMSO-d_6) δ 2.12 (s, 3, aromatic CH_3), 7.60 (s, 1, aromatic). *Anal.* Calcd for $C_{34}H_{52}NO_{10}Na$: C, 62.18; H, 7.98; N, 2.13; Na, 3.49. Found: C, 62.02; H, 8.25; N, 2.11; Na, 3.27.

Base Transformation of 1c into 4-[5-Ethyl-3-methyl-5-(5-ethyl-5-hydroxy-6-methyl-2-tetrahydropyranyl)-2-tetrahydrofuryl]-3-hexanone (3), 5-Hydroxy-6-methyl-4-nitroindole (4), 6-Hydroxy-2,7-dimethyl-5-nitroquinoline (2), and 2-Methyl-4,6-dinitro-5-(7-ethyl-3,5-dimethyl-6-oxo-7-[5-ethyl-3-methyl-5-(5-ethyl-5-hydroxy-6-methyl-2-tetrahydropyranyl)-2-tetrahydrofuryl]-4-heptenyl)phenol (5a).—A solution of 10 g of the dinitrophenol **1c** in 700 ml of 1:1 aqueous dioxane containing 50 g of sodium hydroxide was stirred for 20 hr at room temperature. The solution separated into two phases, and the upper phase was treated with 200 ml of water and 200 ml of ethyl acetate. The organic layer was separated and concentrated to 6.13 g of a viscous oil. The oil was chromatographed on 350 g of silica using a linear gradient from 4 l. of methylene chloride to 4 l. of 1:1 methylene chloride–ether. The first fraction was concentrated and crystallized by the addition of hexane to give 8 mg (0.3%) of 5-hydroxy-6-methyl-4-nitroindole (**4**) as orange needles: mp 185–187°; uv max (methanol) 210 mμ (ε 21,300), 247 (10,200), 274 infl (2890), 398 (9300); ir ($CHCl_3$) 3485, 1630, 1580, 1480 cm^{-1}; nmr ($CDCl_3$) δ 2.38 (s, 3, aromatic CH_3), 7.23 (s, 1, NH), 7.23 (t, 1, J = 2 Hz, CH=CHN), 7.32 (t, 1, J = 2 Hz, CH=CH—N), 7.51 (s, 1, aromatic), 12.01 (s, 1, aromatic OH); mass spectrum (70 eV) m/e 193 (M^+), 175 (loss of OH from *o*-nitrophenol system). *Anal.* Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.19; N, 14.57. Found: C, 56.71; H, 3.97; N, 14.22.

The second fraction gave, on evaporation, 4.07 g (76%) of the ketone **3**, which was identical with the compound isolated[1] from retroaldol cleavage of **1a** by uv max (2-propanol) 283 mμ (ε 57); ir ($CHCl_3$) 3600, 1710 cm^{-1}; and mass spectrum m/e 354 (M^+). *Anal.* Calcd for $C_{21}H_{38}O_4$: C, 71.14; H, 10.80. Found: C, 71.37; H, 10.61.

The third fraction was concentrated and, after addition of hexane, gave 501 mg of the sodium salt of the α,β-unsaturated ketone **5a** as yellow needles: mp 222–223°; $[\alpha]_D$ +66° (c 1, $CHCl_3$); ir ($CHCl_3$) 1615 and 1605 cm^{-1}; uv max (2-propanol) 232 mμ (ε 21,700), 388 (10,850); nmr ($CDCl_3$) δ 1.76 (s, 3, CH_3C=), 2.20 (s, 3, aromatic CH_3), 6.53 (d, 1, J = 10 Hz, C = CHCH), 7.95 (s, 1, aromatic); mass spectrum m/e 640 (M^+). *Anal.* Calcd for $C_{33}H_{49}N_2O_9Na$: C, 61.86; H, 7.71; N, 4.37; Na, 3.59. Found: C, 62.09; H, 7.84; N, 4.28; Na, 3.29.

The aqueous phase was acidified with hydrochloric acid to pH 2.0 and extracted twice with ethyl acetate. The extracts were combined and concentrated to 1.8 g of crude solid. Chromatography on 200 g of silica gave a further 360 mg of **5a** for a total yield of 861 mg (9%).

An earlier fraction gave 366 mg (11%) of 6-hydroxy-2,7-dimethyl-5-nitroquinoline (**2**) which crystallized as yellow needles mp 175–176°, from methylene chloride–hexane; ir ($CHCl_3$) 3250, 1660, 1620, 1570, 1520 cm^{-1}; uv max (2-propanol) 221 mμ (ε 38,690), 296 sh (4580), 330 (6760), 370 sh (4100); nmr ($CDCl_3$) δ 2.50 (s, 3, aromatic CH_3), 2.72, (s, 3, aromatic CH_3), 7.42, 9.00 (AB, 2, J_{ortho} = 8 Hz, aromatic), 8.02 (s, 1, aromatic), 12.46 (s, 1, aromatic OH); mass spectrum m/e 218 (M^+), 201 (loss of OH from *o*-nitrophenol). *Anal.* Calcd for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.53; H, 4.61; N, 12.89.

5-Hydroxy-6-methyl-4-nitroindole (4).—To 588 mg (4.0 mmol) of 5-hydroxy-6-methylindole[6] dissolved in 25 ml of concentrated sulfuric acid at 5° was added an ice-cold solution of 350 mg (4.1 mmol) of sodium nitrate in 10 ml of concentrated sulfuric acid while maintaining the reaction temperature at 2–5°. After an additional 5 min, the amber-black solution was poured onto 500 ml of ice water. The resulting suspension was extracted with three 200-ml portions of methylene chloride–ethyl acetate (1:1) and the organic phases were backwashed with 100 ml of 5% sodium bicarbonate solution. The combined organic phases were dried (Na_2SO_4), filtered, evaporated under reduced pressure to give a brown solid which was dissolved in 100 ml of methylene chloride, and filtered through a column of 5 g of silica gel prepared in hexane. The column was eluted with chloroform until no residue was obtained on evaporation of the solvent. The red solid (585 mg) thus obtained was crystallized from ether to give 450 mg (59%) of 5-hydroxy-6-methyl-4-nitroindole (**4**) as orange needles, mp 186–187°. This material was identical by mixture melting point, tlc, ir, uv, nmr, and mass spectrum with the compound isolated from the base treatment of **1c**.

6-Methoxy-2,7-dimethylquinoline (7a).—To a solution of 145 g (1.06 mol) of 3-methyl-4-methoxyaniline[7] (**6**) in 500 ml of concentrated hydrochloric acid was added 200 g of paraldehyde. The stirred mixture was warmed in an oil bath to 60°. Another 50 g of paraldehyde was added and the reaction mixture heated to reflux (oil bath 130°) within 1 hr. Heating and stirring were continued for 3.5 hr at 140°. The mixture was allowed to cool to 80° and then was poured into an aqueous solution of excess potassium carbonate. The alkaline solution and its precipitates were extracted with 1 l. of chloroform. The organic layer was washed with water, dried (Na_2SO_4), and concentrated *in vacuo*. The remaining black oil was distilled at reduced pressure to yield 77.5 g (29%) of approximately 75% pure **7a** (by nmr), bp 122–27° (0.250 mm). The compound formed a picrate, mp 243–244.5°, which crystallized from methanol. *Anal.* Calcd for $C_{18}H_{16}N_4O_8$ (416.34): C, 51.92; H, 3.87; N, 13.46. Found: C, 51.95; H, 4.06; N, 13.19.

6-Hydroxy-2,7-dimethylquinoline (7b).—A solution of 70 g of crude (75%) **7a** (0.28 mol) in 400 ml of 48% hydrobromic acid was stirred and heated at reflux (oil bath 130°) for 4 hr. Then 100 ml of 48% hydrobromic acid was added and the reaction mixture was heated at 150° for another 4 hr. The mixture was poured over ice. Concentrated ammonia was added until the solution was slightly alkaline. The white precipitate was separated by filtration, washed with water followed by 50% ethanol, and dried *in vacuo* giving 47.0 g of crude material, mp 269–272°. This was extracted with 500 ml of methanol under reflux, cooled, and filtered to yield 32.0 g of **7b**, mp 273–275°, and from the mother liquor an additional 4.8 g, mp 270–273°, was obtained. Total yield was 36.8 g (76%) of **7b**: ir (KBr) 3160–2400, 1950, 1800 cm^{-1}; uv max (2-propanol) 213 mμ (ε 43,600), 234 (37,600), 273 (2950), 283 (2800), sh 327 (5000), 337 (5400); nmr (DMSO) δ 2.35 (s, 3, 7-CH_3), 2.57 (s, 3, 2-CH_3) 7.13 (s, 1, H_5), 7.21, 7.95 (AB, 2, J = 8.5 Hz, $H_{3,4}$) 7.68 (s, 1, H_8); mass spectrum m/e 173 (M^+). *Anal.* Calcd for $C_{11}H_{11}NO$ (173.20): C, 76.27; H, 6.40; N, 8.09. Found: C, 76.27; H, 6.73; N, 8.04.

6-Methoxy-2,7-dimethyl-5-nitroquinoline (7c).—To a stirred solution of 19.5 g (0.078 mol) of approximately 75% (purity) **7a** in 50 ml of concentrated sulfuric acid, 11.0 g (0.108 mol) of potassium nitrate was added at room temperature in small portions over a period of 1 hr. The mixture was then warmed

(8) The ultraviolet spectra were measured with a Cary recording spectrophotometer Model 14M. Nuclear magnetic resonance spectra were obtained with a Varian Associates Model A-60 or HA-100 spectrophotometer. Chemical shifts are reported in δ with the following abbreviations: s, singlet; m, multiplet; t, triplet; b, broad. Optical rotations were measured with a Perkin-Elmer polarimeter Model 141 using a 1% solution at 25°. The mass spectra were taken with a CEC-21-110 mass spectrometer at 70 eV.

to 40° for 3 hr and poured over ice. After neutralization with ammonium hydroxide, the organic material was extracted twice with 200 ml of chloroform. The organic layer was washed twice with 200 ml of water, dried (Na_2SO_4), evaporated, and taken up in 100 ml of ether. This solution was treated with charcoal, heated, and washed thoroughly with ether through 40 g of Florisil. On concentration at reduced pressure and crystallization, 7.37 g (41%) of tan needles, mp 88–89.5°, was obtained. The mother liquor yielded another 1.05 g of less pure material. Recrystallization of the first crop from ether afforded **7c**: mp 88.5–90°; ir ($CHCl_3$) 1526, 1345 cm^{-1}; uv max (2-propanol) 228 mμ (ε 51400), 277 (4450), sh 311–314 (5000), 324–325 (6400); nmr (DMSO) 2.52 (s, 3, 7-CH_3), 2.67 (s, 3, 2-CH_3), 3.94 (s, 3-OCH_3), 7.55, 7.96 (AB, 2, J = 8.5 Hz, $H_{3,4}$), 8.06 (s, 1, H_8); mass spectrum m/e 232 (M^+). *Anal.* Calcd for $C_{12}H_{12}N_2O_3$ (232.23): C, 62.06; H, 5.21; N, 12.06. Found: C, 61.83; H, 5.34; N, 11.97.

6-Hydroxy-2,7-dimethyl-5-nitroquinoline (2). **Method A.**—To a solution of 32.0 g (184.8 mmol) of **7b** in 100 ml of concentrated sulfuric acid, stirred in an ice bath, a solution of 20.4 g (200 mmol) of potassium nitrate in 50 ml of concentrated sulfuric acid was added dropwise within 30 min. The reaction mixture was stirred for 2 hr in an ice bath and then for 2 hr at room temperature. The reaction mixture was poured over ice, neutralized with ammonium hydroxide, and extracted with 1.5 l. of chloroform. The organic layer was washed twice with 500 ml of water, dried (Na_2SO_4), washed thoroughly with chloroform through 100 g of Florisil, and finally concentrated to 300 ml to yield 33.8 g of **2**, mp 177–178.5°, as small plates. From the mother liquor another 2.95 g, mp 178°, was obtained; the total yield was 36.75 g (91.5%). This material was identical by mixture melting point, tlc, and spectra with the material isolated from the base treatment of **1c**.

Method B.—A mixture of 0.5 g (2.15 mmol) of **7c** and 15 ml of 40% hydrobromic acid was heated at reflux for 3 hr (oil bath temperature 150°), then was poured over ice, neutralized with ammonium hydroxide, and extracted twice with 200 ml of chloroform. The combined chloroform layers were washed with 100 ml of water, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was crystallized from ethanol and gave 0.39 g (83%) of **2**, yellow needles, mp 177–178.5°.

5-Amino-6-hydroxy-2,7-dimethylquinoline.—A solution of 4.36 g (2.0 mmol) of **2**, in 50 ml of concentrated hydrochloric acid was warmed together with 20 g of stannous chloride dihydrate on a steam bath until the solution became colorless. This mixture was neutralized with sodium carbonate and extracted with 500 ml of chloroform. The emulsion which formed was filtered through Celite. The chloroform layer was separated, dried (Na_2SO_4), and concentrated to yield 250 mg (6.6%) of a brownish powder: mp 231–233°; ir (KBr) 3400, 3350, 3260, 2700–2500 cm^{-1}; mass spectrum m/e 188 (M^+). *Anal.* Calcd for $C_{11}H_{12}N_2O$ (188.22): C, 70.18; H, 6.43; N, 14.88. Found: C, 70.23; H, 6.45; N, 15.02.

5-Acetamido-6-acetoxy-2,7-dimethylquinoline.—A solution of 150 mg (0.8 mmol) of 5-amino-6-hydroxy-2,7-dimethylquinoline and 5 ml of acetic anhydride was warmed on the steam bath for 10 min. After cooling, ether was added and the crystals, which were separated by filtration, were washed with ether to yield 180 mg (83%): mp 239.5–240°; ir (KBr) 3275, 1750, 1658 cm^{-1}; nmr (DMSO) 2.16 (s, 3, 7-CH_3), 2.33 (s, 6, 2CH_3C=O), 2.66 (s, 3, 2-CH_3), 7.37, 8.07 (AB, 2, J_{ortho} = 8 Hz, $H_{3,4}$) 7.80 (s, 1, H_8), 9.80 (s, 1, NH); mass spectrum m/e 272 (M^+). *Anal.* Calcd for $C_{15}H_{16}N_2O_3$ (272.29): C, 66.16; H, 5.92; N, 10.29. Found: C, 66.11; H, 5.99; N, 10.29.

2,4,7-Trimethoxyloxazolo[4,5-*f*]quinoline (8).—Pyrolysis of 100 mg (0.37 mmol) of 5-acetamido-6-acetoxy-2,7-dimethylquinoline in a metal bath at 250° resulted in the evolution of acetic acid. After 5 min, the reaction was finished and the crude semicrystalline oil was dissolved in an ether–methylene chloride mixture and washed with methylene chloride through 0.5 g of Florisil. The almost colorless solution was concentrated under reduced pressure. The crude residue crystallized from ether to give 35 mg (45%) of **8**: mp 134–134.5°; nmr ($CDCl_3$) δ 2.64, 2.70, 2.71 (s, 9, 3CH_3) 7.32, 8.55 (AB, 2, J_{ortho} = 8.5 Hz, $H_{3,4}$), 7.71 (s, 1, H_8); mass spectrum m/e 212 (M^+). *Anal.* Calcd for $C_{13}H_{12}N_2O$ (212.24): C, 73.56; H, 5.70; N, 13.20. Found: C, 73.76; H, 5.72; H, 13.27.

Registry No.—**1a**, 25999-31-9; **1b** sodium salt, 31478-24-7; **1c** sodium salt, 31478-25-8; **2**, 31504-47-9; **3**, 31478-26-9; **4**, 31478-27-0; **5a** sodium salt, 31478-28-1; **7a**, 31478-29-2; **7a** picrate, 31478-30-5; **7b**, 31478-31-6; **7c**, 31478-32-7; **8**, 31478-33-8; 5-amino-6-hydroxy-2,7-dimethylquinoline, 31478-34-9; 5-acetamido-6-acetoxy-2,7-dimethylquinoline, 31478-35-0.

Acknowledgment.—We are indebted to the Physical Chemistry Department, Hoffmann-La Roche Inc., Nutley, N. J., under the supervision of Dr. P. Bommer, for the analytical and spectral data.

The Decahydro-1*H*-dibenzo[*a*,*h*]quinolizine System

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Having obtained the four isomers of the inside yohimbane system,[1] we turned our attention to their benzene analogs. When 3,4-dimethoxyphenethylamine and 2-formylcyclohexaneacetic acid were heated in acetic acid for a short time the open unsaturated lactam **1** was obtained. Longer heating of either the starting materials or lactam **1** resulted in cyclization to give lactam **2** as the predominant product, lactam **3** as the secondary product, and lactam **4** in trace yield. The lactams were reduced to the corresponding bases **8**, **10**, and **6**, respectively.

In the indole series the main product of the condensation had been the trans-anti isomer. However, the indole lactams may have been formed by a Pictet–Spengler cyclization followed by lactamization thus favoring a different isomer than in this case, where lactamization is the first step.

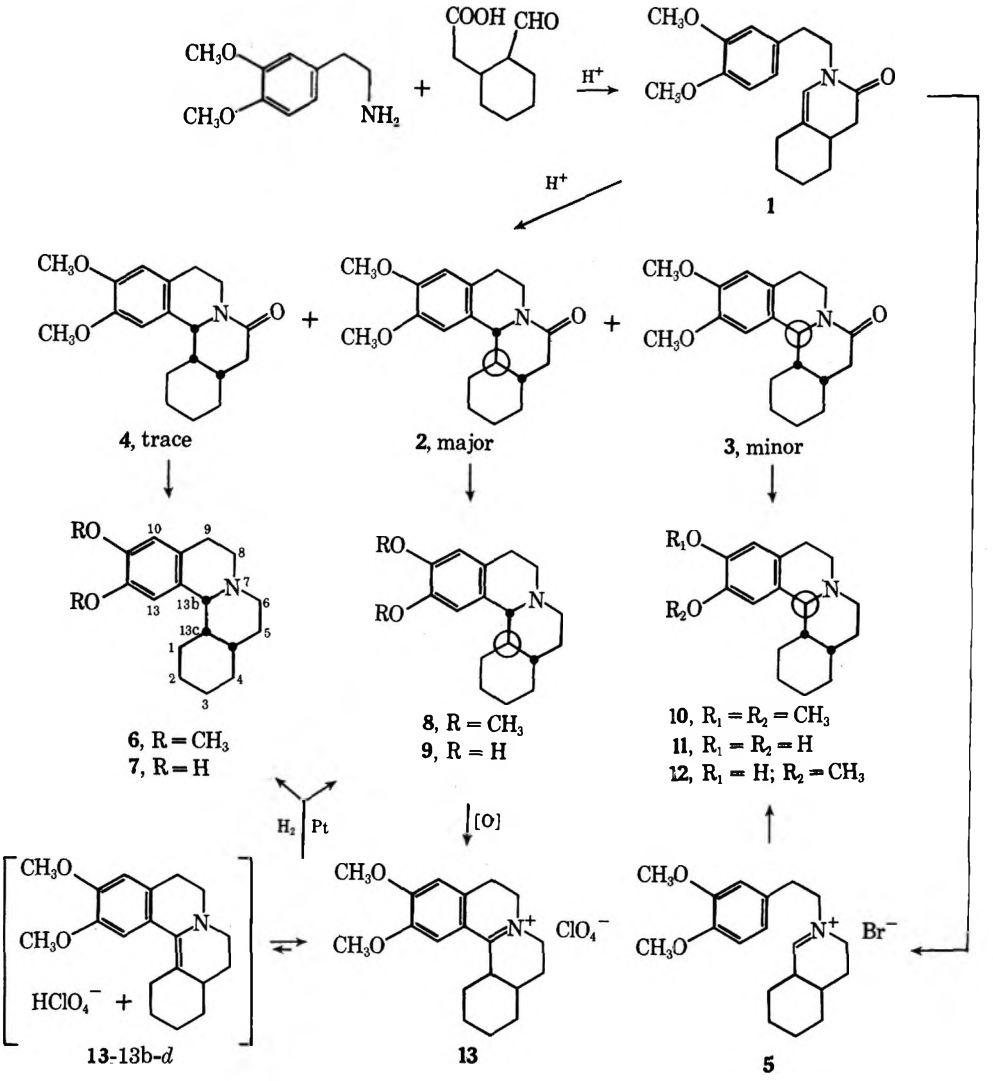
The uncyclized lactam **1** was reduced to the enamine **5** which on acid treatment undergoes hydrolysis of one methoxyl group and cyclization to the base **12**. The three dimethoxy bases **6**, **8**, and **10** were hydrolyzed to their corresponding dihydroxy derivatives **7**, **9**, and **11**. Further hydrolysis of **12** afforded the dihydroxy compound **11**, whose stereochemistry corresponds to the secondary product of the condensation reaction.

Having three isomers in hand we attempted to obtain the final one by the scheme which had produced the two isomers not obtained from the condensation in the indole series. Base **8** was oxidized to the dehydro compound **13**. Hydrogenation of **13** with platinum in alcohol gave back isomer **8** as the principal product along with isomer **6** and a small amount of isomer **10**. Sodium borohydride reduction gave essentially the same result. Zinc–acid reduction afforded a mixture containing a larger amount of isomer **10** (Scheme I).

The main difference between the indole and benzene series, other than the electronic nature of the two aromatic systems, is the steric relation of the hydrogens at C-1 to the adjacent hydrogen of the aromatic system. In the indole cis series we have shown that the syn

(1) G. C. Morrison, W. A. Cetenko, and J. Shavel, Jr., *J. Org. Chem.*, **32**, 2768 (1967).

SCHEME I



isomer is predominantly in the conformation which has a trans quinolizidine, and the anti isomer is a mixture of the three possible conformations. In these conformations the steric factor is relatively unimportant since the distance between the closest hydrogens at C-1 and the indole NH is over 2 Å. This is supported experimentally by the fact that on going from the indole NH to NCH_3 series there was little or no effect on the conformation make-up. Therefore in the cis benzene series the conformations of the isomers should be the same as for their corresponding indole isomer, since the distance between the hydrogen at C-1 and the adjacent aromatic hydrogen is reduced only 0.4 Å. The infrared spectrum of **10** shows no Bohlmann bands. The nmr spectrum displays a signal at 3.8 ppm for one hydrogen (buried under the methoxyl) and a methylene envelope with a half-width of 9 cps. This data corresponds perfectly to that for the cis-anti isomer in the indole series. Isomer **6** shows Bohlmann bands of moderate intensity, no signal in the 3.2–4.5-ppm region, disappearance of a singlet at 3.15 ppm (W_H = 7 cps) in the C-13b-*d* derivative, and a methylene envelope half-width of 32 cps. Again this corresponds to the cis-syn data in the indole series.

In the trans indole series the distance between the closest hydrogen at C-1 and the indole NH is 1.3 Å in both the trans-syn isomer and the favored trans quinolizidine conformation of the trans-anti isomer. The cis quinolizidine conformation of the trans-anti isomer has no serious steric interaction. In both isomers insertion of a *N*-methyl group reduces this distance to approximately zero and results in a shift to the cis quinolizidine conformation for the anti isomer and to the ring D boat conformation for the syn isomer. In the benzene series the distance between the hydrogen at C-1 and the adjacent aromatic hydrogen is 0.9 Å. This increased steric interaction may or may not affect the conformational preferences; therefore, both conformations of the trans-anti isomer must be considered and possibly even the boat conformation for the trans-syn isomer.

The spectral data for **8** are no Bohlmann bands, no signal in the 3.5–4.5-ppm region, and a methylene envelope half-width of 40 cps. The methylene envelope data are further support for the assignment of a trans C–D ring fusion. The remaining nmr and infrared data are in conflict on the basis of the classical interpretations: no Bohlmann bands for cis quinolizidine[2] and no signal above 3.8 for trans quinolizidine.[3] The only documented exception to the Bohlmann rule is that of Meyers.[4] However, the dividing line of 3.8 ppm for

(2) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).
(3) M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Amer. Chem. Soc.*, **86**, 3364 (1964).
(4) J. C. Sircar and A. I. Meyers, *J. Org. Chem.*, **32**, 1248 (1967).

cis and trans quinolizidines is at best an approximation since long-range shielding effects are certain to have an effect on this position. For example, we have shown that in the case of trans-anti *N*-methyl inside yohimban, which exists in a cis quinolizidine conformation (most likely exclusively), the quinolizidine crotch hydrogen resonates at 3.65 ppm. On going from cis-anti *N*-methyl inside yohimban to the cis-anti benzene series there should be no change in conformation. However, the chemical shift of the crotch hydrogen is −0.2 ppm. Applying this correction the expected position of the cis quinolizidine conformation of the trans-anti isomer should be 3.45 ppm.

A close examination of the methylene envelope of **8** suggests a poorly resolved doublet at 3.4 ppm (peak separation of 5 cps) which corresponds well to the calculated position. To support the assignment of this pattern to the crotch hydrogen of **8** we have carried out the reduction of the dehydro compound **13** with sodium borodeuteride. The main product isolated was **6** deuterated at C-13b. By thin layer chromatography a small sample of C-13b deuterated **8** was obtained in reasonable purity. Although the nmr spectrum of this material was poorly resolved, it was essentially the same as the spectrum of **6** except for the lack of the doublet at 3.4 ppm. The splitting pattern of **8** is typical of 180° coupling rather than 60° coupling;[1] therefore, we have assigned **8** as the trans-anti isomer in the cis quinolizidine conformation. The fact that we were unable to obtain the cis-syn isomer by any of our procedures is probably due to its lower thermodynamic stability in the benzene series.

Experimental Section[5]

The melting points were determined using a Thomas-Hoover apparatus which had been calibrated against known standards. The infrared spectra were recorded with a Baird Model 455 instrument on chloroform solutions. The nmr spectra were determined with a Varian Associates A-60 spectrometer on deuteriochloroform solutions unless noted.

2-(3,4-Dimethoxyphenethyl)-4,4a,5,6,7,8-hexahydro-3(2*H*)-isoquinolone (1).—A solution of 67 g of homoveratrylamine and 63 g of 2-formycyclohexaneacetic acid[1] in 440 ml of acetic acid was refluxed for 2.5 hr. The acetic acid was removed *in vacuo*. The residue was treated with 200 ml of 10% sodium hydroxide solution and 1.5 l. of methylene chloride. The methylene chloride layer was washed with water and dried over sodium sulfate, and the solvent was removed. The residue was digested with 400 ml of ethyl acetate and allowed to cool. The mixture was filtered and the ethyl acetate solution was evaporated to dryness. The residue was chromatographed on 2.5 kg of basic alumina. Elution with benzene–methylene chloride 1:1 gave, after recrystallization from Skellysolve B, 18.1 g (28%) of a crystalline solid, mp 91–92°.

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.63; H, 8.07; N, 4.47.

***trans-anti-*, *cis-anti-*, and *cis-syn*-1,2,3,4,4a,5,8,9,13b,13c-Decahydro-11,12-dimethoxy-6*H*-dibenzo[*a*,*h*]quinolizin-6-ones (2, 3, and 4).**—A solution of 163 g of homoveratrylamine and 162 g of 2-formylcyclohexaneacetic acid in 1.1 l. of acetic acid was refluxed for 24 hr. The acetic acid was removed *in vacuo*. The residue was treated with 1 l. of 10% sodium carbonate solution and 2.7 l. of methylene chloride. The methylene chloride layer was washed with water and dried with sodium sulfate, and the solvent was removed. The residue, after crystallization from 3.8 l. of ethyl acetate, afforded 158 g (56%) of a solid, mp 168–170°. Recrystallization from ethyl acetate gave an analytical sample of the trans-anti isomer **2**, mp 170–171°.

(5) The authors are indebted to Mr. A. Lewis and his associates, to Dr. C. Greenough for the spectral data, and to Mrs. U. Zeek for analytical determinations.

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.58; H, 8.03; N, 4.71.

Concentration of the mother liquor to 600 ml gave a second crop, 104 g, mp 134–140°, which was chromatographed on 4.0 kg of alumina. Elution of the column with methylene chloride gave, after recrystallization from Skellysolve B, 18 g (6%) of the cis-anti isomer **3**, mp 146–147°.

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.45; H, 7.94; N, 4.49.

The mother liquor from the crystallization was evaporated to dryness and the residue was chromatographed on 1.2 g of alumina. Elution with benzene–methylene chloride 1:1 gave, after recrystallization from ethyl acetate, 0.05 g (0.02%) of the cis-syn isomer **4**, mp 152–155°.

2-(3,4-Dimethoxyphenethyl)-3,4,4a,5,6,7,8,8a-octahydroisoquinolinium Bromide (5).—To a solution of 10.2 g of lithium aluminum hydride in 800 ml of ether was added a solution of 17.8 g of **1** in 1.4 l. of ether. The solution was refluxed for 3 hr and allowed to stand for 20 hr. The excess hydride was destroyed by the dropwise addition of water and the mixture was filtered. On acidification of the ethereal solution with hydrogen bromide there was deposited a solid which, after recrystallization from acetonitrile, afforded 9.3 g (43%) of solid, mp 192–194°. Further recrystallization gave an analytical sample, mp 195–196°.

Anal. Calcd for $C_{19}H_{28}BrNO_2$: C, 59.69; H, 7.38; N, 3.66. Found: C, 59.63; H, 7.26; N, 3.94.

***trans-anti*-2,3,4,4a,5,6,8,9,13b,13c-Decahydro-11,12-dimethoxy-1*H*-dibenzo[*a*,*h*]quinolizine (8).**—To a solution of 18 g of lithium aluminum hydride in 750 ml of tetrahydrofuran was added a solution of 110 g of **2** in 2.4 l. of tetrahydrofuran and the resulting solution was refluxed for 5 hr. The excess hydride was destroyed by the dropwise addition of water and the mixture was filtered. The tetrahydrofuran solution was stripped to dryness. Recrystallization of the residue from Skellysolve B gave 91 g (86%) of a solid, mp 101–102°.

Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.96; H, 9.06; N, 4.57.

***cis-syn*-2,3,4,4a,5,6,8,9,13b,13c-Decahydro-11,12-dimethoxy-1*H*-dibenzo[*a*,*h*]quinolizine (6).**—Reduction of 30 mg of **4** by the procedure used for the trans-anti isomer gave a solid. Thin layer chromatography on silica gel using a 1:1 benzene–ethyl acetate system in an ammonia atmosphere showed that this sample was identical with that obtained from the reduction of 1,2,3,4,4a,5,6,8,9,13c-decahydro-11,12-dimethoxydibenzo[*a*,*h*]-quinolizinium perchlorate.

***cis-anti*-2,3,4,4a,5,6,8,9,13b,13c-Decahydro-11,12-dimethoxy-1*H*-dibenzo[*a*,*h*]quinolizine (10).**—Reduction of 9.9 g of **3** by the procedure used for the trans-anti isomer gave, after recrystallization from Skellysolve B, 6.9 g (75%) of a solid, mp 118.5–119°. Further recrystallization gave an analytical sample, mp 119–120°.

Anal. Calcd for $C_{18}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.82; H, 9.11; N, 4.57.

***cis-anti*-2,3,4,4a,5,6,8,9,13b,13c-Decahydro-11-hydroxy-12-methoxy-1*H*-dibenzo[*a*,*h*]quinolizine (12).**—A solution of 6.5 g of **5** in 6 *N* hydrochloric acid was refluxed for 6 hr. The pH of the reaction mixture was adjusted to 9 with 40% sodium hydroxide solution, and the mixture was extracted with ether. The ethereal solution was washed with water and dried over sodium sulfate and the solvent was removed. Crystallization of the residue from benzene gave 0.6 g (12%) of solid, mp 134–135°.

Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.42; H, 8.91; N, 4.43.

***trans-anti*-2,3,4,4a,5,6,8,9,13b,13c-Decahydro-11,12-dihydroxy-1*H*-dibenzo[*a*,*h*]quinolizine (9).**—A solution of 2.0 g of **8** in 55 ml of hydrobromic acid was refluxed for 6 hr in a nitrogen atmosphere. The reaction mixture was neutralized to pH 8.5 with dilute ammonium hydroxide and extracted with methylene chloride. The methylene chloride layer was washed with water and dried over sodium sulfate, and the solvent was removed. Recrystallization of the residue from ethyl acetate gave 0.92 g (50%) of a solid, mp 223–224°.

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.62; H, 8.53; N, 4.97.

***cis-anti*-2,3,4,4a,5,6,8,9,13b,13c-Decahydro-11,12-dihydroxy-1*H*-dibenzo[*a*,*h*]quinolizine Hydrobromide (11). Method A.**—A solution of 8.0 g of 10 in 200 ml of hydrobromic acid was refluxed for 6 hr. On standing there was deposited a solid which,

after recrystallization from ethanol, afforded 7.4 g (79%) of a solid, mp 288–290°.

Anal. Calcd for $C_{17}H_{23}NO_2 \cdot HBr$: C, 57.63; H, 6.83; N, 3.95. Found: C, 57.52; H, 6.89; N, 3.94.

Method B.—A solution of 0.10 g of **12** in 15 ml of hydrobromic acid was refluxed for 6 hr. On standing, there was deposited 0.11 g of a crystalline solid, mp 288–290°. This sample was shown to be identical with that obtained in method A by the method of mixture melting point.

***cis-syn*-2,3,4,4a,5,6,8,9,13b,13c-Decahydro-11,12-dihydroxy-1*H*-dibenzo[*a*,*h*]quinolizine Hydrobromide (7).**—A solution of 7.0 g of **6** in 175 ml of hydrobromic acid was refluxed for 8 hr. On standing there was deposited a solid which on recrystallization from ethanol afforded 6.9 g (84%) of a solid, mp 329–331°.

Anal. Calcd for $C_{17}H_{23}N_2O_2 \cdot HBr$: C, 57.63; H, 6.83; N, 3.95. Found: C, 57.43; H, 6.76; N, 3.97.

1,2,3,4,4a,5,6,8,9,13c-Decahydro-11,12-dimethoxydibenzo-[*a*,*h*]quinolizinium Perchlorate (13).—To a solution of 50 g of **8** in 1 l. of 5% acetic acid was added a solution of 530 g of mercuric acetate in 1.5 l. of 5% acetic acid. After the addition had been completed the solution was heated at 95° for 3 hr with stirring. The hot reaction mixture was saturated with hydrogen sulfide and filtered. Treatment of the filtrate with perchloric acid gave, after recrystallization from methanol, 44 g (66%) of a solid, mp 180–182°. Further recrystallization gave an analytical sample, mp 187–188°.

Anal. Calcd for $C_{19}H_{25}NO_2 \cdot HClO_4$: C, 57.07; H, 6.55; N, 3.50. Found: C, 56.83; H, 6.56; N, 3.78.

Hydrogenation of 1,2,3,4,4a,5,6,8,9,13c-Decahydro-11,12-dimethoxydibenzo[*a*,*h*]quinolizinium Perchlorate (13).—To a solution of 30 g of **13** in 60 ml of water and 800 ml of ethanol was added 3.0 g of platinium oxide and the mixture was hydrogenated at atmospheric pressure. Uptake ceased after the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration. After removal of the solvent the residue was treated with 300 ml of 10% sodium hydroxide solution and 2.3 l. of ether. The ether layer was washed with water and dried over sodium sulfate and the solvent was removed. The residue was chromatographed on 600 g of alumina. Elution of the column with benzene gave 6.0 g (27%) of *cis-syn*-2,3,4,4a,5,6,8,9,13b,13c-decahydro-11,12-dimethoxy-1*H*-dibenzo[*a*,*h*]quinolizine (**6**), mp 120–122°.

Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.70; H, 9.01; N, 4.73.

Elution of the column with chloroform–methanol gave 5.4 g of material which contained mostly trans-anti-2,3,4,4a,5,6,8,9,13b,13c-decahydro-11,12-dimethoxy-1*H*-dibenzo[*a*,*h*]quinolizine (**8**) as shown by thin layer chromatography.

Preparation of the C-13b-*d* Derivatives of *cis-syn*- and *trans-anti*-2,3,4,4a,5,6,8,9,13b,13c-Decahydro-11,12-dimethoxy-1*H*-dibenzo[*a*,*h*]quinolizine.—To a solution of 4.9 g of **13** in 45 ml of deuterium oxide was added 1.8 g of sodium borodeuteride over a 10-min interval. The reaction mixture was extracted with methylene chloride. The methylene chloride layer was dried over sodium sulfate and the solvent was removed. The residue (4.9 g) was chromatographed on 160 g of alumina. Elution of the column with benzene gave 1.7 g of *cis-syn*-2,3,4,4a,5,6,8,9,13b,13c-decahydro-11,12-dimethoxy-1*H*-dibenzo[*a*,*h*]quinolizine-13b-*d*, mp 121–122°.

Anal. Calcd for $C_{19}DH_{26}NO_2$: C, 75.45; H, 9.33; N, 4.63. Found: C, 75.59; H, 9.37; N, 4.39.

Elution of the column with 1% methanol in ether gave 0.6 g which was rechromatographed on 40 g of alumina. Elution with methylene chloride gave 0.31 g which was subjected to preparative thin layer chromatography on silica gel. The plates were developed with ethyl acetate–benzene (1:1). The desired zone was removed from the plate and extracted with methylene chloride. The methylene chloride was removed and the residue dissolved in Skellysolve B. On standing there was deposited 0.06 g of a *trans-anti*-2,3,4,4a,5,6,8,9,13b,13c-decahydro-11,12-dimethoxy-1*H*-dibenzo[*a*,*h*]quinolizine-13b-*d*, mp 95–98°.

Registry No.—**1**, 31446-56-7; **2**, 31446-57-8; **3**, 31446-58-9; **4**, 31446-59-0; **5**, 31446-60-3; **6**, 31446-61-4; **7**, 31446-62-5; **8**, 31446-63-6; **9**, 31446-64-7; **10**, 31446-65-8; **11**, 31446-66-9; **12**, 31446-67-0; **13**, 31446-68-1; **13**-13b-*d* (cis-syn,) 31446-69-2; **13**-13b-*d* (trans-anti), 31446-70-5.

Preparation of Amidines from *gem*-Dichloroaziridines[1,2]

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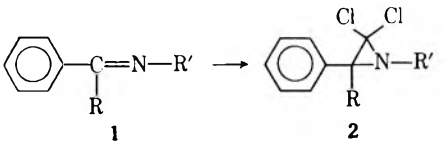
The first preparation of a *gem*-dichloroaziridine was reported by Fields and Sandri in 1959.[3] They synthesized 1,3-diphenyl-2,2-dichloroaziridine (**2a**) by the addition of dichlorocarbene, generated by the reaction of chloroform with sodium methoxide, to benzylidine-



1 **2**

aniline (**1a**). A number of other methods have been used to generate the dichlorocarbene in this reaction and the methods are summarized in Table I. The new

TABLE I

gem-DICHLOROAZIRIDINES[a]

Imine	R	R'	Aziridine	Yield, %	Method[b]	Ref
1a	Hydrogen	Phenyl	**2a**	55	A	3
				80	B	*c*
				61	C	*d*
				68, 91[e]	D	*f*
1b	Phenyl	Phenyl	**2b**	*g*	D	*h*
1c	Hydrogen	1-Naphthyl	**2c**	39	A	*i*
				44	B	*i*
1d	Phenyl	Benzyl	**2d**	65[j]	A	*i*
				7	B	*i*
1e	Ethyl	Phenyl	**2e**	56	A	*i*
				52	B	*i*
1f	Ethyl	1-Naphthyl	**2f**	68	A	*i*
				31	B	*i*

[a] This table also contains the other reported *gem*-dichloroaziridine systems. [b] The reaction of sodium methoxide with chloroform (A), ethyl trichloroacetate (B), hexachloroacetone (C), and the reaction of potassium *tert*-butoxide with chloroform (D). [c] J. A. Deyrup and R. B. Greenwald, *J. Amer. Chem. Soc.*, **87**, 4538 (1965). [d] P. K. Kadaba and J. O. Edwards, *J. Org. Chem.*, **25**, 1431 (1960). [e] Yields reported for R' = *p*-chlorophenyl and *p*-methoxyphenyl, respectively. [f] A. G. Cook and E. K. Fields, *ibid.*, **27**, 3686 (1962). [g] Not reported. [h] J. A. Deyrup and R. B. Greenwald, *Tetrahedron Lett.*, 321 (1965). [i] This report. [j] This yield was obtained in one run; typical yields for this reaction were *ca.* 4%.

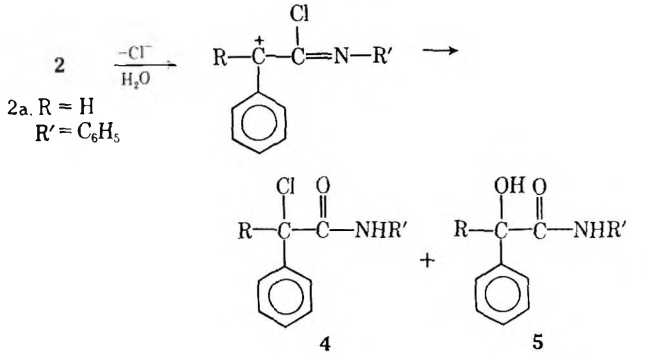
alkyl- and aryl-substituted *gem*-dichloroaziridines reported in Table I were prepared by two of these methods. Although the yields are comparable for the two methods, the aziridines were more readily purified from the reaction which employed chloroform as the carbene source.

Hydrolysis.—The hydrolysis of 1,3-diphenyl-2,2-dichloroaziridines (**2a**) has been reported to afford α-chloro-α-phenylacetamide (**4a**) in quantitative

(1) Presented in part at the 41st Meeting of the Colorado–Wyoming Academy of Science, Greeley, Colo., May 1,2, 1970.

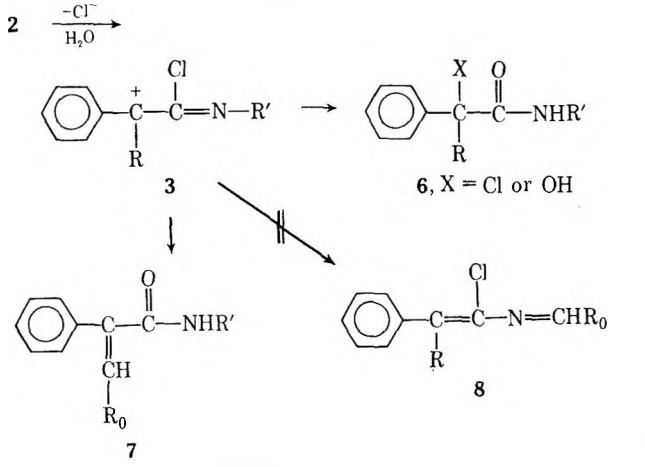
(2) We are plaesed to acknowledge the support of the Research Corporation by a Frederick Gardner Cottrell grant.

(3) E. K. Fields and S. M. Sandri, *Chem. Ind. (London)*, 1216 (1959).



yields, while the homogeneous hydrolysis affords a mixture of amides **4** and **5**. The mechanism of the ring-opening reaction has been studied in detail and cation **3** has been suggested as an intermediate.[4] Prior to this report only products of substitution of the intermediate cation **3** had been observed in the hydrolytic ring opening of known *gem*-dichloroaziridines. However, as shown in Scheme I, when alkyl groups are substituted on the aziridine the intermediate cation in the ring opening can also give rise to products by elimination pathways.

SCHEME I



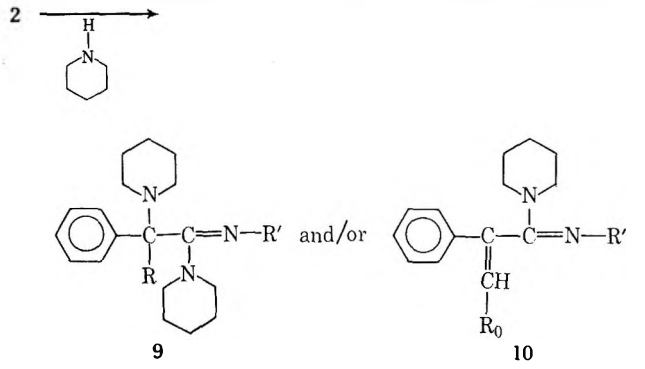
To test the plausibility of the elimination pathways, the hydrolysis of two alkyl-substituted *gem*-dichloroaziridines, **2d** and **2e**, was examined. The hydrolysis of 1,3-diphenyl-3-ethyl-2,2-dichloroaziridine (**2e**) gave the α,β-unsaturated amide **7** (R_0 = methyl) in 35% yield demonstrating the feasibility of elimination. Analysis of the mother liquors by nmr failed to detect any additional unsaturated amide. Hydrolysis of aziridine **1d** gave the α-hydroxyamide **6** (R = phenyl, R′ = benzyl, X = OH) in high yields. Products resulting from the hydrolysis of **8** were not observed.

Aminolysis.—The aminolysis of *gem*-dichloroaziridines provides a new, convenient synthesis of amidines.[5] The *gem*-dichloroaziridine is dissolved in the amine and the solution is slowly heated to and maintained at 100–130° for several hours. The amine hydrochloride which is formed in the reaction is removed from the cooled reaction mixture by filtration or by an aqueous work-up. The amidine is generally isolated by crystallization. The aryl-substituted *gem*-dichloroaziridines (**2a** and **2c**) afford α-aminoamidines (**9**) in reasonable yields. The 3-alkyl-substituted *gem*-dichloroaziridines afforded α,β-unsaturated amidines (**10**) as the predominant isolated product. The amidines which have been prepared by this new method are summarized in Table II.

TABLE II

AMIDINES PREPARED FROM *gem*-DICHLOROAZIRIDINES

Aziridine	Amine	Amidine	R	R′	R_0	Yield, %
2a	Piperidine	9a	H	C_6H_5		59
2a	Morpholine	9b	H	C_6H_5		36
2a	Pyrrolidine	9c	H	C_6H_5		72
2c	Piperidine	9d	H	1-Naphthyl		74
2e	Piperidine	10a		C_6H_5	CH_3	51
2f	Piperidine	10b		1-Naphthyl	CH_3	50



The amidines reported in Table II and the hydrolysis products, **6** and **7**, support the intermediacy of cation **3** in this type of ring-opening reaction. The potential of cation **3** to serve as a useful reaction intermediate in organic chemistry is being examined.

Experimental Section

All melting points are uncorrected and were determined on a Mel-Temp melting point apparatus. The nuclear magnetic resonance spectra were recorded on a Varian Associates A-60A spectrometer using tetramethylsilane as an internal standard. Infrared spectra were determined in potassium bromide on a Perkin-Elmer Model 137 spectrophotometer. The microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind., and Huffman Laboratories, Inc., Wheatridge, Colo.

N-1-(1-**Phenylpropylidene**)-1-**naphthylamine** (**1f**).—To a solution of 30 g (0.21 mol) of 1-naphthylamine and 28 g (0.21 mol) of propiophenone in 100 ml of dry toluene was added *p*-toluenesulfonic acid (*ca.* 0.1 g). The flask was connected to a water separator fitted with a condensor and drying tube and the solution was heated at the reflux temperature for 18 hr. The solvent was removed *in vacuo* from the cooled solution and crystallization of the residue from methanol afforded 33 g (61%) of the crude imine, mp 102–104°. Short-path distillation, flask temperature 220° (0.2 mm), followed by crystallization from hexane afforded an analytical sample of the light yellow imine: mp 103–104°; ir (KBr) 1625 cm^{-1} (C=N); nmr (CCl_4) δ 8.3–6.6 (m, 12, aromatic), 2.6 (broad q, 2, J = 7 Hz, CH_2CH_3), 1.0 (broad t, 3, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_{19}H_{17}N$: C, 87.98; H, 6.62. Found: C, 87.73; H, 6.54.

General Synthesis of *gem*-Dichloroaziridines. Method A.—Chloroform (0.08 mol) was slowly added dropwise to a magnetically stirred mixture of sodium methoxide (0.08 mol), imine (0.02 mol), and purified hexane (10–20 ml). The mixture was stirred for several hours, hexane or ether was added (*ca.* 25 ml), and the solution was filtered.[6] The *gem*-dichloroaziridine was isolated from the filtrate by crystallization.

(4) R. E. Brooks, J. O. Edwards, G. Levey, and F. Smith, *Tetrahedron*, **22**, 1279 (1966).

(5) For a review of amidine chemistry see (a) L. Weintraub, S. R. Oles, and N. Kalish, *J. Org. Chem.*, **33**, 1679 (1968); R. I. Fryer, J. V. Earley, G. F. Field, W. Zally, and L. H. Sternbach, *ibid.*, **34**, 1143 (1969), and references cited therein; (b) R. L. Shriner and F. W. Newmann, *Chem. Rev.*, **35**, 351 (1944).

(6) (a) In those cases where the imine was slightly soluble in hexane, it was dissolved in a hexane–ether solution. (b) The mixture may be poured into water, extracted with ether, dried ($MgSO_4$), and filtered.

Method B.—The procedure was the same as method A except that during the dropwise addition of ethyl trichloroacetate the mixture was cooled in an ice bath. Using the above procedures the following *gem*-dichloroaziridines were prepared.

1-(1-Naphthyl)-3-phenyl-2,2-dichloroaziridine (2c).—Crystallization from ethyl acetate afforded the light yellow crystalline aziridine: mp 120–121°; nmr (CCl_4) δ 7.3 (m, 12, aromatic) and 3.75 (s, 1, aziridinyl H).

Anal. Calcd for $C_{18}H_{13}Cl_2N$: C, 68.80; H, 4.18; N, 4.56. Found: C, 68.75; H, 4.45; N, 4.47.

1-Benzyl-3,3-diphenyl-2,2-dichloroaziridine (2d).—Crystallization from hexane–ethyl acetate afforded the white crystalline aziridine: mp 136–137°; nmr ($DCCl_3$) δ 7.3 (m, 15, aromatic) and 3.97 (s, 2, CH_2).

Anal. Calcd for $C_{21}H_{17}Cl_2N$: C, 71.18; H, 4.85; N, 3.95. Found: C, 71.04; H, 4.91; N, 3.95.

1,3-Diphenyl-3-ethyl-2,2-dichloroaziridine (2e).—Crystallization from hexane afforded the white crystalline aziridine: mp 82–83°; nmr (CCl_4) δ 7.2 (m, 10, aromatic), 1.9 (m, 2, CH_2CH_3), and 1.07 (m, 3, CH_2CH_3).

Anal. Calcd for $C_{16}H_{15}Cl_2N$: C, 65.67; H, 5.18; N, 4.79. Found: C, 65.72; H, 5.18; N, 4.67.

1-(1-Naphthyl)-3-phenyl-3-ethyl-2,2-dichloroaziridine (2f).—Crystallization from hexane–ethyl acetate afforded the white crystalline aziridine: mp 90.5–92°; nmr (CCl_4) δ 7.4 (m, 12, aromatic), 2.1 (m, 2, CH_2), and 1.17 (t, 3, CH_3).

Anal. Calcd for $C_{20}H_{17}Cl_2N$: C, 70.17; H, 5.02; N, 4.09. Found: C, 69.94; H, 5.15; N, 4.17.

2-Phenyl-2-butenanilide.—A solution of 0.639 g (0.0022 mol) of 1,3-diphenyl-3-ethyl-2,2-dichloroaziridine (**1e**), water (5 ml), and tetrahydrofuran (15 ml) was heated at the reflux temperature overnight. The solution was poured into water, extracted with ether, dried ($MgSO_4$), and filtered. The solvent was removed *in vacuo* and the residue was crystallized from ethyl acetate–hexane to afford 0.180 g (35%) of the crude amide, mp 141–146°. Recrystallization afforded 0.148 g (29%) of the pure amide: mp 152–153°; ir (KBr) 1650 cm^{-1} (C=O); nmr ($DCCl_3$) δ 7.3 (m, 10, aromatic), 6.13 (q, 1, J = 7 Hz, C=CH), and 1.98 (d, 3, J = 7 Hz, =$CHCH_3$).

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.97; H, 6.38. Found: C, 81.02; H, 6.15.

***N*-Benzylbenzilamide.**—A solution of 0.245 g (0.0067 mol) of 1-benzyl-3,3-diphenyl-2,2-dichloroaziridine (**2d**), *p*-dioxane (10 ml), and water (1 ml) was heated at the reflux temperature for 9 hr, poured into water, and extracted with ether. The combined ether extracts were dried ($MgSO_4$) and concentrated to afford a light yellow oil. Crystallization of the oil from ethyl acetate–hexane afforded 0.137 g (62%) of the amide, mp 99–100° (lit.[7] mp 99–100°). An additional 0.016 g (7%) of the crude amide was isolated: mp 97–99°; ir (KBr) 1650 cm^{-1} (C=O); nmr ($DCCl_3$) δ 7.3 (m, 16, aromatic and NH), 4.45 (d, 2, J = 6 Hz, CH_2NH), and 3.9 (s, 1, OH).

General Synthesis of Amidines from *gem*-Dichloroaziridines.—A solution of the *gem*-dichloroaziridine (0.02 mol) and the amine (5–10 ml) was slowly heated to and maintained at 100–130° for several hours. The amine hydrochloride was removed from the cooled solution by filtration.[8] The filtrate was concentrated *in vacuo* and crystallization of the residue afforded the crude amidines which were purified by crystallization.

1-[*N*,2-Diphenyl-2-(1-piperidino)acetimidoyl]piperidine (9a).—The amidine was isolated in 59% yield after a reaction period of 1.5 hr by crystallization from ethyl acetate, mp 104–105.5°. Recrystallization afforded an analytical sample: mp 105–106.5°; ir (KBr) 1625 cm^{-1} (C=N); nmr (CCl_4) δ 7.0 (m, 10, aromatic), 4.63 (s, 1, CH), 3.58 (m, 4, CH_2N), 2.53 (m, 4, CH_2N), and 1.35 (m, 12, CH_2).

Anal. Calcd for $C_{24}H_{31}N_3$: C, 79.72; H, 8.66. Found: C, 79.70; H, 8.65.

4-[*N*,2-Diphenyl-2-(4-morpholino)acetimidoyl]morpholine (9b).—The amidine was isolated in 36% yield after a reaction period of 3 hr by crystallization from ethyl acetate, mp 170–172°. Recrystallization afforded an analytical sample: mp 172–174°; ir (KBr) 1625 cm^{-1} (C=N); nmr ($DCCl_3$) δ 7.5–6.7 (m, 10, aromatic), 4.67 (s, 1, CH), 3.9–3.2 (m, 12, CH_2O and CH_2N), and 2.6 (m, 4, CH_2N).

Anal. Calcd for $C_{22}H_{27}N_3O_2$: C, 72.42; H, 7.42; N, 11.44. Found: C, 72.54; H, 7.34; N, 11.20.

1-[*N*,2-Diphenyl-2-(1-pyrrolidino)acetimidoyl]pyrrolidine (9c).—The amidine was isolated in 72% yield after a reaction period of 3 hr by crystallization from hexane, mp 118–121°. Recrystallization afforded an analytical sample: mp 120.5–122.5°; ir (KBr) 1600 cm^{-1} (C=N); nmr ($DCCl_3$) δ 6.90 (m, 10, aromatic), 4.52 (s, 1, CH), 4.0–2.1 (m, 8, CH_2N), and 1.75 (m, 8, CH_2).

Anal. Calcd for $C_{22}H_{27}N_3$: C, 79.24; H, 8.15. Found: C, 78.98; H, 8.41.

1-[*N*-(1-Naphthyl)-2-phenyl-2-(1-piperidino)acetimidoyl]piperidine (9d).—The amidine was isolated in 74% yield after a reaction period of 12 hr by crystallization from hexane: mp 144–145.5; ir (KBr) 1600 cm^{-1} (C=N); nmr (CCl_4) δ 8.0–6.5 (m, 12, aromatic), 4.68 (s, 1, CH), 3.7 (m, 4, CH_2N), 2.5 (m, 4, CH_2N), and 1.5 (m, 12, CH_2).

Anal. Calcd for $C_{28}H_{33}N_3$: C, 81.49; H, 8.08. Found: C, 81.31; H, 8.08.

1-[*N*-Phenyl-2-phenyl-2-butenimidoyl]piperidine (10a).—The amidine was isolated in 51% yield after a reaction period of 9 hr by crystallization from hexane, mp 82.5–85°. Recrystallization afforded an analytical sample: mp 86.5–87.5°; ir (KBr) 1600 cm^{-1} (C=N and C=C); nmr (CCl_4) δ 7.4–6.3 (m, 10, aromatic), 6.0 (q, 1, J = 7 Hz, CH=C), 3.5 (m, 4, CH_2N), and 1.60 (m, 9, CH_2 and CH_3).

Anal. Calcd for $C_{21}H_{24}N_2$: C, 82.84; H, 7.96. Found: C, 82.96; H, 7.88.

1-[*N*-(1-Naphthyl)-2-phenyl-2-butenimidoyl]piperidine (10b).—The amidine was isolated after a reaction period of 3 hr by crystallization from hexane in 50% yield, mp 113–116°. Crystallization afforded an analytical sample: mp 116.5–118°; ir (KBr) 1625 (C=N) and 1600 cm^{-1} (C=C); nmr (CCl_4) δ 8.1, 7.6–6.9 6.3 (m, 12, aromatic), 6.02 (q, 1, J = 7 Hz, =$CHCH_3$), 3.6 (m, 4, CH_2N), 1.68 (m, 6, CH_2), and 1.48 (d, 3, J = 7 Hz, $CHCH_3$).

Anal. Calcd for $C_{25}H_{26}N_2$: C, 84.69; H, 7.41. Found: C, 84.68; H, 7.56.

Registry No.—**1f**, 31528-94-6; **2c**, 31528-95-7; **2d**, 31528-96-8; **2e**, 31528-97-9; **2f**, 31528-98-0; **9a**, 31528-99-1; **9b**, 31529-00-7; **9c**, 31529-01-8; **9d**, 31529-02-9; **10a**, 31529-03-0; **10b**, 31529-04-1; 2-phenyl-2-butenanilide, 31529-05-2; *N*-benzylbenzilamide, 13415-45-7.

Acknowledgment.—The authors wish to thank Dr. W. E. Parham for his helpful comments prior to and during the course of this study and Drs. J. A. Beel and R. D. Bach for their support and encouragement.

(7) V. E. Johnsen, C. R. Jacobsen, R. A. LaForge, and C. Hanna, *J. Pharm. Sci.*, **51**, 799 (1962).

(8) The amine hydrochloride may be removed by pouring the solution into a mixture of 10% sodium hydroxide and ether and stirring until the solid material dissolves. The ether layer is separated and dried and the solvent removed *in vacuo* to afford the crude amidine.

Reaction of Acetone Azine and *p*-Toluenesulfonyl Azide

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Contribution No. 1637 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

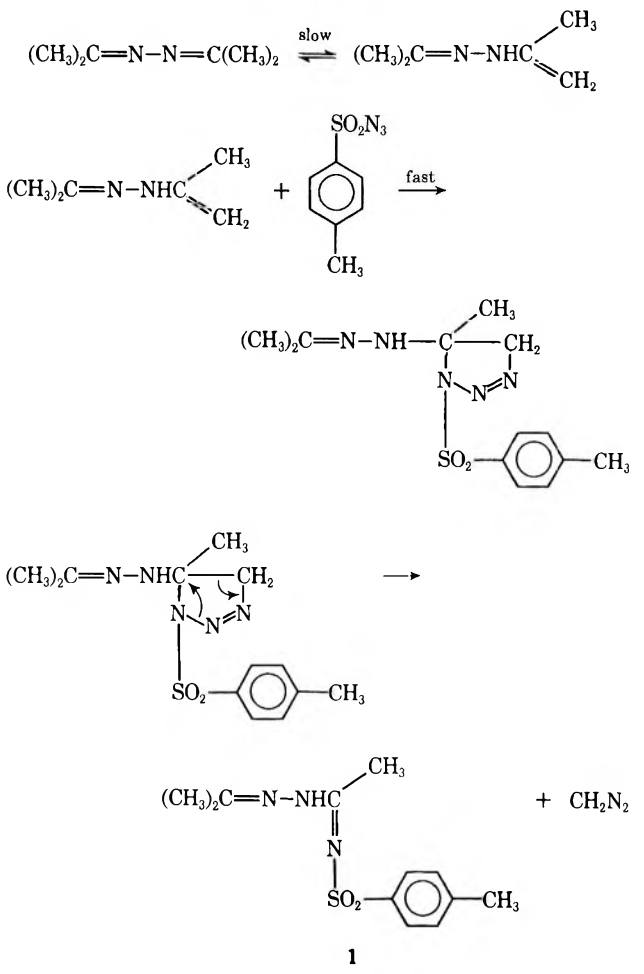
Received October 31, 1969

Acetone azine and *p*-toluenesulfonyl azide reacted to produce a compound which had the elements of both azine and azide minus nitrogen and a methyl group of the azine. The product has been assigned the structure of *N*-[1-(isopropylidenehydrazino)ethylidene]-*p*-toluenesulfonamide (**1**). The reaction occurred very slowly at reflux in tetrahydrofuran solution, and a 12%

yield of **1** was obtained after 7 days. The reaction occurred at approximately the same rate at which deuterium (from D_2O) was incorporated into the azine. The structure of **1** was confirmed by the nmr spectrum which showed the absorptions of four different methyl groups, the infrared spectrum which showed the absorption of the NH group, and the ultraviolet absorption spectrum.

Scheme I is suggested for the reaction. The slow incorporation of deuterium into acetone azine is

SCHEME I



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in agreement with the postulated equilibrium between the azine and the substituted hydrazone. The hydrazone would be expected to undergo rapid deuterium exchange and thus provide a means for the entrance of deuterium into the azine. The azide should add rapidly to the enamine derivative to give the triazoline.[1,2] Analogous fragmentations of triazolines to diazo compounds have been observed previously.[1-3] Diazomethane was not isolated from the reaction but suggestive evidence for its formation was obtained by the isolation of methyl *p*-nitrobenzoate from the reaction of acetone azine, *p*-toluenesulfonyl azide, and *p*-nitrobenzoic acid.

Experimental Section

***N*-[1-(Isopropylidenehydrazino)ethylidene]-*p*-toluenesulfonamide (1).**—A solution of 12 g of acetone azine and 20 g of *p*-toluenesulfonyl azide in 50 ml of tetrahydrofuran was heated at reflux for 7 days. Gas was slowly evolved. The mixture was cooled and the solvent was removed under reduced pressure. The residue was stirred with methanol and filtered to give white, crystalline **1**, 3.19 g (12%), mp 154–156.5°. Recrystallization from methanol gave material which melted at 158–159°: uv λ_{max}^{EtOH} 264 mμ (ε 23,400), 224 (13,100); nmr ($CDCl_3$) δ 1.98 (3), 2.05 (3), 2.22 (3), 2.42 (3), 7.58 (4).

Anal. Calcd for $C_{12}H_{17}O_2N_3S$: C, 53.91; H, 6.41; N, 15.72; S, 11.99; mol wt, 267. Found: C, 53.62, 53.75; H, 6.38, 6.48; N, 15.57, 15.45; S, 11.90, 11.80; mol wt (mass spectrum), 267.

From the original methanol filtrate there was obtained in successive crops a total of 6.18 g (36%) of *p*-toluenesulfonamide, mp 125–126° from benzene.

Acetone Azine in Deuterium Oxide.—A solution of acetone azine in deuterium oxide was heated at 65°. After 4 days the intensity ratio of the two azine methyl groups to the exchange peak of H_2O in D_2O in the nuclear magnetic resonance spectrum was 6.3, indicating exchange of 14% of the original methyl hydrogens for deuterium. After 9 days the ratio was 4.6 (18% exchange) and after 16 days the ratio was 3.2 (24% exchange).

Registry No.—**1**, 31600-81-4; acetone azine, 627-70-3; *p*-toluenesulfonyl azide, 941-55-9.

Acknowledgment.—We wish to thank Dr. Howard E. Simmons for helpful discussions

(1) R. Fusco, G. Bianchetti, D. Pocar, and R. Ugo, *Chem. Ber.*, **96**, 802 (1963).
(2) J. Kuvera and Z. Arnold, *Tetrahedron Lett.*, 1109 (1966).
(3) M. Regitz and F. Menz, *Chem. Ber.*, **101**, 2622 (1968).

On the Structure of the Diels–Alder Adduct of Ditropyl and Dimethyl Acetylenedicarboxylate

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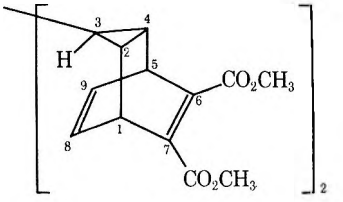
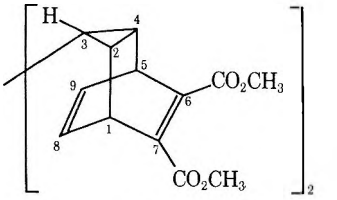
Recently we assigned structure I to the Diels–Alder adduct of ditropyl and 2 mol of dimethyl acetylenedicarboxylate,[1] by employing both nmr evidence and reactivity arguments. However, the configuration at



1a



1b

C-3 (and C-3′) could not be unequivocally established. Thus, the nmr signal at τ 9.08 which we confidently assign to the hydrogen at C-3 (and C-3′) moves upfield to τ 9.49 when all of the double bonds are hydrogenated. Since, in the most likely anti-3-exo arrangement[2] Ia,

(1) G. H. Wahl, Jr., and K. Weiss, *J. Org. Chem.*, **35**, 3902 (1970).
(2) M. J. Goldstein and A. H. Gevirtz, *Tetrahedron Lett.*, 4417 (1965).

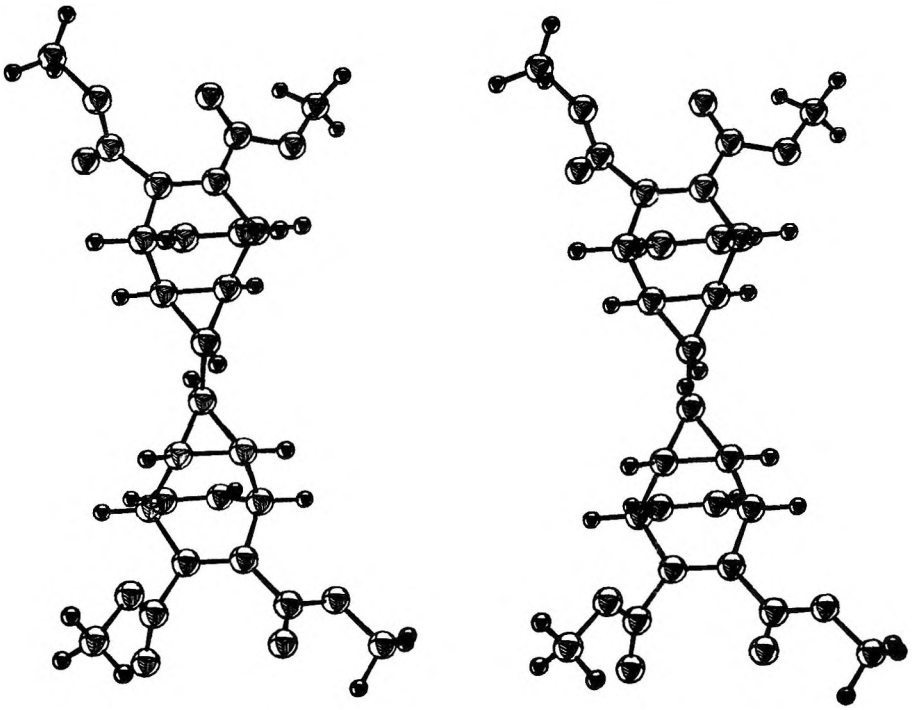


Figure 1.—ORTEP stereoscopic view of tetramethyl (3,3′-bitricyclo[3.2.2.0^{2,4}]nonε-6,8-diene)-6,6′,7,7′-tetracarboxylate (Ia).

H-3 is held rigidly in the π cloud of the proximate double bond, it might be expected that this arrangement would confer extra shielding on this hydrogen.[3] Furthermore, after hydrogenation, which removes this feature, the resonance should shift downfield. Since the reverse effect is found,[1] the anti-3-endo configuration Ib in which H-3 (and H-3′) would not be expected to experience as large a shielding effect from the adjacent double bond must be considered.

The structure of the Diels–Alder adduct was unambiguously established as Ia (see Figure 1) by a routine, single crystal X-ray analysis. Intensity data (1 Å) (maximum sin θ/λ = 0.5) was collected on a Syntex $P\bar{1}$ diffractometer using copper radiation.[4] Phasing was accomplished using a reiterative application of Sayre's equation.[5,6] A trial structure was obtained with the first E map, and this trial structure refined smoothly to a final R index of 0.068. The final cycle of full matrix least-squares refinement contained the scale factor, coordinates, and anisotropic temperature factors for all the nonhydrogen atoms.[7] The hydrogen positions were located using difference Fourier techniques. While the hydrogen parameters were included in the structure factor calculations, they were not subjected to refinement. Crystal and data collection parameters are presented in Table I. All bond distances and angles were normal and are not presented here. Full details of the X-ray analysis can be obtained from one of the authors (J. B.).

TABLE I

CRYSTAL AND DATA COLLECTION PARAMETERS

Crystallization medium, methanol	Scan mode, $\theta/2\theta$
Cell dimensions, a = 6.312 Å,	Scan rate, 2°/min in 2θ
b = 11.89 Å, c = 30.59 Å,	Background count time, 0.5 (scan time)
β = 97.88 Å	Density calcd, 1.362 g/cc
	Density obsd, 1.32 g/cc

Space group, $P2_1/c$ (4 molecules/unit cell)

This unequivocal assignment of structure and the results of other studies[2,8] permit the conclusion that the three-membered ring which is generated in most Diels–Alder reactions of cycloheptariene and its 7-substituted derivatives will usually be situated in an anti geometry with respect to the dieneophile. Moreover, the predominant or exclusive epimer formed from 7-substituted cycloheptatrienes will possess the anti-3-exo configuration. Finally, the above-mentioned nmr arguments[3] for assigning stereochemistry should be used with extreme caution.[9]

Registry No.—Ia, 31528-84-4.

Acknowledgments.—Partial support of this work from the North Carolina State University Engineering Foundation and Faculty Research and Professional Development Fund is acknowledged with pleasure. We are grateful to Professor Karl Weiss for helpful discussion of this manuscript.

(3) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, p 231.

(4) Monochromatic radiation was obtained by use of a graphite monochromator.

(5) D. Sayre, *Acta Crystallogr.*, **5**, 60 (1952).

(6) The phasing process was facilitated by the use of a computer program written by R. E. Long, UCLA. Of the 16 possible solutions generated by the program, the one which converged in the fewest number of cycles (seven) and had the highest internal consistency index (0.69372) proved to be correct.

(7) Of the 2355 reflections collected, 1937 reflections had F's greater than twice their standard deviation. These 1937 reflections were used in the least-squares refinement. Refinement was terminated when the calculated shifts were one-tenth the standard deviation for the positional parameters.

(8) G. H. Wahl, Jr., *J. Org. Chem.*, **33**, 2158 (1968).

(9) Y. E. Rhodes, P. E. Schueler, and V. G. DiFate, *Tetrahedron Lett.*, 2073 (1970). These authors present nmr data on related model systems which suggest that the distant double bond deshields H-3 about as effectively as the closer π system shields it.

The Structure of a 3:2 Adduct from the Reaction of Dimethyl Acetylenedicarboxylate and Cyclohexyl Isocyanide

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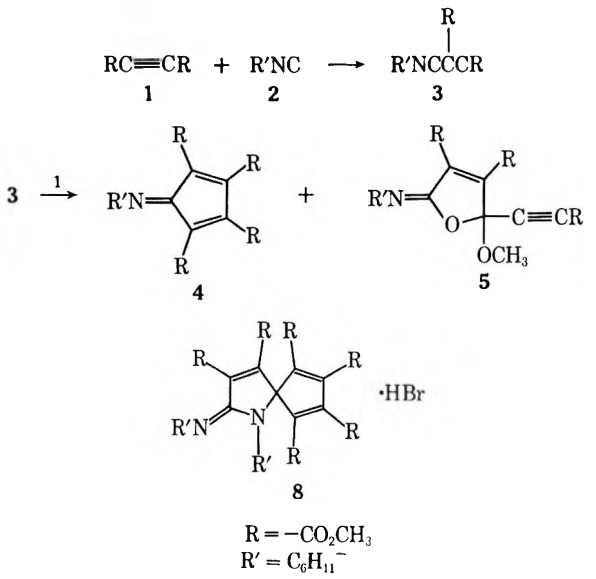
Reaction of dimethyl acetylenedicarboxylate (**1**) with organic isocyanides (**2**) usually yields a large number of products, although low temperatures and an excess of **2** apparently favor the formation of 2:1 adducts (**4** and **5**) derived from alternative additions of a second molecule of **1** to the initially formed 1:1 dipolar species **3**.[1]



Chemical information on the origin and structure of some of the other products was obtained in a recent study[2] of the reaction of **1** with cyclohexyl isocyanide (**2**, R′ = C_6H_{11}–). A yellow 3:2 adduct **6** ($C_{32}H_{40}O_{12}N_2$, mp 155–156°) was isolated and found to undergo subsequent isomerization, upon heating at 130° in xylene, to a red isomer **7** (mp 136–137°) which, in turn, undergoes further thermal rearrangement to yet other isomers. Since 3:2 adducts had not been previously studied, we undertook a crystal structure analysis of the hydrobromide salt of **7**. Our results therefore establish simultaneously the molecular structure of a reactant and product of these complicated condensation reactions.[3]

The crystal data for the hydrobromide are $C_{32}H_{40}O_{12}N_2 \cdot HBr$; mp 155° dec; $a = 25.00 \pm 0.02$, $b = 10.98 \pm 0.02$, $c = 13.47 \pm 0.02$ Å, $\beta = 104.4 \pm 0.1°$; $Z = 4$; $\rho_{meas} = ca.\ 1.28$ g cm^{-3} and space group $P2_1/a$. Intensities from levels $h0l$–$h5l$ and $0kl$–$4kl$ were measured diffractometrically (Cu Kα) from two crystals (~0.15-mm cubes), converted to $|F|^2$ without correction for absorption, and merged to a common scale.

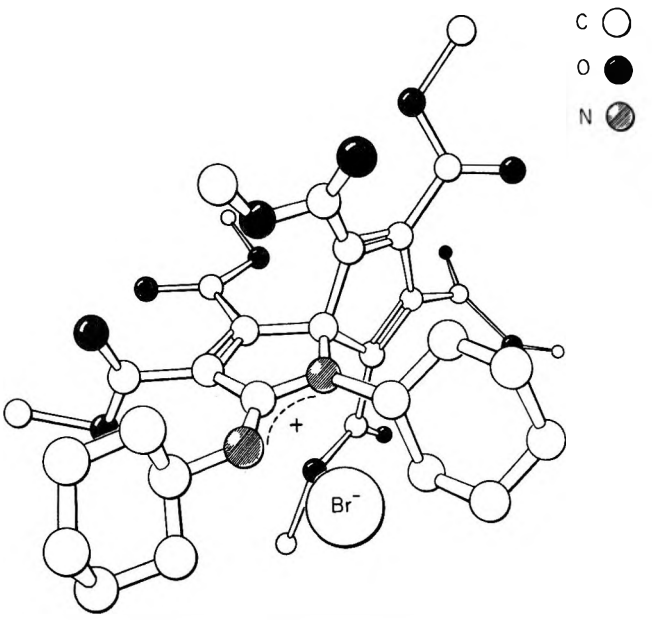


Figure 1.—The solid-state molecular structure and conformation of the hydrobromide salt **8**.

Although the three independent interbromine vectors were easily identified in a Patterson synthesis, their source could not be uniquely attributed to specific symmetry elements since the halogen was positioned on or very near the glide plane. An ambiguity thus arose between the location of the inversion centers and screw axes relative to the bromide ion. No independent structural information other than the chemical origin and atomic composition of **7** was available, and it was therefore not possible to resolve this ambiguity from additional considerations of the molecular packing requirements of possible trial structures. A Fourier map therefore was computed with phases from an arbitrary choice between the two possible bromine X coordinates ($R = 0.57$). Excessive caution in selecting trial molecular moieties near and across the false mirror planes in this map (symmetry $P2_1/m$) led us unknowingly to ignore the correct molecular structure which, in fact, was present along with many other false peaks. Chemical considerations of possible molecular structures for **7** eventually led to an interpretation of this map based on the nearly symmetric spiro structure **8** oriented with a close coincidence of the pseudo molecular mirror and the false Fourier mirror planes. Although successive Fourier syntheses were consistent with the spiro structure, the crystal structure based on all 47 nonhydrogen atoms could not be refined below $R \sim 0.25$. Since, in addition, several unreasonably short intermolecular distances were indicated across the inversion centers and screw axes, the entire hydrobromide structure was translated by $\vec{a}/4$ (6.25 Å) to the alternative unit cell site. This crystal structure and the *original* assignment of the molecular structure as **8** were verified completely through least-squares refinements of all coordinates and temperature parameters (only the Br^- was refined anisotropically). The final agreement between the 2500 observed and calculated structure factors is $R = 0.11$.

The cyclopentadienyl and 3-pyrrolinyl rings are planar and mutually perpendicular within experimental error while the cyclohexane rings are in the chair conformation with equatorial nitrogen substituents (Figure 1).

(1) E. Winterfeldt, *Angew. Chem.*, **78**, 757 (1966); *Angew. Chem., Int. Ed. Engl.*, **5**, 741 (1966).

(2) We wish to thank Professor M. V. George of the Department of Chemistry, Indian Institute of Technology, Kanpur, India, for calling our attention to his studies of this reaction and for providing crystals of the hydrobromide salt.

(3) Financial support by the U. S. Air Force Office of Scientific Research (Grant No. AFOSR-68-1509) is gratefully acknowledged.

The plane of the heterocycle (approximately coincident with the crystallographic glide plane) is nearly a mirror plane of each of the four rings. However, this molecular symmetry is violated by the essentially flat carbomethoxyl groups which are rotated unsymmetrically about the C–C bonds through various angles (in the pyrrolinyl ring, 87, 2°; adjacent in the cyclopentadienyl ring, 25, 40, 55, 4°) in order to relieve nonbonded steric interactions. The equal geminal C—N bond lengths (1.33 Å) and the coplanarity of all atoms bonded to the two nitrogen atoms suggest a delocalized amidine structure. Both cyclohexyl rings appear oriented so as to allow close approach of the protonated amidine to the bromide ion. The latter ion also lies essentially in the heterocyclic plane within hydrogen bonding distance (3.32 Å) of the exocyclic nitrogen atom which presumably bears the proton. The other Br^----N distance is 4.46 Å.

The structure of this 3:2 adduct can be formally derived by the addition of the dipolar 1:1 adduct **3** to the C=N bond of the 2:1 adduct **4**. However, in the absence of further chemical information, we cannot comment on the structure of its isomeric precursor **6**.

Registry No.—**1**, 762-42-5; **2** (R′ = C_6H_{11}), 931-53-3; **7**, 31528-92-4; **7** HBr, 31528-93-5.

Configuration and Conformation of the Dibromides Obtained from the Reaction of Bromine with 2-Ethoxy-5,6-dihydro-2*H*-pyran[1]

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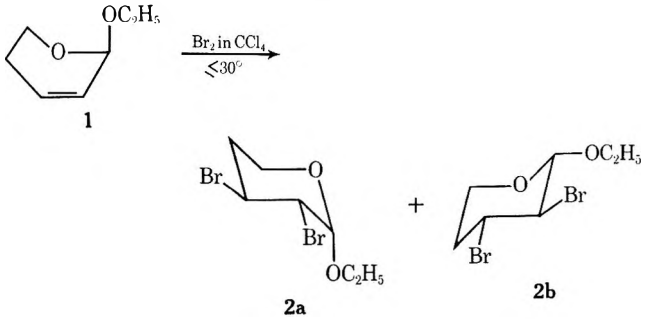
It has been reported[5] that the reaction of bromine with 2-ethoxy-5,6-dihydro-2*H*-pyran (**1**) produces a mixture of "two geometrical isomers of 2-ethoxy-3,4-dibromotetrahydropyran" (Scheme I). Although the

SCHEME I



separation of these isomers has been described,[5] no conformational assignment was made apart from the assumption that the two vicinal bromine atoms were mutually trans.[5] Our program of study of 2-alkoxydihydro- and tetrahydropyrans required a knowledge of the configurational and conformational details of these dibromides in order to determine their influence on the relative stability of the α and β anomers (the anomeric effect[6–8]) and on the course of the base-catalyzed dehydrohalogenation of the dibromides. This note reports our findings concerning the configuration and conformation of these dibromides.

Low-temperature ($\leq 30°$) bromination of **1** either in carbon tetrachloride or methylene chloride gave a mixture of dibromides in 71% yield (*cf.* 68%[5]). Bromination in methylene chloride at −80° or −40 to −45° provided a mixture in which the two isomers **2a** and **2b** were present in the approximate ratio 3:1, determined by the proton magnetic resonance (pmr) spectrum of the isolated crude mixture. An increase in reaction temperature to −30° changed the proportion to ~2:1. Bromination in carbon tetrachloride at either −45 or −30° gave **2a** and **2b** in the ratio ~2:1.

The minor constituent, **2b**, a solid, was separated in the pure state from the liquid mixture by crystallization as reported previously.[5] This did not give quantitative separation. However, most of the remainder of **2b** could be obtained from the residue left when the mother liquor was distilled. The major component, **2a**, a liquid obtained by vacuum fractional distillation of the mother liquor, was found to be contaminated by a small amount (<5%) of **2b** which extensive and careful fractional distillation failed to remove. However, subsequent gas–liquid chromatography (glc) of this distilled fraction did provide pure **2a**. Elemental analyses of the individual isomers agreed with that required for a dibromo-2-ethoxytetrahydropyran.

The configuration and conformation of the solid isomer **2b** was examined by pmr. The 100-MHz spectrum obtained in deuteriochloroform and referred to tetramethylsilane showed the anomeric proton signal as a doublet centered at τ 5.52 ($J_{2,3} \sim 7.0$ Hz). In either acetonitrile or acetonitrile saturated with tetra-*n*-butylammonium bromide, the anomeric proton signal was found at τ 5.54 with $J_{2,3} \sim 7.8$ Hz. The large coupling, as well as the change observed when acetonitrile was used as solvent, shows that the C-2 ethoxy group and the C-3 bromine atom are trans and equatorial.[9] By irradiation at appropriate frequencies, in spin decoupling experiments, it was possible to locate the signals for both H-3 and H-4. A first-order analysis showed a large coupling, $J_{3,4} \sim 9.8$ Hz, indicating that these two protons are trans diaxially disposed and therefore that the two bromine atoms attached to C-3 and C-4 are trans and equatorial. The above information clearly shows that the solid isomer has the configuration shown by **2b** and that the preferred conformation of **2b** is that in which all the substituents are equatorial.

The 100-MHz pmr spectrum of the liquid isomer, **2a**, in deuteriochloroform possessed a doublet for the anomeric proton signal at τ 5.12 ($J_{2,3} \sim 2.8$ Hz) which is nearly the same as that obtained in acetonitrile or ace-

(1) In part from the thesis of F. Sweet, presented to the Faculty of Graduate Studies, University of Alberta, Edmonton, Alberta, Canada, in partial fulfillment of the requirements for the Ph.D. degree.
(2) Postdoctoral Fellow, 1968–1970.
(3) Postdoctoral Fellow, 1969–1971.
(4) Author to whom correspondence should be directed.
(5) G. F. Woods and S. C. Temin, *J. Amer. Chem. Soc.*, **72**, 139 (1950).
(6) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, pp 375–377.
(7) C. B. Anderson and D. T. Sepp, *Chem. Ind. (London)*, 2054 (1964).
(8) E. L. Eliel and C. A. Giza, *J. Org. Chem.*, **33**, 3754 (1968).
(9) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.* **80**, 6098 (1958).

tonitrile saturated with tetra-*n*-butylammonium bromide (τ 5.10, $J_{2,3} \sim 2.8$ Hz). By irradiation of the H-2 nucelus at τ 5.12, the quartet centered at τ 5.89 collapsed to a doublet ($J_{3,4} \sim 10$ Hz), showing that the quartet at τ 5.89 was due to H-3. The large coupling (10 Hz) between H-3 and H-4 proved that these two protons are trans and diaxial and therefore the two bromine atoms are trans and diequatorial. The value of 2.8 Hz for $J_{2,3}$ establishes that the protons on C-2 and C-3 are either gauche (equatorial–axial) or trans diequatorial. Since it has been shown that the C-2 ethoxy group in **2b** is equatorial, and that **2a** and **2b** are isomeric, both having substituents only on C-2, C-3, and C-4, it follows that **2a** differs from **2b** in the configuration at C-2. Accordingly, the ethoxy group at C-2 in **2a** must be axial and thus the configuration and preferred conformation of the liquid isomer is that shown by **2a** in Scheme I.

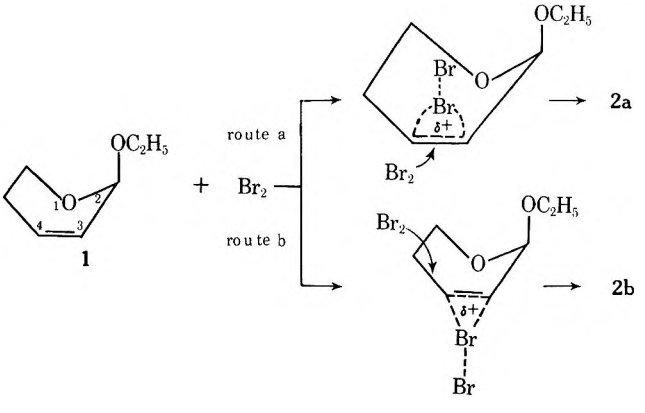
Further support for the structure and conformation of the two isomeric dibromides as shown by **2a** and **2b** in Scheme I is provided by the relative pmr chemical shifts of the signals for the anomeric protons. It is known that an anomeric proton in the axial position provides a signal in the nmr spectrum at higher field than does the anomeric proton in an equatorial orientation.[9] In accord with this is the signal position of the anomeric proton of **2b** at τ 5.52 while that of **2a** is at τ 5.10. Strong bands at 730 and 740 cm^{-1} in the infrared spectra of **2a** and **2b**, respectively, also are indicative of equatorial C–Br stretching. No absorption was found in the region of 550 cm^{-1}, characteristic of axial C–Br.

Whether the proportion of the two isomers obtained is a result of direct bromination of **1**, or of the preferential formation of one isomer which isomerizes in part to the other isomer, is not clear. The same proportion of the two isomers was obtained either when the mixture was worked up immediately following complete addition of the bromine, or when the mixture was allowed to stand for 60 hr after the bromine addition and then worked up. Attempts at isomerization or equilibration by heating either **2a** or **2b** from 12 to 14 hr in refluxing absolute ethanol containing *p*-toluenesulfonic acid gave no appreciable change in either isomer. The marked stability of these dibromides to hydrolysis has already been noted.[5] However, when a methylene chloride solution of pure **2b** at $-30°$ was treated for 0.5 hr with dry hydrogen bromide gas, and the resulting solution was first allowed to stand for an additional 2.5 hr at $-30°$, then come to room temperature over a 4-hr period, and finally kept in a refrigerator overnight, a crude material was obtained whose 100-MHz pmr spectrum showed **2a** and **2b** to be present in the ratio 1.5:1.0, respectively. Similar treatment of **2a** containing 14% of **2b** as contaminant (**2a**:**2b** $\approx$ 6:1) gave a crude product containing **2a** and **2b** in the proportions of $\sim$10:1. Under these conditions, **2b** is converted to **2a** but the reverse conversion appears to be much more difficult. It is significant that, in both cases involving treatment of **2a** or **2b** with dry hydrogen bromide in methylene chloride, the pmr spectrum of the crude product contained signals (unidentified) not found in the pmr spectrum of the crude product of bromination of **1**. This indicates that the normal conditions of bromination of **1** are not so severe as those involving isomerization of **2a** or **2b** with hydrogen bromide.

To determine whether isomerization of **2b** to **2a** might have been caused by hydrogen bromide present in the bromine, or by the hydrogen bromide produced by a side reaction such as substitution, 0.1 molar equiv of bromine was added over a 1-hr period to a solution of **2b** in methylene chloride kept at $-30°$, and the mixture was then allowed to approach room temperature for 1 hr. During this time all the color of bromine slowly disappeared. The pmr spectrum of the isolated crude material showed no evidence whatsoever of the formation of **2a**.

The evidence above in our view indicates that the proportion of isomers **2a** and **2b** does arise from a direct bromination process. Bearing on this problem is our finding[10] that the double bond of 2-methoxy-5,6-dihydro-2*H*-pyran, the methyl homolog of **1**, is attacked by osmic acid apparently only from the side trans to the C-2 methoxy group, thus indicating that this dihydropyran strongly prefers to react in the conformation in which the methoxy group at C-2 is pseudoaxial. If this is so, then compound **1** (Scheme I) should prefer a similar conformation. Pertinent to this is the report[11] that the 2-alkoxy group in both *cis*- and *trans*-2-alkoxy-5,6-dihydro-2*H*-pyran-6-carboxylic esters prefers the pseudoaxial conformation. As well, we have shown[12] that 2-methoxy-5,6-dihydro-2*H*-pyran in ether–methanol reacts with 1,3-dibromo-5,5-dimethylhydantoin to give the two isomers 3β-bromo-2α,4α-dimethoxytetrahydropyran and 3α-bromo-2α,4β-dimethoxytetrahydropyran, thus showing that the bromine atom invariably ends up on C-3, the carbon atom of the double bond closer to the anomeric center C-2, while the methoxy group is attached to C-4 (Scheme II in ref 12). If a bromonium

SCHEME II



ion is involved in this latter reaction as has been suggested,[12] and this occurs also in the reaction of bromine with **1**, and taking into account our findings,[12] it is clear that **2a** could be formed by route a shown in Scheme II, while **2b** could then be formed by the alternate route (b) in Scheme II. In each case, the bromine atom of the bromonium ion becomes attached to C-3. The greater proportion of **2a** must then mean that bromine prefers to attack the double bond from the side cis to the C-2 ethoxy group in spite of the apparent

(10) R. M. Srivastava and R. K. Brown, *Can. J. Chem.*, **49**, 1339 (1971).
(11) O. Achmatowicz, Jr., J. Jurczak, A. Konowal, and A. Zamojski, *Org. Magn. Resonance*, **2**, 55 (1970).
(12) M. J. Baldwin and R. K. Brown, *Can. J. Chem.*, **47**, 3099 (1969).

steric opposition[10] due to this substituent. It is conceivable that an association occurs between the bromine molecule and the electron pairs of the ethoxy group and this causes the predominance in attack by bromine on the double bond on the same side of the ring as is occupied by the ethoxy group.

Experimental Section

All melting points and boiling points are uncorrected. The micro boiling point was determined by using a two-bulb microdistillation apparatus whose lower bulb was immersed in an oil bath. The bath was heated slowly, and, when the liquid started to boil, the temperature of the bath was recorded as the boiling point. Gas–liquid chromatography (glpc) analyses were made with an F & M Model 700 instrument using 0.125 × 12 in. columns. For isolation purposes, an Aerograph Autoprep Model A-700 was employed. Helium was the carrier gas. Solvents were removed by rotary evaporator under vacuum unless otherwise stated. The 60-MHz pmr spectra were obtained with a Varian 60-MHz spectrometer. The 100-MHz spectra and decoupling experiments were made with a Varian HR 100-MHz spectrometer. Tetramethylsilane was the reference material. The infrared spectra were obtained with a Perkin-Elmer Model 421 grating spectrometer.

trans-**3-Bromo-2-ethoxytetrahydropyran** was prepared by the same method used to make *trans*-3-bromo-2-methoxytetrahydropyran[13] but using absolute ethanol rather than methanol as solvent. From 84 g (1.0 mol) of 3,4-dihydro-2*H*-pyran there was obtained 85 g (41%) of crude 3-bromo-2-ethoxytetrahydropyran. This was distilled and the fraction (60 g) boiling at 64–66° (2.8 mm) was collected, n^{21}D 1.4760 [lit.[14] bp 94–96° (18 mm); n^{25}D 1.4752 for material made by the reaction of 2,3-dibromotetrahydropyran with dry ethanol and ammonia].

Both the pmr ($CDCl_3$) and the glc spectra showed our material to be a mixture of cis and trans isomers in the ratio of 1:4, respectively.

Preparation of 3-bromo-2-ethoxytetrahydropyran by the method of Woods and Sanders[14] gave a cis–trans ratio of 2:1.

3,4-Dibromo-2-ethoxytetrahydropyran (**2**).—This compound was prepared by the following modification of the published procedure.[5]

The bromination was carried out in carbon tetrachloride at −45 to −40° rather than at −30°. When all the bromine had been added, the reaction flask was removed from the cooling bath and the solution was stirred for 1 hr, during which time the mixture came to room temperature. The mixture was washed six times with an aqueous solution of a mixture of sodium sulfite (~15%) and sodium carbonate (~15%) and then thrice with water. The last water wash still showed a faint acidic reaction to litmus. The organic solution was dried (Na_2SO_4) and then freed from the drying agent and solvent. The pmr spectrum of the crude residue in $CDCl_3$ showed that it was nearly all a 2:1 mixture of **2a** and **2b**. The weight of this crude material indicated that the bromination had occurred nearly quantitatively.

To avoid extensive decomposition during the subsequent distillation step due to residual acid, the crude material was dissolved in ether and the solution was washed six times with aqueous sodium carbonate (~30%) and then thoroughly with water. The ether solution was dried over a mixture of anhydrous sodium sulfate and sodium carbonate. Removal of the drying agent and solvent gave a colorless liquid (83% crude yield) which was distilled and the fraction collected which boiled at 77–81° (0.2–0.5 mm), yield 71%. At room temperature, this slowly turned yellow. The infrared spectrum (neat) showed two very weak bands at 1700 and 1615 cm^{-1} indicative of a trace of contamination (<1%) by a substance containing a carbonyl group. This impurity was then removed by washing a carbon tetrachloride solution of the oil, first with aqueous sodium carbonate (25%), then with aqueous sodium bisulfate (25%), and finally with water. The oil then isolated could be distilled without decomposition, yielding a stable, pure substance.

Separation of the solid isomer, **2b**, was accomplished by precipitation from cold pentane.[5] The recrystallized material (from pentane) melted at 58–58.5° (lit.[5] mp 60–61°).

The ir spectrum (Nujol mull) showed a strong, sharp band at 740 cm^{-1} (equatorial C–Br); 100-MHz pmr ($CDCl_3$) τ 5.52 (d, 1, J = 7.0 Hz, HC_2O), 5.94 (sextet, J = 9.8 and 5.0 Hz, HC_4Br), 6.10 (q, 1, J = 9.8 and 7.0 Hz, HC_3Br), 6.45 (m, 4, $-CH_2O$, $-C_6H_2O$), 7.75 (m, 2, $-C_5H_2-$), 8.74 (t, 3, J = 7.0 Hz, $-CH_3$).

The mother liquid was distilled with a spinning-band column and provided **2a**, bp 74° (0.5 mm), contaminated with **2b** (<5% by 100-MHz pmr). Glc on a column of 20% butanediol succinate on Gas-Chrom P (60–80 mesh) at 170° with a helium gas flow rate of 80 ml/min showed two peaks, one of which was minute, but the isolated major component **2a** invariably contained decomposition products. Glc on a 0.25 in. × 5 ft column of 20% diethylene glycol succinate on Gas-Chrom W (60–80 mesh) with column and injection port temperatures at 145 and 180°, respectively, and helium carrier gas flow at 100 ml/min and with 10-μl quantities at each injection gave satisfactory isolation of pure **2a** (major peak), bp 74–74.5° (0.5 mm), by two-bulb microdistillation, n^{23}D 1.5155 [lit.[5] bp 123° (12 mm); n^{25}D 1.5158].

Anal. Calcd for $C_7H_{12}O_2Br_2$: C, 29.19; H, 4.20; Br, 55.50. Found: C, 29.48; H, 4.37; Br, 55.42.

The ir spectrum (neat) showed a strong, sharp band at 730 cm^{-1} (equatorial C–Br); 100-MHz pmr ($CDCl_3$) τ 5.12 (d, 1, J = 2.8 Hz, HC_2O), 5.50 (sextet, 1, J = 10.0 and 4.8 Hz, HC_4Br), 5.89 (q, 1, J = 10.0 and 2.8 Hz, HC_3Br), 6.32 (m, 4, $-CH_2O$, $-C_6H_2O$), 7.70 (m, 2, $-C_5H_2-$), 8.74 (t, 3, J = 7.0 Hz, $-CH_3$).

When the bromination was carried out at −30° in carbon tetrachloride, the proportion of **2a** to **2b** in the crude product was found by its pmr spectrum to be ~2:1. Bromination in methylene chloride at −45 to −40° gave **2a**:**2b** ≈ 3:1 whereas bromination in this solvent at −30° gave **2a**:**2b** ≈ 2:1.

Attempted Isomerization of 2a and 2b. A. In Acidified Ethanol.—A solution of 250 mg of the liquid isomer **2a** in 10 ml of absolute ethanol containing 100 mg of *p*-toluenesulfonic acid monohydrate was heated under reflux for 24 hr. The solution was cooled and made alkaline with 10% ethanolic potassium hydride (5 ml). The solvent was removed and the residue was treated with 50 ml of diethyl ether. The precipitated salt was removed and the filtrate was washed with water (three 5-ml portions) and dried (Na_2SO_4). Removal of the drying agent and solvent afforded 200 mg of **2a**. The pmr spectrum in $CDCl_3$ gave no indication of the presence of **2b**.

Similarly, **2b** was heated under reflux for 12 hr and the product was worked up as above. The pmr spectrum of the isolated material showed no evidence of the presence of **2a**. The spectrum did show a new broadened singlet at τ 5.14, but this was not due to **2a**, since the anomeric proton of **2a** produces a doublet at τ 5.10. This contamination was of the order of 10–15%.

B. In Methylene Chloride in the Presence of Hydrogen Bromide.—A solution of 400 mg of pure **2b** in 10 ml of dry methylene chloride was cooled to −30° in a Dry Ice–acetone bath. Dry hydrogen bromide gas was passed through the solution for 5 min. The mixture then was stirred and kept at −30° for 2.5 hr and then the cooling bath was removed and the stirred solution allowed to come to room temperature over a period of 4 hr. After being kept in the refrigerator overnight, during which time it became yellow, the solution was diluted with 10 ml of methylene chloride, then washed with 10% aqueous sodium carbonate (three 10-ml portions) and finally with water (four 10-ml portions). The organic layer was dried (Na_2SO_4) and freed from drying agent and solvent and gave 280 mg of oil. The 60-MHz pmr spectrum showed a new doublet at τ 5.12 (J = 2.8 Hz) indicative of the anomeric proton of **2a**. Comparison of the integrated areas of the anomeric proton signals at τ 5.12 (for **2a**) and 5.52 (for **2b**) with that at τ 8.74 for the triplet for the protons of the methyl group shows that the proportion of **2a**:**2b** ≈ 1.5:1.0. In addition, two minor signals of unknown origin appeared at τ 4.57 (d, J ≈ 2.0 Hz) and 3.52 (d, J ≈ 2.8 Hz).

A solution of 400 mg of **2a** containing 14% of **2b** (**2a**:**2b** ≈ 6.16:1.0) in methylene chloride was treated as described above for pure **2b**. Light yellow liquid (337 mg) was obtained. The integrated areas of the anomeric proton signals showed the presence of **2a**:**2b** ≈ 10.1:1.0. New signals appeared at τ 3.53 (d, J = 3 Hz) and in the region τ 7.70.

Registry No.—**1**, 13687-95-1; **2a**, 31599-27-6; **2b**, 31599-28-7; bromine, 7726-95-6.

(13) F. Sweet and R. K. Brown, *Can. J. Chem.*, **46**, 707 (1968).
(14) G. F. Woods and H. Sanders, *J. Amer. Chem. Soc.*, **68**, 2483 (1946).

Acknowledgment.—We thank the National Research Council of Canada for financial assistance in this work. Our thanks are extended to Mrs. D. Mahlow of this department for the elemental analyses, to Mr. R. Swindlehurst and associates in this department for the 60-MHz spectra, to Mr. Swindlehurst for the infrared spectra, and to Mr. G. Bigham and associates of this department for the decoupling experiments and the 100-MHz spectra.

The Reaction of *p*-Chlorobenzotrifluoride with Methylsulfinyl Carbanion

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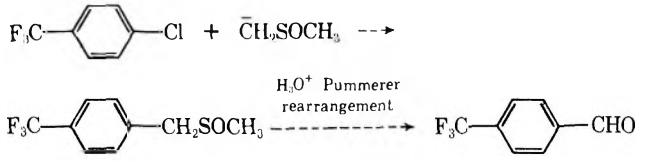
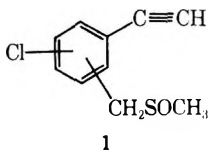
Received April 23, 1971

The preparation of *p*-trifluoromethylbenzaldehyde by the Grignard reaction using *p*-bromobenzotrifluoride and dimethylformamide has been reported.[1,2] The method suffers from the fact that the starting bromo compound is very expensive. Attempts here and elsewhere[1] to use the relatively inexpensive chloride have resulted in the isolation of only miniscular yields of *p*-trifluoromethylbenzaldehyde.[3] A search for an alternate method for its synthesis was therefore undertaken.

One approach was suggested by the report by Corey and Chaykovsky[4] that chlorobenzene reacts with methylsulfinyl carbanion to give methylbenzyl sulfoxide. Accordingly, the following sequence was investigated.



Treatment of *p*-chlorobenzotrifluoride with sodium methyl sulfinyl carbanion gave a dark, foul-smelling, oily product from which a solid slowly crystallized. Infrared and nmr analyses of the purified solid indicated the presence of a benzyl methyl sulfoxide part structure, but both spectra also indicated the presence of a monosubstituted acetylene. Elemental analysis gave empirical formula $C_{10}H_9ClOS$. These data strongly pointed to a structure such as **1**.



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Several attempts to convert the substance to one more easily characterizable, *e.g.*, by reduction of the acetylene group and/or acid-catalyzed rearrangement of the sulfoxide group, were unsuccessful.

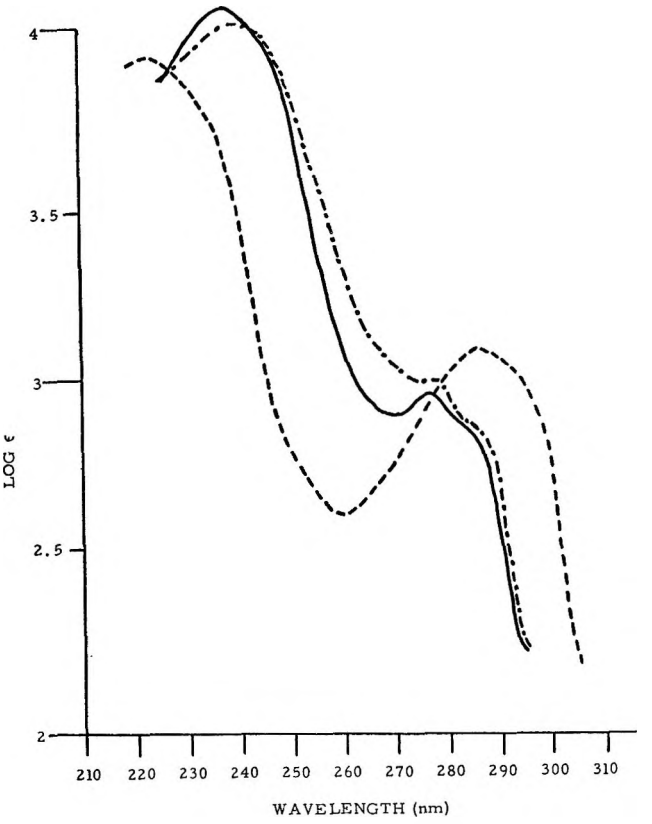
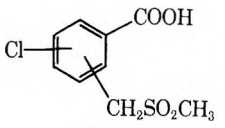


Figure 1.—Ultraviolet spectra: oxidation product (—·—·); 5-Chloro-*o*-toluic acid (– – –); 4-chloro-*o*-toluic acid (——).

Ultraviolet spectral comparison to *m*- and *p*-chlorophenylacetylenes[5] was inconclusive (λ_{max}^{MeOH} 237, 248, 255 nm for the unknown; λ_{max}^{MeOH} 243, 248, 253 nm for *p*-chlorophenylacetylene; *m*-Chlorophenylacetylene shows λ_{max}^{MeOH} 237, 241, 247 nm).

Finally, oxidation with potassium permanganate gave a carboxylic acid sulfone **2** whose ultraviolet and nmr spectra were then compared to those of 4-chloro-*o*-toluic acid (**3**) and 5-chloro-*o*-toluic acid (**4**).[6]



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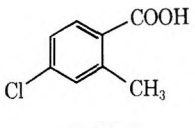

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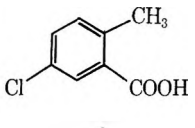

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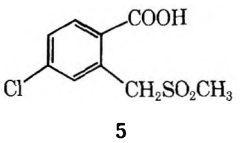
The ultraviolet and nmr comparisons are shown in Figures 1 and 2, respectively. The excellent correlation between the oxidation product and 4-chloro-*o*-toluic acid (3) leaves little doubt that the structure of the former is correctly shown as **5**, *i.e.*, 2-methylsulfonylmethyl-4-chlorobenzoic acid. The crystalline



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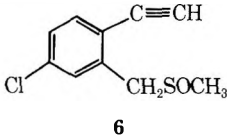

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(1) H. E. Ramsden, *et al.*, *J. Org. Chem.*, **22**, 1202 (1957).
(2) R. Filler and H. Novar, *ibid.*, **25**, 733 (1960).
(3) G. F. Holland, *et al.*, *J. Med. Chem.*, **6**, 519 (1963), report the use of *p*-chlorobenzotrifluoride to prepare this aldehyde. Unfortunately, no details are given.
(4) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).
(5) These were prepared from the corresponding acetophenones by the method of C. Dufraisse and A. Desquesnes, *Bull. Soc. Chim. Fr.*, **49**, 1880 (1931). See also, M. M. Otto, *J. Amer. Chem. Soc.*, **56**, 1393 (1934).
(6) We thank K & K Laboratories of Plainview, N. Y., for samples of these compounds which were unambiguously prepared from 4-chloro-2-methylaniline and 5-chloro-2-methylaniline, respectively.

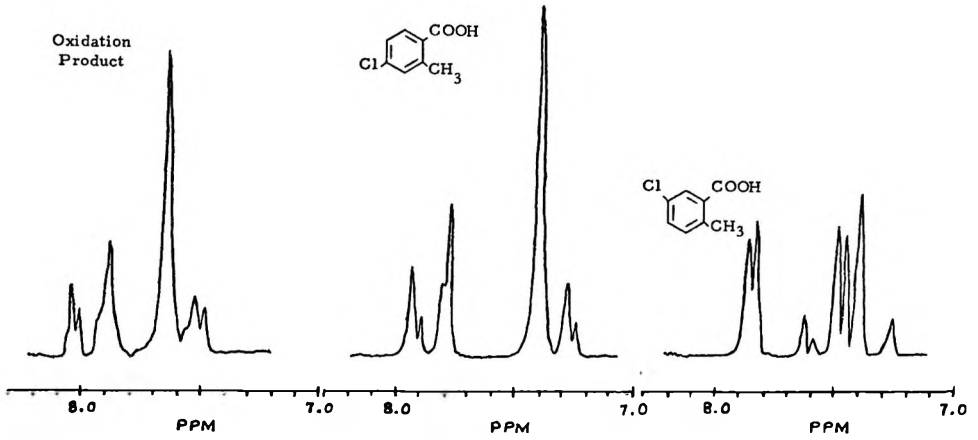
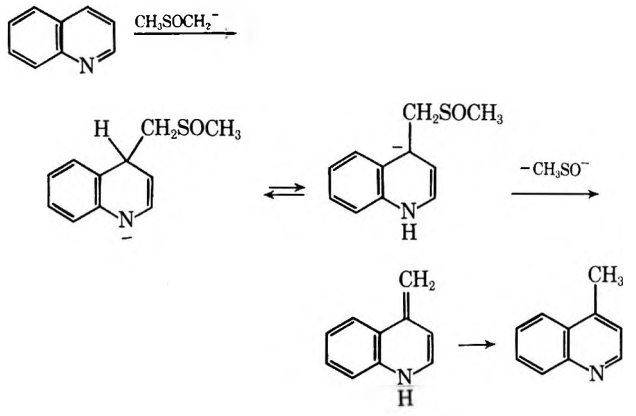


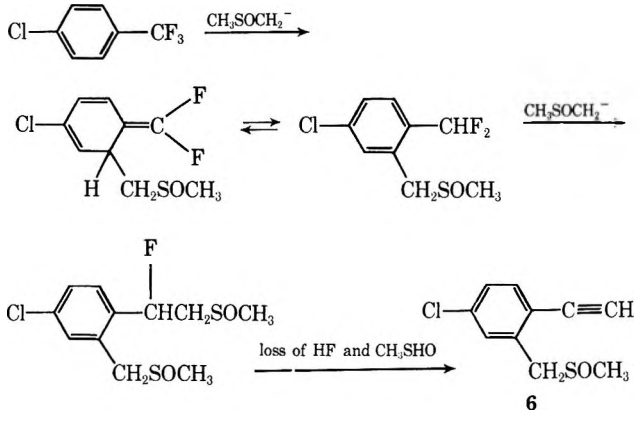
Figure 2.—Nmr spectra: oxidation product; 4-chloro-*o*-toluic acid; 5-chloro-*o*-toluic acid.

product isolated from the reaction of methylsulfinyl carbanion with *p*-chlorobenzotrifluoride is, therefore, **6**, *i.e.*, 5-chloro-2-ethynylbenzyl methyl sulfoxide.

Methylsulfinyl carbanion is known to add to some aromatic systems to give methylated products.[7] For example, the reaction sequence with quinoline to give 4-methylquinoline was pictured as follows.



With *p*-chlorobenzotrifluoride, the sequence of events might be as follows.



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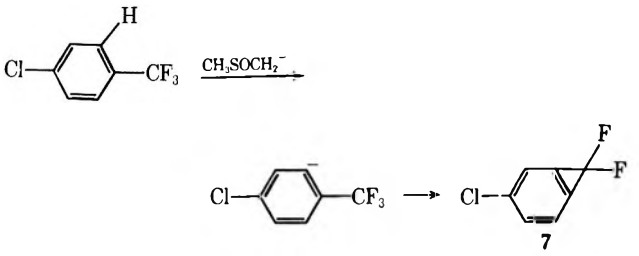
Corey and Chaykovsky[4] have suggested the possibility of a benzyne intermediate in the transformation of chlorobenzene to methyl benzyl sulfoxide, and the involvement of an analogous species, such as **7**, is also a possibility in the present work.



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Further clarification of the mechanism of this reaction is the subject of further investigation.

Experimental Section[8]

5-Chloro-2-ethynylbenzyl Methyl Sulfoxide (6).—A mixture of 28.8 g (1.2 mol) of sodium hydride, freed from oil by washing with petroleum ether, and 156 g (2 mol) of distilled, water-free dimethyl sulfoxide in 350 ml of THF was stirred and refluxed until hydrogen gas evolution ceased (about 2.5 hr). The mixture was cooled to −5°, under nitrogen, in an ice bath and treated dropwise with 36 g (0.2 mol) of *p*-chlorobenzotrifluoride in 25 ml of THF.[9] The temperature was kept at below 8° during the addition.

After stirring for about 2 hr, the bath was removed and the temperature allowed to reach room temperature. The reaction mixture was poured into a mixture of ice and water and extracted with benzene. The extracts were dried and treated with charcoal, and the solvent was distilled *in vacuo*, leaving a dark oily residue which deposited a solid on trituration with ether. The solid was collected (9 g) and recrystallized from ethyl acetate–hexane to give 5.1 g (12%) of **6**, mp 104–108°. Recrystallization from ethyl acetate–hexane gave 5 g of material: mp 112–114°; ir (KBr) 3200 (C≡C**H**), 2100 cm^{-1} (C≡C**H**); uv (MeOH) 237 nm (ε 14,900), 248 (15,620), 255 (14,550); nmr ($CDCl_3$) δ *ca.* 7.4 (m, 3, aromatic), 4.19 (s, 2, CH_2SO), 3.47 (s, 1, C≡C**H**), 2.52 ppm (s, 3, $SOCH_3$).

Anal. Calcd for $C_{10}H_9ClOS$: C, 56.47; H, 4.26; Cl, 16.67; S, 15.08. Found: C, 56.35; H, 4.30; Cl, 16.63; S, 15.20.

2-Methylsulfonylmethyl-4-chlorobenzoic Acid (5).—To a suspension of 1.1 g (0.005 mol) of 5-chloro-2-ethynylbenzyl methyl sulfoxide in 30 ml of water was added, with swirling and heating on a steam bath, 3.2 g (0.02 mol) of $KMnO_4$ in several portions. After a few minutes, the mixture was cooled, filtered through Celite, and acidified. The resulting precipitate was collected and washed with water to give 0.5 g (38%) of **5**: mp 193–196° (recrystallization from absolute ethanol raised the melting point 201–203°); ir (KBr) 1666 cm^{-1} (C=O); uv max (MeOH) 236

(7) See, *e.g.*, G. A. Russell and S. A. Weiner, *J. Org. Chem.*, **31**, 248 (1966), and references cited therein.

(8) All melting points are uncorrected and were taken on a Thomas-Hoover capillary melting point apparatus. The nmr spectra were taken on a Varian A-60 spectrometer with tetramethylsilane as internal standard. The elemental analyses were performed by Scandinavian Microanalytical Laboratories, Herlev, Denmark.

(9) *Caution:* The reaction is very exothermic, and, if the addition is not carried out slowly, a violent eruption may occur.

nm (ε 9660), 279 (960), 286 (745); nmr (DMSO-d_6) δ *ca.* 7.8 (m, 3, aromatic), 5.07 (s, 2, CH_2SO_2), 2.91 ppm (s, 3, SO_2CH_3).

Anal. Calcd for $C_9H_9ClO_4S$: C, 43.46; H, 3.65; Cl, 14.26; 14.26; S, 12.90. Found: C, 43.47; H, 3.65; Cl, 14.45; S, 12.76.

Registry No.—**3**, 7499-07-2; **4**, 7499-06-1; **5**, 31579-08-5; **6**, 31579-09-6; *p*-chlorobenzotrifluoride, 98-56-6; methylsulfinyl carbanion, 13810-16-7.

Acknowledgment.—We wish to thank Dr. Harold R. Almond for the spectroscopic data and his assistance in their interpretation.

An Investigation of the Formation of By-Products in the Nitration of Pentachlorobenzene

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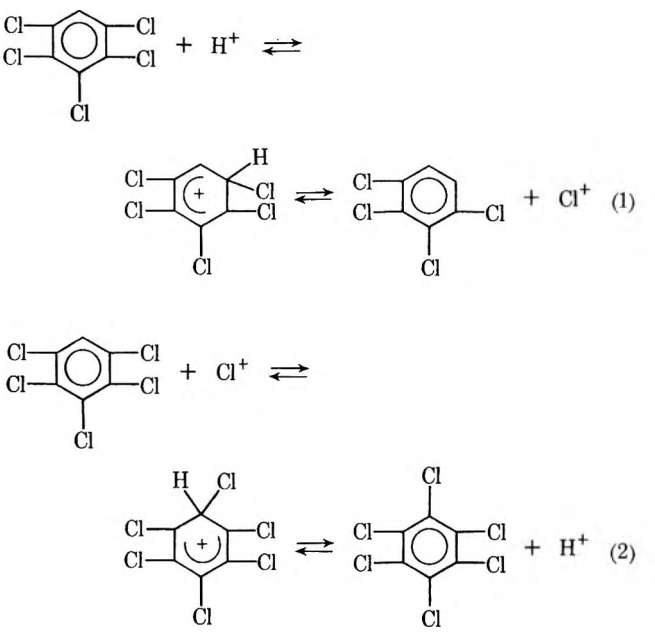
Received December 28, 1970

Pentachloronitrobenzene (PCNB) is an extensively used soil fungicide produced by both foreign and domestic manufacturers. A variety of methods have been used in the production of PCNB,[1-3] but it is commonly prepared by the direct nitration of pentachlorobenzene (PCB).

We have observed in our investigation of this process that the desired PCNB is produced in 83–89% yield based on the amount of PCB reacting, some unchanged PCB being recovered due to sublimation thus removing it from the nitrating mixture. Careful analysis of the reaction mixture by gas chromatography showed that a by-product, hexachlorobenzene (HCB), is formed during the course of reaction.

It was first suspected that the possible displacement of a chloronium ion from the PCB by a proton from the acids employed, with subsequent attack of this chloronium ion on PCB, would lead ultimately to formation of HCB. This mechanism may be represented by eq 1 and 2. This route was discarded as a likely mechanism when only two products, HCB and PCNB, were found in the reaction mixture; no detectable amount of tetrachlorobenzene was produced in the nitration of PCB. In addition, no hexachlorobenzene or tetrachlorobenzene could be detected when PCB was heated with fuming sulfuric acid, even for extended periods of time.

In subsequent studies of the nitration of PCB, the presence of molecular chlorine as a reaction product was established. It has then been postulated that the molecular chlorine arose *via* destructive oxidation of PCB since it is known that ring oxidation is sometimes a significant side reaction in the direct nitration of aromatic systems.[4] The destructive oxidation process



(2)

of PCB would be expected to give, in addition to molecular chlorine, low-molecular-weight fragments. Infrared and nmr analysis of the off-gas from the nitration process established the presence of the products identified generally as low-molecular-weight carboxylic acids. No aromatic products were observed in the off-gas. Subsequent attack of the molecular chlorine on PCB would lead to the formation of the observed HCB. The process involves chlorination of the aromatic system in the absence of catalyst (ZnX_2, FeX_3, etc.) normally employed in halogenations. The reaction path followed is probably similar to that suggested in earlier halogenation studies by Keefer and Andrews.[5,6] The molecular chlorine reacts with the PCB to form an aromatic halogen π complex, which collapses into a σ complex as a result of attack on the halogen–halogen bond by a polar reagent. It has been suggested[5] that in the absence of a catalyst the halogen itself may fill the role of the polar reagent. However, under the conditions of the nitration of PCB, there are a number of species formed that are stronger electrophilic reagents than chlorine and are more likely to function as the polar reagent.

It has also been observed that HCB is formed in small amounts when PCB is heated with fuming nitric acid, the amount of HCB formed in a given time being increased by the introduction of anhydrous chlorine. Treatment of PCB with anhydrous chlorine in the presence of hydrochloric acid or anhydrous hydrogen chloride gave no detectable amount of HCB in reaction periods up to 1.5 hr. This lends support to the concept that chlorination of PCB to form HCB is promoted by some polar reagent formed during the nitration process or by nitric acid itself.

Experimental Section

Gas chromatographic analyses were performed on a Hewlett-Packard F & M Model 700 chromatograph. Columns used in this study were 10% OV-17 silicone on Chromosorb G, H. P., 80–100 mesh, 5% Carbowax 20M on Anakrom AS, 80–90 mesh, and 5% Aroclor 1232 on Chromosorb T, 40–60 mesh. Ir spectra

(1) H. Furst, H. Dietz, P. Ehrentrant, and P. Rammelt, German (East) Patent 10,655 (Oct. 19, 1955); *Chem. Abstr.*, **52**, P-16288*e* (1956).

(2) E. A. Lojewski, U. S. Patent 30,26358 (March 20, 1962); *Chem. Abstr.*, **57**, 7170*f* (1962).

(3) M. Hedayatullah, C. Olle, and L. Dienville, *C. R. Acad. Sci., Ser. C*, **264**, 106 (1967); *Chem. Abstr.*, **66**, 104756*e* (1968).

(4) J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1956, p 332.

(5) R. M. Keefer and L. J. Andrews, *J. Amer. Chem. Soc.*, **78**, 5626 (1956).

(6) L. J. Andrews and R. M. Keefer, *ibid.*, **79**, 5172 (1957).

were obtained with a Perkin-Elmer Model 337 spectrophotometer. Nmr spectra were obtained on a Varian A-60D spectrometer and in reference to benzene as an internal standard.

Nitration of Pentachlorobenzene (Runs 1, 2, and 3).—Pentachlorobenzene (25.0 g, 0.1 mol) was heated to 140°. The nitrating mixture, consisting of 9.0 ml of fuming nitric acid (Baker analyzed reagent) in 31.0 ml of fuming sulfuric acid (Baker analyzed reagent, 30–33%), was added to the liquid pentachlorobenzene, maintaining a temperature of 140–145° during the addition. After addition of the nitrating mixture was completed, the temperature was held at 150–155° for a period of 1.5 hr. The reaction mixture was cooled to room temperature and the solid product was collected by suction filtration, followed by thorough washing with cold water. The product was dried under reduced pressure.

Run 4.—The procedure was identical with that employed in runs 1–3, except 75.0 g of pentachlorobenzene was used. The nitrating mixture consisted of 27.0 ml of fuming nitric acid and 93.0 ml of fuming sulfuric acid. Gas chromatographic analysis of the reaction mixture on the OV-17 and on the more polar Carbowax columns showed only two products, pentachloronitrobenzene (PCNB) and hexachlorobenzene (HCB). Identification was based upon retention times on the two columns and the lack of evidence from either column of additional components when standard HCB was added to the mixture of products. Experimental results are summarized in Tables I and II.

TABLE I

Run	Unchanged PCB, g	Yield of PCNB, g	% yield, PCNB
1	3.4	22.2	89.5
2	4.7	21.5	83.7
3	4.0	20.6	83.0
4	18.5	55.5	85.9

TABLE II

GAS CHROMATOGRAPHIC ANALYSIS

Run	Reactant (PCB), %	Product mixture, % by wt PCNB	HCB
1	100	99	1
2	100	98.5	1.5
3	100	98.1	1.9
4	100	98.4	1.6

Collection and Inspection of Off Gases.—The gases liberated during the nitration of pentachlorobenzene were collected as follows.

Fraction 1: off-gases passed into a 50-ml portion of benzene for a 30-min period.

Fraction 2: off-gases passed into a fresh 50-ml portion of chloroform for a 30-min period.

Fraction 3: off-gases passed into a 10% aqueous solution of silver nitrate for a 2-min period. A heavy precipitate, identified as silver chloride, formed.

Fraction 4: off-gases passed into a fresh 50-ml portion of chloroform for a 20-min period.

Ir, Nmr, and Gc Analysis (Fractions 1, 2, and 4).—Ir spectra of fractions 1, 2, and 4 exhibited an intense band at 5.74 μ and a broad, intense band at 3.3 μ indicative of C=O stretching and OH stretching, respectively, in a carboxylic acid dimer. No absorption was observed in the aromatic region of the spectra of fractions 2 and 4.

The nmr spectrum of fraction 1 exhibited a singlet at δ 10.33, representing the carboxylic acid proton. Spectra of fractions 2 and 4 exhibited no acid proton signal, likely due to the use of chloroform as a solvent. Spectra of fractions 2 and 4 also exhibited no aromatic proton signal.

Samples taken from the off-gas stream in front of the solution phase collector were chromatographed on Arochlor 1232. The presence of chlorine in these samples was established by retention time and by increase in chlorine peak area, without evidence of resolution, on addition of chlorine to the off-gas mixture.

Treatment of Pentachlorobenzene with Fuming Sulfuric Acid.—A 5.0-g sample of pentachlorobenzene was added to 18.0 ml of fuming sulfuric acid and the mixture was heated at 150–160° for periods of 1–8 hr. The mixture was cooled to room temperature and poured over crushed ice. The product was collected by suction filtration, thoroughly washed with cold water, and dried. Solid material (5.0 g) was collected. The product was subjected to gas chromatographic analysis and was found to be pure pentachlorobenzene. No trace quantities of other materials were detected.

Treatment of Pentachlorobenzene with Fuming Nitric Acid.—The procedure was identical with that employed in using fuming sulfuric acid. The product was subjected to gas chromatographic analysis and hexachlorobenzene, pentachloronitrobenzene, and pentachlorobenzene were found to be present. The procedure was repeated and anhydrous chlorine was passed through the mixture. It was observed that the amount of hexachlorobenzene forming in a given time increased.

Treatment of Pentachlorobenzene with Hydrogen Chloride and Chlorine.—A 5.0-g sample of pentachlorobenzene was melted and anhydrous hydrogen chloride and chlorine were passed through the melt for 1.5 hr. The mixture was cooled to room temperature, thoroughly washed with water, and collected. The product was subjected to gas chromatographic analysis and was found to be unchanged pentachlorobenzene. No detectable quantities of other materials were detected. The process was repeated using 20.0 ml of concentrated hydrochloric acid rather than anhydrous hydrogen chloride. The result was the same as above.

Registry No.—PCB, 608-93-5; PCNB, 82-68-8; HCB, 118-74-1.

Acknowledgment.—The authors wish to express appreciation to the University of South Alabama Research Committee for financial support. We also thank Dr. S. F. Thames of the University of Southern Mississippi for running the nmr spectra for us.

A Novel Rearrangement of 2-Isocyanato-4-(alkylthio) Acid Chlorides

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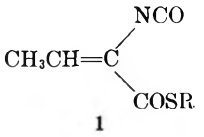
Received May 20, 1971

α-Isocyanato acid chlorides have been prepared from amino acids, phosgene, and hydrogen chloride.[1] While studying a series of reactions of these materials with various amines, the need arose for 2-isocyanato-(4-methylthio)butyryl chloride. Utilizing the method of Iwakura, Uno, and Kang,[1] methionine was converted to the expected α-isocyanato acid chloride. This was evidenced by the infrared spectrum of the crude product which exhibited peaks at 4.5 (NCO) and 5.65 μ (COCl). However, upon attempted purification by vacuum distillation a vigorous evolution of hydrogen chloride was found to occur. After the evolution of the gas had ceased, the distillation proceeded without further incident.

The infrared spectrum of the reaction product finally obtained after distillation exhibited an intense peak at 4.5 μ characteristic of the isocyanate grouping but lacked the characteristic acid chloride absorbance at 5.65 μ. There was, however, an additional intense absorption at 6.05 μ attributable to a thiol ester grouping. The nuclear magnetic resonance spectrum of this unknown material consisted of a doublet at 1.91 (3 H), a singlet at 2.42 (3 H), and a quartet at 6.53 ppm (1 H) downfield from an internal tetramethylsilane standard in

(1) Y. Iwakura, K. Uno, and S. Kang, *J. Org. Chem.*, **30**, 1158 (1965).

carbon tetrachloride. Infrared and nmr spectral data in conjunction with elemental analysis conclusively demonstrated the structure of the unknown material to be methyl 2-isocyanato-2-butenethiolate (**1**, R = CH_3).



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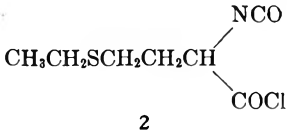
When an identical reaction was carried out using ethionine in place of methionine, distillation at reduced pressure afforded two materials. These were identified as the expected α-isocyanato acid chloride **2** and the



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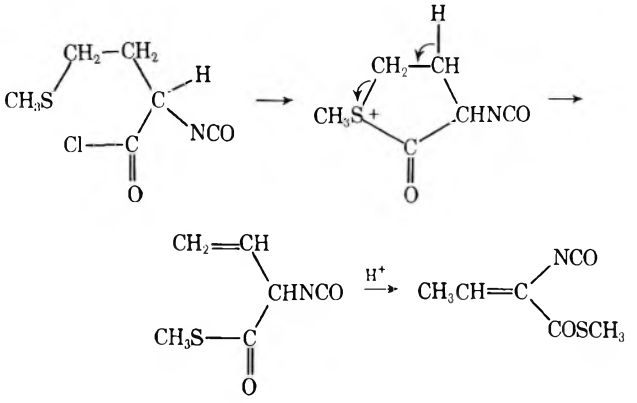
corresponding rearrangement product **1** (R = C_2H_5). While no mechanistic studies of this rearrangement have been undertaken, it is quite likely that in intramolecular rearrangement occurs *via* a sulfonium ion intermediate. A possible mechanism is shown below.



An investigation of the intermolecular interaction between acyl chlorides and sulfur has been shown to form thiolactones and alkyl halides *via* an acyl sulfonium salt.[2] Thus, 4-(*n*-propylthio)butyryl chloride provides γ-thiobutyrolactone and *n*-propyl chloride. In contrast, the present study reveals that formation of the 2-isocyanatoacylsulfonium chloride undergoes loss of hydrogen chloride to form an unsaturated 2-isocyanatothiol ester.

Experimental Section

Infrared and nuclear magnetic resonance spectra were determined on a Beckman IR-5 spectrophotometer and a Varian Model A-60 spectrometer, respectively.

Preparation of Methyl 2-Isocyanato-2-butenethiolate.—Methionine (50 g) was suspended in 500 ml of dry dioxane; phosgene was then passed through the mixture at 45° for 4 hr. The solution was cooled to 0° and dry hydrogen chloride passed through the mixture for 2 hr; the resultant mixture was allowed to stand overnight. The solution was then heated to 50° and phosgene was passed through for 4 hr, and then the solution was allowed to stand for 2 days. The solvent was removed *in vacuo* and the residue was distilled at 70–80° (*ca.* 1 mm). Prior to the distillation temperature, evolution of hydrogen chloride occurred. The product (10.2 g, 21%) was identified as the title compound by its infrared and nmr spectra in conjunction with elemental analysis.

(2) W. E. Truce and D. J. Abraham, *J. Org. Chem.*, **28**, 964 (1963).

Anal. Calcd for $C_6H_7NO_2S$: C, 45.84; H, 4.49; S, 20.40. Found: C, 45.62; H, 4.51; S, 20.18.

When the reaction was carried out in an identical fashion using ethionine, distillation at 70–75° (0.45 mm) provided 20 g of a 3:2 mixture of compounds **2** and **1** (R = C_2H_5). Further distillation at 77° (0.35 mm) provided 9.7 g (18%) of pure **1** (R = C_2H_5). The nmr spectrum of the latter had proton resonances centered at 1.3 (t, 3 H), 1.9 (d, 3 H), 2.95 (q, 2 H), and 6.4 ppm (q, 1 H).

Registry No.—**1** (R = CH_3), 31600-83-6; **1** (R = C_2H_5), 31600-84-7; **2**, 31600-85-8.

Trifluoroacetic Anhydride Ring Opening Addition to Cyclic Ethers

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Contribution No. 1784 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

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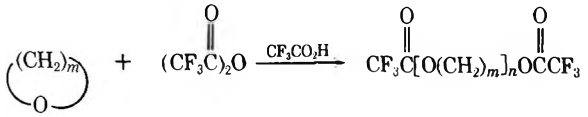
Cyclic ethers such as ethylene oxide (EO) and tetrahydrofuran (THF) are readily opened by acids to the corresponding adducts;[1,2] for example, acetic acid condenses rapidly with EO to give 2-acetoxyethanol. Recently, on attempting a trifluoroacetylation with trifluoroacetic anhydride (TFAA) in THF, we obtained mainly the products resulting from addition of TFAA to THF and an oligomer.[3] This reaction is definitely acid catalyzed since higher yields at lower reaction temperature result by addition of a catalytic amount of trifluoroacetic acid. In the series of cyclic ethers the relative yields of oligomer *vs.* 1:1 adduct vary with the



size of the ring. Relative concentration and possibly temperature are also important, but insufficient data have been collected to establish any quantitative conclusions. The reaction was run under autogenous pressure in a sealed autoclave in order to attain temperatures over 100° that appeared to be required for reasonable reaction rate. No significant yield of product was found in refluxing THF at atmospheric pressure. For ethylene oxide (m = 2), products with n = 1, 2, 3, 4, and greater are isolated. For tetramethylene oxide (m = 3) and THF (m = 4), both 1:1 and 2:1 adducts are obtained. For tetrahydropyran, only the 1:1 adduct was found. The product yields are given in Table I and physical and analytical data on all new compounds are listed in Table II.

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(2) R. C. Elderfield, *Heterocycl. Compounds*, **1**, 175 (1950).

(3) The ring opening addition of acetic anhydride to THF has been reported: Netherlands Patent Application 6,516,827 (Farwerke Hoechst A.-G., July 1966) [*Chem. Abstr.*, **66**, 2194b (1967)]; R. M. Ispiryan, L. I. Belen'kii, Ya. I. Gol'farb, *Izv. Akad. Nauk Kaz. SSR, Ser. Khim.*, **11**, 513 (1967) [*Chem. Abstr.*, **69**, 66866t (1968)].

TABLE I

REACTION OF CYCLIC ETHERS WITH TRIFLUOROACETIC ANHYDRIDE (TFAA)

Ether	Amount, g (mol)	TFAA,[a] g (mol)	Conditions	Product	n	Yield, g	Yield, % based on ether	Yield, % based on TFAA[a]
Ethylene oxide	8.9 (0.20)	42 (0.20)	50 ml of CCl_3F solvent, 120°, 20 hr	$CF_3C(OCH_2CH_2)_nOCCF_3$	1	11.6	22.8	22.8
					2	17.6	59	29.5
	44.5 (1.0)	42 (0.20)	120°, 20 hr		1	9.3	3.7	18.3
					2	23.2	15.6	40.0
					3	12.8	11.1	18.5
					(4)[b]	7.7	8.2	(10.0)
Trimethylene oxide	11.6 (0.20)	42 (0.20)	50 ml of CCl_3F solvent, 120°, 18 hr	$CF_3C[O(CH_2)_3]_nOCCF_3$	1	14.0	25.6	25.6
					2	18.1	55.4	27.7
Tetrahydrofuran	14.4 (0.20)	42 (0.20)	120°, 18 hr	$CF_3C[O(CH_2)_4]_nOCCF_3$	1	1.9	3.4	3.4
					2	0.3	0.9	0.5
	14.4 (0.20)	42 (0.20)	180°, 18 hr		1	41.7	73.9	73.9
					2	6.2	17.5	8.7
	72 (1.0)	42 (0.20)	120°, 18 hr		1	6.6	2.3	11.7
					2	5.0	2.8	7.0
	72 (1.0)	42 (0.20)	1.0 g of CF_3CO_2H, 120°, 18 hr		1	14.6	5.2	25.9
					2	26.5	15.0	37.4
Tetrahydropyran	17.2 (0.2)	42 (0.20)	200°, 18 hr	$CF_3C[O(CH_2)_5]_nOCCF_3$	1	45.3	76.5	76.5
	17.2 (0.2)	42 (0.20)	120°, 18 hr			0	0	0

[a] TFAA = trifluoroacetic anhydride. [b] The fraction of bp 112° (0.225 mm) appeared to be primarily oligomer with $n = 4$.

TABLE II

PHYSICAL AND ANALYTICAL DATA ON ETHER–TFAA ADDUCTS

Compd	n	Registry no.	Bp, °C (mm)	$n^{25}D$	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	F, % Calcd	F, % Found
$CF_3C(OCH_2CH_2)_nOCCF_3$	1	2613-44-7	47 (6.5)	1.3275	$C_6H_4F_6O_4$[a]						
	2	31580-02-6	71 (1.5)	1.3516	$C_8H_8F_6O_5$	32.2	32.1	2.70	2.88	38.2	37.1
	3	31528-86-6	61 (0.02)	1.3696	$C_{10}H_{12}O_6F_6$	35.1	35.8	3.54	3.77	33.3	32.4
$CF_3C[O(CH_2)_3]_nOCCF_3$	1	7647-95-2	95.5 (30)	1.3388	$C_7H_6O_4F_6$	31.4	31.2	2.26	2.24	42.5	42.3
	2	31528-88-8	134 (30)	1.3604	$C_{10}H_{12}F_6O_5$	36.8	37.1	3.71	3.76	35.0	34.9
$CF_3C[O(CH_2)_4]_nOCCF_3$	1	31528-89-9	43–44 (0.1)	1.3459	$C_8H_8F_6O_4$	34.1	33.8	2.85	2.86	40.4	40.5
	2	31528-90-2	70–75 (0.1)	1.3709	$C_{12}H_{16}F_6O_5$	40.9	40.0	4.55	4.65	32.2	32.5
$CF_3C[O(CH_2)_5]_nOCCF_3$	1	453-44-1	50 (0.25)	1.3538	$C_9H_{10}F_6O_4$	36.5	36.5	3.41	3.5	38.5	37.5

[a] Lit. bp 151–153°, $n^{25}D$ 1.3286 (at least 95% pure): S. D. Ross and M. Finkelstein, *J. Org. Chem.*, **22**, 847 (1957). Preparation was from a large excess of trifluoroacetic anhydride and ethylene glycol.

The reaction no doubt goes by ring-opening protonation of the ether since trifluoroacetic acid was shown to be a catalyst. To attempt to determine whether polymer was derivable under the reaction conditions using a larger THF–anhydride ratio, ratios of 10:1–100:1 (molar) were used. Under the latter conditions, conversion was low to give predominantly the adduct with two THF units.

Experimental Section

The typical procedure for reaction was to charge the reactants into a 240-ml stainless steel pressure vessel and heat at autogenous pressure, at temperature and time given in Table I. The reaction mixture was distilled.

No significant reaction occurred when THF and TFAA containing a catalytic amount of trifluoroacetic acid were refluxed for 24 hr at atmospheric pressure.

The physical and analytical data on all new compounds are in Table II. The ir and nmr (proton and ^{19}F) spectra were in agreement with the proposed structure. In the ir, the trifluoroacetate carbonyl had a strong absorption at 1740 cm^{-1}. The ^{19}F nmr for the CF_3 group was a sharp singlet in the range of 75.8–75.9 ppm relative to CCl_3F (internal standard and solvent, 5% concentration).

Registry No.—Trifluoroacetic anhydride, 407-25-0.

Reaction of Nitronium Fluoroborate with Olefins in Acetonitrile

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The Ritter reaction[2] is a convenient method of preparing amines or amides by reaction of olefins in acidic

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(2) (a) J. J. Ritter and P. P. Minieri, *J. Amer. Chem. Soc.*, **70**, 4045 (1948); (b) T. Clark, J. Devine, and D. W. Dicker, *J. Amer. Oil Chem. Soc.*, **41**, 78 (1964).

media with hydrogen cyanide or nitriles. Treatment of olefins with halogens in nitrile solvents leads to α-halogenated amides;[3] other modifications of the Ritter reaction with *N,N*-dichlorosulfonamides or peracids in nitrile media have also been reported.[4]

We wish to report an extension of the Ritter reaction in which the electrophilic reagent is nitronium or nitryl fluoroborate, NO_2BF_4. This salt is known to nitrate and to initiate the polymerization of olefins.[5] These nitrative polymerizations are effected when NO_2BF_4 is contacted with neat olefins in the liquid state. We have found that olefins react with NO_2BF_4 in anhydrous acetonitrile at −15° to give products which on hydrolytic work-up afford vicinal nitroacetamido derivatives **1**. The products from primary, secondary, and tertiary olefins are acyclic, in contrast to the results with nitrosyl fluoroborate.[4b] Side products such as unsubstituted amides formed by simple Ritter reactions are easily separated by distillation at low pressure.

$$RR'C{=}CHR'' + NO_2BF_4 \xrightarrow[2.\ H_2O]{1.\ CH_3CN} RR'\overset{NO_2}{\underset{NHCOCH_3}{C}}CHR''$$

In this manner, propylene is converted to 1-nitro-2-acetamidopropane (**1a**, R = CH_3; R′ = R″ = H)[6] (50%), isobutylene to 1-nitro-2-methyl-2-acetamidopropane (**1b**, R = R′ = CH_3; R″ = H) (23%), and butene-2 to 2-nitro-3-acetamidobutane (**1c**, R = R″ = CH_3; R′ = H) (13%). In the latter case, the identical product was obtained from either the cis or trans olefin. Although it was ascertained that no isomerization of the olefin occurred prior to reaction, other details of the work-up procedure during which isomerization of the nitroacetamide might occur preclude any definitive conclusions of the structure of the reaction intermediate.

Experimental Section

Melting points are uncorrected. Elemental analyses, nmr, and mass spectroscopy were performed by AID laboratory of Esso Research and Engineering Co. Acetonitrile was purified by distillation from P_2O_5. Nitryl fluoroborate was purchased from Alfa Inorganics.

A solution of 13.3 g (0.1 mol) of NO_2BF_4 in 200 ml of anhydrous acetonitrile was treated with 0.2 mol of olefin at −25° under nitrogen with stirring. Upon completion of the addition of olefin, 10 ml of water was introduced. The reaction was stirred for 0.5 hr and gradually warmed to ambient temperature under nitrogen. The mixture was diluted with 50 ml of benzene and the solvent was removed by evaporation at reduced pressure. The residue was extracted with methylene chloride and washed free of acid with aqueous sodium bicarbonate solution, then with brine, dried ($MgSO_4$), evaporated, and distilled under reduced pressure.

Propylene gave 7 g (50% yield) of 1-nitroacetamidopropane (**1a**): mp 103–104° (lit.[6] mp 104°); nmr (acetone-d_6) δ 1.25 (d, 3, CH_3CH, J = 6.5 Hz), 1.9 (s, 3, CH_3CO), 4.7 (m, 3, NCH_2CHN), and 7.5 ppm (broad, 1, NH). *Anal.* Calcd for $C_5H_{10}N_2O_3$: C, 41.08; H, 6.83; N, 19.29; mol wt, 146. Found: C, 41.04; H, 7.07; N, 18.92; mol wt, 146 (mass spectrum).

Isobutylene gave 3.7 g (23%) of 1-nitro-2-methyl-2-acetamidopropane (**1b**): mp 86° ($CHCl_3$–hexane); nmr ($CDCl_3$) δ 1.5 [s, 6, $(CH_3)_2C$], 2.0 (s, 3, CH_3CO), 4.9 (s, 2, CH_2), and 6.6 ppm (broad, 1, NH). *Anal.* Calcd for $C_6H_{12}N_2O_3$: C, 44.94; H, 7.55; N, 17.49. Found: C, 44.55; H, 17.52; N, 17.17.

Both *cis*- and *trans*-butene-2 afforded the same product, but there was no isomerization of unreacted olefin observed during the course of reaction, as indicated by vpc. The brown oil obtained (7.3 g) was distilled to give a fraction, bp 70–75° (0.2 Torr), 1.5 g (12%), which was *N*-*sec*-butylacetamide: $n^{25}D$ 1.437 (lit.[7] $n^{25}D$ 1.436): ir ($CHCl_3$) 3260, 1650, 1545, and 870 cm^{-1}; nmr ($CDCl_3$) δ 0.90 (t, 3, CH_3CH_2), 1.10 (d, 3, CH_3CH), 1.45 (q, 2, CH_2), 1.98 (s, 3, $COCH_3$), 3.88 (q, 1, CH), and 7.0 ppm (broad, 1, NH). The second fraction, bp 105–106° (0.2 Torr), 2.1 g (13%), was 3-nitro-2-acetamidobutane (**1c**): mp 50–52° (ether, hexane), white crystals, mp 53.5° (sublimation, 30°, 0.2 Torr); ir ($CHCl_3$) 3260, 1650, 1545, 1385, and 1370 cm^{-1}; nmr ($CDCl_3$) δ 1.12 (q, 3, CH_3CHNH, J = 6.5 and 1.5 Hz), 1.55 (d, 3, CH_3CHNO_2), 2.0 (s, 3, CH_3CO), and 4.7 ppm (m, 2, CHCH). *Anal.* Calcd for $C_6H_{12}N_2O_3$: C, 44.99; H, 7.55 N, 17.49; mol wt, 160. Found: C, 44.81; H, 7.57; N, 17.57; mol wt, 160 (mass spectrum).

Registry No.—**1a**, 31593-56-3; **1b**, 31662-22-3; **1c**, 31593-57-4; *N*-*sec*-butylacetamide, 1189-05-5; nitronium fluoroborate, 13826-86-3; propylene, 115-07-1; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6; isobutylene, 115-11-7.

Acknowledgment.—The authors are indebted to Mr. R. Kelly, Miss M. A. Miciak, and Mr. J. J. Porcelli for experimental assistance.

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(6) C. A. Grob, C. Wagner, and P. Zoller, *Helv. Chim. Acta*, **67**, 1689 (1955).

(7) H. Windaus, *Ber.*, **40**, 81 (1907).

Formation of Sulfones in the Thermal Decomposition of Ylides Derived from *p*-Toluenesulfonylhydrazides

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Ylides of the type I were first prepared by Wawzonek and Meyer, who described the thermolysis at 185–195° of the example I (R = Me).[2] They obtained a large amount of a polymer of the *p*-toluenesulfonamide–formaldehyde type, along with *p*-toluenesulfonamide, ammonia, trimethylamine, and formaldehyde. Subsequently Robson and Speakman prepared *N*-trimethylammoniododecanesulfonamidate (II) and demonstrated by suitable trapping experiments that the two products observed on pyrolysis, a trapped nitrene (dimethyl sulfoxide or triphenylphosphine) and dodecanesulfonesulfonamide, were formed by cleavage of the N–N bond to yield a sulfonyl–nitrene intermediate III,[3] which would also account for the products observed in the former case (I, R = Me) (Chart I).

In the course of our investigations of the [2,3] sigmatropic rearrangements of nitrogen ylides,[4,5] we had occasion to prepare ammoniosulfonamidate (I, R = 3-methyl-2-butenyl; mp 138° dec) and have discovered that its thermolysis proceeds in a very different way to

(1) A. P. Sloan Fellow, 1969–1971.

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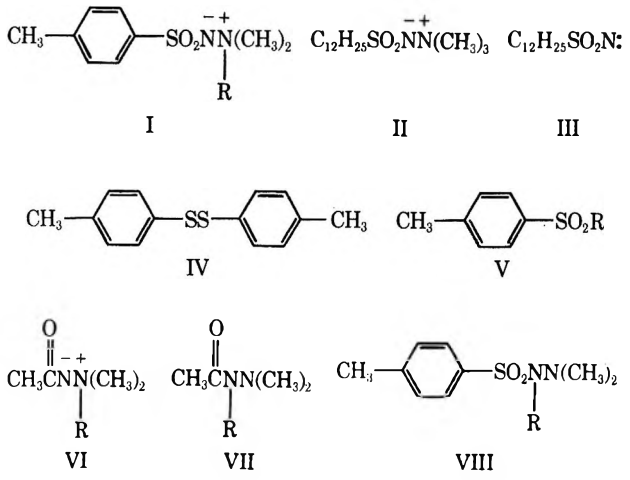
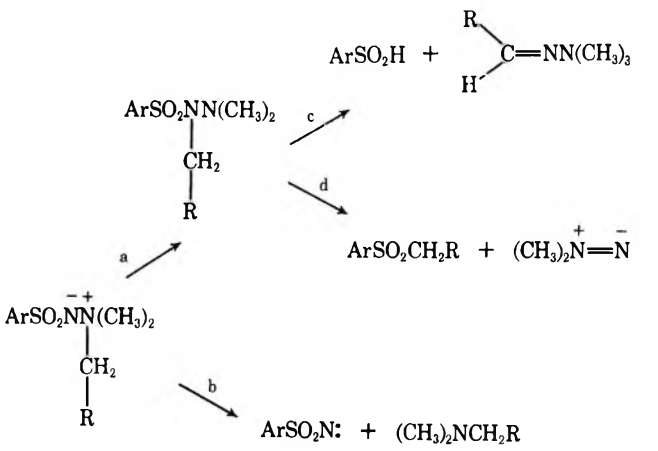
CHART I



SCHEME I



those earlier described.[2,3] Thus, pyrolysis at the melting point yielded 4-methylphenyl disulfide (IV, 21%) and sulfone (V, R = 3-methyl-2-butenyl, 22%), along with a volatile fraction which is as yet unidentified but by glpc analysis consists of at least 15 components. Similarly, the benzyl ylide I (R = benzyl) was pyrolyzed to the disulfide IV (4%); sulfone V (R = benzyl, 22%, benzaldehydedimethylhydrazone (5%), *p*-toluenesulfonamide (13%), and a volatile fraction containing *N*,*N*-dimethylbenzylamine (5%). Thus in contrast to the earlier work,[2,3] the pyrolysis of ylides I, in which group R is capable of radical stabilization, leads to major amounts of products, the disulfide IV and sulfone V, formed by complete ejection of the nitrogenous fragment rather than heterolytic cleavage to a nitrene. Since it is known that acylammonioamidates, such as VI (R = benzyl or 3-methyl-2-butenyl), do undergo a facile thermal Stevens rearrangement, by a radical pathway,[4,6] to hydrazides such as VII (R = benzyl or 3-methyl-2-butenyl), it seems likely that in this case also the reaction is prefaced by a similar conversion to the rearrangement product VIII (R = benzyl or 3-methyl-2-butenyl). The hypothetical Scheme I shows how reasonable further transformations *via* paths c and d of this species would yield the hydrazone and sulfone products. Apparently the nitrene route[3] is operative to some extent also, judging by the formation of sulfonamide and amine, path b. The origin of disulfide IV is more difficult to understand, but there is precedence for its formation in the Bamford–Stevens reaction of benzaldehydetosylhydrazone,[7,8] which was rationalized as a deoxygenation of *p*-toluenesulfinate by phenyl carbene. In this series the sulfonylnitrene or dimethyldiazene could be similarly effective deoxygenators, Scheme I.

The product studies noted here suggest that a labile substituent on nitrogen in ylides of type I permits the operation of a previously unobserved pathway in the pyrolytic behavior of such species. They are compatible with the operation of a Stevens type process yielding a substance such as VIII, which may undergo further thermal reactions resulting in complete loss of the nitrogenous portion.

(6) S. Wawzonek and E. Yeaker, *J. Amer. Chem. Soc.*, **82**, 5718 (1960); D. G. Morris, *Chem. Commun.*, 1345 (1969).

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Experimental Section

Melting points were taken on a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were carried out by Midwest Micro-Labs in Indianapolis, Ind. Gas chromatography was performed with a Varian Model 700 equipped with recorder, column temperature 130°, column 30% Carbowax on Chromosorb W (45–60 mesh, 20 ft by 0.375 in.).

Preparation of 1,1-Dimethyl-2-(*p*-toluenesulfonyl)hydrazine.—The procedure of Wawzonek and Meyer[2] was used and the material was obtained as white crystals (57%), mp 78–79° (lit.[2] 79–81°).

Preparation of 1,1-Dimethyl-1-(3-methyl-2-butenyl)-2-(*p*-toluenesulfonyl)hydrazonium Bromide.—1-Bromo-3-methyl-2-butene (20.4 g, 0.136 mol) was added to 26.7 g (0.124 mol) of 1,1-dimethyl-2-(*p*-toluenesulfonyl)hydrazine stirring in 45 ml of acetone. After the solution had been stirred for 24 hr at room temperature and filtered, it yielded 35.9 g (80%) of white solid: mp 107–108°; ir (Nujol) 2700, 1600, 1180 cm^{-1}; nmr ($CDCl_3$) ϵ 1.87 (s, 6), 2.45 (s, 3), 3.07 (s, 1, exchanges), 3.61 (s, 6), 4.71 (d, 2, J = 8 Hz), 5.45 (t, 1, J = 7 Hz), 7.38 (d, 2, J = 8 Hz).

Preparation of 1,1-Dimethyl-1-(3-methylbut-2-enyl)-2-(*p*-toluenesulfonyl)hydrazonium Ylide (I, R = 3-Methyl-2-butenyl).—Potassium *tert*-butoxide (3.46 g, 31.0 mmol) in 22 ml of absolute ethanol was added dropwise to 7.32 g (20.2 mmol) of the hydrazonium bromide stirring in 150 ml of absolute ethanol at room temperature. Stirring for 0.5 hr, followed by filtration and concentration of the filtrate, yielded 5.33 g (93%) of white amorphous solid. Recrystallization from dioxane gave 3.41 (69%) of white prisms: mp 137–138° dec; ir (Nujol) 1270 (s), 1130 (m), 1090 cm^{-1} (m); uv λ_{max} 235 (8600); nmr ($CDCl_3$) ϵ 1.72 (s, 3), 1.80 (s, 3), 2.37 (s, 3), 3.08 (s, 6), 4.03 (d, 1, J = 8 Hz), 5.47 (t, 1, J = 7 Hz), 7.21 (d, 2, J = 8 Hz, 7.79 (d, 2, J = 8 Hz); mass spectrum 70 eV (m/e) no molecular ion, 214, 171, 155, 91.

Anal. Calcd for $C_{14}H_{22}O_2S$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.30; H, 7.70; N, 9.77.

Treatment of this ylide with zinc in water–acetic acid yielded *p*-toluenesulfonamide and *N*,*N*-dimethyl-*N*-(3-methylbut-2-enyl) amine.

Thermolysis of I (R = 3-Methylbut-2-enyl).—Thermolysis was performed by placing 0.951 g of this ylide in a Pyrex 11-mm tube sealed at one end (immersed in an oil bath) and a portion (U shape) immersed in a Dry Ice–acetone bath (−78°). A vacuum (0.04 mm) was applied to the system and the temperature of the oil bath gradually raised. At 140° a vigorous bubbling took place and immediately a yellow condensate, 0.206 g (22%), was collected in the U tube; the nmr indicated *N*-methyl protons, but both glpc and nmr analysis showed little or no *N*,*N*-dimethyl-*N*-(3-methylbut-2-enyl)amine when compared with an authentic sample. The pyrolysis was continued for 20 min and the black residue, 0.705 g, was transferred to a Kügelrohr distillation apparatus and distilled (oven) at 170° (0.05 mm), 0.456 g of yellow oil being collected and 0.192 g of black nonidentifiable tar remaining as residue. Chromatography over alumina of the

distilled oil (benzene) gave 81 mg of crystalline *p*-tolyl disulfide (IV): mp 43–45° [mp (Eastman *p*-tolyl disulfide IV) 43–45°]; mmp 43–45°; ir and nmr identical. A later fraction (25% $CHCl_3$–75% C_6H_6), 0.132 g, was redistilled, mp 80–81°, white needles. Comparison with authentic *p*-toluene-3-methylbut-2-enyl sulfone prepared by the alkylation of *p*-toluenesulfinic acid with 1-bromo-3-methyl-2-butene showed that the compounds were identical in all respects. Nmr evidence on the crude ylide distillate indicated only the disulfide and sulfone present, and integration yielded weight per cents of 21 and 22%, respectively.

Preparation of 1,1-Dimethyl-1-benzyl-2-(*p*-toluenesulfonyl)-hydrazonium Bromide.—To 12.8 g (59.6 mmol) of 1,1-dimethyl-2-(*p*-toluenesulfonyl)hydrazine in a 50-ml flask was added 20 g (117 mmol) of benzyl bromide. The mixture was warmed on a steam bath until dissolved and allowed to stand for 10 hr at room temperature. The white solid formed was triturated with ether and filtered to yield 14.2 g (62%) of white salt. Recrystallization from ethanol yielded a white powder: mp 105–106°; ir (Nujol) 2750 (broad), 1600, 1700, 1090 cm^{-1}; nmr ($CDCl_3$) δ 2.37 (s, 3), 3.69 (s, 6), 5.52 (s, 2), 7.1–8.1 (m, 9), 9.0–10.5 (broad, 1).

Preparation of 1,1-Dimethyl-1-benzyl-2-(*p*-toluenesulfonyl)-hydrazonium Ylide (I, R = benzyl).—The previously prepared hydrazonium bromide (3.59 g, 9.32 mmol) was dissolved in 20 ml of absolute ethanol and 1.15 g (1.1 equiv) of potassium *tert*-butoxide in 10 ml of ethanol was added while stirring. After the solution was stirred for 4 hr at room temperature, it yielded a white solid, 3.92 g (113%). This was dissolved in hot chloroform and filtered, and the chloroform was removed giving a white solid, 2.12 g (75%). Recrystallization from ethanol yielded white prisms: mp 176–177° dec; ir (Nujol) 1600, 1260, 1130, 1090, 1000 cm^{-1}; nmr ($CDCl_3$) ϵ 2.30 (s, 3), 3.08 (s, 6), 4.55 (s, 2), 7.0–7.7 (m, 9).

Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.22. Found: C, 63.08; H, 6.49; N, 9.18.

Pyrolysis of the Ylide I (R = Benzyl).—When 1.403 g of this ylide (I, R = benzyl) was pyrolyzed (same manner and apparatus as previously described) at 185° for 15 min, 0.133 g of yellow oil was collected in the trap (−78°). This was not completely characterized, but nmr evidences indicated that *N*,*N*-dimethylbenzylamine was a major component. The nonvolatile portion, 1.24 g, a black oil, was chromatographed over alumina. Four components were identified: (benzene) 59 mg (4.2%) of *p*-tolyl disulfide; (benzene) 63 mg (4.5%) of benzaldehyde (the dimethylhydrazone was identical with that of the authentic sample); (25% chloroform–75% benzene) 313 mg (22.3%) of *p*-tolyl benzyl sulfone (V, R = benzyl) [recrystallized from carbon tetrachloride; mp 144–145° (lit.[9] 144.5°), nmr ($CDCl_3$) ϵ 2.40 (s, 3), 4.10 (s, 2) 6.95–7.69 (m, 9)]; and (2% ethyl acetate–98% chloroform) 183 mg (13.1%) of *p*-toluenesulfonamide [mp 136–137° (from water); mixture melting point with the authentic sample was undepressed].

Attempted Preparation of 1,1-Dimethyl-2-benzyl-2-(*p*-toluenesulfonyl)hydrazine (VIII, R = Benzyl).—Reaction of the lithium salt of 1,1-dimethyl-2-(*p*-toluenesulfonyl)hydrazine in ether with benzyl bromide (1 equiv) gave the previously described ylide I (R = benzyl) in 60% yield. With potassium *tert*-butoxide (1 equiv) in ethanol, this ylide also formed. Refluxing potassium *tert*-butoxide (1 equiv) in *tert*-butyl alcohol with the hydrazine (1 equiv) and benzyl bromide (1 equiv) yielded *p*-toluenebenzyl sulfone (V, R = benzyl) as the sole product.

Registry No.—I (R = 3-methyl-2-butenyl), 31529-11-0; I (R = benzyl), 31529-12-1; 1,1-dimethyl-1-(3-methyl-2-butenyl)-2-(*p*-toluenesulfonyl)hydrazonium bromide, 31529-13-2; 1,1-dimethyl-1-benzyl-2-(*p*-toluenesulfonyl)hydrazonium bromide, 31529-14-3.

Acknowledgments.—We wish to thank the U. S. Public Health Service, the National Science Foundation, the Petroleum Research Fund, administered by the American Chemical Society, Eli Lilly and Co., and Hoffmann-La Roche, Nutley, N. J., for support of this research.

(9) R. A. Henry and D. W. Moore, *J. Org. Chem.*, **32**, 4145 (1967).

Carbomethoxy Radical from Photodecomposition of Carbomethoxymercury Compounds

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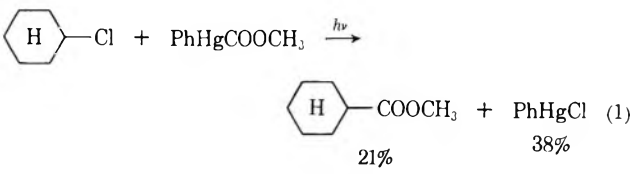
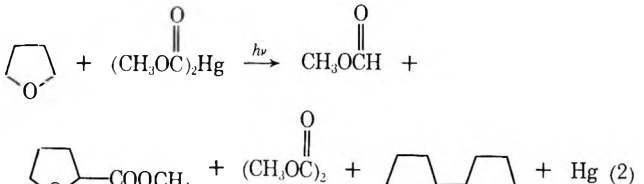
Although many species have been investigated in the study of free-radical chemistry, little work has been reported on carbomethoxy or carbethoxy radicals. These radicals are reportedly unstable and decompose readily to form carbon monoxide and alkoxy radicals or carbon dioxide and alkyl radicals. Gray and Thynne[1] reported that the activation energy of decomposition is only a few kilocalories/mole.

In a course of a study on the photochemical reaction of some mercury compounds,[2] it was found that the photochemical reaction of phenyl(carbomethoxy)mercury with cyclohexyl chloride gave methyl cyclohexylcarboxylate and phenylmercuric chloride, together with some metallic mercury (eq 1).[3] In a similar reaction



Fanta[4] found that a photodecomposition of carbomethoxymercuric iodide in benzene produced methyl benzoate and toluene. However, it has not been elucidated whether this carbomethoxylation proceeds *via* formation of a free carbomethoxy radical and can be applied to saturated aliphatic compounds. Thus, we carried out the photochemical reaction of some carbomethoxymercury compounds in tetrahydrofuran (THF).

In a typical experiment, bis(carbomethoxy)mercury (0.015 mol) was irradiated in THF (82 ml) with a low-pressure mercury lamp for 12 hr under nitrogen. The products formed were methyl formate (50%), methyl tetrahydrofuroate (21%), dimethyl oxalate (5.3%), and α,α'-bistetrahydrofuranyl (43%), in addition to metallic mercury (quantitative yield) (eq 2). The results of photolysis of some organomercury compounds in THF are shown in Table I.

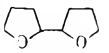


In the photolysis of carbomethoxymercury compounds, the formation of the esters may be evidence for the carbomethoxy radical and successful carbomethoxyl-

(1) P. Gray and J. C. J. Thynne, *Nature*, **191**, 1357 (1962).
(2) T. Sakakibara, Y. Odaira, and S. Tsutsumi, *Tetrahedron Lett.*, 503 (1968).
(3) Unpublished result.
(4) G. F. Fanta, *J. Org. Chem.*, **29**, 1610 (1964).

TABLE I

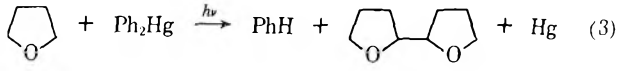
PHOTOCHEMICAL REACTION OF ORGANOMERCURY COMPOUNDS WITH TETRAHYDROFURAN

Reactant L-Hg-L′	Products, %[a] Hg	Hg_2Cl_2			L-H (L′-H)	L-L	Evolved gas, ml
L = L′ = $COOCH_3$ (I)	100		21	43	50	5.3	230[b]
L = $COOCH_3$; L′ = Ph (II)	100		6	36	35 (96)	0.6	200
L = $COOCH_3$; L′ = Cl (III)		92	6	10	37	Trace	200
L = Ph; L′ = Cl (IV)		59	Trace	8	94	None	
L = L′ = Ph (V)	97		None	92	97	None	

[a] Yields of orgnic products were based on reacted organomercury compound. [b] Gaseous products consisted of CO (55%), CO_2 (22%), and CH_4 (24%).

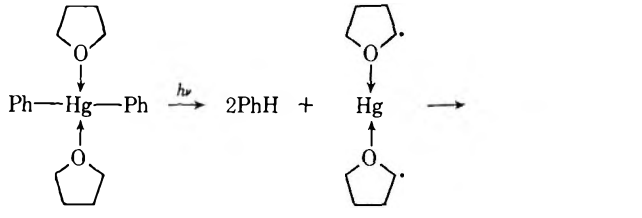
ation of an aliphatic compound. In photodecomposition of the mercury compounds II and III, the formed carbomethoxy radicals mainly decomposed to give carbon monoxide or carbon dioxide, etc., and the esters were obtained in lower yields, while in photodecomposition of I the esters were given in better yields. This shows that the carbomethoxy radicals produced in photolysis of I and of II (or III) do not necessarily have the same stability or reaction behavior.

In the photochemical reaction of diphenylmercury (V) in THF, the products, α,α′-bistetrahydrofuranyl and benzene, were obtained in nearly quantitative yields (eq 3). This apparently shows that the phenyl radicals

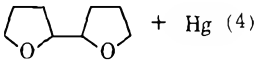


(3)

produced by photolysis of V may abstract the α hydrogen of THF to give benzene and α-tetrahydrofuranyl radicals, which may dimerize exclusively to form α,α′-bistetrahydrofuranyl. However, when THF was gradually diluted by cyclohexane, the formation of α,α′-bistetrahydrofuranyl sharply decreased relatively to that of bicyclohexyl (Table II). That is, the increasing dilution of THF may decrease the formation of the α-tetrahydrofuranyl radical while increasing that of cyclohexyl radical. We have already suggested that certain organomercury compounds may form the complexes with THF.[2] The present result also suggests the formation of a ground-state complex of THF with diphenylmercury, such as VI. If this is the case, the dilution of THF may cause the dissociation of the complex into V and THF to decrease the formation of the α-tetrahydrofuranyl radical in the photoreaction (eq 4).



VI



(4)

Concerning the formation of α,α′-bistetrahydrofuranyl, the photochemical reaction of diphenylmercury and phenylmercuric chloride (IV) gave conflicting results. Although both IV and V gave benzene in nearly quantitative yields, α,α′-bistetrahydrofuranyl was predominantly formed only in the reaction of V (Table I). In IV, high-boiling carbonyl compounds were the principal products. The α-tetrahydrofuranyl radical is known to isomerize thermally to the corresponding carbonyl radical.[5] Thus, the radical produced in the reaction of V favorably dimerized with little isomerization. Moreover, the absence of cross-coupling products from the reaction of V and THF contrasted sharply with their presence from the reaction of I and THF. Consequently, the results in Table I show that the carbomethoxy radical and the α-tetrahydrofuranyl radical produced from I or V (VI) are sufficiently stable to couple with each other under the conditions of this reaction.

TABLE II

FORMATION RATIO OF α,α′-BISTETRAHYDROFURANYL TO BICYCLOHEXYL BY PHOTOLYSIS OF Ph_2Hg IN THE MIXED SOLVENT OF TETRAHYDROFURAN AND CYCLOHEXANE

Reactants (molar ratio), Tetrahydrofuran/cyclohexane	Products (molar ratio), α,α′-Bistetrahydrofuranyl/bicyclohexyl
1.00	10
0.70	3.8
0.25	0.48
0.057	0.056

All these results suggest that the abnormal reaction behavior of α-tetrahydrofuranyl radicals of carbomethoxy radicals may be owing to an effect of the mercury atom on the radical coupling. Namely, two α-tetrahydrofuranyl radicals formed in photolysis of VI may rapidly react with each other around the mercury atom before isomerization (eq 4), while, in the photochemical reaction of I in THF, the nonfree carbomethoxy radicals and α-tetrahydrofuranyl radicals trapped on the mercury atom may rapidly react with each other, with comparatively little decomposition, to give the esters in moderate yields. This apparent *mercury template* effect may be significant and play an important role in homo coupling or cross coupling of unstable radicals.

Experimental Section

Mercury Compounds.—Carbomethoxymercury compounds and diphenylmercury were prepared by the methods of Dessy, *et al.*,[6] and Calvery,[7] respectively. Phenylmercuric chloride was obtained in quantitative yield from equimolar mixtures of V and mercuric chloride in methanol. The uv spectra of carbomethoxymercury compounds are shown in Figure 1.

Solvents.—Tetrahydrofuran was refluxed over sodium hydroxide for 6 hr and distilled and then distilled from sodium before use. Cyclohexane was purified by the method described in "Organic Solvents."[8]

(5) T. J. Wallace and R. J. Gritter, *J. Org. Chem.*, **27**, 3067 (1962); *Tetrahedron*, **19**, 657 (1963).

(6) F. E. Paulik and R. E. Dessy, *Chem. Ind. (London)*, 1650 (1962).

(7) H. O. Calvery, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 196", p 228.

(8) J. A. Riddick and E. E. Toops, Jr., "Organic Solvents," 2nd ed Wiley, New York, N. Y., 1955, p 307.

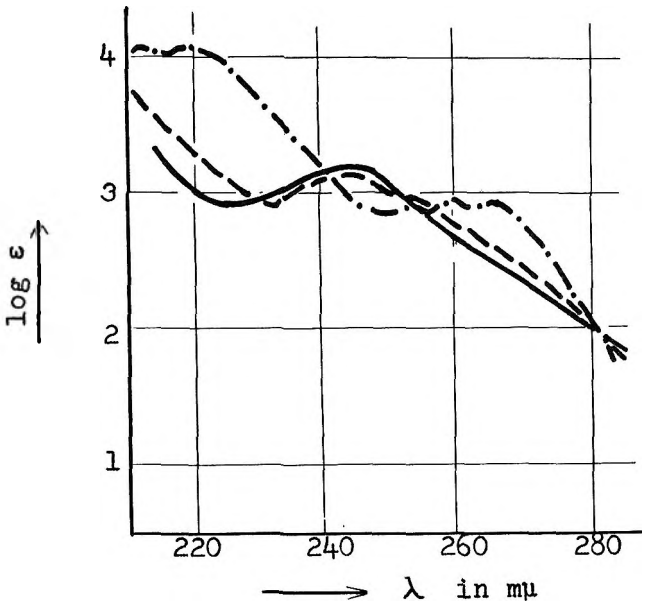


Figure 1.—Uv spectra of carbomethoxymercury compounds I (——), II (-·-·-), and III (- - -) in ethanol.

Authentic Materials.—Methyl tetrahydrofuroate, α-phenyltetrahydrofuran, and α,α′-bistetrahydrofuranyl were prepared by catalytic hydrogenation of methyl furoate,[9] by the methods of Shima, *et al.*,[10] and Mitsui, *et al.*,[11] respectively. Methyl formate, dimethyl oxalate, and bicyclohexyl were commercially availabel (from Wako Pure Chemical Industries, Ltd.).

Photochemical Reaction of Bis(carbomethoxy)mercury in THF.—*Bis(carbomethoxy)mercury (4.8 g, 0.015 mol)* was irradiated in THF (82 ml) for 12 hr by a 120-W low-pressure mercury lamp under nitrogen at room temperature. During the reaction, metallic mercury precipitated. Evolved gas was introduced into a cylindrical gas holder filled with a saturated aqueous solution of sodium chloride. The gaseous products (230 ml) consisted of carbon monoxide (55%), methane (24%), and carbon dioxide (22%) by glpc, using a 3-m, activated carbon column (80°, He carrier). After distillation of the reaction mixture, a lower boiling fraction, bp 30–68°, contained 0.9 g of methyl formate, which was identified by comparison with authentic material on glpc, using a 1.5-m, tricresyl phosphate on Celite 545 column (80°, He carrier gas flow rate of 46 ml/min). The glpc retention time was 1.2 min. The higher boiling fraction (1.75 g), bp 40–124° (24 mm), consisted of α,α′-bistetrahydrofuranyl (0.92 g), *methyl* tetrahydrofuroate (0.42 g), and dimethyl oxalate (0.10 g), which were identified by comparison with authentic materials on glpc, using a 1.5-m, silicone DC 550 on Celite 545 column (147°, H_2 carrier gas flow rate of 65 ml/min). The glpc retention times were 11.7, 6.5, and 2.4 min, respectively. Further identification by glpc using another column, 1.5 m, polyethylene glycol 6000 on Celite 545 (200°, H_2 carrier) supported the above results. The products, methyl formate, methyl tetrahydrofuroate, and α,α′-bistetrahydrofuranyl, were isolated by further distillation and preparative glpc, although dimethyl oxalate could not be isolated due to the small amount. The infrared spectra of products isolated were identical with those of authentic materials. The distillation residue was 0.2 g.

The photochemical reactions of carbomethoxymercuric chloride and phenyl(carbomethoxy)mercury were carried out under the same conditions and the reaction mixture was similarly treated.

Photolysis of Diphenylmercury in THF and Cyclohexane.—Diphenylmercury (3.5 g, 0.01 mol) was photolyzed in the mixed solvents (100 ml) at various molar ratios of THF and cyclohexane for 5 hr by a 120-W low-pressure mercury lamp. The reaction mixtures were treated as described above, and the yields of THF dimer and bicyclohexyl in higher boiling fractions were determined by glpc analysis.

(9) B. H. Wojcik, *Ind. Eng. Chem.*, **40**, 210 (1948).
(10) K. Shima and S. Tsutsumi, *Bull. Chem. Soc. Jap.*, **36**, 121 (1963).
(11) S. Mitsui and H. Saito, *Nippon Kagaku Zasshi*, **81**, 289 (1960).

Registry No.—I, 10507-39-8; II, 19638-01-8; III, 17261-26-6; IV, 100-56-1; V, 587-85-9; THF, 109-99-9.

Reaction of Diethyl Bromomalonate with Sodium Phenoxide

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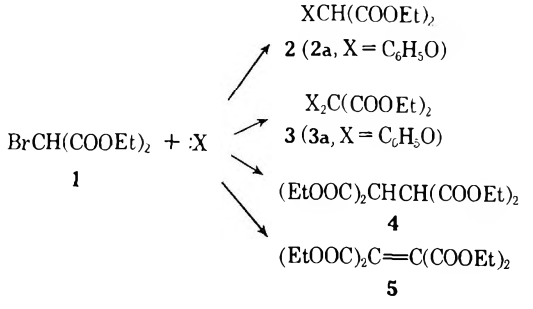
Received March 24, 1971

The major product(s) of the reaction of diethyl bromomalonate (**1**) with nucleophiles has been found to be dependent upon the base employed (Scheme I). Thus,

SCHEME I



the diazido compound **3** (X = N_3) is formed in the reaction with sodium azide,[2] and tetraethyl 1,1,2,2-ethanetetracarboxylate (**4**) is obtained with the sodium salts of diethyl phosphite,[3] diethyl thiophosphite,[4] and thiophenol.[5] Reagents which give the unsaturated ester, tetraethyl ethenetetracarboxylate (**5**), have been summarized.[6] Both monoaroxy- and diaroxymalonates (**2** and **3**, X=ArO) are produced when bromo ester **1** is treated with phenoxide, 3-methylphenoxide, or 4-nitrophenoxide ion.[7] The ratio of these two products formed in the reaction was reported to be solvent-dependent.

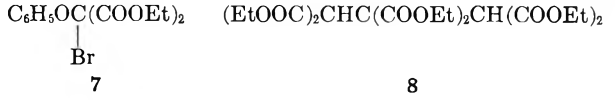
The purpose of the present work was to establish a reaction path for the formation of diphenoxymalonate (**3a**) in the reaction of **1** with sodium phenoxide. In addition, it was of interest to investigate further the effect of solvent on the course of the reaction.

Results and Discussion

The reaction of **1** with sodium phenoxide was carried out in the following solvents: absolute alcohol, 85% alcohol, tetrahydrofuran, benzene, and ether.

(1) Abstracted in part from the M.S. Theses, Creighton University, of (a) S. M. P., 1968; (b) F. O. H., 1969.
(2) H. Bretschneider and N. Karpitschka, *Monatsh. Chem.*, **84**, 1091 (1953).
(3) A. E. Arbuzov and V. S. Abramov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 223 (1946).
(4) A. N. Pudovik and R. I. Tarasova, *Zh. Obshch. Khim.*, **34**, 293 (1964); *Chem. Abstr.*, **60**, 10579 (1964).
(5) K. H. Takemura and D. J. Tuma, *J. Org. Chem.*, **34**, 252 (1969).
(6) A. H. Blatt, Ed., "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 273.
(7) J. B. Niederl and R. T. Roth, *J. Amer. Chem. Soc.*, **62**, 1154 (1940).

In addition to the previously reported aroxymalonates (**2a** and **3a**), the crude reaction product was found to contain the tetracarboxylates **4** and **5**, together with diethyl malonate (**6**), diethyl α-bromophenoxymalonate (**7**), and hexaethyl 1,1,2,2,3,3-propanehexacarboxylate



7 **8**

(**8**). The results of our experiments are summarized in Table I.

TABLE I

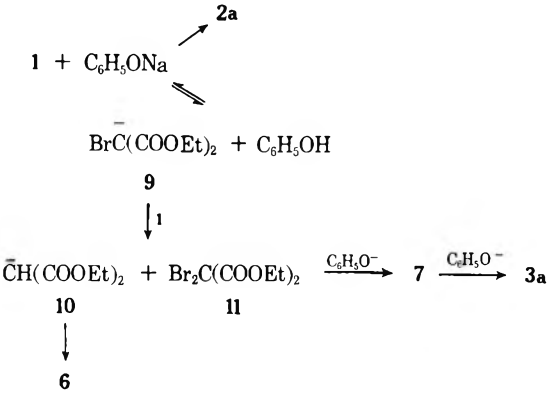
PRODUCTS OF REACTION OF DIETHYL BROMOMALONATE WITH SODIUM PHENOXIDE[a]

	Weight per cent of reaction product[b]						
Solvent	**2a**	**3a**	**4**	**5**	**6**	**7**	**8**
Absolute alcohol	43	28	4	11	9	3	2
85% alcohol[c]	40	27	3	10	15		
Tetrahydrofuran	41	30	10	3	4		10
Benzene	23	41	4	12	14	4	1
Ether	13	37	9	11	16	5	8

[a] Equimolar quantities (0.030 mol) in 50 ml of solvent, heated for 1 hr. [b] Excluding any traces of bromomalonate and phenol present; average of two to three experiments. [c] Several unidentified materials present.

The formation of diphenoxymalonate (**3a**) and α-bromophenoxymalonate (**7**) is most easily explained by reactions of phenoxide ion with dibromomalonate (**11**).[8] We therefore propose the sequence of reactions in Scheme II to account for **3a** and **7**, together with the

SCHEME II



monophenoxy compound **2a** and diethyl malonate (**6**) which are also products of the reaction.

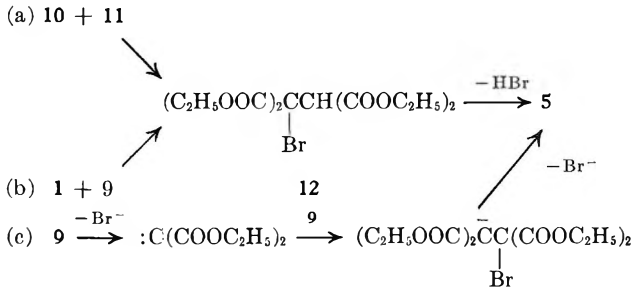
Diethyl bromomalonate (**1**) may be considered as an ambident substrate. Possible sites for reaction with nucleophiles include bromine, α carbon, and α hydrogen. Attack on bromine has been observed.[5] The generally expected displacement on carbon leads to **2a**. We suggest that, in the reaction of phenoxide ion with **1**, reversible attack on hydrogen also occurs to give bromomalonate anion **9**. The latter then combines with the bromine of a second molecule of **1** to give malonate anion (**10**) and dibromomalonate (**11**).

(8) The possibility of **2a** as an intermediate in the formation of **3a** has been excluded on the basis of the reaction of **1** with sodium phenoxide in the presence of 4-nitrophenoxymalonate. There was no evidence for the formation of phenoxy(4-nitrophenoxy)malonate.[1b]

The behavior of chloromalonate is consistent with these ideas. This halo ester with sodium phenoxide in absolute alcohol gave more than 88% of monophenoxy compound **2a**. Only a trace amount of diphenoxymalonate (**3a**) was detected.[9] Although conversion of choromalonate to its anion would be expected to proceed more readily than with **1**, the subsequent reaction at halogen to give the dihalomalonate is greatly diminished. The latter can be attributed to the decreased polarizability of chlorine as compared to bromine.[5,10]

Other products arising from the reaction of **1** with phenoxide may be accounted for by reactions which relate readily with those given in Scheme II. Bromo ester **1** and malonate anion (**10**) can give the saturated tetracarboxylate **4**.[11] Three reaction paths are possible for the formation of the unsaturated ester **5** (Scheme III). In two of these, a and b, **5** is pro-

SCHEME III



duced by elimination of hydrogen bromide from the intermediate bromotetracarboxylate **12**. Compound **12** can arise from malonate anion (**10**) and dibromomalonate (**11**) (route a), or from attack of bromomalonate anion (**9**) at the carbon of **1** with displacement of bromide ion (route b).[12] In route c, loss of bromide from anion **9** yields a carbenoid intermediate (overall α elimination from **1**). The reaction of the latter with **9**, followed by loss of halide ion, leads to unsaturated ester **5**.[13] We are unable to exclude any of these three possible reaction routes.

The hexaester **8** can be formed in two ways: the Michael addition of diethyl malonate (**6**) to unsaturated ester **5**,[14] or the reaction of malonate anion (**10**) with dibromomalonate (**11**). The latter was employed in the preparation of **8** in this work. Which of the two routes is followed in our experiments with **1** is undetermined.

In their studies of the reaction of **1** with sodium phenoxide, Niederl and Roth[7] found that the ratio of monophenoxy- (**2a**) to diphenoxymalonate (**3a**) produced

(9) In some experiments, trace amounts of the unsaturated ester **5** were also found. In all cases minor quantities of several unidentified substances were also present.

(10) It is interesting to note that diazidomalonate (**3**, X = N_3) was obtained from **1**,[2] and also from dichloromalonate, but chloromalonate gave no identifiable organic product with sodium azide [M. O. Forster and R. Muller, *J. Chem. Soc.*, 126 (1910)].

(11) C. A. Bischoff, *Ber.*, **29**, 1276 (1896).

(12) D. Bethell, *J. Chem. Soc.*, 666 (1963). A mechanism analogous to (b) was suggested for the formation of bifluorenylidene from 9-bromofluorene and base.

(13) The reactions of 4-nitrobenzyl derivatives with base to give 4,4′-dinitrostilbene have been explained by similar reaction routes. See S. B. Hanna, Y. Iskander, and Y. Riad, *J. Chem. Soc.*, 217 (1961); C. G. Swain and E. R. Thornton, *J. Amer. Chem. Soc.*, **83**, 4033 (1961); I. Rothberg and E. R. Thornton, *ibid.*, **85**, 1704 (1963).

(14) S. Ruhemann and A. V. Cunnington, *J. Chem. Soc.*, 1013 (1898).

was 2:3 in absolute alcohol and 3:2 in 85% alcohol.[15] We have noted little difference in the relative amounts of the two products in these two solvents (Table I). In both, **2a** was found to predominate, the product ratio being in each case about 3:2.

It is noteworthy that the diphenoxy compound **3a** was the major product in those reactions in which sodium phenoxide was insoluble in the solvent (ether and benzene).[16] However, when the phenol salt was soluble (alcoholic and tetrahydrofuran solvents), the principal product was the monophenoxy compound **2a**. It appears that the protic or aprotic nature of the solvent is relatively unimportant. The possibility that these solvent effects might be attributed to differences in the concentration of phenoxide ion available for reaction with bromo ester **1** was considered. The slow addition of phenoxide to **1** had no significant effect upon the ratio of **2a** to **3a**. At the present, the solvent effects noted remain unexplained.

Experimental Section

Melting points were determined on a Fisher–Johns hot state and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded on a Beckman IR-8 spectrophotometer, and nuclear magnetic resonance spectra in carbon tetrachloride (unless otherwise specified) on a Varian T-60 spectrometer. Chemical shifts are expressed in parts per million downfield relative to TMS (δ scale). Glpc analyses were made with an Aerograph A-90-P gas chromatograph using an 8 ft × 0.25 in. column of 20% SE-30 on Chromosorb W at a column temperature of 115°, programmed to 225°, using helium (100 cc/min) as carrier.

Materials.—Reagent grade diethyl bromomalonate (**1**) (Aldrich Chemical) was redistilled, bp 54–55° (0.08 mm), n^{20}D 1.4512. Glpc analysis showed less than 2% dibromo compound. Sodium phenoxide (>97% purity) was prepared as previously described.[17] Reagent grade solvents were employed. Tetrahydrofuran was distilled from lithium aluminum hydride and stored under nitrogen.

Diethyl monophenoxymalonate (2a) was isolated in 50% yield from the reaction of sodium phenoxide and diethyl chloromalonate in alcohol. The crude reaction product (glpc analysis) contained 88% of **2a**. The recrystallized product (alcohol) melted at 51–52° (lit.[7] mp 52–53°): ir (KBr) 1755, 1220, 1100, and 1030 cm^{-1}; nmr 7.05 (m, 5 H), 5.03 (s, 1 H), 4.19 (q, 4 H), and 1.25 (t, 6 H).

Diethyl diphenoxymalonate (3a) was prepared from dibromomalonate and sodium phenoxide in alcohol: bp 158–161° (0.3 mm) [lit.[18] bp 250–260° (60 mm)]; n^{24}D 1.5272; ir (neat) 1765, 1220, 1080, 755, and 695 cm^{-1}; nmr 7.22 (m, 10 H), 4.17 (q, 4 H), and 1.03 (t, 6 H).

Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.21; H, 5.92.

Tetraethyl 1,1,2,2-ethanetetracarboxylate (4) was obtained from **1** and sodium diethyl phosphite as previously described,[3] mp 76° (lit.[3] mp 76°).

Tetraethyl ethenetetracarboxylate (5) was synthesized according to the published procedure,[6] mp 52–53° (lit.[6] mp 52.5–53°).

Diethyl α-bromophenoxymalonate (7) was isolated in 10% yield from equimolar quantities of dibromomalonate and sodium phenoxide in alcohol: bp 135–137° (0.4 mm); n^{24}D 1.5125; ir (neat) 2985, 1750, 1230, 1135, 1050, 1020, 760, and 695 cm^{-1}; nmr 7.22 (m, 5 H), 4.30 (q, 4 H), and 1.27 (t, 6 H).

Anal. Calcd for $C_{13}H_{15}BrO_5$: C, 47.15; H, 4.57. Found: C, 47.40; H, 4.83.

Hexaethyl 1,1,2,2,3,3-propanehexacarboxylate (8) was prepared in 38% yield from dibromomalonate and diethyl sodiomalonate in alcohol: bp 178–179° (0.1 mm) [lit.[18] bp 246° (15 mm)]; n^{26}D 1.4532; ir (CCl_4) 1745, 1245, 1115, and 1040 cm^{-1}; nmr ($CDCl_3$) 4.30 (q, 12 H), 4.33 (s, 2 H), and 1.30 (t, 18 H). The quartet and singlet were superimposed; the quartet and triplet peaks appeared as unresolved doublets.

Anal. Calcd for $C_{21}H_{32}O_{12}$: C, 52.94; H, 6.77. Found: C, 53.08; H, 6.91.

Reaction of Diethyl Bromomalonate (1) with Sodium Phenoxide.—In a typical run, 7.2 g (0.030 mol) of **1** in 10 ml of solvent was added in one portion with stirring to 3.5 g (0.030 mol) of sodium phenoxide in 40 ml of solvent. The addition of **1** resulted in an exothermic reaction with rapid precipitation of sodium bromide. (In ether solvent, it was necessary to moderate the reaction by dropwise addition of **1**.) The mixture was heated (bath 90–95°) and stirred under nitrogen for 1 hr.

In the case of water-soluble solvents, the solvent was removed under reduced pressure (water aspirator) at 100°, and the residue was treated with water. With solvents insoluble in water, the reaction mixture was diluted directly with water. The organic materials were isolated in the usual manner by extraction with ether. The crude oily product (6–7.5 g) was dissolved in toluene for glpc analysis. Components were identified by retention times and by admixture with authentic materials. Weight ratios of the substances present were established from peak areas, with appropriate modifications based upon preliminary studies with known mixtures.

The dropwise addition (20-min period) of sodium phenoxide in 40 ml of alcohol to **1** dissolved in 15 ml of solvent afforded a crude product which contained **2a** and **3a** in the ratio of 3:1.8.

Registry No.—**1**, 685-87-0; **2a**, 4525-70-6; **3a**, 4525-71-7; **7**, 31593-62-1; **8**, 5435-96-1; sodium phenoxide, 139-02-6.

(15) The analytical methods employed were based upon differential solublilities of the substituted malonic acids and preferential amide formation. In our hands, using known mixtures of **2a** and **3a**, these methods gave unsatisfactory results (unpublished observations).

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An Improved Method of Resolution of Coniine[1]

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The hemlock alkaloids[2] constitute a large group of optically active 2-substituted piperidines of which coniine (2-*n*-propylpiperidine) is the major representative. Considerable current interest in these substances is due not only to the conflicting hypotheses for their biogenesis[3-5] but also to the recent extension of methods of optical rotatory dispersion and circular dichroism to the determination of their absolute configuration.[6-9]

The need for large quantities of optically pure enantiomers of coniine revealed that the published method[10]

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of optical resolution using tartaric acid was unsatisfactory for several reasons. These included the difficulty of inducing crystallization without seed crystals of the authentic diastereoisomeric salt, the need for many repeated crystallizations of the acid tartrate to achieve purity, and the low yield of the final resolved base.

The method of optical resolution was therefore reinvestigated using a number of optically active acids[11] as resolving agents. Mandelic acid was found to be the reagent of choice. Under the correct experimental conditions, crystallization commenced after a few minutes to give the less soluble diastereoisomeric salt in excellent yield. It had constant melting point and rotation after only one crystallization. The use of (−)- and (+)-mandelic acid,[12] respectively, afforded the enantiomeric salts, (+)-coniine (−)-mandelate and (−)-coniine (+)-mandelate, without difficulty. When basified, these yielded (+)- and (−)-coniine, shown to be both chemically and optically homogeneous by gas–liquid partition chromatographic techniques.[13]

The method is readily applicable to other alkyl-substituted piperidines; *e.g.*, 2-methyl- and 2-ethylpiperidine[9,14] were resolved into optically pure enantiomers in an equally facile manner.

Experimental Section

Resolution of (±)-Coniine.—Racemic coniine (6.35 g) and (−)-mandelic acid (7.6 g, 1 mol) were mixed with cooling, and methanol (20 ml) was added. The mixture was warmed to effect solution, cooled, and then treated with anhydrous ether (45 ml). After a few minutes crystals began to separate. After 22 hr at 0° the crystals were collected and dried *in vacuo*, yield 5.68 g. Recrystallization was effected by dissolving the salt (10 g) in dry methanol (30 ml) and adding dry ether (60 ml). After 22 hr at 0° the (+)-coniine (−)-mandelate was collected and dried *in vacuo* (9.1 g): feathery needles; mp 127.5°; $[\alpha]^{22}D$ −59.0° (*c* 0.5, 95% EtOH). Both the melting point and the rotation were unchanged by further recrystallization. The filtrate A was treated as described below.

Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.59; H, 8.95; N, 5.25.

The above salt (9.0 g) in water (75 ml) was cooled in ice and basified slowly with solid potassium hydroxide. The liberated (+)-coniine was extracted thrice with ether and the combined extracts were dried over powdered KOH. The ether was evaporated *in vacuo* at room temperature. The residual (+)-coniine distilled (yield 3.25 g, 86% based on salt) at 65–66° (20 mm): bp 164° (755 mm) [lit.[10,15] bp 64° (18 mm), 166–166.5° (1 atm)]; $[\alpha]^{25}D$ +8.4° (*c* 4.0, $CHCl_3$) [lit.[16] $[\alpha]^{25}D$ +8.0° (*c* 4.0, $CHCl_3$)]; $[\alpha]^{23}D$ +14.6° (neat) [lit.[10] $[\alpha]^{19}D$ +15.2° (neat)]. Glpc on a Carbowax column at 125° showed a single peak.

The ether–methanol filtrate A on evaporation of the solvents gave a syrupy residue which was dissolved in water and basified as above, yielding a base, bp 164–165° (755 mm), rich in (−)-coniine. This base (6.35 g) and (+)-mandelic acid (7.6 g, 1 mol) were dissolved in dry methanol (20 ml) and the warm solution was treated with dry ether (50 ml). After 22 hr at 0° the crystals of (−)-coniine (+)-mandelate were collected, dried (9.1 g), and recrystallized from methanol (27 ml) by careful addition of ether (54 ml), giving the pure salt, mp 127° (7.7 g), as feathery needles, $[\alpha]^{23}D$ +60.0° (*c* 0.5, 95% EtOH), unchanged by further crystallization. The same salt was obtained from racemic coniine and (+)-mandelic acid.

Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.71; H, 9.12; N, 5.34.

This salt (61.4 g) in water (300 ml) was cooled in ice and basified as described above, giving (−)-coniine distilling at 165° (756 mm) (24.4 g, 87% yield based on salt): $[\alpha]^{23}D$ −8.1° (*c* 4.0, $CHCl_3$), $[\alpha]^{23}D$ −14.2° (neat), $[\alpha]^{23}D$ −5.0° (*c* 2.0, 95% EtOH). Glpc on a Carbowax column at 125° showed a single peak.

2-Methyl- and 2-Ethylpiperidine.—Application of the same method gave (+)-2-methylpiperidine, $[\alpha]^{25}D$ +7.2° (*c* 6, 95% ethanol) [lit.[17] $[\alpha]^{15}D$ +31.2° (neat)], and (+)-2-ethylpiperidine, $[\alpha]^{25}D$ +6.6° (*c* 14, 95% ethanol) [lit.[18] $[\alpha]^{23}D$ +21.3° (neat)].

Registry No.—(±)-Coniine, 3238-60-6; (+)-coniine, 458-88-8; (−)-coniine, 5985-99-9; (+)-coniine (−)-mandelate, 31608-17-0; (−)-coniine (+)-mandelate, 31608-18-1.

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Catalyzed Hydrogenation of Tolane and Stilbene in Liquid Ammonia

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The reaction between the ammoniated electron and liquid ammonia has been shown to be reversible in the

$$e^-_{am} + NH_3 \rightleftharpoons NH_2^- + {}^1/_2H_2 \qquad (1)$$

presence of certain solid catalysts and to have an equilibrium constant of 5×10^4 $atm^{1/2}$ at room temperature.[1] There are many compounds which are highly reactive toward ammoniated electrons[2] but which are essentially inert toward molecular hydrogen. We therefore felt that a liquid ammonia system containing potassium amide and a catalyst for reaction 1 might serve as a useful medium for "activating" molecular hydrogen. We have studied the reactions of stilbene (1,2-diphenylethylene) and tolane (diphenylacetylene) in this system at −45° and at room temperature. Both compounds are known to undergo reduction by the ammoniated electron[2-4] and we hoped that reaction sequences such as the following (illustrated by stilbene) would take place.

$$H_2 + 2NH_2^- \rightleftharpoons 2e^-_{am} + 2NH_3$$

$$2e^-_{am} + C_6H_5CHCHC_6H_5 + 2NH_3 \longrightarrow C_6H_5CH_2CH_2C_6H_5 + 2NH_2^-$$

Experimental Section

Reagents.—Hydrogen and argon (99.999%, Pacific Oxygen Supply) were used without further purification. Potassium metal (Baker and Adamson) was sealed in glass tubing and purified by heating it under high vacuum and allowing it to flow through constrictions in the glass. This procedure removed oil

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TABLE I
REACTION OF HYDROGEN WITH TOLANE AND STILBENE. DATA FOR FLOW EXPERIMENTS AT −45°

Substrate (mmol)	Fe_2O_3 catalyst, mg	KNH_2, mmol	Gas	Reaction time, hr	Conversion, % $(C_6H_5CH)_2$	Conversion, % $(C_6H_5CH_2)_2$	Substrate recovered, %
$(C_6H_5C)_2$ (5.3)	120	30	Ar	20	0	0	96
$(C_6H_5C)_2$ (3.1)	114	0	H_2	25	0	0	98
$(C_6H_5C)_2$ (2.25)	0	20	H_2	160	0	0	98
$(C_6H_5C)_2$ (2.2)	123	50	H_2	8	3	26	68
$(C_6H_5C)_2$ (1.34)	190[a]	100	H_2	27	4	30	63
$(C_6H_5CH)_2$ (1.8)	232	48	Ar	6		0	97
$(C_6H_5CH)_2$ (1.0)	219	0	H_2	8		0	97
$(C_6H_5CH)_2$ (3.7)	0	45	H_2	8		0	98
$(C_6H_5CH)_2$ (3.1)	240	60	H_2	12		80	16
$(C_6H_5CH)_2$ (2.1)	198[a]	100	H_2	20		90	6

[a] $Fe(NO_3)_3 \cdot 9H_2O$ used instead of Fe_2O_3.

and oxides from the metal, and allowed easy weighing and transferring of the metal.

Either Fe_2O_3 (Baker Analyzed Reagent) or $Fe(NO_3)_3 \cdot 9H_2O$ (Baker and Adamson) was reduced to a black solid by potassium in liquid ammonia, and used as the catalyst for reaction 1. Tolane (mp 61–62°, Aldrich Chemicals) and *trans*-stilbene (mp 123–124°, Eastman Organic Chemicals) were checked for purity by gas chromatography (Aerograph Model A-90-P) and found to be at least 99% pure. Deoxybenzoin (mp 54–56°, Matheson Coleman and Bell) was used without further purification. For simplicity, *trans*-stilbene is referred to as stilbene throughout this paper.

Products were separated by gas chromatography (G.E.-S.F.-96 silicone on firebrick at 190°), isolated in small traps, and identified by mass spectrometry and (in the case of solids) by melting point determination.

Flow Experiments.—The apparatus used for bubbling hydrogen through liquid ammonia systems was essentially a gas-washing bottle (with a sintered-glass bubbler) fitted with inlet and outlet stopcocks, a side arm, and an O-ring joint for closure. Traces of oil and water were removed from the hydrogen by passing it through a −78° trap attached to the inlet to the reaction vessel. The flow rate of hydrogen was estimated by use of a mineral oil bubbler attached to the outlet. The substance to be hydrogenated was placed in the side arm. The solid catalyst [Fe_2O_3 or $Fe(NO_3)_3 \cdot 9H_2O$] and a glass-enclosed magnetic stirring bar were placed in the vessel. About 100 ml of ammonia was distilled into the apparatus from a reservoir containing sodium and sodium amide. The apparatus was placed in a dewar of liquid ammonia, which maintained a temperature of approximately −45°. The bubbling of hydrogen through the ammonia was started; the O-ring joint was disconnected, and the glass tubing containing the purified potassium was dropped into the vessel. The joint was then quickly reconnected, and shortly thereafter the hydrogen flow was stopped. When the blue color of the solvated electron disappeared, the compound to be reduced was introduced from the side arm. Magnetic stirring was begun, and the hydrogen bubbling was resumed.

To stop the reaction, the vessel was opened and ammonium chloride or water was added to destroy the potassium amide. The ammonia was allowed to evaporate and the products and the iron catalyst were washed with 25 ml of water into a sintered glass crucible and dried by suction filtration. The solids were extracted with 25 ml of benzene. A portion of the benzene solution was passed through a gas chromatograph, and each fraction was collected in a small trap for identification by mass spectrometry and melting point determination.

The reactivity of tolane and stilbene toward hydrogen in the absence of potassium amide was determined. The catalyst was prepared as above (*i.e.*, reduced by potassium) and was then washed free of potassium amide by repeatedly decanting the supernatant solution into a side arm and distilling the ammonia back onto the catalyst. The rest of the procedure was unchanged. Similarly, the reduction was attempted without the iron catalyst. The formation of potassium amide was catalyzed by an iron wire which was subsequently removed with a magnet.

Static Experiments.—Experiments employing static pressures of hydrogen or argon were performed at −45° in a 500-ml round-bottomed flask. After introduction of a stirring bar, the catalyst, and a piece of pure potassium, ammonia was distilled into the vessel. The metal–ammonia solution was allowed to decompose, and the solution was degassed by freezing, pumping, and thawing. An accurately known quantity (8–10 mmol) of hydrogen or argon was admitted, and the compound to be reduced was introduced from a side arm. The products were separated and identified as described above.

Room-Temperature Experiments.—To determine the reactivity of stilbene (or tolane) toward potassium amide at room temperature in the absence of solid catalyst and hydrogen, a solution of 3–5 mmol of stilbene (or tolane) in 50 ml of ammonia containing a 10- to 30-fold excess of potassium amide was prepared in a sealed tube fitted with a breakable tip.[5] To stop the reaction, water was distilled into the tube through a stopcock attached to the breakable tip. The ammonia was allowed to evaporate; the tube was broken in a nitrogen glove bag, and the product was transferred to a funnel and washed with 10 ml of degassed distilled water. The white, air-sensitive solid product was then dried at room temperature under high vacuum. The melting point, mass spectrum, and Nujol mull infrared spectrum were obtained.

Results and Discussion

The results of experiments at −45° are shown in Table I. Reduction of stilbene produced 1,2-diphenylethane in high yield. Reduction of tolane produced stilbene and 1,2-diphenylethane (the major product). In the absence of either hydrogen, potassium amide, or catalyst, no products were formed.

We verified that hydrogen is consumed when tolane is reduced. When 8–10 mmol of hydrogen was added at −45° to an apparatus containing a degassed ammonia solution of substrate, iron catalyst, and potassium amide, a significant amount (up to 0.81 mmol/mmol of substrate) of hydrogen was consumed. In the absence of potassium amide, however, only a small amount (0.03 mmol/mmol of substrate) of hydrogen was apparently consumed. Because of the difficulty in measuring the difference between relatively large amounts of hydrogen, this latter quantity is probably not significant.

Walling and Bollyky have shown that the homogeneous *tert*-butoxide-catalyzed hydrogenation of benzophenone probably involves an H^- intermediate.[6] In view of the fact that hydrogen shows some acidity in potassium amide–ammonia solutions,[7] a similar homogeneous mechanism is conceivable for our reductions. However, because we found that a heterogeneous catalyst was required for our reductions, such a mechanism is ruled out.

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Olefins are the principal products when iron is used as a heterogeneous catalyst for the gas-phase hydrogenation of acetylenes.[8] In our study of the reduction of tolane, the alkane was the principal product even before half of the tolane had reacted. This result indicates that stilbene is reduced to the alkane more rapidly than tolane is reduced to stilbene (see Table I). Strel'tsova and Shilov found the same order of reactivity when acidic protons were available (in the form of ethanol, for example) in the homogeneous reduction of tolane by potassium metal in liquid ammonia.[3] In fact, they obtained no stilbene as product. However, in the absence of a protonic acid, Strel'tsova and Shilov found the reverse order of reactivity. When half the stoichiometric amount of sodium for reduction of tolane to 1,2-diphenylethane was used, essentially pure stilbene was isolated as the reduction product. The highly basic, heterogeneous system of this study surprisingly yields the same kinetic results as the relatively acidic homogeneous system of Strel'tsova and Shilov.

Our experimental results can be explained in terms of a mechanism involving the following initial steps. (Here M denotes an active site on the catalyst surface.)

$$2M + H_2 \rightleftharpoons 2MH$$

$$MH + NH_2^- \rightleftharpoons M^- + NH_3$$

$$M^- \rightleftharpoons M + e^-_{am}$$

Subsequent steps are uncertain; they involve the substrate accepting either electrons (from M^- or e^-_{am}) or hydride ions (from MH^-). Although the details of the overall hydrogenation mechanism are uncertain, it seems very likely that the first two steps (the bonding of hydrogen atoms to the catalyst and the formation of a low oxidation state form of the catalyst) are involved.[9,10] The facts that these steps fit the data for *both* reaction 1 and the hydrogenations and that they are common features of hydrogenations[9] are strong support for their involvement.

When stilbene was treated at room temperature for several days with a potassium amide–ammonia solution, a product was obtained that had a melting point of 57–60° and a mass spectrum with a parent peak at *m/e* 195 (corresponding to the elemental composition $C_{14}H_{13}N$) and a fragmentation pattern suggesting either phenylbenzyl ketimine (1,2-diphenylethylidenimine) or 2,3-diphenylaziridine.[11] Because of the air sensitivity of the compound, only poor infrared spectra could be obtained. There definitely was no strong absorption in the 1100–1250-cm^{-1} region; therefore the compound cannot be 2,3-diphenylaziridine, which does have a very strong absorption at about 1200 cm^{-1}.[12] Phenylbenzyl ketimine (mp 57°) is known to decompose in air to produce deoxybenzoin.[13] When our product was allowed to come in contact with the atmosphere, a material was obtained which gave a mass spectrum identical with that obtained for a known sample of deoxybenzoin.

A similar analysis of the product obtained from the room temperature reaction of tolane with excess potassium amide in liquid ammonia again showed the product to be phenylbenzyl ketimine. When liquid ammonia solutions containing stilbene or tolane and potassium amide were allowed to stand for several weeks, high molecular weight species were produced in yields of a few per cent. These compounds were observed in the gas chromatogram of the product mixture, but were not identified.

The reaction of tolane with ammonia to form phenylbenzyl ketimine is a straightforward example of a well-known class of reactions: the reaction of acetylenes with amines and ammonia to form ketimines.[14] The reaction of stilbene with a potassium amide–ammonia solution to form phenylbenzyl ketimine probably involves the addition of ammonia to form 1,2-diphenyl-1-aminoethane followed by the amide-catalyzed conversion of the amine to the ketimine.[15] The high molecular weight products found when tolane and stilbene were in potassium amide-ammonia solutions for several weeks may be due to polymerization of the unstable phenylbenzyl ketimine or to the base-catalyzed polymerization of unreacted stilbene or tolane in a reaction similar to the polymerization of styrene in ammonia.[16]

Registry No.—Tolane, 501-65-5; stilbene, 103-30-0.

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Halogen Metathesis in Fluorocarbons

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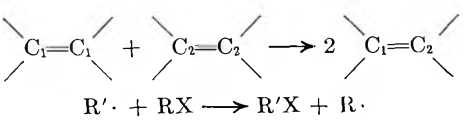
The term metathesis is used in chemistry to describe reactions in which groups are transferred or exchanged. In organic chemistry the term has been used for the "scrambling" of olefins[1,2] and acetylenes[3] or the radical abstraction of an atom to produce another radical. The term can be extended to other reactions

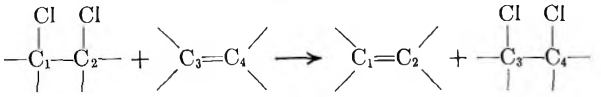


$$R'\cdot + RX \longrightarrow R'X + R\cdot$$

where there is a transfer of groups. For example, the transfer of chlorine in fluorocarbons fits within this defi-

(1) J. L. Wang and H. R. Menapace, *J. Org. Chem.*, **33**, 3794 (1968).
(2) Goodyear Tire and Rubber Co., British Patent 1,125,529 (Aug 28, 1968); *Chem. Abstr.*, **69**, 105851f (1968).
(3) F. Pennella, R. L. Banks, and G. C. Bailey, *Chem. Commun.*, 1548 (1968).

nition. We now describe this reaction and refer to it as *halogen metathesis.*



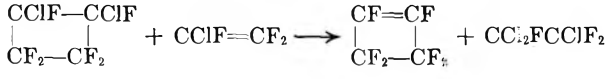
The reaction of chlorotrifluoroethylene with 1,1,2,2-tetrachloro-1,2-difluoroethane exemplifies this reaction.

$$CClF{=}CF_2 + CCl_2FCCl_2F \longrightarrow CCl_2FCClF_2 + CClF{:}CClF$$

At 300° and a contact time of 60 sec over a carbon catalyst essentially all of the chlorotrifluoroethylene is reacted. The amount remaining was too small to measure by mass spectral analysis. The yield of 1,2-dichloro-1,2-difluoroethylene was 94.4%.

An estimation of the thermodynamic functions relating to this reaction indicates that (a) little or no change of entropy or heat capacity is involved and (b) the enthalpy of reaction is probably close to 8 kcal/mol (see later discussion and Table I). This would indicate an equilibrium constant, based on $\log_{10}K_{eq} = -\Delta F/RT$, of 2.8×10^6. It would be expected that the reaction would go essentially to completion.

A second example of this reaction is the preparation of hexafluorocyclobutene from the reaction of 1,2-dichlorohexafluorocyclobutane with chlorotrifluoroethylene. For this reaction the thermodynamic functions again predict an equilibrium constant which is near completion for the reaction. Under the conditions



studied, however, this equilibrium has not been approached. The highest yield, based on the 1,2-dichlorohexafluorocyclobutane fed, was 18% (13% of the product).

This reaction is quite similar to the bromine transfer described by Tarrant and Tandon,[4] which was observed when free radical addition reactions were being studied.

$$CH_2{=}CH_2 + CFClBrCFClBr \longrightarrow CH_2BrCH_2Br + CClF{=}CClF \quad (20\%)$$

$$CH_2{=}CH_2 + CF_3CFBrCClBrCF_3 \longrightarrow CH_2BrCH_2Br + CF_3CF{=}CClCF_3 \quad \text{(quantitative)}$$

Catalysis.—Chlorine metathesis is promoted by alumina and carbon with high surface areas and many small pores.

The preferred catalytic material appears to be activated carbon which has been treated with a chlorofluoroalkane at about 300° until the formation of acid has nearly ceased. This material was used for the reaction between 1,1,2,2-tetrachloro-1,2-difluoroethane and chlorotrifluoroethylene at 300°. The chlorine metathesis occurred readily and there was a minimum of by-product formation.

The only other material which we examined with significant catalytic activity for chlorine metathesis was activated alumina,[5] but it required a temperature of 500° instead of the 300° used for activated carbon. Sodium fluoride on the alumina improves its activity. These results indicate that the decrease in acidic sites on alumina decreases side reactions with an apparent increase in chlorine metathesis.

It is possible that these materials provide a physical environment for this specific reaction, rather than actually participating in the reaction. Similar results by Tarrant and Tandon[5] in which bromine compounds undergo metathesis under radical conditions suggest that a radical mechanism may be functioning.

Additional work is needed to confirm these tentative conclusions.

Thermodynamics.—An indication of the thermodynamic differences is available from the heats of chlorination of various olefins which might be involved either as reactants or products.[6] The values for the heats of chlorination of several olefins are given in Table I. Those olefins with a large heat of chlorination should be good "chlorine sinks" and saturated dichloro compounds corresponding to olefins with smaller heats of chlorination should act as chlorine sources. Tetrafluoroethylene would serve as the best "chlorine sink," but chlorotrifluoroethylene should be useful for preparing any of the other olefins except tetrafluoroethylene and perhaps hexafluoropropylene.

TABLE I

HEATS OF CHLORINATION OF HALOGENATED OLEFINS

Olefin	Heat of reaction	Ref
$CF_2{=}CF_2$	−57.32	*a*
$CClF{=}CF_2$	−48.83	*a*
$CF_3CF{=}CF_2$	−47.15	*a*
$C_2F_5CF{=}CF_2$	−44.95	*b*
$C_3F_7CF{=}CF_2$	−45.64	*b*
$(CF_3)_2C{=}CF_2$	−42.22	*b*
$CCl_2{=}CF_2$	−41.08	*a*
$CF{=}CFCF_2CF_2$	−37.38	*c*
$CH_2{=}CH_2$	−41.5	*d*
$CH{\equiv}CH$ (1 Cl_2)	−53.9	*e*

[a] J. R. Lacher, J. J. McKinley, C. M. Snow, L. Michel, G. Nelson, and J. D. Park, *J. Amer. Chem. Soc.*, **71**, 1330 (1949). [b] J. R. Lacher, A. Kianpour, and J. D. Park, *J. Phys. Chem.*, **61**, 584 (1957). [c] Reference 10. [d] C. R. Patrick, *Tetrahedron*, **4**, 26 (1958). [e] S. W. Benson, F. R. Cruickshank, D. M. Golden, G. R. Haugen, H. E. O'Neal, A. S. Rodgers, R. Shaw, and R. Walsh, *Chem. Rev.*, **69**, 279 (1969).

(4) P. Tarrant, *et al.*, "Research on Synthesis of Unsaturated Fluorocarbon Compounds," AD 662712, March 1967; *Chem. Abstr.*, **68**, 93047*n* (1967); *cf.* J. P. Tandon, Dissertation, University of Florida, Aug 1966.

(5) Alcoa F-1 alumina was used.

(6) There is a lack of some of the thermodynamic functions of the compounds involved in these reactions, and a range of values for others. For example, no thermodynamic values are available for 1,1,2,2-tetrachloro-1,2-difluoroethane and there is no data for the heat capacity of 1,2-dichloro-1,2-difluoroethylene above 300°K. On the other hand, care must be taken with reported values. The reported values for the heat of formation of chlorotrifluoroethylene range from −114[7] to −130.2[8] kcal/mol. Rodgers[9] in 1967 chose a "best value" of −117.5 ± 2 kcal/mol, which fits with a "best value" for the heat of formation of 1,1,2-trichloro-1,2,2-trifluoroethane, −166.1 kcal/mol, and the reported heat of chlorination.[10]

(7) P. G. Maslov and Yu. P. Maslov, *Khim. Tekhnol. Topl. Masel*, **3**, 50 (1958); *Chem. Abstr.*, **53**, 1910*h* (1959).

(8) V. P. Kolesov, I. D. Zenkov, and S. M. Skuratov, *Zh. Fiz. Khim.*, **37**, 224 (1963).

(9) A. S. Rodgers, *J. Phys. Chem.*, **71**, 1996 (1967).

(10) J. R. Lacher, J. J. McKinley, C. Walden, K. Lea, and J. D. Park, *J. Amer. Chem. Soc.*, **71**, 1334 (1949).

TABLE II
CHLORINE METATHESIS OF CHLOROTRIFLUOROETHYLENE WITH 1,2-DICHLOROHEXAFLUOROCYCLOBUTANE

Expt no.	Catalyst	Vol,[a] cc	Mole ratio, C_2ClF_3/$C_4Cl_2F_6$	Temp, °C	Contact time, sec	Material balance, wt %	Product composition, mol % $CClF{=}CF_2$	$CClF(CF_2)CClF$	$CF{=}CF$ $(CF_2)_2$	CCl_2FCClF_2	$CClF_2CF{=}CFCF_3$[b]	$CCl{=}CCl$ $(CF_2)_2$[b]
1	NaF on F-1 alumina	15	1.4	500	8.2	81.9	35.3	52.0	3.0	9.3		
2	Same	15	1.2	500	9.1	95.3	37.8	53.5	2.0	6.2		
3	Carbon	300	0.80	300	66.7	78.8	2.0	42.5	10.0	22.2	5.1	18.2

[a] The reaction was carried out in a Pyrex tube or a stainless steel 1-in. tube. [b] The structure of these two compounds was assigned on the basis of their mass spectra.

The heats of chlorination are smaller for compounds with more chloro or perfluoroalkyl groups. One possibility of a less expensive "chlorine sink" than tetrafluoroethylene is acetylene.

By-Products.—The formation of by-products appears to be thermally induced. Although the amounts are small below 450°, there is a marked increase with temperature.

Previous studies of the thermal reactions of chlorotrifluoroethylene at 300–500° by Atkinson and Stedman[11] had shown that the first-formed 1,2-dichlorohexafluorocyclobutane appeared to open to form 1,4-dichlorohexafluorobutene-2. Miller[12] indicated that pyrolysis of chlorotrifluoroethylene at 560° seemed to give the products shown below. At 650° hexafluorocyclobutane was also observed.

$$CClF{=}CF_2 \xrightarrow{560^\circ} \underset{34\%}{CClF(CF_2)CClF} + \underset{30\%}{CF_2{=}CFCClFCClF_2} + \underset{10\%}{CF_2{=}CFCClFCF_2} + \underset{10\%}{CF_2{=}CFCCl_2F}$$

By-products which have been identified in the experiment utilizing chlorotrifluoroethylene and 1,2-dichlorohexafluorocyclobutane were 1-chloroheptafluoro-2-butene, 3,4-dichlorohexafluoro-1-butene, and 1,2-dichlorotetrafluorocyclobutene. Those identified from the reaction of chlorotrifluoroethylene with 1,1,2,2-tetrachloro-1,2-difluoroethane were 2-chloroheptafluoro-2-butene, 2,3-dichlorohexafluoro-2-butene, and 1,2-dichlorohexafluorocyclobutane.

Experimental Section

Reaction of Chlorotrifluoroethylene with 1,2-Dichlorohexafluorocyclobutane.—Three experiments were carried out to demonstrate the direct reaction of these two materials by chlorine metathesis. In the first two the catalyst was 15 cc of NaF-coated Alcoa F-1 Alumina in a 16-mm Pyres tube. The third used Columbia CXA 6-8 mesh carbon in a 1-in. stainless steel tube. The conditions used and the results observed are presented in Table II.

Reaction of Chlorotrifluoroethylene with 1,1,2,2-Tetrachloro-1,2-difluoroethane.—The 1-in. stainless steel tube mentioned above was charged with Columbia CXA 6-8 mesh activated carbon. This had been used in the third experiment mentioned above, discharged, and allowed to stand for 3 weeks. The catalyst was recharged and heated to 300° in a nitrogen purge. 1,1,2,2-Tetrachloro-1,2-difluoroethane was fed over the catalyst for 5.5 hr to condition it. At first there was much acid in the condensate, but this decreased rapidly after 2 hr. A mixture of 47 g of chlorotrifluoroethylene and 77.5 g of 1,1,2,2-tetrachloro-1,2-difluoroethane was passed over the catalyst over a 2-hr period. The contact time was 60 sec at a temperature of 300°. Products were collected in Dry Ice cooled traps and analyzed by gas chromatography and mass spectroscopy.

(11) B. Atkinson and M. Stedman, *J. Chem. Soc.*, 512 (1962).
(12) W. T. Miller, U. S. Patent 2,733,277 (Jan 31, 1956).

The products included 47.7 g (94.4%) of 1,2-dichloro-1,2-difluoroethylene, 37.4 g of 1,1,2-trichloro-1,2,2-trifluoroethane, 4.5 g of recovered 1,1,2,2-tetrachloro-1,2-difluoroethane, a trace of chlorotrifluoroethylene, and 5.3 g of 1,2-dichlorohexafluorocyclobutane.

Registry No.—Chlorotrifluoroethylene, 79-38-9; 1,2-dichlorohexafluorocyclobutane, 356-18-3; 1,1,2,2-tetrachloro-1,2-difluoroethane, 76-12-0.

Facile Synthesis of Tricyclo[5.3.1.$0^{3,8}$]undecane and Spiro[5.5]undecane Systems from a Common Intermediate

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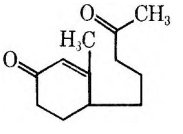
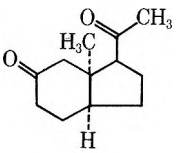
Barton and his coworkers[1] and Johnson's group[2] reported that the cyclization of the unsaturated diketone of type I led stereoselectively to the *cis*-hydrindanone II.

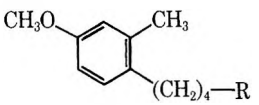

I


II

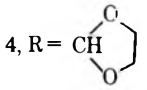
In an attempt to investigate the stereochemical outcome of cyclization of the compound carrying the side chain with one more methylene unit in I, we have examined cyclization of 3-methyl-4-(4′-formylbutyl)-2-cyclohexenone (**6**) under a variety of conditions. The cyclohexenone aldehyde **6** employed in this study was prepared as follows. The Wolff–Kishner reduction of γ-(2-methyl-4-methoxybenzoyl)butyric acid[3] afforded δ-(2-methyl-4-methoxyphenyl)valeric acid (**1**). Lithium aluminum hydride reduction of the methyl ester of the acid **1** gave an alcohol **2**, which, on Pfitzner–Moffatt oxidation yielded an aldehyde **3**. The corresponding acetal **4** was submitted to the Birch reduction and the resulting enol ether was hydrolyzed with

(1) D. H. R. Barton, A. S. Campos-Neves, and A. I. Scott, *J. Chem. Soc.*, 2698 (1957).
(2) W. S. Johnson, S. Shulman, K. L. Williamson, and R. Pappo, *J. Org. Chem.*, **27**, 2015 (1962).
(3) D. Chakravarti and N. K. Roy, *J. Indian Chem. Soc.*, **42**, 607 (1965).

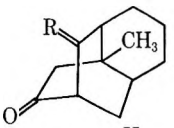
oxalic acid to afford the β,γ-unsaturated ketone acetal, which was converted to the α,β-unsaturated ketone acetal **5**. The structure of the acetal **5** was secured by spectral data. Deacetalization of **5** in hot aqueous acetic acid afforded the desired cyclohexenone aldehyde **6**.

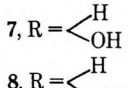


1, R = COOH
2, R = CH_2OH
3, R = CHO

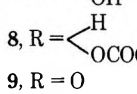


4, R =



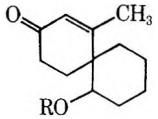


7, R =

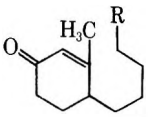


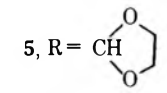
8, R =

9, R = O



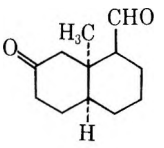
12, R = H
13, R = $COCH_3$



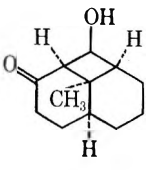


5, R =

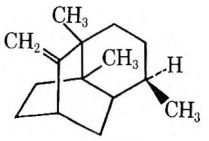
6, R = CHO



10



11



seychellene

The intramolecular Michael condensation of **6** was examined using various amines and alkoxides. Cyclization was effected with pyrrolidine in methanol at room temperature and a crystalline product, $C_{12}H_{18}O_2$, was obtained in 70% yield. While the ultraviolet spectrum showed no absorption, the infrared spectrum ($CHCl_3$) of the cyclized product exhibited bands at 3640, 3400, and 1720 cm^{-1}, and the nuclear magnetic resonance spectrum revealed a singlet due to a tertiary methyl group at δ 1.02, a broad singlet of a hydroxyl at δ 2.5 which disappeared on addition of deuterium oxide, and a broad doublet (J = 4.5 Hz) of a hydrogen on carbon bearing the hydroxyl at δ 4.00. These spectral data suggest that the product is a saturated keto alcohol. The structure of the cyclized product was, therefore deduced to be **7**. Further, the cyclization product **7** formed the monoacetate **8** with acetic anhydride and pyridine, and was oxidized with chromium trioxide–pyridine to the diketone **9**, which showed two carbonyl bands at 1740 and 1710 cm^{-1} in the infrared spectrum. The infrared spectral data of the diketone **9** exclude the possibility of **11** for the structure of the cyclized product. The cyclization of **6** to form **7** could also be carried out in *tert*-butyl alcohol containing potassium *tert*-butoxide, but in a yield less than in the pyrrolidine–methanol solution.

Since the cyclized product **7** corresponds to the tricyclic carbon skeleton of a unique sesquiterpene, seychellene,[4,5] this mode of cyclization would be potentially useful for the synthesis of the sesquiterpene.

The formation of the tricyclic compound **7** from the cyclohexenone aldehyde **6** implies that the *cis*-decalone **10** was initially formed, which underwent further intramolecular aldol condensation. Although the reaction mixture was analyzed periodically by thin layer chromatography and vapor phase chromatography during the cyclization reaction in pyrrolidine–methanol, intermediates or other products could not be observed. Presumably the *cis*-decalone **10** was directly formed from **6** without intervention of the corresponding *trans*-decalone.

On the other hand the acid-catalyzed cyclization of the cyclohexenone aldehyde **6** proceeded in a different manner: on treatment of **5** in hydrochloric acid in aqueous tetrahydrofuran under reflux a crystalline compound $C_{12}H_{18}O_2$ was obtained, the structure of which was proved to be **12** containing a spiro[5.5]undecane skeleton on the basis of the spectral data. The compound **12** retains the original α,β-unsaturated ketone group [ν_{max} 1660, 1615 cm^{-1}; λ_{max} (CH_3OH) 241 nm (ϵ 12,000)] and a secondary hydroxyl group [ν_{max} 3660, 3470 cm^{-1}; δ_{CDCl_3} 3.9 (CHOH) as a multiplet]. On acetylation with acetic anhydride–pyridine the monoacetate **13** [δ 5.1 ($CHOCOCH_3$) as a multiplet] was obtained.

Experimental Section

General.—Melting points were uncorrected. The ultraviolet spectra were measured in methanol with a Perkin-Elmer Model 202 spectrophotometer. The infrared spectra were recorded with a JASCO Model IRS spectrophotometer. Nuclear magnetic resonance spectra were determined on a JNMC-60H (60 MHz) spectrometer: chemical shifts are expressed in parts per million downfield from tetramethylsilane as internal standard (δ). The mass spectra were obtained on a Hitachi RMU-6D mass spectrometer operating with an ionization energy of 70 eV. Vapor phase chromatographic analyses (vpc) were carried out on a Hitachi K-52 instrument using a flow rate of 20 ml/min on 2 m × 3 mm columns packed with 5% SE-30 on Chromosorb W at 230°. Thin layer chromatography (tlc) was performed on silica gel GF_{254} (E. Merck, A.G.). For column chromatography Mallinckrodt silicic acid (100 mesh, Mallinckrodt) was used. The organic solutions were dried over anhydrous sodium sulfate, and evaporated under reduced pressure.

δ-(2-Methyl-4-methoxyphenyl)valeric Acid (1).—A mixture of 17.3 g (73.3 mmol) of γ-(2-methyl-4-methoxybenzoyl)butyric acid,[3] mp 133–135°, 8 ml of $NH_2NH_2 \cdot H_2O$, 14 g of 85% KOH, and 100 ml of diethylene glycol was refluxed under nitrogen for 2 hr, and then was allowed to distil until the temperature of the solution reached 210°. The solution was kept at 210° for a further 2 hr. After cooling, the solution was diluted with 20 ml of water and then 15 ml of dimethyl sulfate was added. The mixture was heated under reflux for 1 hr, and after cooling poured slowly into a mixture of excess HCl and ice. The precipitate obtained was collected by filtration, washed with water, and dried. Recrystallization from benzene afforded 13.2 g (82%) of **1**, mp 109–111°.

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.08; H, 8.10.

5-(2′-Methyl-4′-methoxyphenyl)pentan-1-ol (2).—Treatment of the valeric acid **1** with excess diazomethane in ether afforded the methyl ester. To a suspension of 1.0 g (26 mmol) of $LiAlH_4$ in 50 ml of ether was added dropwise a solution of 7.6 g (32 mmol) of crude methyl ester of **1** in 20 ml of ether with stirring

(4) N. Tsubaki, K. Nishimura, and Y. Hirose, *Bull. Chem. Soc. Jap.*, **40**, 597 (1967); G. Wolffe, and G. Ourisson, *Tetrahedron Lett.*, 3849 (1968).

(5) For the synthesis of seychellene, see E. Piers, R. W. Britton, and W. deWaal, *Chem. Commun.*, 1069 (1969); K. J. Schmalzl and R. N. Mirrington, *Tetrahedron Lett.*, 3219 (1970).

at −20° in a Dry Ice–acetone bath. After the mixture was stirred at 0° for 1 hr, 5 ml of ethyl acetate in 10 ml of ether was added. A saturated aqueous solution of sodium potassium tartarate was slowly added to the mixture until the gray granular precipitate was formed. The ethereal solution was separated by decantation and the precipitate was washed with two 20-ml portions of ether. The combined ethereal solution was washed with a saturated NaCl solution and dried. Evaporation of solvent afforded a crude product, which was distilled to afford 6.2 g (67%) of **2**: bp 155–156° (2 mm); ir ($CHCl_3$) 3680 (OH), 3550 cm^{-1} (OH); mass spectrum *m/e* 208 (parent ion). The analytical sample was fractionally distilled through a Vigreux column.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.70; H, 9.51.

5-(2′-Methyl-4′-methoxyphenyl)pentan-1-al (3).—A solution of 2 g of 100% phosphoric acid in 2.5 ml of DMSO was added dropwise under ice-bath cooling to a mixture of 10.0 g (49.5 mmol) of the alcohol **2**, and 30 g of dicyclohexylcarbodiimide in 40 ml of benzene and 45 ml of DMSO with stirring. After the addition of the phosphoric acid solution the mixture was kept at room temperature with stirring for 5 hr. The mixture was diluted with 100 ml of ether and a solution of 14 g of oxalic acid in 40 ml of methanol was added. The resulting mixture was stirred for 2 hr and the precipitated dicyclohexylurea was filtered. The filtrate was washed with water twice, a saturated $NaHCO_3$ solution three times, and a saturated NaCl solution, and dried. Evaporation of solvent afforded 15.7 g of an oily product containing dicyclohexylurea. The crude product was chromatographed on 200 g of silicic acid with $CHCl_3$; each fraction eluted was examined by tlc. Fractions containing the aldehyde **3** were combined and evaporated to afford 8.5 g (86%) of a colorless liquid **3**, which showed one peak in vpc analysis: ir ($CHCl_3$) 2840 (CHO), 2720 (CHO), 1725 cm^{-1} (CHO). The product **3** was directly employed without further purification for the next step. The 2,4-dinitrophenylhydrazone was obtained as orange needles, which was recrystallized from ethanol, mp 108–110°.

Anal. Calcd for $C_{19}H_{22}O_5N_4$: C, 59.06; H, 5.74; N, 14.50. Found: C, 59.08; H, 5.69; N, 14.79.

Preparation of the Acetal (4) of the Aldehyde (3).—A mixture of 4.0 g (19 mmol) of **3**, 6 ml (107 mmol) of ethylene glycol, and 100 mg of *p*-toluenesulfonic acid in 50 ml of toluene was kept under reflux for 4 hr with stirring in a system containing a water separator. After cooling solid $NaHCO_3$ was added to the mixture for neutralization. The mixture was washed with water and a saturated NaCl solution, and dried. Evaporation of solvent afforded a colorless liquid, which was distilled to give 3.8 g (78%) of the acetal **4**, exhibiting one peak in vpc: bp 158–160° (2 mm); nmr (CCl_4) δ 6.89 and 6.49 (AB type q, 2, J = 9.0 Hz, aromatic H), 6.55 (s, 1, aromatic H), 4.70 (t, 1, J = 4.5 Hz, acetal methine), 3.76 (m, 4, $-OCH_2CH_2O-$), 3.69 (s, 3, CH_3O), 2.24 (s, 3, aromatic CH_3); mass spectrum *m/e* 250 (parent ion).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.03; H, 8.99.

3-Methyl-4-(4′-formylbutyl)-2-cyclohexenone (6).—To a solution of 3.0 g (12 mmol) of **4** in 150 ml of *tert*-butyl alcohol, 150 ml of THF, and 300 ml of liquid ammonia was added 15 g of lithium wire with stirring over a period of 30 min. After the addition was complete, the dark blue mixture was stirred at the refluxing temperature (*ca.* −33°) for 10 hr, and then allowed to stand overnight at room temperature. Methanol was slowly added first to decompose excess lithium, and water was added. The resulting mixture was concentrated to give a white residue, to which 100 ml of benzene and 50 ml of water were added. The benzene layer was separated and the aqueous layer was further extracted with three 50-ml portions of benzene. The combined benzene solution was concentrated, giving a residue, which was dissolved in 20 ml of a saturated aqueous solution of oxalic acid and 100 ml of methanol. The resulting solution was stirred at room temperature for 1 hr and concentrated, affording a residue, which was extracted with four 50-ml portions of benzene. The benzene solution was washed with water twice and a saturated NaCl solution, and dried. On removal of solvent there was obtained 2.7 g of crude β,γ-unsaturated ketone: ir ($CHCl_3$) 1712 cm^{-1}.

A solution of 2.6 g of the β,γ-unsaturated ketone in 95 ml of methanol containing 105 mg of sodium methoxide was stirred at room temperature for 2 hr, neutalized with oxalic acid, and concentrated, giving a yellow residue. The benzene solution of the residue was washed with water and a saturated NaCl solution, and dried. Evaporation of solvent afforded 2.1 g of crude ketone **5**, which was chromatographed on 100 g of silicic acid with $CHCl_3$; fractions containing **5**, detected by tlc and vpc analyses were combined, giving 1.5 g (*ca.* 52% from **4**) of colorless liquid **5**: ir ($CHCl_3$) 1660 (conjugated C=O), 1630 cm^{-1} (conjugated C=C); nmr ($CDCl_3$) δ 5.38 (q, 1, J = 0.5 Hz, $CH{=}CCH_3$), 4.87 (t, 1, J = 4.5 Hz, acetal methine), 3.93 (m, 4, $-OCH_2CH_2O-$), 1.98 (d, 3, J = 0.5 Hz, $CH{=}CCH_3$); mass spectrum *m/e* 238 (parent ion).

A solution of 1.45 g of **5** obtained above in 30 ml of acetic acid–water (2:1 v/v) was heated at 90° for 4 hr, and diluted with 50 ml of water and 100 ml of benzene. To the mixture was added solid $NaHCO_3$, making the aqueous layer basic. The organic layer was separated and the aqueous phase was extracted with three 20-ml portions of benzene. The combined benzene solution was washed with water, dried, and evaporated, affording 1.0 g (*ca.* 43% from **4**) of slightly yellow liquid **6**: ir ($CHCl_3$) 2840 (CHO), 2720 (CHO), 1660 (conjugated C=O), 1630 cm^{-1} (conjugated C=C). The α,β-unsaturated ketone aldehyde **6** obtained above, the purity of which was examined by vpc, was used directly in the next step.

2-Hydroxy-8-methyltricyclo[5.3.1.0^{3,8}]undecan-10-one (7).—A. Cyclization in Pyrrolidine–Methanol.—A solution of 60 mg (0.31 mmol) of **6** in 4 ml of methanol containing 15 mg (0.22 mmol) of pyrrolidine was stirred at room temperature for 24 hr and concentrated, affording a yellow oil. The residue was dissolved in 0.5 ml of a saturated aqueous oxalic acid solution and 5 ml of $CHCl_3$. The organic layer was washed with water and a saturated NaCl sclution, dried, and evaporated to give 54 mg of a crystalline solid. Analysis by tlc showed formation of a single compound. Column chromatogaphy on 2 g of silicic acid with $CHCl_3$–CH_3OH (96:4 v/v) afforded 43 mg (*ca.* 70%) of crystals. Recrystallization from benzene–petroleum ether (bp 30–60°) gave pure **7**: mp 161–162°; ir ($CHCl_3$) 3640 (OH), 3400 (broad, OH), 1720 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.00 (br d, 1, J = 4.5 4.5 Hz, CHOH), 2.5 (br s, 1, CHOH, disappeared on addition of D_2O), 1.02 (s, 3, $C-CH_3$); mass spectrum *m/e* 194 (parent ion).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.08; H, 9.36.

B. Cyclization in *tert*-Butyl Alcohol–Potassium *tert*-Butoxide.—A solution of 142 mg (0.73 mmol) of **6** in 9.6 ml of *tert*-butyl alcohol containing 110 mg (1.0 mmol) of potassium *tert*-butoxide was stirred at 30° for 18 hr under nitrogen. The brown solid deposited in the mixture was filtered. The filtrate was neutralized by aqueous oxalic acid, concentrated, and extracted with three 10-ml portions of $CHCl_3$. The combined organic phase was washed with water and a saturated NaCl solution, dried, and evaporated, giving 75 mg of a crystalline solid, which showed a main spot in tlc. Column chromatography on 3 g of silicic acid as described in A was carried out to give 50 mg (35%) of colorless crystals **7**.

Acetylation of the Tricyclic Compound 7.—A mixture of 24 mg (0.124 mmol) of **7** in 0.3 ml of acetic anhydride and 0.4 ml of pyridine was kept at room temperature for 24 hr and diluted with 10 ml of benzene. The resulting mixture was successively washed with dilute HCl solution, a saturated $NaHCO_3$ solution, water, and a saturated NaCl solution, and dried. Evaporation of solvent afforded a solid, which was purified by preparative tlc with chloroform–ethyl acetate (1:1 v/v). Crystalline solid eluted from silica gel with ethyl acetate was recrystallized from hexane, giving 21 mg (72%) of the acetate **8**: mp 115–117°; ir ($CHCl_3$) 1735 (ester C=O), 1720 cm^{-1} (C=O); nmr ($CDCl_3$) δ 5.05 (dd, 1, J = 4.5, 1.5 Hz, $CHOCOCH_3$), 2.55 (m, 1, CHC=O), 2.00 (s, 3, CH_3COO), 1.02 (s, 3, CCH_3); mass spectrum *m/e* 236 (parent ion).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.11; H, 8.55.

Oxidation of the Tricyclic Compound 7.—To a solution of 14 mg (0.057 mmol) of **7** in 0.3 ml of pyridine was added 88 mg of chromium trioxide in 1.5 ml of pyridine at 0°. The mixture was kept at room temperature for 17 hr, concentrated, and diluted with 2 ml of ethyl acetate and 2 ml of water. The resulting precipitate was filtered and washed with four 2-ml portions of ethyl acetate. The combined ethyl acetate solution was washed with a saturated NaCl solution and dried. Evaporation of solvent afforded 11 mg of a colorless oil, which showed one spot in tlc. Column chromatography on 1 g of silicic acid with $CHCl_3$ gave 9 mg (64%) of amorphous powder **9**: ir ($CHCl_3$) 1745 (C=O), 1710 cm^{-1} (C=O); mass spectrum *m/e* 192 (parent ion).

1-Methyl-7-hydroxyspiro[5.5]undec-1-en-3-one (12).[6]—A solution of 55 mg (0.25 mmol) of **5** in 0.9 ml of 6 *N* HCl and 1.8 ml of THF was refluxed for 2 hr, and after cooling extracted with three 5-ml portions of benzene. The combined benzene solution was washed with water until the aqueous layer became neutral and with a saturated NaCl solution and dried. Evaporation of solvent afforded a crystalline residue, which showed a main spot in tlc. Preparative tlc using ethyl acetate afforded 26 mg (58%) of colorless needles, which was recrystallized from hexane–benzene, affording pure **12**: mp 103–104°; uv max (CH_3OH) 241 nm (ϵ 12,000); ir ($CHCl_3$) 3400 (OH), 1660 (conjugated C=O), 1615 cm^{-1} (conjugated C=C); nmr ($CDCl_3$) δ 5.91 (q, 1, J = 1.0 Hz, C**H**=CCH_3), 3.9 (m, 1, C**H**OH), 2.02 (d, 3, J = 1.0 Hz, CH=C**CH**$_3$); mass spectrum m/e 194 (parent ion).

(6) Since the product **12** was obtained from both **5** and **6** under the same condition, the result employing **5** is described.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.93; H, 9.24.

Acetylation of the Spiro Compound 12.—A mixture of 36 mg (0.18 mmol) of **12** in 0.25 ml of acetic anhydride and 0.5 ml of pyridine was stirred at room temperature for 24 hr, diluted with 10 ml of benzene. By the same work-up as described in the acetylation of **7**, an oily product was obtained, which showed a single spot in tlc. Preparative tlc using ethyl acetate afforded 25 mg of purified **13** as a colorless semisolid: ir ($CHCl_3$) 1730 (ester C=O), 1663 (conjugated C=O), 1615 cm^{-1} (conjugated C=C); nmr ($CDCl_3$) δ 5.90 (q, 1, J = 1.0 Hz, C**H**=CCH_3), 5.1 (m, 1, C**H**O$COCH_3$), 1.98 (s, 3, CH_3COO), 1.91 (d, 3, J = 1.0 Hz, CH=C**CH**$_3$); mass spectrum m/e 234 (parent ion).

Registry No.—**1**, 31603-60-8; **2**, 31603-61-9; **3**, 31603-62-0; **3** 2,4-DNP, 31603-63-1; **4**, 31603-64-2; **5**, 31603-65-3; **6**, 31603-66-4; **7**, 31603-67-5; **8**, 31603-68-6; **9**, 31603-69-7; **12**, 31603-70-0; **13**, 31603-71-1.

Additions and Corrections

Vol. 34, 1969

Erling Grovenstein, Jr., Thomas C. Campbell, and Tomoo Shibata: Photochemical Reactions of Dimethyl Acetylenedicarboxylate with Benzene and Naphthalene.

Pages 2419 and 2425. Compound VI, dimethyl 2,3-benzobicyclo[2.2.2]octatriene-5,6-dicarboxylate or dimethyl 1,4-dihydro-1,4-ethenonaphthalene-2,3-dicarboxylate, from thermal reaction of naphthalene with dimethyl acetylenedicarboxylate, we now find has mp 105.0–105.5° rather than the lower value (76.5–77.5°) previously reported.

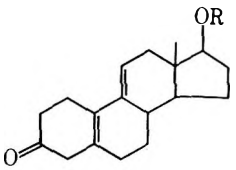
William G. Dauben, Milton Lorber, and Dwight S. Fullerton: Allylic Oxidation of Olefins with Chromium Trioxide–Pyridine Complex.

Page 3591. Column 2, line 6. The nmr spectra ldata listed for isopiperitenone (**12**) are those found for carvone (**13**). The correct data are as follows: nmr (δ, CCl_4) 5.73 (m, 1, C=CH-CO), 4.83 (m, 1, C=CH_2), 4.66 (m, 1, C=CH_2), 2.82 (m, 1, CHCO–), 1.93 (d, 3 H, CH_3C=C), 1.71 (sharp m, 1, CH_2C=C).

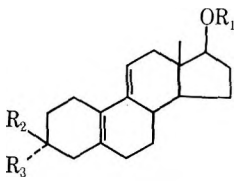
Vol. 35, 1970

Samuel G. Levine and Nancy H. Eudy: The Conformation of Ring A in 5(10),9(11)-Estradienes.

Page 549. Column 2. Several errors appear in formulas **5**–**11** which should be given as



5, R = H
6, R = Ac



7, $R_1 = R_3 = H$; $R_2 = OH$
8, R_1 = Ac; $R_2 = H$; $R_3 = OH$
9, R_1 = Ac; $R_2 = OH$; $R_3 = H$
10, R_1 = Ac; $R_2 = H$; $R_3 = OAc$
11, R_1 = Ac; $R_2 = OAc$; $R_3 = H$

J. M. Springer, C. W. Hinman, E. J. Eisenbraun, P. W. K. Flanahan, and M. C. Hamming: The Reaction of 1-Tetralones with Potassium Hydroxide–Sodium Hydroxide.

Page 1263. In Scheme IV, the third structure should have the hydroxyl at C-2 and not at C-1.

Edward E. Smissman, J. Pengman Li, and Mary Weir Creese: Neighboring-Group Participation in Pyrolytic *trans* Eliminations.

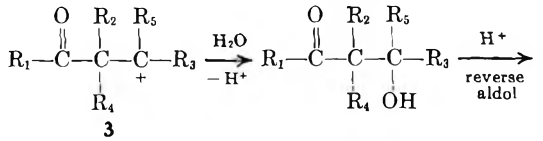
Page 1353. Column 2, line 24. The "lower" should be changed to "higher."

Edward E. Smissman, John R. J. Sorenson, William A. Albrecht, and Mary Weir Creese: Thiomethylation.

Page 1357. Title. "William A. Albrecht" should read "William L. Albrecht."

Dennis D. Faulk, Walter H. Corkern, Ikuo Ookuni, and Arthur Fry: Acid-Catalyzed Disproportionation Reactions of Aliphatic Ketones. Scope and Mechanisms.

Page 1518. Column 1. The fourth line of formulas contains typographical errors, and should be corrected to read as follows.



3

E. J. Moriconi and C. P. Dutta: Chlorosulfonyl Isocyanate Addition to Bicyclo[2.1.0]pentane.

Page 2445. Column 2. The melting point of 2-aza-3-ketobicyclo[2.2.1]heptane (compound **5**) should read 45–47° (not 32–34° as reported).

Charles D. Hurd: M. S. Karasch.

August issue, dedicatory article immediately preceding page 2465. Reference to Dr. Hurd's article on M. S. Karasch was inadvertently omitted from the December index, 1970.

Robert L. Lichter and John D. Roberts: ^{15}N Magnetic Resonance. X. Angular Dependence of Vicinal ^{15}N–H Coupling Constants in Amino Acids.

Page 2806. Equation 7 should read

$$J_{NA} = p_a J_t^N + (p_b + p_c) J_g^N$$

Page 2807. Footnote 11 should read as follows.

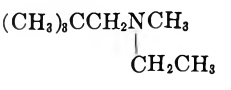
(11) The reported values for ^{14}N were corrected by

$$|\gamma^{14}N/\gamma^{15}N| = 0.713$$

for this purpose.

Stanley H. Pine, Brian A. Catto, and Frederick G. Yamagishi: The Stevens Rearrangements of *N*,*N*,*N*-Trimethylneopentylammonium Iodide.

Page 3663. Structural formula **5** should have been



D. C. Dittmer, G. E. Kuhlmann, and G. C. Levy: Photolysis and Pyrolysis of the Episulfoxide of Dibenzoylstilbene.

Page 3676. The second line of the paper should read "oxidation of a cis isomer would yield two meso episulfoxides; oxidation of a trans isomer would yield a pair of enantiomorphs."

Marvin L. Poutsma and Pedro A. Ibarbia: Radical Addition of *tert*-Butyl Hypochlorite to Conjugated Enynes.

Page 4044. Column 1, last line. "reversible" should read "irreversible."

P. Haake and Joseph W. Watson: The Mechanism of Acid Hydrolysis of Lysidine and *N*-(2-Aminoethyl)acetamide.

Page 4065. Column 1, eq 1. Structure **4** has an extraneous 2. **4** is given correctly on pages 4066 and 4067.

Page 4065. Column 2, Table III, line 3. Table heading should read 10^5k (sec^{-1}).

Page 4065. Column 2, line 21 of text. The formula should read $(CH_3)_2NH_2^+$.

Page 4066. Column 1, Table IV. The data columns 2, 3, and 4 are placed under the wrong column headings and the data for the column "*M*, H_2SO_4" has been omitted. (i) Data column 4 should be under the column heading "δ" pertaining to the "methyl." (ii) Data columns 2 and 3 should be under column headings "$-\delta$" and "Width" pertaining to the "Methylene," respectively. (iii) The column headings "% H_2SO_4" and "*M*, H_2SO_4" should be replaced by the column heading "% H_2SO_4 (*M*, H_2SO_4)" with the first six data entries in the first column being 32.0 (4.0), 44.0 (6.0), 63.0 (10.0), 76.0 (13.0), 88.0 (16.0), 95.0 (18.0). (iv) Footnote *b* of Table IV should read "Chemical shifts in cps from the central peak of the dimethylammonium cation triplet."

Page 4067. Column 1, line 2. Parenthetical statement should read "($H_0 = -13.16$)."

A. Streitwieser, Jr., and David Holtz: Acidity of Hydrocarbons. XXXIV. Rate of Proton Abstraction from *p*-Trifluoromethyltoluene by Lithium Cyclohexylamide in Cyclohexylamine.

Page 4290. The registry number for LiCHA should be 4819-94-7.

Vol. 36, 1971

David N. Harpp, John G. Gleason, and David K. Ash: The Chemistry of Thiolsulfonates and Related Derivatives. Nucleophilic Reactions on Sulfenyl Sulfur.

Page 326. Column 1. Lines 35 and 36. Nmr should read "τ 5.5 (m, 2 H), 7.65 (m, 4 H)."

J. K. Crandall and R. J. Watkins: Thermal Transformations of Medium Ring Olefins.

Page 915. Column 1, line 33. "**18**" should read "**11.**"

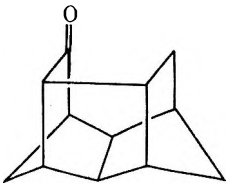
S. Morris Kupchan and Masao Maruyama: Reductive Elimination of Epoxides to Olefins with Zinc–Copper Couple.

Page 1188. Columns 1 and 2, Table I. Compounds **14** and **15** were designated erroneously as 11,12-diones, rather than 11,20-diones. Thus **14** is 16α,17α-oxido-3α-acetoxy-16β-methyl-5β-pregnane-11,20-dione, and **15** is 3α-acetoxy-16-methyl-5β-pregn-16-ene-11,20-dione.

Page 1190. Column 1, lines 66, 67, and 72. The designations of compounds **14** and **15** should be corrected as described above.

Robert K. Howe, P. Carter, and S. Winstein: Formation and Transannular Reactions of Cyclopropane Half-Cage Alcohols.

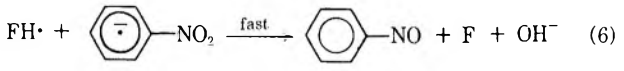
Page 1317. The structure for **4** should be



Morton J. Gibian and A. L. Baumstark: The Reduction of Aromatic Nitro and Related Compounds by Dihydroflavins.

Page 1390. Scheme I should appear as shown in column 2.

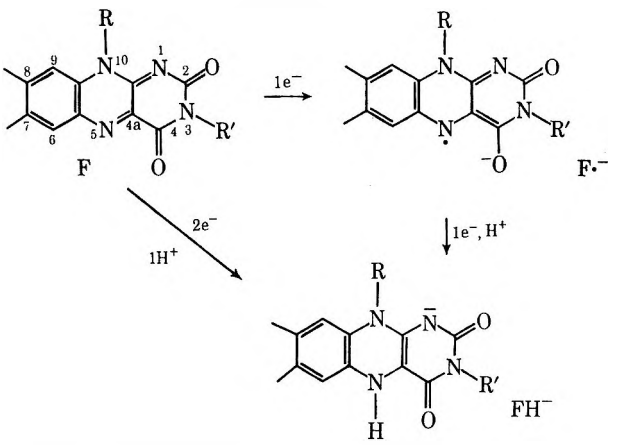
Page 1392. Equation 6 should appear as follows.



T. J. van Bergen and Richard M. Kellogg: Reactions of Aryl Grignard Reagents with Pyridine 1-Oxide. The Structure of the Addition Products.

Page 1705. An article by P. Schiess, P. Ringela, and H. L. Chia, *Chimia*, 24 (1970), has been brought to our attention. These authors, on chemical grounds, deduced that the product from addition of phenyl Grignard reagent to lutidine *N*-oxide exists in ring-opened form.

SCHEME I[a]



[a] Only one tautomeric or resonance form for each state has been drawn. Flavins are 7,8-dimethylisoalloxazines.

H. E. Zaugg and R. W. DeNet: 3-Monosubstituted 1-Benzoyl-2,2-dichloroaziridines. Methanolysis, Thermolysis, and Benzoylation.

Page 1938, column 2. Structure **14** is in error. The nitrogen and oxygen atoms should be interchanged.

D. E. Boone, E. J. Eisenbraun, P. W. Flanagan, and R. D. Grigsby: The Acid-Catalyzed Alkylation and Cyclialkylation of the Cymenes with Isobutylene and Related olefins.

Page 2043. In Figure 1, top trace, structure **4** should be 1,1,3,5-tetramethyl-3-ethylindan.

Roger S. Macomber: Return-Rearrangement in Solvolyses. Triangular Kinetic Schemes.

Page 2183. Reference 7. Second equation has an incorrect subscript: $[ROTs]_0k_1$. It appears correctly as eq 4 in the body of the paper.

Robert L. Soulen, David B. Clifford, F. Fleming Crim, and Joann A. Johnston: Nucleophilic Vinylic Substitution. I. The Synthesis and Reactions of 2-Substituted 3,3-Dichloroacrylonitriles.

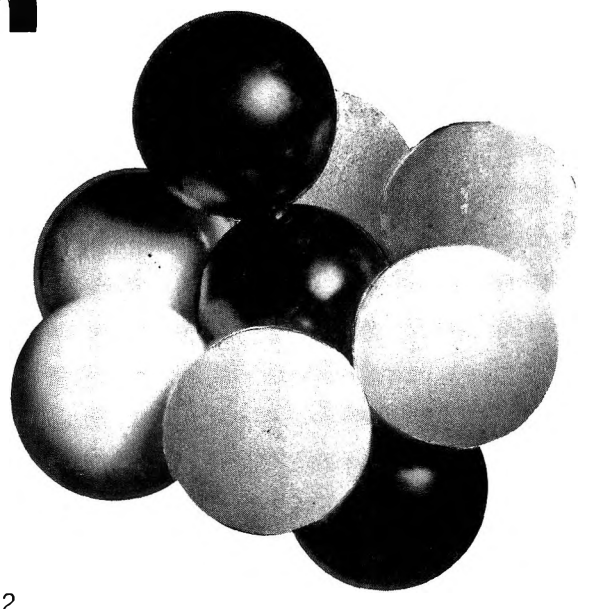
Page 3386. In last line of abstract "phenylphosphorine" should be "phenylphosphine."

Elliot Block and Robert Stevenson: Lignan Lactones. Synthesis of (±)-Collinuson and Justicidin B.

Page 3453. Column 1, first line of title. "(≡)" should be "(±)." Paragraph 1, line 8. "(≡)" should be "(±)."

Page 3454. Column 1, fifth line from bottom. "(≡)" should be "(±)".

Molecular Sieve Zeolites



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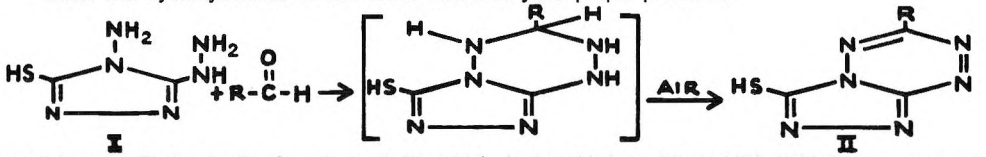

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(1) R. G. Dickinson and N. W. Jacobsen, Chem. Comm. 1719 (1970).

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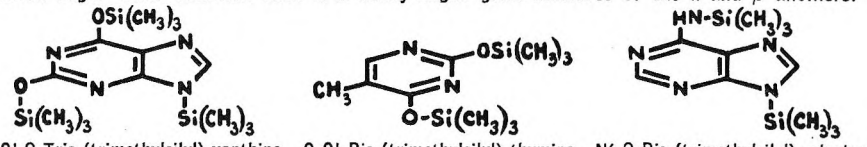

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1. a. Takuzo Nishimura, Bunji Shimizu, and Issei Iwai (Sankyo Co. Ltd., Tokyo), Chem. Pharm. Bull. Tokyo, **11** (11) 1470-7 (1963).
   b. Takuzo Nishimura and Issei Iwai, ibid., **12** (3), 352-6 (1964).
2. H. Vorbrüggen, P. Strehlke and G. Schulz, Angew. Chem. internat. Edit., **8**, 976 (1969).
3. U. Niedballa and H. Vorbrüggen, ibid., **9**, 461 (1970).

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