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THE JOURNAL OF Organic Chemistry®

VOLUME 37, NUMBER 17

AUGUST 25, 1972

The Synthesis and Solvolysis of 1-Phenylethyl Disubstituted Phosphinates[1]

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Received January 25, 1972

A series of 1-phenylethyl esters of phosphinic acids has been prepared and their mode of solvolysis studied. Correlation of the rate constants for the solvolysis of 1-arylethyl diphenylphosphinates in 80% ethanol–water at 75° with σ^+ constants gave a ρ of -5.10, demonstrating that alkyl–oxygen fission occurs. This value is compared with the value obtained from other 1-arylethyl esters and chlorides. The rate data for the solvolysis of 1-phenylethyl esters: diphenylphosphinate (1), phenylphosphinate (2), methylphenylphosphinate (3), bis(*m*-nitrophenyl)phosphinate (4), diisopropylphosphinate (5), and dimethylphosphinate (6) are compared to the rates of other 1-phenylethyl esters and halides under the same conditions. Products from the solvolysis of 2 are compared to the products obtained from 1-phenylethyl chloride (7) under the same conditions (80% ethanol–water, 75°). The solvolysis of 5 showed an acid-catalyzed component. The products from the solvolysis of 1, 2, and 5 in 25% ethanol–water at 75° were 3% styrene, 12% 1-phenylethyl ethyl ether, and 85% 1-phenylethanol, which agrees well with the conclusion that a common carbonium ion is formed in each case and forms products independent of the phosphinate from which it originated.

Although there are a large number of leaving groups in solvolysis reactions, there has been little attention focused on the development of leaving groups whose reactivity is intermediate between *p*-nitrobenzoates (PNB) and chlorides. In measuring the rates of a series of compounds undergoing solvolysis there may be a tremendous range of reactivity and it would be very desirable to have a reasonably spaced range of reactivity of leaving groups available. Gaps in the present series are conveniently filled by phosphinate esters.

In order to investigate the relative rates of solvolysis of phosphinate leaving groups with respect to other leaving groups, various esters of 1-phenylethanol were synthesized. This system was chosen so that the solvolytic reactivity could be studied under mild conditions. The literature also contains abundant rate data on a variety of 1-phenylethyl chlorides, bromides, nitrates, acetates, tosylates, and *p*-nitrobenzoates which can be compared to the solvolysis rates for the phosphinates.

Correlation of the rates of solvolysis of the 1-arylethyl diphenylphosphinates with the σ^+ electrophilic substituent constants of Brown and Okamoto[2] provide the desired evidence to demonstrate alkyl–oxygen fission.

Results and Discussion

The 1-arylethyl esters of diphenylphosphinic acid were prepared by the reaction of chlorodiphenylphosphine with the appropriate alcohol followed by oxidation of the phosphorus from the trivalent to the pentavalent state. The substituent groups in the alcohol moiety were *p*-methyl, *p*-chloro, *m*-chloro, and *p*-nitro. The rates of solvolysis of these esters are presented in Table I. The fact that the rates of formation of the phosphinic acid showed good first-order kinetics and that the rates of solvolysis correlate very well with σ^+ with a ρ value of -5.10 substantiate the premise that alkyl–oxygen fission with formation of a carbonium ion is occurring.

The values of ρ obtained for other 1-phenylethyl systems are presented in Table II. The large negative ρ values indicate that a substantial positive charge is formed in the transition state of each of the solvolysis reactions. The large negative ρ value for substituted 1-phenylethyl chlorides agrees well with the conclusion drawn by Shiner[3] from deuterium isotope effects that the more reactive chlorides solvolyze by an SN1 mechanism with very little nucleophilic participation by solvent.

Based on the observation from Table II that even the very slow solvolysis of 1-phenylethyl acetates remains SN1 in mechanism, the various other phosphinates can be presumed to solvolyze by the same mechanism.

With two exceptions all the phosphinates studied showed excellent first-order behavior. The rate of hydrolysis of 1-phenylethyl phenylphosphinate (2) was found to be sensitive to the addition of base. Competing SN1 solvolysis and a basic hydrolysis mechanism have been identified in the reaction of 2;[4] a pH

(1) Supported in part by a grant from the National Science Foundation, GP-6133X.

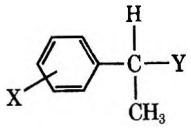
(2) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

(3) V. J. Shiner, Jr., W. E. Buddenbaum, B. L. Murr, and G. Lamaty, *J. Amer. Chem. Soc.*, **90**, 418 (1968).

(4) D. S. Noyce and J. A. Virgilio, *J. Org. Chem.*, **37**, 1052 (1972).

TABLE I

THE RATES OF SOLVOLYSIS OF 1-PHENYLETHYL ESTERS AND HALIDES IN ETHANOL–WATER MIXTURES (v/v)

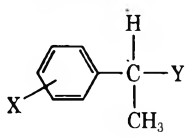


Registry no.	Run no.	X	Y	Solvent, % EtOH–H_2O	Temp, °C	k, sec^{-1}
34887-65-5	1	H	$O_2P(C_6H_5)_2$	80	75.0	8.32×10^{-6}
	2	H	$O_2P(C_6H_5)_2$	80	90.0	4.83×10^{-5}
	3	H	$O_2P(C_6H_5)_2$	30	75.0	3.32×10^{-4}
34887-66-6	4	p-CH_3	$O_2P(C_6H_5)_2$	80	75.0	3.71×10^{-4}
34887-67-7	5	p-Cl	$O_2P(C_6H_5)_2$	80	75.0	4.93×10^{-6}
34887-68-8	6	m-Cl	$O_2P(C_6H_5)_2$	30	75.0	6.21×10^{-6}
	7	m-Cl	$O_2P(C_6H_5)_2$	50	75.0	1.52×10^{-6}
	8	m-Cl	$O_2P(C_6H_5)_2$	80	75.0	1.04×10^{-7} [a,b]
34887-69-9	9	p-NO_2	$O_2P(C_6H_5)_2$	80	110.0	Very slow
33521-92-5	10	H	$O_2P(H)C_6H_5$	80	75.0	5.73×10^{-5}
34887-71-3	11	H	$O_2P(C_6H_4$-m-$NO_2)_2$	80	75.0	1.52×10^{-3}
34887-72-4	12	H	$O_2P(CH_3)C_6H_5$	80	75.0	3.08×10^{-6}
34887-73-5	13	H	$O_2P(CH_3)_2$	80	75.0	1.03×10^{-6}
	14	H	$O_2P(CH_3)_2$	0	75.0	2.24×10^{-4} [c]
34887-74-6	15	H	$O_2P[CH(CH_3)_2]^2$	0	75.0	4.24×10^{-5} [d]
	16	H	$O_2P[CH(CH_3)_2]_2$	0	75.0	8.63×10^{-5} [e]
	17	H	$O_2P[CH(CH_3)_2]_2$	10	75.0	6.27×10^{-5} [e]
	18	H	$O_2P[CH(CH_3)_2]_2$	25	75.0	1.50×10^{-5} [e]
	19	H	$O_2P[CH(CH_3)_2]_2$	40	75.0	9.39×10^{-6} [e]
	20	H	$O_2P[CH(CH_3)_2]_2$	50	75.0	1.24×10^{-6} [e]
	21	H	$O_2P[CH(CH_3)_2]_2$	80	75.0	2.3×10^{-8} [a,f]
1524-12-5	22	H	O_2CCF_3	80	75.0	5.54×10^{-3} [d]
672-65-1	23	H	Cl	80	75.0	2.20×10^{-3} [d]
	24	H	Cl	30	25.0	4.90×10^{-3} [g]
2362-36-9	25	p-CH_3	Cl	95	25.0	3.82×10^{-5} [h]
	26	p-CH_3	Cl	80	25.0	5.89×10^{-4} [h]
	27	p-CH_3	Cl	60	25.0	6.30×10^{-3}
	28	p-CH_3	Cl	30	25.0	4.01×10^{-1} [a,i]
20001-65-4	29	p-Cl	Cl	30	25.0	5.82×10^{-4} [d]
34887-78-0	30	m-Cl	Cl	30	45.0	8.82×10^{-5} [d]
	31	m-Cl	Cl	30	75.0	3.30×10^{-3} [d]
	32	m-Cl	Cl	30	25.0	5.34×10^{-6} [j]

[a] Calculated from previous data using the Grunwald–Winstein correlation. [b] $m = 0.58$. [c] Measured at constant pH (7.0). [d] Measured at constant pH (7.5). [e] This rate constant is slightly too fast due to acid catalysis. [f] $m = 1.0$. [g] A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, 79, 1597 (1957). [h] Reference 3. [i] $m = 0.91$. [j] Calculated from previous data, $E_a = 26.5$.

TABLE II

THE VALUE OF ρ FOR THE SOLVOLYSIS OF 1-PHENYLETHYL ESTERS AND HALIDES



Y	Solvent	Temp, °C	ρ
$O_2P(C_6H_5)_2$	80% EtOH–H_2O	75.0	−5.10
$O_2P(H)C_6H_5$	30% EtOH–H_2O	45.0	−4.25
Cl	30% EtOH–H_2O	25.0	−6.89
O_2CCH_3[b]	30% EtOH–H_2O	25.0	−5.96[a]

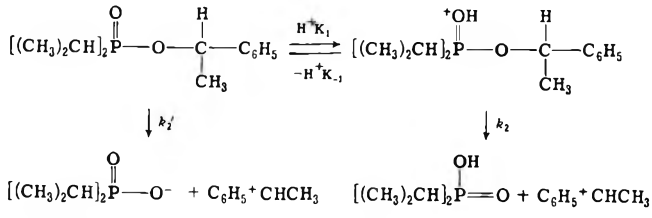
[a] E. A. Hill, M. L. Gross, M. Stasiewicz, and M. Manion, *J. Amer. Chem. Soc.*, 91, 7381 (1969). [b] Registry number: 93-92-5.

study has demonstrated that in acidic solution the predominant mechanism is SN1 while in basic solution (above a pH of 9) the predominant mechanism is attack of hydroxide ion at phosphorus.

The solvolysis of **5** at a constant pH of 7.5 follows good first-order kinetics. In unbuffered solutions, the rate of solvolysis of **5** is not strictly first order but shows a weak autocatalytic component. The incursion of an acid-catalyzed path for **5** was not completely unexpected. In a homologous series of phosphinates in which the alkyl group is varied, the basicity of the phosphoryl oxygen should increase as the inductive effect of the alkyl groups increase. Thus in **5** the basicity of the phosphoryl oxygen has been increased by the two isopropyl groups to a point where it will be more readily protonated in acidic media.

The solvolytic reaction of **5** can be represented by Scheme I.

SCHEME I



The rate expression for this scheme can be expressed by eq 1.

$$\text{Rate} = k_2K[R_2P(O)OR][H^+] + k_2'[R_2P(O)OR] \quad (1)$$

Since one of the kinetic runs was carried out at the constant pH of 7.5, the value of k_2' in water at 75° was determined to be 4.24×10^{-5} sec^{-1}. The value of k_2K was calculated from the rate of reaction at 60% completion to approximately equal 1.7×10^{-1}.

In view of the acid-catalyzed component observed for **5**, the products from the solvolysis of 1-phenylethyl diphenylphosphinate (**1**), of **2**, of **5**, and of 1-phenylethyl chloride (**7**) were analyzed to ensure that **5** was not solvolyzing by an abnormal mechanism. The Sn1 solvolysis products for **2** in 80% ethanol–water at 75° consist of 60% 1-phenylethyl ethyl ether and 40% 1-phenylethanol, in close correspondence to the products observed for **7** under the same reaction conditions (53% ether and 47% alcohol). The products of the solvolysis of **5** in 25% ethanol–water at 75° were compared to the products obtained from **1** and **2**, which solvolyze by a Sn1 mechanism under these conditions. The products from the solvolysis of **1**, **2**, and **5** were 3% styrene, 12% 1-phenylethyl ethyl ether, and 85% 1-phenylethanol. This agrees well with the conclusion that a common carbonium ion is formed in each case and forms products independent of the phosphinate from which it originated. Since the leaving group in the case of **5** is to some extent diisopropylphosphinic acid rather than the anion, the product distribution is not very sensitive to the change in charge type of the leaving group.

Several of the phosphinate esters, 1-phenylethyl methylphenylphosphinate (**3**) and **2**, are mixtures of diastereoisomers. However, a comparison of the nmr spectrum of the initial phosphinate and the phosphinate after 50% reaction for **2** showed that, within experimental accuracy, the ratio of diastereoisomers was unchanged. This implies that the two diastereoisomers are reacting at the same rate or that an equilibrium amount (through possible equilibrium of the trivalent species) is maintained.

Table III lists the relative rates of a large variety of leaving groups obtained from the solvolysis of the 1-phenylethyl system. Estimated rates are clearly labeled and should be used with caution, since they are derived from other systems and involve substantial extrapolation. Table III shows that the availability of leaving groups is quite diverse and extends over a range of reactivity of 10.[14]

As Table III shows, the phosphinate leaving groups are important in that they provide a graded reactivity series between the *p*-nitrobenzoate and chloride leaving group. In terms of availability, the diphenyl-, monophenyl-, and methylphenylphosphinates are easily prepared in high yield,[4] using dicyclohexylcarbodiimide.

There have been a number of studies on the rates of solvolysis of other phosphinate esters.[5-9] However, conclusive mechanism studies are often incomplete. In the homologous series of esters which have been studied, the compounds that solvolyze by an Sn1 mechanism can be easily detected, for they have an unusually rapid rate and a lower (less negative) entropy value. By these criteria *tert*-butyl ethylphosphinate, *sec*-butyl bis(chloromethyl)phosphinate,[6] and allyl bis(chloromethyl)phosphinate[7] definitely solvolyze by an Sn1 mechanism. The substitution of two chloromethyl groups in phosphinates promotes Sn1 reactions by making the phosphinate leaving group a much weaker base.

Further evidence for carbonium ion formation in heterolysis is shown in the very recent studies by Haake and Diebert[10] on pyrolysis of phosphinate esters.

Table III

The Relative Rates of Solvolysis of 1-Phenylethyl Esters and Halides in 80% Ethanol–Water at 75°

$C_6H_5CH(CH_3)X$ X =	k, sec^{-1}	Relative rate	Footnotes
CH_3COO	3.1×10^{-9}	1.4×10^{-6}	*a*
p-$NO_2C_6H_4COO$	1.2×10^{-8}	5.5×10^{-6}	*b*
F	2×10^{-8}	9×10^{-6}	*c*
$[(CH_3)_2CH]_2POO$	2.3×10^{-8}	1.0×10^{-5}	This work
$(CH_3)_2POO$	1.03×10^{-6}	4.7×10^{-4}	This work
$C_6H_5(CH_3)POO$	3.08×10^{-6}	1.4×10^{-3}	This work
$(C_6H_5)_2POO$	8.32×10^{-6}	3.8×10^{-3}	This work
$C_6H_5(H)POO$	5.73×10^{-5}	2.6×10^{-2}	This work
(m-$NO_2C_6H_4)_2POO$	1.52×10^{-3}	6.9×10^{-1}	This work
Cl	2.20×10^{-3}	1.0	This work
CF_3COO	5.54×10^{-3}	2.5	This work
O_2NO	1.59×10^{-2}	7.2	*d*
Br	3.13×10^{-2}	14	*e*
I	2×10^{-1}	91	*b*
2,4,6-$(NO_2)_3C_6H_2O$	1.2	5.5×10^{2}	*f*
Tetra(1-phenylethyl)pyrophosphate	2.0	9.1×10^{2}	*g*
$CH_3S(O)_2O$	6.7×10	3.0×10^{4}	*h*
p-$CH_3C_6H_4S(O)_2O$	8.1×10	3.7×10^{4}	*i*
p-$NO_2C_6H_4S(O)_2O$	9.7×10^{2}	4.4×10^{5}	*j*
$CF_3S(O)_2O$	3.0×10^{5}	1.4×10^{8}	*k*

[a] Estimated from the ratio of rates for 1-phenylethyl acetate [E. A. Hill, *et al.*, *J. Amer. Chem. Soc.*, **91**, 7381 (1969)] and 1-phenylethyl phenylphosphinate in 30% ethanol-water and the rate of 1-phenylethyl phenylphosphinate in 80% ethanol-water. [b] Estimated from data for 1-*p*-anisylethyl *p*-nitrobenzoate in 70% acetone-water [H. L. Goering, R. G. Briody, and G. Sandrock, *J. Amer. Chem. Soc.*, **92**, 7401 (1970)] and in 80% ethanol-water [D. S. Noyce and G. V. Kaiser, *J. Org. Chem.*, **34**, 1008 (1969)]. [c] Estimated rate obtained from A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 82. A Cl/F ratio of 10^5 and a Cl/I ratio of 10^{-2} were used to obtain the specific rates. [d] Calculated from data of Baker and Heggs [J. W. Baker and T. G. Heggs, *J. Chem. Soc.*, 616 (1955)]. [e] Calculated from data at other temperatures [A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, **79**, 1602 (1957)]. [f] Estimated from data of M. L. Sinnott and M. C. Whiting, *Chem. Commun.*, 1917 (1968), using a tosylate/picrate ratio of 8.5. [g] Estimated from data of G. O. Dudek and F. H. Westheimer, *J. Amer. Chem. Soc.*, **81**, 2641 (1959); 10^3 benzyl. [h] Estimated from data of P. K. Crossland, S. R. Hartshorn, and V. J. Shiner, Jr., Abstracts, 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 29, 1971, #40, using a ratio of 3×10^4 for mesylate/Cl ratio. [i] Estimated from data of H. M. R. Hoffman, *J. Chem. Soc.*, 6753, 6762 (1965). [j] Estimated from typical tosylate/nosylate ratios. [k] Estimated from data of T. M. Su, N. F. Sliwinski, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 5386 (1969), using a OTF/OTOS ratio of 3×10^4.

(5) V. E. Bel'skii, G. Z. Motygullin, V. N. Eliseenkov, and N. I. Rizpolozhenskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 565 (1970); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 520 (1970).

(6) V. E. Bel'skii, M. V. Efremova, I. M. Shermergorn, and A. N. Pudovik, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 307 (1969); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 263 (1969).

(7) V. E. Bel'skii, M. V. Efremova, and Z. V. Lustina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1293 (1969), *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1192 (1969).

(8) V. E. Bel'skii, M. V. Efremova, and I. M. Shermergorn, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1654 (1966); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1597 (1966).

(9) V. E. Bel'skii, M. V. Efremova, and A. R. Panteleeva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2278 (1968); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 2154 (1968).

(10) P. Haake and C. E. Diebert, *J. Amer. Chem. Soc.*, **93**, 6931 (1971).

They found that *tert*-butyl diphenylphosphinate suffered pyrolysis 7000 times more rapidly than isopropyl diphenylphosphinate, and suggested a carbonium ion intermediate for the pyrolysis.

Thus, carbon–oxygen heterolysis is a reasonably prevalent mode of reaction for phosphinate esters, particularly in structural situations where the alkyl moiety provides a modest stabilization for the carbonium ion.

Experimental Section[11]

Materials.—Chlorodiphenylphosphine, dichlorophenylphosphine, phenylphosphinic acid, and 1-phenylethanol are commercially available. The appropriately substituted 1-phenylethanols were synthesized from the corresponding acetophenone by sodium borohydride reduction. Substituted 1-phenylethyl chlorides were obtained from the corresponding alcohol by reaction with thionyl chloride or phosphorus chlorides.

1-Phenylethyl Diphenylphosphinate (1).—To a stirred solution of 5.0 g (0.023 mol) of chlorodiphenylphosphine (Aldrich) and pyridine (1.8 g, 0.023 mol) in 300 ml of anhydrous ether was added 2.8 g (0.023 mol) of 1-phenylethanol (Aldrich). After refluxing for 1 hr, the solution was allowed to cool for 30 min and 10.0 g (0.023 mol) of lead tetraacetate (Matheson Coleman and Bell) was added in small portions. The mixture was refluxed for 1 hr and after cooling to room temperature the solution was filtered. The filtrate was washed with 2 × 200 ml of water and the resulting colorless oil was crystallized from mixed hexanes–ether, giving 3.50 g (49%) of ester 1, nmr ($CDCl_3$) δ 7.5 (m, 15), 5.5 (2 q, 1), and 1.65 (d, 3).

Anal. Calcd for $C_{20}H_{19}O_2P$: C, 74.60; H, 5.90; P, 9.62. Found: C, 74.46; H, 5.94; P, 9.58.

1-(*p*-Methylphenyl)ethyl Diphenylphospinate (8).—Ester 8 was synthesized by the same method as 1 using 1-(*p*-methylphenyl)ethanol. The ester was isolated as a colorless oil after chromatography, nmr ($CDCl_3$) δ 7.6 (m, 10), 7.1 (s, 4), 5.55 and 5.41 (2 q, 1), 2.23 (s, 3), 1.60 (d, 3).

Anal. Calcd for $C_{21}H_{21}O_2P$: C, 74.99; H, 6.29; P, 9.21. Found: C, 74.84; H, 6.15; P, 9.06.

1-(*p*-Chlorophenyl)ethyl Diphenylphospinate (9).—Similarly, from 1-(*p*-chlorophenyl)ethanol and chlorodiphenylphosphine, ester 9 was obtained in 40% yield, mp 68.5–70°, nmr ($CDCl_3$) δ 7.6 (m, 10), 7.2 (s, 4), 5.57 and 5.42 (2 q, 1), 1.60 (d, 3).

Anal. Calcd for $C_{20}H_{18}ClO_2P$: C, 67.33; H, 5.08; Cl, 9.94; P, 8.68. Found: C, 67.14; H, 4.95; Cl, 9.90; P, 8.53.

1-(*m*-Chlorophenyl)ethyl Diphenylphosphinate (10).—*n*-Butyllithium (12.4 ml, 1.6 *M* in *n*-hexane, 0.0178 mol, Foote Mineral) was added dropwise to a stirred solution of 1-(*m*-chlorophenyl)-ethanol (3.0 g, 0.019 mol) in 200 ml of anhydrous diethyl ether under nitrogen in a Dry Ice–acetone bath. After the addition was complete, chlorodiphenylphosphine (4.32 g, 0.0191 mol) was added dropwise and the solution was warmed to room temperature. After 30 min the solution was concentrated and the slurry was dissolved in 200 ml of ether. The solution was washed with a solution of 10 ml of hydrogen peroxide (30%) in 200 ml of water, followed by 2 × 200 ml of water. The ether extract was dried ($MgSO_4$), filtered, and concentrated to yield 6.63 g (97%) of ester 10, nmr ($CDCl_3$) δ 7.5 (m, 14), 5.61 and 5.46 (2 q, 1), and 1.32 (d, 3).

Anal. Calcd for $C_{20}H_{18}ClO_2P$: C, 67.33; H, 5.08; Cl, 9.94; P, 8.68. Found: C, 67.24; H, 4.98; Cl, 9.89; P, 8.58.

1-(*p*-Nitrophenyl)ethyl Diphenylphosphinate (11).—Ester 11 was synthesized by the same method as 1 using 1-(*p*-nitrophenyl)-ethanol. The resulting colorless oil was purified by crystallization from mixed hexanes to yield 58% of ester 11, mp 101.5–102.5°, nmr ($CDCl_3$) δ 7.7 (m, 14), 5.70 and 5.50 (2 q, 1), and 1.65 (d, 3).

Anal. Calcd for $C_{20}H_{18}NO_4P$: C, 65.40; H, 4.94; N, 3.81; P, 8.43. Found: C, 65.15; H, 4.98; N, 3.97; P, 8.40.

Bis(*m*-nitrophenyl)phosphinic Acid (12).—The method of Dorken[12] was used with modifications. Chlorodiphenylphosphine (10 g, 0.046 mol) was added very cautiously to 20 ml of concentrated sulfuric acid at 0°. After the vigorous oxidation had subsided, 20 ml of 90% nitric acid was added dropwise over a period of 30 min. After stirring at room temperature for 2 hr the solution was poured onto an ice–water mixture. The white solid was filtered and dried to yield 4.5 g (45%) of bis(*m*-nitrophenyl)-phosphinic acid, mp 260–270°. Recrystallization from glacial acetic acid yielded 4.0 g of bis(*m*-nitrophenyl)phosphinic acid, mp 268–270° (lit.[12,13] mp 268° and 271–273°).

1-Phenylethyl Bis(*m*-nitrophenyl)phosphinate (13).—A solution of bis(*m*-nitrophenyl)phosphinic acid (5.0 g, 0.016 mol), *N*,*N*′-dicyclohexylcarbodiimide (3.3 g, 0.016 mol), and 1-phenylethanol (1.95 g, 0.016 mol) in 200 ml of anhydrous benzene was refluxed for 18 hr. After the solution had cooled to room temperature, the *N*,*N*′-dicyclohexylurea was removed by filtration and the benzene was removed on a rotary evaporator. The colorless oil was dissolved in 100 ml of diethyl ether and a small amount of solid material was removed by filtration. The ether was removed on a rotary evaporator to yield 4.0 g (66%) of ester 13: mp 97–100°; nmr ($CDCl_3$) δ 7.7 (m, 8), 7.5 (m, 5), 5.65 (m, 1), and 1.75 (d, 3).

Anal. Calcd for $C_{20}H_{17}N_2O_6P$: C, 58.26; H, 4.15; N, 6.79; P, 7.52. Found: C, 58.37; H, 4.21; N, 6.83; P, 7.64.

1-Phenylethyl Phenylphosphinate (14)[4].—Ester 14 was synthesized in the same manner as ester 13, yield 99%.

Methylphenylphosphinyl Chloride.—The method of Mislow[14] was used without modification.

1-Phenylethyl Methylphenylphosphinate (15).—1-Phenylethanol (3.6 g, 0.029 mol), methylphenylphosphinyl chloride (5.0 g, 0.029 mol), and pyridine (2.4 g, 0.03 mol) were dissolved in 100 ml of dry diethyl ether and the solution was refluxed for 1 hr. After the solution cooled, the pyridine hydrochloride was removed by filtration and the ether was removed on a rotary evaporator. The resulting colorless oil was passed through a silica gel column first using mixed hexanes followed by a solution of 50% ether–mixed hexanes which eluted 3.5 g (45.5%) of 1-phenylethyl methylphenylphosphinate (15), nmr ($CDCl_3$) δ 7.5 (m, 10), 5.4 (m, 1), 1.5 (m, 6).

Anal. Calcd for $C_{15}H_{17}O_2P$: C, 69.22; H, 6.59; P, 11.90. Found: C, 69.39; H, 6.41; P, 11.99.

Tetramethyldiphosphine Disulfide.—The method of Pollart and Harwood[15] was used without modification.

Dimethylphosphinyl Chloride.—The method of Pollart and Harwood[15] was used with modifications. Tetramethyldiphosphine sulfide (31.5 g, 0.17 mol) was suspended in 500 ml of methylene chloride and thionyl chloride (71.4 g, 0.60 mol) was added dropwise over a period of 1 hr. After the addition was complete, the solution was stirred for 1 hr. The solution was filtered, concentrated, and distilled to yield 23.0 g (60%) of dimethylphosphinyl chloride: bp 95° (20 mm); mp 66–68°; highly hydroscopic solid (lit.[16] mp 66.8–68.4°, bp 202–204°); nmr (CCl_4) δ 2.08 (d, J_{CH_3P} = 14 Hz).

1-Phenylethyl Dimethylphosphinate (16).—To a stirred solution of 1-phenylethanol (6.23 g, 0.050 mol) in 200 ml of anhydrous diethyl ether under nitrogen in a Dry Ice–acetone bath was added dropwise over 15 min 32 ml of *n*-butyllithium (1.6 *M* in *n*-hexane, 0.10 mol, Foote Mineral). After the addition was complete, dimethylphosphinyl chloride (5.75 g, 0.051 mol) was added dropwise and the solution was stirred for 30 min. The solution was warmed to room temperature and the ether was removed on a rotary evaporator. The residue was dissolved in 100 ml of methylene chloride, the solution was filtered and concentrated, and the residual oil was passed through a silica gel column using mixed hexanes, 20% ether–mixed hexanes, 40% ether–mixed hexanes, 60% ether–mixed hexanes, 80% ether–mixed hexanes, ether, and finally 20% methylene chloride–ether, which eluted 1.8 g (18%) of ester 16, nmr (CCl_4) δ 7.37 (s, 5), 5.64 and 5.54 (2 q, 1), 1.83 (d, 3), 1.10 (d, 3, *J* = 14 Hz, PCH_3) and 1.10 (d, 3, *J* = 14 Hz, PCH_3). Ester 16 adhered to the column much more tenaciously than any of the previous phosphinates or the alkylaryl phosphinates.

(11) Melting points and boiling points are uncorrected. Routine infrared spectra were obtained using a Perkin-Elmer Infracord Model 137. Nmr spectra were obtained using a Varian A-60, T-60, or HA-100 instrument with tetramethylsilane as the internal standard. The elemental analyses were carried out by the Microanalytical Laboratory of the University of California at Berkeley.

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Diisopropylphosphine Oxide.—The method of Crofts and Kosolopoff[17] was used with modifications. Magnesium (97.2 g, 4.0 mol) was placed in 1500 ml of dry diethyl ether under nitrogen and isopropyl bromide (492.0 g, 4.0 mol) was added dropwise at such a rate as to maintain a constant reflux of ether. After the addition was complete and visible reaction had ceased, diethyl phosphonate (160.0 g, 1.16 mol, Aldrich) was added over a period of 4 hr. The mixture was stirred for 12 hr and then refluxed for 1 hr. After the addition of a saturated solution of ammonium chloride (500 ml), the ether layer was separated and the aqueous phase was extracted with 3 × 500 ml of methylene chloride. The combined extracts were dried ($MgSO_4$), filtered, and concentrated, and the colorless oil was distilled to yield 97.0 g (63%) of diisopropylphosphine oxide: bp 188° (30 mm) [lit.[18] bp 54–55° (1.5 mm)]; nmr ($CDCl_3$) δ 1.1 (m, 12), 2.0 (m, 2), and two triplets at 2.7 and 11.6 (total 1 H, J = 633 Hz, PH, and J = 3 Hz, PH, CH).

Diisopropylphosphinic Acid.—The method of Crofts and Kosolopoff[17] was used with modifications. Hydrogen peroxide (30%, 14 ml) was added cautiously with stirring to diisopropylphosphine oxide (10.0 g, 0.075 mol). Since the reaction was not very exothermic the solution was placed in an oil bath at 75° for 24 hr. The colorless oil was dissolved in 200 ml of diethyl ether, dried ($MgSO_4$), filtered, and concentrated to yield 9.7 g (87%) of diisopropylphosphinic acid: nmr ($CDCl_3$) δ 1.07 and 1.28 (2 d, 12, J = 16 Hz, PCH_3), 1.88 (m, 2), and 13.95 (s, 1). The acid was used without further purification.

Diisopropylphosphinyl Chloride. A.—Phosphorus pentachloride (13.5 g, 0.065 mol) was added in small portions to a solution of diisopropylphosphinic acid (9.7 g, 0.065 mol) in 200 ml of methylene chloride. After the addition was complete, the solution was stirred for 1 hr and the solution was concentrated. The yellow oil was distilled to yield 9.0 g (83%) of diisopropylphosphinyl chloride: bp 65° (0.2 mm) [lit.[19] bp 77° (3 mm)]; nmr ($CDCl_3$) δ 1.14 and 1.45 (2 d, 12, showing some fine splitting of about 2 cycles, J = 7 Hz, CH_3CH and J = 18 Hz, CH_3P), and 2.20 (m, 2).

B.—Diisopropylphosphine oxide (10.0 g, 0.075 mol) was dissolved in 200 ml of diethyl ether, and thionyl chloride (25.0 g, 0.15 mol) was added dropwise (caution: a very vigorous reaction occurs). After the addition was complete, the solution was stirred for 5 min and the ether and excess thionyl chloride were removed on a rotary evaporator. The yellow oil was distilled to yield 10.4 g (84%) of diisopropylphosphinyl chloride. The product is identical with that in part A.

1-Phenylethyl Diisopropylphosphinate (17).—To a stirred solution of 1-phenylethanol (2.20 g, 0.0178 mol) in 200 ml of anhydrous diethyl ether under nitrogen in a Dry Ice–acetone bath was added dropwise over 5 min 11 ml of *n*-butyllithium (1.6 *M* in *n*-hexane, 0.0178 mol, Foote Mineral). After the addition was complete, diisopropylphosphinyl chloride (3.0 g, 0.0178 mol) was added dropwise and the solution was warmed to room temperature. The solution was concentrated, and the slurry was dissolved in ether. The solution was filtered and concentrated, and the residual oil (4.0 g, 90% yield) was purified by chromatography on a silica gel column using mixed hexanes, 10% ether–mixed hexanes, 20% ether–mixed hexanes, 10% ether–mixed hexanes, 50% ether–mixed hexanes, 60% ether–mixed hexanes, 80% ether–mixed hexanes, ether, 10% methylene chloride–ether, and finally 20% methylene chloride–ether, which eluted 1.2 g (27%) of ester 17, nmr ($CDCl_3$) δ 7.3 (s, 5), 5.55 (m, 1), 1.8 (m, 2), and 1.2 (m, 15). The methyl region was resolved on the HA-100 nmr ($CDCl_3$) of methyl region δ 1.23, 1.07, 0.94, and 0.78 (4 d, 12) and 1.52 (d, 3).

Anal. Calcd for $C_{14}H_{23}O_2P$: C, 66.12; H, 9.12; P, 12.19. Found: C, 65.94; H, 9.10; P, 12.04.

1-Phenylethyl Trifluoroacetate (18).—A solution of trifluoroacetic anhydride (21.0 g, 0.10 mol) in 100 ml of diethyl ether was added dropwise over a period of 1 hr to a solution of pyridine (7.9 g, 0.10 mol) and 1-phenylethanol (12.2 g, 0.10 mol) in 100 ml of ether. The reaction mixture was maintained at 0° by an ice–water bath. After the addition was complete and the solution had warmed to room temperature, the pyridinium trifluoroacetate was removed by filtration, and the ether was removed on a rotary evaporator. The clear oil was distilled to yield 16 g (78%) of ester 18: bp 32° (0.5 mm); nmr ($CDCl_3$) δ 1.60 (d, 3), 5.99 (q, 1), and 7.32 (s, 5).

Anal. Calcd for $C_{10}H_9F_3O_2$: C, 55.04; H, 4.17. Found: C, 54.98; H, 4.36.

Kinetic Methods.—The procedures for the solvolysis rate measurements at nonconstant pH have been described.[20]

For kinetic measurements at constant pH the kinetic samples were prepared by weighing 0.0006 mol of phosphinate ester into a 50-ml vessel. To the vessel was added 50 ml of aqueous ethanol, and the entire vessel was suspended in the constant-temperature bath. If the run was unusually fast, the solvent was equilibrated to the appropriate temperature and the phosphinate in several milliliters of solvent was added. The acid produced was monitored by a pH-Stat (Radiometer Corp.) which consisted of a TTT 1c automatic titrator, a ABU 1c autoburette (with a 2.5 ml burette), a TTA 3c titrator assembly, and a 2c recorder.

The solution was maintained at the appropriate pH by the addition of 0.30 *M* potassium hydroxide in aqueous ethanol.

Product Analysis.—The analysis of products was carried out according to the glpc procedure of Buckson and Smith,[21] who analyzed the ethanolysis products from phenyldimethylcarbinyl chloride and phenyldimethylcarbinyl *p*-nitrobenzoate.

The peaks were identified by comparing retention times to those of dichloromethane solutions of pure samples. The molar responses of 1-phenylethyl ethyl ether, 1-phenylethyl alcohol, and styrene relative to that of 1-phenylethyl chloride, a convenient standard, were determined in separate experiments. In separate experiments it was shown that the alcohol, ether, and styrene were stable under the reaction conditions for *ca.* 10 half-lives.

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Solvolysis of Cyclopropyl Halides. II. 2-Phenylcyclopropyl Bromides[1]

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cis- and *trans*-2-phenylcyclopropyl bromide and 2,2-diphenylcyclopropyl bromide have been prepared and solvolyzed in acetic acid. The sole product of solvolysis in each case is the corresponding ring-opened allylic acetate. The first-order rate constants and the activation parameters have been determined. The reaction is considered in terms of the effect of the leaving group on the ring-opening process.

The solvolyses of cyclopropyl derivatives proceed very slowly[3] with the product of solvolysis in all but a few cases[4] being the ring-opened allylic derivative resulting from cleavage of the 2,3 bond. Studies concerned with the effect of substituents have demonstrated that the reaction proceeds in a concerted manner with appreciable buildup of positive charge on the 2- and 3-carbon atoms.[5-8]

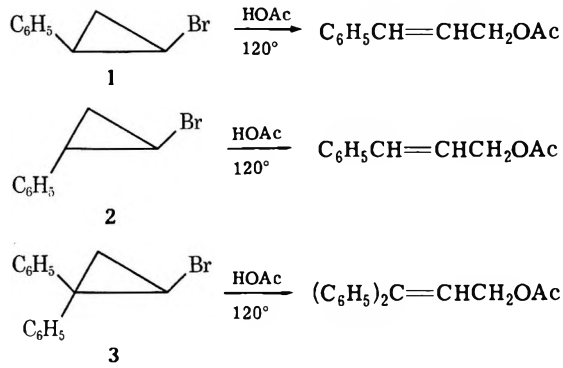
The geometrical requirements for the concerted ring-opening process necessitate rotation about the 1,2 and 1,3 bonds in order to approach the planar allylic cation. A stereochemical differentiation of the ring-opening processes may be made by considering the process as an electrocyclic transformation as proposed by Woodward and Hoffmann.[9] Experimental evidence of a kinetic nature[5-7] and by direct observation of products[10] has supported these predictions.

The cyclopropyl bromides reported here have been studied in order to evaluate the effect of the leaving group on the ring-opening process.

Results and Discussion

cis-2-Phenylcyclopropyl bromide (1) and *trans*-2-phenylcyclopropyl bromide (2) were prepared by the addition of dibromocarbene to styrene followed by partial reduction with tri-*n*-butyltin hydride. The resulting isomeric mixture of 1 and 2 was separated by preparative glpc. The structures were assigned on the basis of their nmr spectra. The chemical shift of the proton on the bromine-bearing carbon is 0.25 ppm higher field when it is located cis to the phenyl group.[5,6] 2,2-Diphenylcyclopropyl bromide (3) was prepared in a similar manner.

The solvolyses of the bromides 1, 2, and 3 were carried out in anhydrous acetic acid in the presence of a slight excess of sodium acetate. The sole product of solvolysis of 1 and 2 was shown to be the thermodynamically stable *trans*-cinnamyl acetate. The sole product from the solvolysis of 3 was shown to be α-phenylcinnamyl acetate.



Control experiments revealed no isomerization of the starting bromides during the course of the reaction.

The kinetics of solvolyses were followed by titration of remaining acetate ion. The rate constants in all cases were first order in starting cyclopropyl bromide concentration. The rate constants, relative rates at 119.4°, and activation parameters are listed in Table I.

TABLE I

KINETICS OF THE SOLVOLYSIS OF CYCLOPROPYL BROMIDES

Compd	Temp, °C	k_1, sec^{-1}	k_{rel}	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, eu
Cyclopropyl bromide	160.3	$6.92 \pm 0.20 \times 10^{-7}$			
cis-2-Phenylcyclopropyl bromide (1)	119.4	$1.46 \pm 0.06 \times 10^{-5}$	1.0	28.9	−9.9
	140.8	$4.58 \pm 0.08 \times 10^{-5}$			
	139.9	$9.64 \pm 0.04 \times 10^{-5}$			
trans-2-Phenylcyclopropyl bromide (2)	108.1	$2.15 \pm 0.04 \times 10^{-5}$			
	119.4	$6.31 \pm 0.39 \times 10^{-5}$	4.3	31.4	+1.7
	130.8	$2.33 \pm 0.38 \times 10^{-4}$			
2,2-Diphenylcyclopropyl bromide (3)	98.4	$2.33 \pm 0.02 \times 10^{-5}$			
	108.4	$6.65 \pm 0.11 \times 10^{-5}$			
	119.4	$1.99 \pm 0.10 \times 10^{-4}$	13.6	29.4	−1.0

The results of the bromide solvolysis along with the corresponding chloride[5] and tosylate[6] provide a series on which leaving group effects may be considered. Table II presents the relative rates as a function of leaving group.[11,12]

The effect of the stereochemistry of the leaving group is qualitatively in agreement with previously observed effects in other systems[5,6,8] and with the Woodward–Hoffmann proposals.[9] The solvolysis rates of cyclo-

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TABLE II

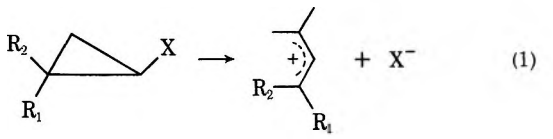
RELATIVE RATES OF SOLVOLYSIS OF α-PHENYL-SUBSTITUTED CYCLOPROPYL DERIVATIVES IN ANHYDROUS ACETIC ACID

Structure	Temp, °C	Chloride[a] k_{rel}	Bromide k_{rel}	Tosylate[b] k_{rel}
Cyclopropyl	160.3		1.0	29
cis-2-Phenylcyclopropyl	150.1	1.0	39	21
trans-2-Phenylcyclopropyl	150.1	1.0	42	57
2,2-Diphenylcyclopropyl	150.1	1.0	39	
Isopropyl[c]	100.1	1.0	25	13,000
2-Adamantyl[d]	25		1.0	16,000

[a] Reference 5. [b] Extrapolated from data in reference 6. [c] Extrapolated and estimated values based on data in reference 11. [d] Reference 12.

propyl halides are greatly enhanced by the presence of a β-phenyl substituent, but there is only a minor dependence of the rates on whether the substituent is cis or trans to the leaving group. The presence of a second phenyl group on the same carbon has little effect.

If the ring is opening by the predicted disrotatory mode shown in eq 1, the trans substituent (R_1) would



(1)

rotate outwardly and would provide conjugative stabilization for the developing positive charge. The substituent cis to the leaving group (R_2) would rotate inwardly with the possible buildup of steric strain as the substituent assumes a cis-allylic configuration.

The fact that the rates of the cis compounds (R_1 = H, R_2 = C_6H_5) are very close to the rates of the trans compounds (R_1 = C_6H_5, R_2 = H) suggests that the ground-state compression strain between the phenyl group and the leaving group cis to it nearly compensates for the strain resulting from the phenyl group moving inwardly.[13]

The importance of this ground-state strain in the acceleration of solvolysis rates gains support from a consideration of the relative solvolysis rates of the *cis*- and *trans*-2-phenylcyclopropyl series. The order for solvolysis of *trans*-2-phenylcyclopropyl derivatives is Cl < Br < OTs, which is the order of leaving-group abilities, whereas the order for *cis*-2-phenylcyclopropyl derivatives is Cl < OTs < Br. The departure of the cis series from the order of leaving group abilities suggests that the size of the leaving group exerts a controlling influence on the relative rates by raising the ground-state energies.

The effect of the leaving group on the solvolysis of aliphatic derivatives is generally very large. 2-Adamantyl derivatives, which have been suggested[12] as models for the pure solvolysis reaction, solvolyze with a tosylate/bromine ratio of 16,000. In contrast to the 2-adamantyl derivatives, the cyclopropyl derivatives listed in Table II show surprisingly small variations in solvolysis rates associated with changes in the leaving group. This behavior is typical of β-substituted cyclopropyl derivatives in which the β substituent is capable of stabilizing the developing positive charge.[8] The "normal" aliphatic dependence of solvolysis rate on leaving group is observed for cyclopropyl systems in which stabilization is provided by α substitution.[8] Thus, the small leaving group dependence for β-substituted cyclopropyl derivatives is associated with the site of stabilization, and not with any unusual characteristics of the bonding between the cyclopropyl ring and the leaving group.

An interpretation of the small effect associated with changes in the leaving group of β-substituted cyclopropyl derivatives requires a consideration of the internal nucleophilic assistance to the leaving group provided by the ring-opening process. The transition state involving appreciable ring opening with dispersal of positive charge to the 2 and 3 carbon atoms may be classed as a k_Δ solvolysis.[14] Isopropyl derivatives are strongly solvent assisted and may be classed as a k_s type solvolysis, while 2-adamantyl derivatives are assumed to undergo solvolysis without solvent assistance or anchimeric assistance and may be classed as a k_c type solvolysis. As can be seen in Table II, isopropyl derivatives have a much lower tosylate/bromide solvolysis ratio (470) than 2-adamantyl derivatives (16,000). The deemphasis of the role of the leaving group in the isopropyl solvolyses is attributed to the charge dispersal to solvent in the transition state. Since the cyclopropyl ring is not expected to undergo bimolecular nulceophilic attack by solvent, the even smaller effect of the leaving groups must be associated with the dispersal of charge provided by the anchimeric assistance of the ring opening.

A more detailed interpretation of the similarity in rates with different leaving groups is possible by postulating an inverse relationship between leaving group ability and the extent of ring opening in the transition state. A relatively poor leaving group such as chloride ion requires considerable internal assistance to its departure, resulting in greater ring opening in the transition state and a large enhancement in rate provided by the β-phenyl substituents. With the tosylate, a much better leaving group, the transition state may be occurring much earlier in the reaction sequence with less ring opening and correspondingly less phenyl stabilization.

In a recent consideration of steric effects in the solvolysis of β-methyl substituted cyclopropyl derivatives,[8] the idea of varied degrees of ring opening was rejected in favor of a constant amount of ring opening in the transition state with varied amounts of bond breaking between the ring and the leaving group. The transition states involving poorer leaving groups would develop considerably more charge on the ring. The inductive effect of the methyl groups can stabilize the additional charge and account for the greater effect of β-methyl substituents without additional ring opening. These conclusions are based on the fact that the solvolysis rate factor for the steric relief of strain between the cis methyl groups of *trans,trans*-2,3-dimethylcyclo-

(13) *cis*-Cinnamyl acetate is the predicted kinetic product from the solvolysis of **1**. Although only *trans*-cinnamyl acetate is observed, it is reasonable to assume that the cis product, if formed, would rapidly isomerize to the trans isomer through the allylic cation. See V. Buss, R. Gleiter, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **93**, 3927 (1971), and references cited therein. An earlier suggestion (ref 5) that the alternate mode of disrotatory ring opening may be operative also remains as a possibility for the solvolysis of **1**.

(14) P. v. R. Schleyer, J. L. Fry, L. K. M. Lam, and C. J. Lancelot, *ibid.*, **92**, 2542 (1970), and references cited therein.

propyl bromide and tosylate is nearly the same in both cases.

While this interpretation[8] explains the leaving group effects and the rate enhancements provided by β-methyl substituents, it does not exclude the initial interpretation set forth. It is reasonable to assume that the steric crowding between the cis methyl groups is greatly reduced in the early stages of ring opening, since both the 2,1,3 bond angle is increasing and the rotation about the 2,1 and 3,1 bonds moves the trans β substituents away from each other. If in fact the bulk of the strain is relieved very early in reaction sequence, then the actual transition states can occur with varied amounts of the ring opening at any subsequent time. The rates would not show any difference in the amount of strain relieved. Furthermore, in the case of β-phenyl substitution a constant amount of ring opening with the resulting variation in charge on the ring would be expected to emphasize the rate-retarding inductive effect of the phenyl groups. This would counteract the delocalizing stabilization and result in a greater dependence of rate on leaving group abilities. On this basis, a compensating amount of ring opening in the transition state to provide internal assistance for poorer leaving groups best accounts for the behavior of β-phenylcyclopropyl derivatives.

Experimental Section

1,1-Dibromo-2-phenylcyclopropane.—To a 3-l. flask equipped with condenser, stirrer, and addition funnel and containing 72.0 g (0.64 mol) of potassium *tert*-butoxide and 200 ml of petroleum ether (bp 60–71°) was added at 0° 183.7 g (1.76 mol) of styrene in 100 ml of petroleum ether. After thorough mixing, 162.4 g (0.65 mol) of bromoform was added over 3 hr. After 12 hr the reaction mixture was hydrolyzed with 200 ml of water and the organic layer was separated, washed with saturated sodium chloride solution, and dried ($MgSO_4$). On concentration and distillation, 50.9 g (28.9%) of 1,1-dibromo-2-phenylcyclopropane was obtained: bp 82–84° (0.55–0.60 mm); $n^{27}D$ 1.5960 [lit.[15] bp 97° (1.0 mm); $n^{22}D$ 1.5988)]; nmr (CCl_4) δ 1.66–2.10 (m, 2), 2.86 (m, 1), 7.34 (m, 5).

***cis*- and *trans*-2-Phenylcyclopropyl Bromide.**—To a 300-ml flask equipped with a stirrer, condenser, and an addition funnel, containing 151.9 g (0.547 mol) of 1,1-dibromo-2-phenylcyclopropane, was added 101.8 g (0.35 mol) of freshly distilled tri-*n*-butyltin hydride[16] over 90 min. The temperature was kept below 40° during the addition. Distillation afforded 53.0 g (77.2%) of the isomeric monobromides in the ratio of 1.4:1.0 (cis:trans), bp 46–52° (0.30–0.33 mm), $n^{27}D$ 1.5716 [lit.[17] bp 48–50 (0.15 mm), $n^{25}D$ 1.5696].

The isomers were separated by preparative glpc techniques to give greater than 98% isomeric purity. *cis*-2-Phenylcyclopropyl bromide (1) had bp 60–62° (0.8 mm); $n^{24}D$ 1.5688; nmr (CCl_4) δ 1.31 (2, assigned to methylene protons), 2.16 (1, benzylic proton), 3.14 (1, proton on bromine-bearing carbon), and 7.16 (5, aromatic protons).

Anal. Calcd for C_9H_9Br: C, 54.85; H, 4.60; Br, 40.55. Found (cis isomer): C, 54.59; H, 4.54; Br, 40.55.

trans-2-Phenylcyclopropyl bromide (2) had bp 56–57° (0.8 mm); $n^{24}D$ 1.5596; nmr (CCl_4) δ 1.30 (2, assigned to methylene protons), 2.20 (1, benzylic proton), 2.89 (1, proton on bromine-bearing carbon), 6.78–7.35 (5, aromatic protons).

Anal. Calcd for C_9H_9Br: C, 54.85; H, 4.60; Br, 40.55. Found (trans isomer): C, 54.79; H, 4.60; Br, 40.71.

1,1-Dibromo-2,2-diphenylcyclopropane.—In a procedure similar to that described above, dibromocarbene generated from 50.0 g (0.45 mol) of potassium *tert*-butoxide and 127.3 g (0.504 mol) of bromoform was added to 191.7 g (1.06 mol) of 1,1-diphenylethylene. On hydrolysis solid 1,1-dibromo-2,2-diphenylcyclopropane separated: 114.6 g (72.4%); mp 150–154° (lit.[18] mp 151–152°); nmr (CCl_4) δ 2.44 (s, 2), 7.34–7.80 (m, 10).

2,2-Diphenylcyclopropyl Bromide (3).—To a 300-ml flask equipped with a stirrer, a condenser, and an addition funnel, containing 35.2 g (0.1 mol) of 1,1-dibromo-2,2-diphenylcyclopropane in 200 ml of petroleum ether (bp 65–79°), was added 29.1 g (0.1 mol) of freshly distilled tri-*n*-butyltin hydride[12] over a period of 1 hr. The temperature was maintained at 20°. After concentration and recrystallization (petroleum ether), 8.0 g (30.0%) of 2,2-diphenylcyclopropyl bromide was obtained: mp 79.5–81.5°; nmr (CCl_4) δ 1.79 (d, 2), 3.61 (t, 1), 7.16–7.28 (m, 10).

Anal. Calcd for $C_{15}H_{13}Br$: C, 65.95; H, 4.80; Br, 29.26. Found: C, 65.82; H, 4.88; Br, 29.55.

Kinetic Procedure.—The general kinetic method employed was that reported by Young, *et al.*[19] The starting bromide concentration ranged from 0.01 *M* to 0.02 *M* in anhydrous acetic acid containing 0.04 *M* sodium acetate. Individual aliquots were sealed in ampoules and heated in a constant-temperature bath regulated to ±0.1°. The concentration of remaining acetate was determined by adding excess *p*-toluenesulfonic acid and back titrating with standard acetate using bromphenol blue as the indicator. The first-order rate constants were determined by the method of least squares.

Registry No.—**1**, 32523-76-5; **2**, 32523-77-6; **3**, 32812-52-5; cyclopropyl bromide, 4333-56-6.

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Halogen-Containing Substituents. II. The Methoxy System. Reactivity Parameters. Charge Distribution and Conformation of the Anisoles[1]

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The side-chain halogenated anisoles $ArOCH_2X$, $ArOCHX_2$, and $ArOCX_3$, with Ar = Ph, *m*-FPh, and *p*-FPh and X = F and Cl, were studied in order to elucidate both the substituent parameters of the side-chain groups and their electronic distributions; the latter were calculated by the CNDO/2 method. Analysis of the results gave an estimation of the apparent conformation of the anisoles with respect to the angle by which the halogenated methyl group is twisted out of the benzene plane.

In the first paper of this series,[1] a study of the electronic properties of halogen-containing methyl groups was presented. With these results established firmly, we are now reporting a study of halogen-containing (F, Cl) methoxy groups, where the primary objective was a systematic evaluation of their electronic properties in terms of the experimental parameters, σ_I and σ_R°. In addition, it was anticipated that comparison of the data for the methyl and methoxy series would provide valuable insight into the factors controlling the electronic behavior of the oxygen linking atom.

The most highly developed method for obtaining such information is Taft's treatment[2,3] of the Hammett equation, which involves examination of the appropriately substituted phenyl system. This treatment ascribes the effect of a substituent to the sum of two independent contributions resulting from inductive and resonance interactions. Such a separation, which has been examined critically by Ehrenson,[4] has found application, among others, in studies of the electronic transmission modes,[5] of the role of π(p-d) conjugation in suitable systems,[6] and recently in the correlation between the empirical and a theoretically calculated scale of resonance.[7]

In the course of determining the ground-state charge distributions for the anisoles by Pople's CNDO/2 method,[8] the question of the precise conformation of the substrates became important. A limited amount of data is available; for example, X-ray analysis has shown that *p*-dimethoxybenzene adopts a trans-planar conformation in the crystal[9] and dipole moment and Kerr constant measurements[10] have shown that in para-substituted anisoles the methyl group is apparently twisted out of the plane of the benzene ring. However, information concerning side-chain substituted anisoles is not available; hence, we have used the CNDO/2 results in conjunction with the experimental parameters to explore new methods for determining conformations in these molecules.

Results and Discussion

The series of anisoles $ArOCH_2X$, $ArOCHX_2$, $ArOCX_3$, with X = F, Cl, and Ar = Ph, *m*-FPh, *p*-FPh (excepting $ArOCH_2F$), were prepared as described in the Experimental Section. The substituent parameters of the groups were determined using both the ^{19}F nmr and the infrared methods. Thus, chemical shifts (δ) of the meta and para fluorines in the fluorophenyl compounds[2,3] were measured and are recorded in Table I together with the σ_I and σ_R° parameters derived from the equations

$$\delta_m = -7.1\sigma_I + 0.60 \quad (1)$$

$$\delta_p - \delta_m = -29.5\sigma_R^\circ \quad (2)$$

The resonance parameters were also obtained using Katritzky's[1,11] infrared method, in which the square root of the intensities of the 1600-cm^{-1} ring-stretching vibrations, $A^{1/2}$, of the appropriate monosubstituted benzene was calculated and the corresponding σ_R° value was derived from the equation

$$\sigma_R^\circ = 0.0079A^{1/2} - 0.027 \quad (3)$$

These values are also given in Table I. Good agreement between the ^{19}F and infrared methods is noteworthy and serves to increase confidence in their application and reliability.

All attempts to prepare the α-fluoroanisoles required for this study were unsuccessful; however, the substituent constants for OCH_2F were obtained by linear interpolation of the plots (not given) of σ_I or σ_R° values *vs.* the number of fluorine atoms in $OCH_{3-n}F_n$ (n = 0–3). In similar plots for the chlorine series, a slight damping effect reminiscent of that for the halogen-containing methyl series[1] was observed and, although this effect was less pronounced here, it is ratio-

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TABLE I

SCALES OF SUBSTITUENT EFFECTS DERIVED FROM ^{19}F NMR AND INFRARED MEASUREMENTS AND FROM MO CALCULATIONS

	^{19}F Nmr[a]				Ir[b]		MO[c]		
Substituent	δ_m	δ_p	σ_I	σ_R°	$A^{1/2}$	$\pm\sigma_R^\circ$	$\Delta q_\pi{}^4$	$\Sigma\Delta q_\pi$	m
OCH_3[d]	−1.05	11.45	0.29	−0.425	57.7	0.430	−396	−647	2
OCH_2F			0.37	−0.350		0.310	−320	−505	5
$OCHF_2$	−2.62	4.32	0.45	−0.269	32.1	0.227	−241	−403	9
OCF_3[e]	−3.20	2.21	0.53	−0.183	27.8	0.193[f]	−187	−383	12
OCH_2Cl	−2.28	7.36	0.41	−0.327	45.2	0.330	−301	−489	16
$OCHCl_2$	−2.95	3.98	0.49	−0.230	35.6	0.255	−211	−354	20
$OCCl_3$	−3.04	1.65	0.51	−0.165	27.5	0.195	−196	−309	21

[a] Shifts are given in parts per million relative to fluorobenzene (probable error ±0.07). Probable errors are ±0.01 in σ_I and ±0.004 in σ_R°. [b] σ_R° values derived from eq 3. [c] The excess π charge at the para carbon, $\Delta q_\pi{}^4$, and on the ring, $\Sigma\Delta q_\pi$, given in 10^{-4} electron, for the chosen conformation, taken from Table II. [d] ^{19}F nmr shifts from ref 2 and 3a. See also ref 3b. [e] σ_I = 0.55 (ref 2) and σ_R° = −0.18 (ref 3). [f] $\pm\sigma_R^\circ$ = 0.250 (ref 11b) is probably in error.

nalized as arising from important pairwise interactions[12] between the chlorine atoms.

The quantitative results given in Table I achieve the principal objective of this investigation. The general trends with increasing halogen substitution of the methoxy group, namely, a decrease in resonance donor capacity and an increase in the magnitude of the inductive effect, are observed. As it happened, the resonance and inductive parameters for this methoxy series are correlated by the simple equation

$$\sigma_I = \sigma_R^\circ + 0.72 \quad (4)$$

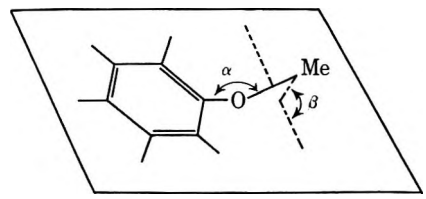
Other workers[13] have noted similar correlations for substituents containing oxygen as the linking atom. These results are analogous to those for Taft's "united-atom-like-first-row-pair donor" (UAFPD) theory[3a] and, although differing in behavior from that found for true UAFPD substituents, suggest that the oxygen atom is exerting the dominant influence in controlling the substituent parameters in the oxygen family. Both Taft[3] and Ehrenson[4] have analyzed this point in detail.

A comparison of the results for the methoxy (OY) with the corresponding methyl[1] (Y) series shows the inductive parameters to be linearly proportional according to the following equation. This result would

$$\sigma_I(OY) = 0.53\sigma_I(Y) + 0.32 \quad (5)$$

not be readily anticipated by an inductive theory based primarily on a direct electrostatic interaction between the substituent and a suitable probe (field effect[2]) but is more indicative of inductive transmission through the bonds with the oxygen atom attenuating, by a factor of approximately one-half, the effect of the halogen-containing methyl group. However, the complex nature of σ_I, as noted earlier,[1] obviates a more refined treatment at this time. No such simple relationship was found between the σ_R° values of the two series, for reasons developed in the following section.

Conformation of Halogenated Anisoles.—The position of a methoxy group relative to an attached benzene moiety is defined by the angles α (C_{Ar}–O–C_{Me}) and β (the angle by which the methyl group is twisted out of the benzene plane). For those anisoles whose geometry



has been discussed, angles of α are usually reported[9,14] around 118–120°. This value is close to that expected for an oxygen bonding *via* sp^2 hybridized orbitals to both carbon atoms, which places the oxygen p_z orbital in perfect location for resonance interaction with the ring,[15] and the degree of conjugation of this orbital with the ring is determined by β. However, molecular polarizability measurements have shown[10] that the angle β can vary within the range of possible values, from 0° in *p*-cyanoanisole to 90° in 2,4,6-tri-X-substituted anisoles (X = CH_3, Cl, Br). The twisting of the methyl group out of the benzene plane results therefore from the balance of the two opposing effects. The first is the electron demand by the aryl system, as evidenced by Figure 1, which was constructed from literature values[3a,10] and shows the approximate linear correlation between the angle β and the σ_R° of the substituent in para-substituted anisoles. This effect tends to place the OCH_3 group coplanar with the ring so as to maximize overlap of the π system with the p_z orbital of oxygen. The second and counteracting effect forces the methyl group out of the benzene plane and has been attributed[16] to steric repulsion between the ortho and side-chain substituents. Another contributing factor, not considered previously, is the repulsion between the oxygen lone pair and the benzene ring, which would be greatest and most destabilizing for an eclipsed conformation (β = 0°). The barrier to rotation for the methoxy group in anisole has been estimated[17] to be

(12) H. J. Bernstein, *J. Phys. Chem.*, **69**, 1550 (1965), and references cited therein. This model has been applied to ^{13}C nmr shifts for halogenated methanes [W. M. Litchman and D. M. Grant, *J. Amer. Chem. Soc.*, **90**, 1400 (1968)] and heats of formation of fluorocarbons [J. R. Lacher and H. A. Skinner, *J. Chem. Soc. A*, 1034 (1968)]. The precise nature of the interaction is unknown but it is probably a complex blend of various factors including steric and polarization contributions.

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(14) (a) C. Romers and B. Hespers, *Acta Crystallogr.*, **20**, 162 (1966); (b) J. Toussaint, *Bull. Soc. Roy. Sci. Liege*, **13**, 111 (1944).

(15) Relatively little discussion of the hybridization of oxygen appears in the literature. Ground-state oxygen $(2s)^2(2p_x)^2(2p_y)(2p_z)$ can undergo reorganization *without* electron promotion to $(sp^2)^2(p)^2(s^2p)^2$. Some justification for this type of hybridization based on MO theory is given by C. Trindle and O. Sinanoğlu, *J. Amer. Chem. Soc.*, **91**, 853 (1969).

(16) M. Horak, E. R. Lippincott, and R. Khanna, *Spectrochim. Acta, Part A*, **23**, 1111 (1967). In addition, references in this paper support the contention that 0° < β < 90°; however, others[17] have advocated a planar model, β = 0°.

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about 6 kcal/mol and also has been detected by other methods.[18]

The resonance donor properties of the halogen-containing anisoles are clearly related to their apparent conformation, and consequently an estimation of the angle β was required for each compound. A new approach to this problem was found in the application of the CNDO/2 method,[8] which calculates the electronic distribution in the compounds from their molecular geometry. Modified versions[19] of QCPE Computer Programs No. 91 and 141 were used for molecules containing first-row and second-row elements, respectively. Unfortunately, the lack of experimental dipole moment data for these compounds generally precluded their use as evidence supporting the accuracy of the calculations. As before,[1] the benzene ring was taken as a regular hexagon with C–C = 1.397 Å and C–H = 1.08 Å. For the substituent, values of C–H = 1.09 Å, C–F = 1.32 Å, and C–Cl = 1.76 Å were used throughout. In all cases, the phenyl C–O and the methyl C–O bonds were taken equal to 1.36 and 1.37 Å, respectively, and the angle α was 118° unless otherwise noted; the angle β was varied between 0° and 90° corresponding to the conformations m, which together with the calculated charge distributions are given in Tables II, III, and IV.

TABLE II

π CHARGE DENSITY ($\times 10^4$) ON THE RING CARBONS OF HALOGENATED ANISOLES FOR VARIOUS CONFORMATIONS[a]

Substituent	m	$\Delta q_\pi{}^1$	$\Delta q_\pi{}^2$	$\Delta q_\pi{}^3$	$\Delta q_\pi{}^4$	$\Delta q_\pi{}^5$	$\Delta q_\pi{}^6$	$\Sigma\Delta q_\pi$	α	β
OCH_3	1	482	−651	266	−404	250	−619	−676	118	0
	2	486	−636	262	−396	248	−611	−647	118	18
	3	478	−509	209	−325	209	−509	−447	118	90
OCH_2F	4	435	−637	269	−365	252	−581	−627	118	18
	5	424	−551	233	−320	231	−522	−505	118	56
	6	387	−497	198	−281	211	−441	−423	118	90
$OCHF_2$	7	350	−554	267	−321	233	−561	−586	118	18
	8	302	−429	206	−246	198	−446	−415	120	75
	9	302	−432	200	−241	200	−432	−403	118	90
	10	417	−585	256	−359	252	−608	−627	160	90
OCF_3	11	261	−529	274	−268	239	−526	−549	118	18
	12	298	−403	206	−187	206	−403	−383	118	90
	13	205	−407	211	−190	206	−412	−387	115	80
	14	321	−559	255	−303	255	−559	−590	160	90
OCH_2Cl	15	394	−578	258	−343	242	−582	−609	118	0
	16	393	−536	236	−301	233	−514	−489	118	45
	17	386	−518	225	−287	227	−488	−455	118	55
	18	379	−503	214	−274	220	−463	−427	118	65
	19	363	−489	198	−259	210	−421	−398	118	90
$OCHCl_2$	20	283	−410	197	−211	197	−410	−354	118	90
$OCCl_3$	21	227	−385	195	−176	195	−385	−329	118	90

[a] The substituent is attached to the 1 position. Each conformation m is defined by the angles α (C_{Ar}-O-C) and β (angle by which the group $CH_{3-n}X_n$ is twisted out of the benzene plane). The excess π charge is $1.0000 - \Delta q_\pi$ and the sum of these values over each ring position (1-6) is given by $\Sigma\Delta q_\pi$.

Although differences within a few degrees for the angle α undoubtedly occur depending on the molecule under examination, practical considerations prohibited taking them into account and hence restricted this study primarily to the results obtained from varying only β.

The CNDO/2 method has been applied previously to a representative set of substituents attached to a phenyl ring: two linear relationships *have been established*[1,7] between the σ_R° values for these substituents and the corresponding calculated values of either the excess π charge at the para carbon, $\Delta q_\pi{}^4$, or the total excess π charge, $\Sigma\Delta q_\pi$, in the phenyl system. These two relationships are given by the lines in Figures 2 and 3, respectively. A similar analysis of the CNDO/2 calculations performed on the side-chain halogenated anisoles gave data for the varying m conformations, which are plotted also in Figures 2 and 3. The important finding was that *one* conformation for each molecule existed, the results from which fitted best *both* of the original[1,7] lines simultaneously. Consequently, these results, which are summarized in Table I, were chosen to represent the apparent conformation of the appropriate anisole. It is emphasized here that the apparent conformation of the appropriate methoxy group refers to its time-averaged position, which de-

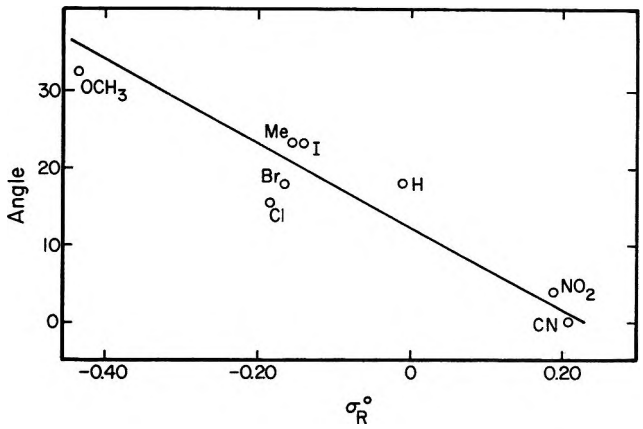

Figure 1.—Correlation between the angle β in para-substituted anisoles and the resonance parameter of the substituent.

TABLE III

σ CHARGE DENSITIES ($\times 10^4$) ON THE RING CARBONS AND HYDROGENS OF HALOGENATED ANISOLES IN VARIOUS CONFORMATIONS m[a]

Substituent Y	m	$\Delta q_\sigma{}^1$	$\Delta q_\sigma{}^2$	$\Delta q_\sigma{}^3$	$\Delta q_\sigma{}^4$	$\Delta q_\sigma{}^5$	$\Delta q_\sigma{}^6$	$\Sigma\Delta q_\sigma{}^C$	$\Sigma\Delta q^H$
OCH_3	1	1396	54	11	198	21	109	1789	1
	2	1393	41	12	194	20	103	1763	4
	3	1397	10	27	159	27	10	1630	15
OCH_2F	4	1459	32	21	183	19	98	1812	64
	5	1457	−3	32	163	25	50	1724	75
	6	1509	4	41	142	26	−3	1719	115
$OCHF_2$	7	1554	−87	26	162	29	95	1779	276
	8	1622	−30	36	127	40	13	1808	217
	9	1611	−5	39	125	39	−6	1803	206
	10	1937	1	35	172	39	8	2192	199
OCF_3	11	1674	−85	31	138	32	105	1895	412
	12	1687	−19	43	107	43	−19	1842	342
	13	1663	−30	41	109	42	2	1827	346
	14	2090	−6	43	147	42	−6	2310	362
OCH_2Cl	15	1509	43	18	169	27	109	1875	238
	16	1509	22	33	158	29	70	1821	113
	17	1511	13	36	151	30	53	1794	116
	18	1513	5	40	146	32	37	1773	175
	19	1513	5	43	138	32	0	1731	169
$OCHCl_2$	20	1607	−2	45	119	44	−2	1811	287
$OCCl_3$	21	1651	−4	52	109	53	−4	1857	334

[a] See footnote *a* in Table II. The σ charge on the ring carbons is $3.0000 - \Delta q_\sigma$. The sum of the excess charge on the phenyl ring hydrogens is given by $\Sigma\Delta q^H$.

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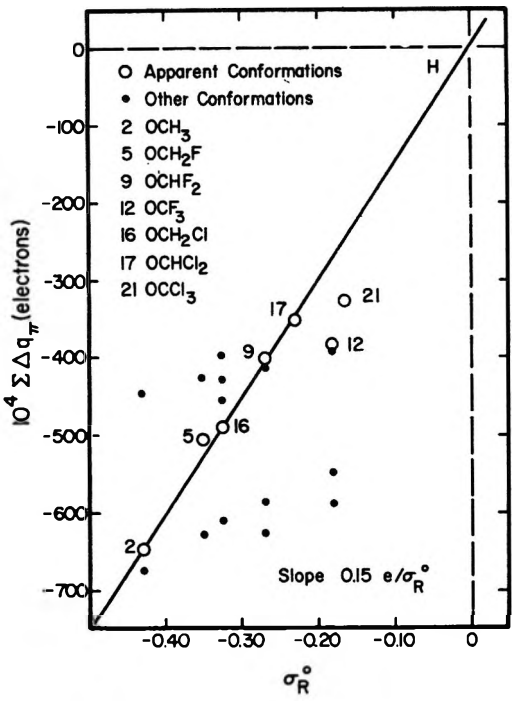

Figure 2.—Correlation between the excess π charge density on the ring of the halogen-containing anisoles and the σ_R° values of the substituents $OCH_{3-n}X_n$. Points in the same vertical correspond to various conformations (m) of the same substituent.

TABLE IV

CHARGE DENSITIES ($\times 10^4$) ON $OCH_{3-n}X_n$ OF GROUPS OF HALOGENATED ANISOLES IN VARIOUS CONFORMATIONS m[a]

Substituent	m	Δq^X	Δq^H	Δq^C	Δq^O
OCH_3	1		−173	1540	−2133
	2		−171	1534	−2144
	3		−180	1573	−2230
OCH_2F	4	−1281	−1027	4680	−2594
	5	−1272	−1040	4700	−2435
	6	−2099	−322	3767	−2647
$OCHF_2$	7	−1936	−1299	6442	−2742
	8	−2192	−328	5716	−2615
	9	−2193	−330	5713	−2604
	10	−1918	−1287	6820	−3463
OCF_3	11	−2211		7519	−2644
	12	−2210		7537	−2708
	13	−2213		7531	−2682
	14	−2204		7910	−3387
OCH_2Cl	15	−1722	80	2053	−1990
	16	−1666	99	2057	−2043
	17	−1672	97	2078	−2058
	18	−1677	95	2088	−2078
	19	−2084	88	2097	−2084
$OCHCl_2$	20	−1363	362	2585	−1965
$OCCl_3$	21	−1105		3074	−1880

[a] See footnote in Table II. Δq^X represents the average excess charge on the halogen. Analogous values for the other atom in the substituent are referenced by the element in the superscript.

pends on the energy differences of all the available conformations.

The value of $\beta = 18°$ found for anisole (conformation $m = 2$ in Table II) is precisely that derived by LeFevre[10] from dipole moment measurements.[20] The α-haloanisoles had $\beta = 56°$ (OCH_2F) and 45° (OCH_2Cl); the remaining compounds, $OCHX_2$ and OCX_3, gave $\beta = 90°$, indicating that the dihalo and

(20) The calculated dipole moment $\mu = 1.46$ D was also closest to the experimental value[10] of 1.24 D (compare 1.83 D for conformation $m = 3$).

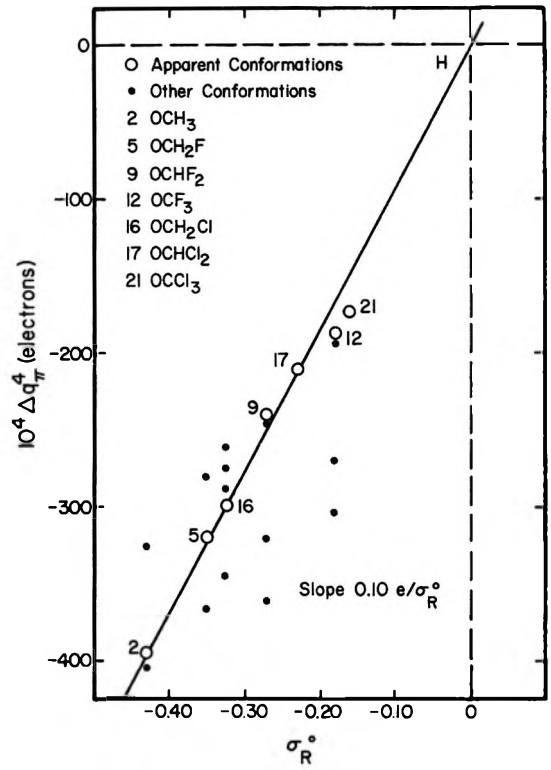

Figure 3.—Correlation between the excess π charge density at the para carbon of anisoles and the σ_R° values of the substituents $OCH_{3-n}X_n$. Points in the same vertical correspond to various conformations (m) of the same substituent.

trihalo groups are perpendicular to the benzene plane, a situation that is consistent with important steric interactions[16] with the ortho hydrogen atom and results in placing the p electrons of the oxygen orthogonal with the benzene π system where overlap is forbidden by symmetry. Rather unexpected experimental support of the latter contention for OCF_3 may be inferred from the results of molecular photoelectron spectroscopy.[21] The largest deviations were found in the case of the OCX_3 groups, which for all conformations studied gave points below the line. However, the calculations showed that even with $\beta = 90°$ ($m = 12$ and 21), resonance transfer of charge[1] to the ring π system was occurring, which is in agreement with the experimental values of σ_R°, and supports the simple model of oxygen hybridization presented herein. Incidently, the apparent conformation derived for OCF_3 differs from those proposed previously[22] and calculations on the latter ($m = 11$ and 14) disagreed with expectation values deduced from Figures 2 and 3.

Charge Distribution in the Benzene Ring.—The CNDO/2 results can be interpreted at various levels,[1,7,8a] but some caution should be exercised.[23] Our results, given in Tables II, III, and IV, are self-explanatory; however, the following trends are noteworthy. (i) The π charges alternate around the ring in a manner predicted by VB theory for ortho,para-directing donor

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substituents.[24] (ii) The charge on the meta carbons (Δq_π^3, Δq_π^5) is relatively insensitive to any variation of the substituent. (iii) The electron deficiency in the σ framework of the benzene ring ($\Sigma\Delta q_\sigma$) is dominated by the large positive value of Δq_σ^1 resulting from the adjacent oxygen atom.[25] (iv) The difference in π charge at various positions, in particular $\Delta q_\pi^1 - \Delta q_\pi^2$, is larger in magnitude than the resonance transfer of charge $\Sigma\Delta q_\pi$ and results from reorganization of charge. This latter feature, which was defined previously in an operational manner[1] as a π-inductive effect, makes some contribution to the σ_I inductive parameter.

Experimental Section

Elemental analyses were performed by the staff of Dr. C. S. Yeh, Purdue University Microanalytical Laboratory. Vapor phase chromatographic (glpc) separations were carried out on a Varian Aerograph 200, using an 8 ft × 0.375 in. aluminum column packed with 20% QF-1 60/80 Chromosorb W (column I) and an 8 ft × 0.375 in. aluminum column packed with 25% SE-30 on 60/80 Chromosorb W (column II). Proton magnetic resonance (nmr) spectra were recorded on a Varian A-60A spectrophotometer using CCl_4 as a solvent and tetramethylsilane as the standard. Ir spectra were measured on a Perkin-Elmer 421.

^{19}F Nmr Calibrations.—All measurements were made as previously reported.[1-3]

Infrared Measurements.—The infrared intensities of the 1600-cm^{-1} stretching vibrations of the anisoles in CCl_4 and cyclohexane solution were measured as reported previously[1,11] and the average values of $A^{1/2}$ derived from five different measurements are recorded in Table I.

Materials.—*m*- and *p*-fluorophenols were purchased from Pierce Chemical Co.

Aryl Chloromethyl Ethers.—These compounds were prepared by a two-step synthesis as described by Barber.[26] The appropriate sodium phenolate was treated with a solution of sodium chloromethane sulfonate, prepared according to the procedure of Schoellkopf,[27] and the resulting sodium aryloxymethane sulfonate was treated further with PCl_5. The resulting oily mixture was poured into ice water, extracted with ether, washed with 1 *N* NaOH solution, dried ($MgSO_4$), and distilled to give pure products. Phenyl chloromethyl ether was obtained in 74% yield: bp 57° (0.5 mm); n^{20}D 1.5368 [lit.[26b] bp 88–90° (15 mm), n^{20}D 1.5362); nmr δ 5.60 (s, J_{CH} = 176.0 Hz).

Anal. Calcd for C_7H_7ClO: C, 59.00; H, 4.90; Cl, 24.90. Found: C, 58.85; H, 4.95; Cl, 24.77.

The *m*- and *p*-fluorophenyl chloromethyl ethers were obtained in 29 and 21% yield, respectively: bp 66° (4 mm) and 65° (4 mm), n^{20}D 1.5122 and 1.5210, and nmr δ 5.72 and 5.72 (s, CH_2), respectively.

Anal. Calcd for C_7H_6ClFO: C, 52.35; H, 3.74; Cl, 22.10; F, 11.84. Found for meta: C, 52.59; H, 3.85; Cl, 21.83; F, 11.71. Found for para: C, 52.43; H, 3.74; Cl, 22.33; F, 11.99.

Aryl Dichloromethyl Ethers.—The three ethers were prepared by a two-step synthesis adapted from that descibed by Laato and Lehtonen.[28] The appropriate phenol was converted into the aryl formate, which was further treated with PCl_5 to give the corresponding aryl dichloromethyl ether in 95–100% yield. The samples were purified by glpc at 180° using column II.

Anal. Calcd for $C_7H_6Cl_2O$: C, 47.41; H, 3.50; Cl, 40.20. Found: C, 47.41; H, 3.19; Cl, 40.22.

Phenyl dichloromethyl ether had n^{20}D 1.5362 (lit.[28] n^{20}D 1.5361) and nmr δ 7.50 (s, J_{CH} = 209.5 Hz).

Anal. Calcd for $C_7H_5Cl_2FO$: C, 43.10; H, 2.56; Cl, 36.42; F, 9.75. Found for para: C, 43.37; H, 2.67; Cl, 36.62; F, 9.74.

The *m*- and *p*-fluorophenyl dichloromethyl ethers had n^{20}D 1.5133 and 1.5132, respectively, and nmr δ 7.28 and 7.28 (s, $OCHCl_2$).

Aryl Trichloromethyl Ethers.—These ethers were prepared from their corresponding phenols by a two-step synthesis according to the procedure described by Iarovenko and Vasileva.[29] The aryl chlorothioformate,[30] prepared by the reaction of thiophosgene with the appropriate phenol, was treated with chlorine at 45–50°. Phenyl trichloromethyl ether was obtained in 90% yield: n^{20}D 1.5415 (lit.[29] n^{20}D 1.5395); bp 92° (10 mm); nmr δ 7.19 (s).

Anal. Calcd for $C_7H_5Cl_3O$: C, 39.81; H, 2.37 Cl, 50.00. Found: C, 39.64; H, 2.53; Cl, 49.20.

The *m*- and *p*-fluorophenyl trichloromethyl ethers were obtained in 96 and 82% yield, respectively: bp 70° (3 mm) and 60° (2 mm); n^{20}D 1.5191 and 1.5191 (lit.[31] n^{20}D 1.5191 for para), respectively.

Anal. Calcd for $C_7H_4Cl_3FO$: C, 36.60; H, 1.74; Cl, 46.40; F, 8.27. Found for meta: C, 36.81; H, 1.55; Cl, 46.24; F, 8.20. Found for para: C, 36.86; H, 1.96; Cl, 46.29; F, 8.50.

Aryl Difluoromethyl Ethers.—According to the procedure of Miller and Thanassi,[32] the appropriate phenols were converted into the title compounds by their reaction with chlorodifluoromethane. Purification of the products was carried out by glpc on column I at 100°. Phenyl difluoromethyl ether had n^{20}D 1.4497 (lit.[32] n^{20}D 1.4473), nmr (neat) δ 6.32 (t, J_{HF} = 75.0 Hz).

The *m*- and *p*-fluorophenyl difluoromethyl ethers were obtained in 45 and 13% yield, respectively, and had n^{20}D 1.4347 and 1.4350, nmr δ 6.40 and 6.38 (t, J_{HF} = 73.5 Hz), respectively.

Anal. Calcd for $C_7H_5F_3O$: C, 51.80; H, 3.08; F, 35.11. Found for meta: C, 51.89; H, 3.26; F, 35.22. Found for para: C, 51.76; H, 3.33; F, 34.81.

Aryl Trifluoromethyl ethers.—The reaction of the corresponding aryl trichloromethyl ether[31] with SbF_3 (mixed with 10% $SbCl_5$) followed by glpc purification at 125° on column II afforded the title compounds in *ca.* 70% yield. Phenyl trifluoromethyl ether had n^{20}D 1.4070 (lit.[31] n^{20}D 1.4073).

Anal. Calcd for $C_7H_5F_3O$: C, 51.80; H, 3.08; F, 35.11. Found: C, 52.00; H, 3.20; F, 34.89.

The *m*- and *p*-fluorophenyl trifluoromethyl ethers had n^{20}D 1.3950 and 1.3951 (lit.[33] n^{25}D 1.3914 and 1.3912).

Registry No.—Phenyl chloromethyl ether, 6707-01-3; *m*-fluorophenyl chloromethyl ether, 34888-01-2; *p*-fluorophenyl chloromethyl ether, 34888-02-3; phenyl dichloromethyl ether, 1195-43-3; *m*-fluorophenyl dichloromethyl ether, 34888-04-5; *p*-fluorophenyl dichloromethyl ether, 34917-96-9; phenyl trichloromethyl ether, 34888-05-6; *m*-fluorophenyl trichloromethyl ether, 34888-06-7; *p*-fluorophenyl trichloromethyl ether, 407-13-6; *m*-fluorophenyl difluoromethyl ether, 34888-08-9; *p*-fluorophenyl difluoromethyl ether, 34888-09-0; phenyl trifluoromethyl ether, 456-55-3; *m*-fluorophenyl trifluoromethyl ether, 1077-01-6; *p*-fluorophenyl trifluoromethyl ether, 352-67-0.

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Chromyl Chloride Oxidations. VII. Kinetics and Mechanism of the Electrophilic Addition to Cycloalkenes[1-3]

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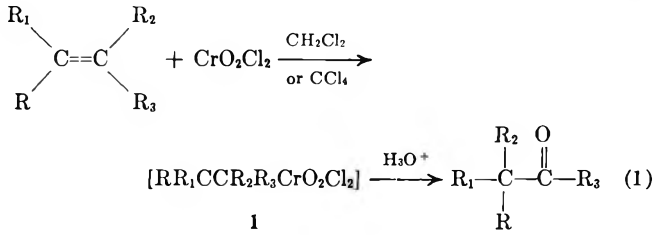
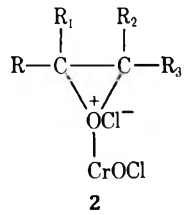
The rapid oxidation of cyclopentene, 1-methyl- and 1,2-dimethylcyclopentene, cyclohexene, 1-, 3-, and 4-methylcyclohexene, 1,3- and 1,4-dimethylcyclohexene, 1-acetylcyclohexene, cycloheptene, 1-methylcycloheptene, cyclooctene, cyclododecene, and bicyclo[2.2.1]hept-2-ene by chromyl chloride has been studied kinetically by means of a spectrophotometric stopped-flow system. The kinetics, which measure the rate of formation of the 1:1 chromyl chloride–cycloalkene adduct, follow the second-order rate law: $v = k[CrO_2Cl_2][\text{cycloalkene}]$. The rate of oxidation increases with the increasing number of methyl groups at the carbon–carbon double bond. The relative rate of oxidation of 1-methylcyclohexene in carbon tetrachloride, chloroform, and methylene chloride is 1.00:4.05:17.4. Large negative entropies of activation ($\Delta S^{\ddagger} = -23.5$ to -42.7 eu) and low enthalpies of activation ($\Delta H^{\ddagger} = 3.21$–$10.6$ kcal/mol) are observed. A consideration of the effects of strain energies, stereochemistry, and ionization potentials on the rates is presented. Comparisons of the relative reactivities of chromyl chloride oxidations with other reactions involving symmetrical and unsymmetrical cyclic activated complexes suggest that the rate-limiting step involves a partially positively charged unsymmetrical three-membered cyclic activated complex. This conclusion does not necessarily hold for bicyclic systems.

The proposed mechanisms and observed products for the chromyl chloride oxidation of carbon–carbon single and double bonds have generated considerable controversy for many years.[4-26] Styrenes have been postulated as intermediates in the chromyl chloride oxidation of arylalkanes (Étard reaction),[17-27] and cycloalkenes have been suggested as intermediates in the oxidation of cycloalkanes.[12,14] Chromyl chloride reacts rapidly with alkenes,[4-11] cycloalkenes,[11-15,24] and styrenes[1,5,8,12,16-23] to give 1:1 chromyl chloride–unsaturate adducts **1** which can be converted to aldehydes and/or ketones in good to excellent yields by reductive hydrolysis with finely powdered zinc dust or with nascent sulfur dioxide.[7,8,28] For example, 2,4,4-trimethyl-1-pentene and 4,4-dimethyl-2-neopentyl-1-pentene are oxidized to 2,4,4-trimethylpentanal and 4,4-dimethyl-2-neopentylpentanal in 75.8 and 80.8% yields, respectively.[7,8,16] Table I shows the products from the chromyl chloride oxidation of some endocyclic and exocyclic cycloalkenes.[28]



(1)

Structure **2** has been suggested for the adduct **1**,[6,11-14]



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and structures **3** and **4** have been proposed as possible cyclic activated complexes for the rate-determining step in the chromyl chloride oxidation of styrenes.[1,20] Kinetic data from the oxidation of alkenes favor the unsymmetrical three-membered cyclic activated complex **4**.[9] Also, preliminary oxidation studies with cyclopentene, cyclohexene, and bicyclo[2.2.2]hept-2-ene suggested that the activated complex could resemble structure **3**, **4**, or **5**.[11]

In an attempt to further elucidate the mechanism of the chromyl chloride oxidation of cycloalkenes, we have examined the kinetics of chromyl chloride addition

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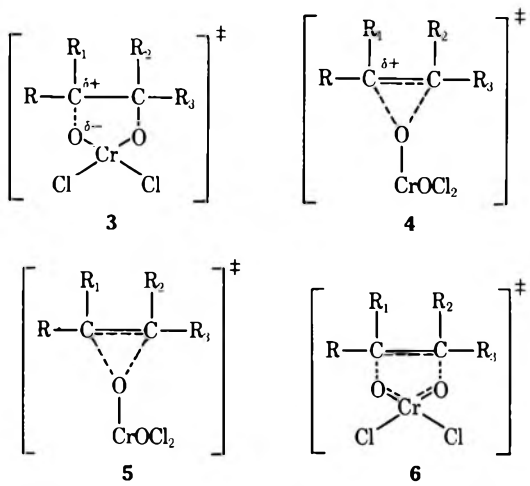
(28) Isolation and/or nonreductive hydrolysis of the hygroscopic and amorphous organometallic complex **1** give(s) rise to a variety of side reactions including chlorination, isomerization, oxidation of the initial product, and carbon–carbon double bond cleavage.[7,8,15]

TABLE I

PRODUCTS OF THE CHROMYL CHLORIDE OXIDATION OF CYCLOALKENES

Endocyclic cycloalkene	Overall yield, %	(% Yield) Products (% Yield)	Overall yield, %	Exocyclic cycloalkene
	56[a]	(84.6) 2-Methylcyclopentanone (72.0) (1.4) Cyclopentanecarboxaldehyde (17.5) (4.2) 2-Chloro-2-methylcyclopentanone (4.7) (9.9) 2-Methylcyclopentan-3-one (5.8)	40[a]	
	68[b]	(52.5) 2-Methylcyclohexanone (29.1)[a] Cyclohexanecarboxaldehyde (47.1)[a] (38.5) 1-Methylcyclopentanecarboxaldehyde (23.8)[a] (9.3) 2-Chloro-2-methylcyclohexanone		
	60[a]	(52.8) 2-Methylcycloheptanone (31.5) (3.9) Cycloheptanecarboxaldehyde (28.3) (26.4) 1-Methylcyclohexanecarboxaldehyde (25.3) (11.1) 2-Methylcyclohepten-3-one (5.7) 2-Chloro-2-methylcycloheptanone Cycloheptanone (12.4) Cyclooctanone (2.5)	68[a]	

[a] Reference 12. [b] Reference 11.



3 4

5 6

to (oxidation of) carbon–carbon double bonds in a variety of cycloalkenes. The kinetics, which measure the rate of formation of the chromyl chloride–cycloalkene adduct **1**, were determined in a spectrophotometric stopped-flow system owing to the very fast rates of oxidation.[1,9,20,29]

Experimental Section

Solutions of cycloalkene and chromyl chloride, in specially purified solvents,[9] were prepared immediately prior to use.

Cycloalkenes.—The cycloalkenes were obtained commercially: cyclopentene,[30] 1-methylcyclopentene,[30] 1,2-dimethylcyclopentene,[31] cyclohexene,[32] 1-methylcyclohexene,[33] 3-methylcyclohexene,[30] 4-methylcyclohexene,[30] 1,3-dimethylcyclohexene,[31] 1,4-dimethylcyclohexene,[31] 1-acetylcyclohexene,[30] cycloheptene,[30] 1-methylcycloheptene,[30] cyclooctene,[34] cyclododecene (mixture of *cis* and *trans* isomers),[34] and bicyclo[2.2.1]hept-2-ene.[30] The cycloalkenes were refluxed for at least 2 hr with $LiAlH_4$,[35] in order to remove any peroxides, before distillation.

Solvent Purification.—Carbon tetrachloride,[36] chloroform,[36] and methylene chloride[36] were purified as previously described.[9]

Chromyl chloride (Alfa Inorganics, Inc.) was distilled and the middle fraction, bp 114.5–115.5°, was used.

Kinetic Measurements.—The rapid rate of oxidation was followed by observing the disappearance of chromyl chloride in a stopped flow reactor[1,9,11,20,29] at 415 and 440 mμ[37,38] under pseudo-first-order conditions (large excess of cycloalkene). Some runs with bicyclo[2.2.1]hept-2-ene were also performed under second-order conditions owing to the extremely fast rate of reaction. The pseudo-first-order rate constants (k_ψ) were obtained from the slopes of plots of $-\ln [\log (T_\infty/T)]$ *vs.* time. T_∞ is the per cent transmission at a point just before the chromyl chloride–cycloalkene adduct **1** begins to precipitate. All rate constants given in the tables are the average of two or more determinations, and were calculated on a CDC 3300 computer.[39] A Forma Model 2095-2 refrigerated and heated bath circulator was used to maintain constant temperature (±0.02°).

Results

Table II summarizes the kinetic data for the chromyl chloride addition to (oxidation of) cyclohexene to give the cycloalkene–chromyl chloride adduct **1**. The

TABLE II

KINETIC DATA FOR THE CHROMYL CHLORIDE OXIDATION OF CYCLOHEXENE AT 10.0° [a]

[Cyclohexene], $\times 10^3 M$	$[CrO_2Cl_2]$, $\times 10^4 M$	k_ψ,[b] sec^{-1}	k_2,[c] M^{-1} sec^{-1}
4.9	4.5	0.006	1.20
9.9	4.5	0.011	1.10
14.8	4.5	0.016	1.09
24.7	4.5	0.020	1.05
29.6	4.5	0.031	1.02
34.6	4.5	0.037	1.20
39.5	4.5	0.048	1.21
39.5[d]	3.9	0.041	1.05
39.5[d]	5.9	0.041	1.02
39.5[d]	7.9	0.046	1.18
39.5[d]	9.9	0.052	1.31
39.5[d]	11.8	0.053	1.35

[a] Carbon tetrachloride solvent, λ = 415 mμ. [b] Pseudo-first-order rate constant. [c] Second-order rate constant = k_ψ/[cyclohexene]. [d] λ = 440 mμ.

(29) K. B. Wiberg and R. D. Geer, *J. Amer. Chem. Soc.*, **87**, 5202 (1965); **88**, 5827 (1966).
(30) Aldrich Chemical Co., Inc.
(31) Chemical Samples Co.
(32) Matheson Coleman and Bell.
(33) K & K Laboratories, Inc.
(34) Sample from Columbian Carbon Co., Inc.
(35) Metal Hydrides Inc.
(36) Mallinckrodt Chemical Works.
(37) O. H. Wheeler, *Can. J. Chem.*, **38**, 2137 (1960).
(38) A. Bartecki, *Rocz. Chem.*, **38**, 1455 (1964).
(39) K. B. Wiberg, "Computer Programming for Chemists," W. A. Benjamin, New York, N. Y., 1965, p 165.

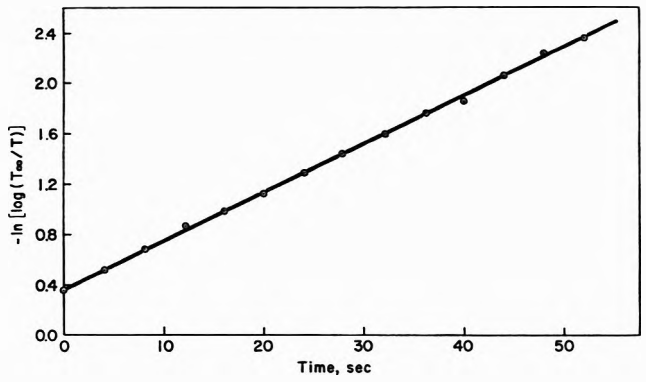


Figure 1.—First-order plot for the reaction of 1-methylcyclohexene with chromyl chloride in carbon tetrachloride; $[CrO_2Cl_2] = 4.5 \times 10^{-4}$ *M*, [1-methylcyclohexene] $= 4.2 \times 10^{-3}$ *M*, λ = 415 mμ, *T* = 0°.

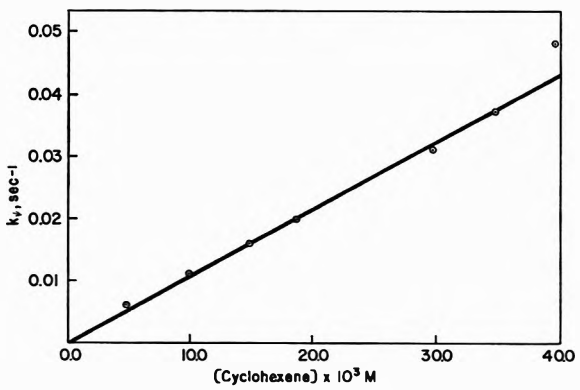


Figure 2.—Effect of cyclohexene concentration on the pseudo-first-order rate constants (k_ψ) for the chromyl chloride oxidation of cyclohexene in CCl_4 at 10.0°.

constancy of the value of the second-order rate constant ($k_2 = k_\psi/$[cyclohexene]), at constant chromyl chloride concentration, over an eightfold range of cyclohexene concentration suggests a first-order dependence on the cycloalkene. It is also seen from Table II that at constant cyclohexene concentration, the pseudo-first-order rate constant (k_ψ) does not alter appreciably over a threefold range of chromyl chloride concentration at 440 mμ. With a tenfold excess of 1-methylcyclohexene good first-order plots were obtained (Figure 1). Thus, further support is given for the first-order dependence on chromyl chloride. Additional support for the first-order dependence on cycloalkene is seen in a plot of k_ψ against cyclohexene concentration (Figure 2) or 1-methylcyclohexene concentration (Figure 3) which gives a straight line that passes through the origin. These data suggest the following rate law.

$$\frac{-d[CrO_2Cl_2]}{dt} = k[\text{cycloalkene}][CrO_2Cl_2] \qquad (2)$$

Effect of Solvents on Rates.—Table III shows the effects of carbon tetrachloride, chloroform, and methylene chloride on the rate of chromyl chloride oxidation of 1-methylcyclohexene at 10.0°. Several empirical parameters for estimating solvent polarity are also presented.

Effect of Strain Energies on Rates.—The effects of strain energy on the chromyl chloride oxidation of the lower cycloalkenes are presented in Table IV.

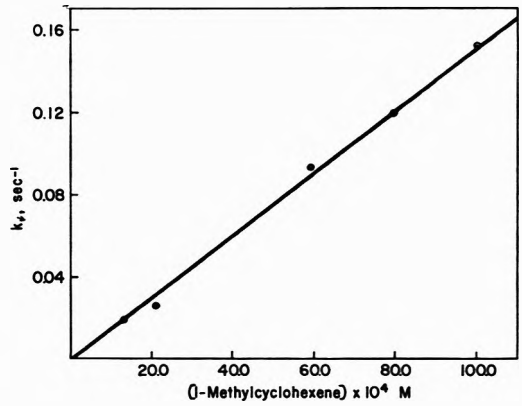


Figure 3.—The linear dependence of the pseudo-first-order rate constants on increasing concentration of 1-methylcyclohexene at constant chromyl chloride concentration in CCl_4 at 10.0°.

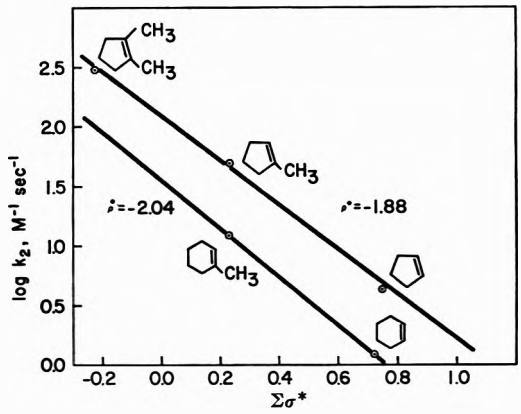


Figure 4.—Relations between rate constants and substitution of methyl groups at carbon-carbon double bonds of cyclopentene and cyclohexene.

TABLE III

EFFECT OF SOLVENTS ON THE RATE OF CHROMYL CHLORIDE OXIDATION OF 1-METHYLCYCLOHEXENE[a]

Solvent	k_2,[b] M^{-1} sec^{-1}	Relative rate	μ[c,d]	ϵ[d,e]	E_T[f]	Z[g]	S[h]
CCl_4[i]	12.1	1.00	0.00	2.24	32.5	52.4	−0.245
$CHCl_3$[j]	49.1	4.05	1.15	4.81	39.2	63.2	−0.200
CH_2Cl_2[k]	211	17.4	1.55	9.08	41.1	64.2	−0.189

[a] $[CrO_2Cl_2] = 4.05 \times 10^{-4}$ *M*, λ = 415 mμ, *T* = 10.0°. [b] Second-order rate constant = $k_\psi/$[1-methylcyclohexene]. [c] Dipole moment. [d] J. A. Riddick and E. Toops, Jr., "Organic Solvents," Vol. VII of "Techniques of Organic Chemistry," A. Weissberger, Ed., Interscience, New York, N. Y., 1965. [e] Dielectric constant. [f] K. Dimroth, C. Reichardt, T. Siepman, and F. Bohlmann, *Justus Liebigs Ann. Chem.*, 661, 1 (1963). [g] E. M. Kosower, *J. Amer. Chem. Soc.*, 80, 3253 (1958). [h] S. Brownstein, *Can. J. Chem.*, 38, 1590 (1960). [i] [1-Methylcyclohexene] $= 42.1 \times 10^{-4}$ *M*. [j] [1-Methylcyclohexene] $= 93.0 \times 10^{-4}$ *M*. [k] [1-Methylcyclohexene] $= 21.9 \times 10^{-4}$ *M*.

Thermodynamic Parameters and Relative Rates.—The rates of the chromyl chloride oxidation of 15 cycloalkenes were determined at several temperatures. Table V summarizes the data for the activation parameters and the relative rates (to cyclohexene) of oxidation, and Figure 4 shows the relation between rates and substitution of methyl groups at the carbon–carbon double bonds of cyclopentene and cyclohexene.

Relation between Rates of Oxidation and Ionization Potentials.—A correlation between ionization potentials and logarithm of relative rates (to 1-hexene) for the

TABLE IV

EFFECT OF STRAIN ENERGIES ON THE CHROMYL CHLORIDE OXIDATION OF CYCLOALKENES

Cycloalkane	$-\Delta H$,[a] kcal/mol	Total[b] strain, kcal/mol	$-\Delta H$,[c] kcal/mol	k_2,[d] M^{-1} sec^{-1}	Cycloalkene
Cyclopentane	793.52[e]	6.5	25.7[f]	4.51	Cyclopentene
Cyclohexane	944.48[e]	0.0	27.10[f]	1.10	Cyclohexene
Cycloheptane	1108.2[e]	6.3	25.85[f]	4.72	Cycloheptene
Cyclooctane	1269.2[e]	9.6	23.62[f]	4.84	*cis*-Cyclooctene
Cyclododecane	1884.2[e,g]	3.4[h]	20.67[f]	1.25[i]	*cis*-Cyclododecene

[a] Heat of combustion for gaseous hydrocarbons to give liquid water at 25.0°. [b] Calculated by subtracting (number of CH_2 groups × 157.4) from the observed heat of formation. [c] Heat of hydrogenation in acetic acid solution at 25.0°. [d] Second-order rate constant for chromyl chloride oxidation at 10.0° [e] S. Kaarsemaker, and J. Coops, *Recl. Trav. Chim. Pays-Bas*, 71, 261 (1952); J. Coops, H. van Kamp, W. A. Lambgrets, B. J. Visser, and H. Dekker, *ibid.*, 79, 1226 (1960). [f] R. B. Turner and W. R. Meador, *J. Amer. Chem. Soc.*, 79, 4133 (1957). [g] Solid state. [h] K. B. Wiberg, *J. Amer. Chem. Soc.*, 87, 1070 (1965). [i] Mixture of cis and trans isomers.

TABLE V

RELATIVE RATES AND THERMODYNAMIC PARAMETERS FOR THE CHROMYL CHLORIDE OXIDATION OF SOME CYCLOALKENES[a]

Registry no.	Cycloalkene	k_2,[b] M^{-1} sec^{-1}	Relative rate	$\Delta H^{\ddagger}$, kcal/mol	$-\Delta S^{\ddagger}$, eu	$\Delta G^{\ddagger}$, kcal/mol
110-83-8	Cyclohexene	1.10	1.0	10.1	23.6	16.5
591-49-1	1-Methylcyclohexene	12.1	11	3.21	42.2	14.9
591-48-0	3-Methylcyclohexene	3.95	3.6	9.90	20.7	15.7
591-47-9	4-Methylcyclohexene	1.35	1.2			
2808-76-6	1,3-Dimethylcyclohexene	36.1	32.8	10.6	14.0	14.5
2808-79-9	1,4-Dimethylcyclohexene	15.1	13.7	7.80	25.5	14.9
932-66-1	1-Acetylcyclohexene	0.15	0.14	8.50	32.1	17.4
142-29-0	Cyclopentene	4.51	4.1[c,d]	8.90[d]	23.5[d]	
693-89-0	1-Methylcyclopentene	48.6	44.2	5.07	32.8	14.2
765-47-9	1,2-Dimethylcyclopentene	299	273	4.39	31.5	13.2
628-92-2	Cycloheptene	4.72	4.3	6.69	31.7	15.5
1453-25-4	1-Methylcycloheptene	182	165			
931-88-4	Cyclooctene	4.84	4.4	3.55	42.7	15.4
1501-82-2[e]	Cyclododecene	1.25[e]	1.1	8.26	28.8	16.3
498-66-8	Bicyclo[2.2.1]hept-2-ene	562	511			

[a] Carbon tetrachloride solvent, T = 10.0°, λ = 415 mμ. [b] Second-order rate constant = k_ψ/[cycloalkene]. [c] Relative rates at 5.0° and 15.0° = 4.9 and 4.5, respectively. [d] Reference 11. [e] Mixture of cis and trans isomers.

TABLE VI

IONIZATION POTENTIALS AND LOG RELATIVE RATES (TO 1-HEXENE) FOR THE CHROMYL CHLORIDE OXIDATION OF SOME UNSATURATED HYDROCARBONS

Unsaturate	k_2,[c] M^{-1} sec^{-1}	k_2/k_2(1-hexene)[b]	log $k_{2\,rel}$[c]	Ionization potential, eV
2,3-Dimethyl-2-butene	287.5	4107	3.613	8.30,[e] 8.4,[f] >8.5[g]
Bicyclo[2.2.1]hept-2-ene	562[h]	8028.6	3.904	8.83,[i] 8.95,[j] 9.20[k]
Styrene	26.9[d]	384.3	2.584	8.43,[l] 8.47[m]
Cyclopentene	4.51[h]	64.4[h]	1.809	9.01,[m] 9.00,[l] 9.3[f]
Cyclohexene	1.22[h]	17.43[h]	1.241	8.72,[n] 9.2[f]
1-Pentene	0.09[d]	1.29	0.110	9.50[m]
cis-2-Pentene	1.11[d]	15.86	1.200	9.11[o]
trans-2-Pentene	1.01[d]	14.43	1.159	9.06[o]
1-Hexene	0.07[d]	1.00	0.000	9.45[e]

[a] Second-order rate constant = k_ψ/[>C=C<] at 10.0°. [b] Second-order rate constant for oxidation of 1-hexene [c] Relative to 1-hexene. [d] References 3 and 9. [e] R. Bralsford, P. V. Harris, and W. C. Price, *Proc. Roy. Soc. Ser. A*, 258, 459 (1960). [f] J. L. Charlton, C. C. Liao, and P. de Mayo, *J. Amer. Chem. Soc.*, 93, 2463 (1971). [g] R. J. Cvetanovic, *J. Chem. Phys.*, 30, 19 (1959). [h] This work. [i] N. Bodor, M. J. S. Dewar, and S. D. Worley, *J. Amer. Chem. Soc.*, 92, 19 (1970). [j] W. C. Steele, B. H. Jennings, G. L. Botyos, and G. O. Dudek, *J. Org. Chem.*, 30, 2886 (1965). [k] D. A. Demeo and A. J. Yencha, *J. Chem. Phys.*, 53, 4536 (1970). [l] M. J. S. Dewar and S. D. Worley, *J. Chem. Phys.*, 50, 654 (1969). [m] K. Watanabe, T. Nakayama, and J. Mottl, *J. Quant. Spectrosc. Radiat. Transfer*, 2, 369 (1962). [n] M. I. Al-Joboury and D. W. Turner, *J. Chem. Soc.*, 4434 (1964). [o] J. Collin and F. P. Lossing, *J. Amer. Chem. Soc.*, 81, 2064 (1959).

chromyl chloride oxidation of nine unsaturated hydrocarbons is shown in Table VI and Figure 5.

Comparison of the Ratio of Relative Reactivities.—Table VII shows a comparison of the ratio of relative reactivities for reactions proceeding *via* three-membered and five-membered cyclic activated complexes.

Discussion

The kinetic data above clearly show that the chromyl chloride oxidation of cycloalkenes is first order with respect to reductant and to oxidant. This also is consistent with the observed second-order rate law for the chromyl

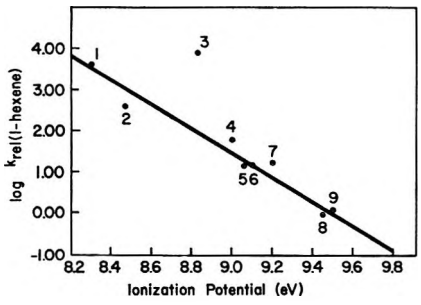
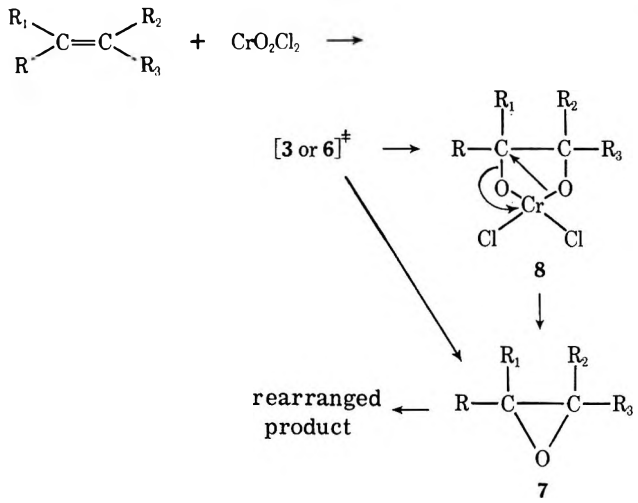


Figure 5.—Relation between log relative rate of chromyl chloride oxidation (to 1-hexene) and ionization potentials. The unsaturated compounds for the number points are as follows: 1, 2,3-dimethyl-2-butene; 2, styrene; 3, bicyclo[2.2.1]hept-2-ene; 4, cyclopentene; 5, *trans*-2-pentene; 6, *cis*-2-pentene; 7, cyclohexene; 8, 1-hexene; 9, 1-pentene.

chloride oxidation of alkenes[9] and styrenes.[1,20] Since structurally rearranged products are obtained from the oxidation of unsaturated hydrocarbons, it is reasonable to assume that positively charged product-determining intermediates are formed after the rate-determining steps. These intermediates could resemble **2** or they could be the corresponding epoxides.[1,40-45] Rearrangement of the epoxide **7** under the hydrolytic conditions would lead to the observed aldehydes and ketones.[7]

Although the intermediacy of epoxides **7** in the chromyl chloride oxidation of carbon–carbon double bonds remains to be demonstrated, it is possible that they could be formed from the proposed cyclic activated complexes **3**–**6**, from a cyclic chromium(IV) ester **8** (Scheme I), or from an intermediate carbonium ion **9** (Scheme II).

SCHEME I



If the addition of chromyl chloride to cycloalkenes is expected to be electrophilic in nature, then an increase of electron availability in the carbon–carbon double bond should increase the rate of reaction. Table

TABLE VII
RELATIVE REACTIVITIES OF CYCLOPENTENE (A), CYCLOHEXENE (B), AND BICYCLO[2.2.1]HEPT-2-ENE (C) IN REACTIONS INVOLVING THREE- AND FIVE-MEMBERED CYCLIC ACTIVATED COMPLEXES

Reaction	Temp, °C	Size of cyclic activd complex	k_2, M^{-1} min^{-1} A	B	C	Ratio of relative rates A/B	Δ[a]	C/B	Δ[a]	C/A	Δ[a]
Chromyl chloride oxidation	10[b,c]	3[b]	4.51[d]	1.10[d]	562[d]	4.1	1.0	511	1.0	125	1.0
Chromic acid oxidation	25[e]	3	0.931	0.724	3.97	1.3	3.1	5.5	93	4.3	29
Epoxidation	25.8[f,g]	3	0.183–0.195[g]	0.129[g]		1.5	2.7				
	25[h]	3		0.0192[d,h]	0.0228[d,h]			1.2	426		
Bromine addition	25[i]	3	0.040	0.030		1.3	3.1				
Dibromocarbene addition		3				1.25[j]	3.3				
Silver complex formation	40[k]	3	7.3	3.6	62	2.0	2.0	17	30	8.5	14.7
Diphenylnitrilimine cycloaddition	~80[l,m]	5				~12	0.34	284	1.8	~24	5.2
Benzonitrile oxide cycloaddition	20[n]	5				19	0.22	1800	0.28	93	1.3
Phenyl azide cycloaddition	25[d,o]	5	1.86×10^{-7}	0.033×10^{-7}	188×10^{-7}	57	0.07	5700	0.09	101	1.2
	25[d,p]	5	1.83×10^{-7}	(3.3×10^{-9})[d,o,q]	2.15×10^{-5}	56	0.07	6500	0.08	115	1.1
Picryl azide cycloaddition	25[d,p]	5	1.08×10^{-4}	2.55×10^{-6}	2.04×10^{-2}	42	0.1	8000	0.06	190	0.6

[a] Δ is the ratio of the chromyl chloride oxidation ratio and the ratio of the comparative reaction. [b] This work. [c] Reference 11. [d] Time unit is sec^{-1}. [e] 0.002 *M* sulfuric acid in 95% w/w acetic acid. A. K. Awasthy and J. Roček, *J. Amer. Chem. Soc.*, **91**, 991 (1969). [f] D. Swern, *Chem. Rev.*, **45**, 49 (1949). [g] Peracetic acid in acetic acid solution. J. Böeseken and J. Stuurman, *Rec. Trav. Chim. Pays-Bas*, **56**, 1034 (1937). [h] Perlauric acid in chloroform. K. D. Bingham, G. D. Meakins, and G. H. Whitham, *Chem. Commun.*, 445 (1966). [i] Acetic acid solvent. P. W. Robertson, J. K. Heyes, and B. E. Swedlund, *J. Chem. Soc.*, 1014 (1952). [j] Potassium *tert*-butoxide and bromoform. P. S. Skell and A. Y. Garner, *J. Amer. Chem. Soc.*, **78**, 5430 (1956). [k] Equilibrium constant (l./mol) for formation of silver nitrate–unsaturate complex in 1,2-dihydroxyethane. M. A. Muks and F. T. Weiss, *ibid.*, **84**, 4697 (1962). [l] Boiling benzene solvent except for cyclopentene. R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes," S. Patai, Ed., Interscience, New York, N. Y., 1964, p 819. [m] A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, D. Grashey, and E. Spindler, *Chem. Ber.*, 100, 2192 (1967); R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, **17**, 3 (1962). [n] Ether solvent. Table VII, ref *l*, p 826. [o] Carbon tetrachloride solvent. R. Huisgen, G. Szeimies, and L. Möbius, *Chem. Ber.*, 100, 2494 (1967). [p] Chloroform solvent. A. S. Bailey and J. E. White, *J. Chem. Soc. B*, 819 (1966). [q] Carbon tetrachloride solvent. R. Huisgen, L. Möbus, G. Muller, H. Stangl, G. Szeimies, and J. M. Vernon, *Chem. Ber.*, **98**, 3992 (1965).

(40) Epoxides have been isolated in the chromyl acetate oxidation of alkenes and styrenes,[41,42] and in the chromic acid oxidation of allylic alcohols,[43] cyclohexene,[44] and styrenes.[45]

(41) M. A. Davis and W. J. Hickinbottom, *J. Chem. Soc.*, 2205 (1958).

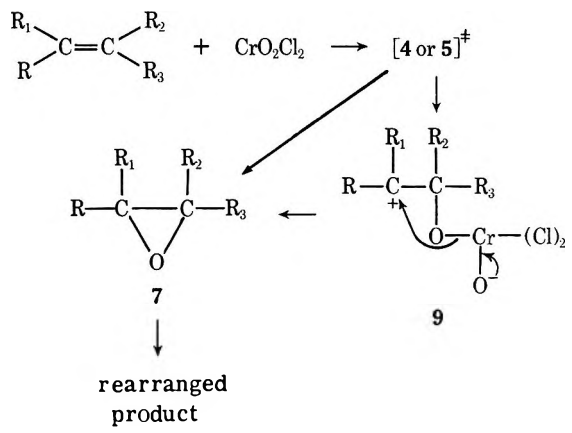
(42) W. A. Mosher, F. W. Steffgen, and P. T. Lansbury, *J. Org. Chem.*, **26**, 670 (1961).

(43) P. S. Kalsi, K. S. Kumar, and M. S. Wadia, *Chem. Ind. (London)*, 71 (1971).

(44) J. Roček and J. C. Drozd, *J. Amer. Chem. Soc.*, **92**, 6668 (1970).

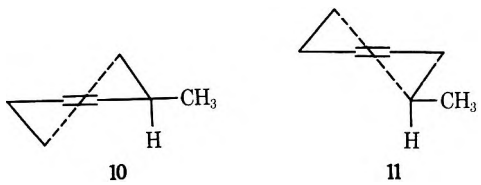
(45) W. J. Hickinbottom and G. E. M. Moussa, *J. Chem. Soc.*, 4195 (1957); G. E. M. Moussa, *J. Appl. Chem.*, **12**, 385 (1962).

SCHEME II



V shows that 1-methylcyclohexene is oxidized 12 times as fast as cyclohexene. In contrast, the electron-attracting acetyl group on the cyclohexene ring slows the rate by a factor of approximately seven. It is also seen that 1-methylcyclopentene and 1,2-dimethylcyclopentene are approximately 11 and 66 times as reactive as cyclopentene. In these respects the chromyl chloride oxidation closely resembles electrophilic reactions (*e.g.*, bromine addition, chromic acid oxidation, epoxidation) which involve three-membered cyclic activated complexes.

It is of interest to note that 3-methyl- and 4-methylcyclohexene (**10**, **11**) are oxidized slightly faster than



10 **11**

cyclohexene. In contrast, remote alkyl substituents retard the rates of epoxidation with *m*-chloroperbenzoic acid[46] and the addition of 2,4-dinitrobenzenesulfenyl chloride[47] to various cyclohexene derivatives. The similarity in the rates of oxidation among cyclohexene, **10**, and **11** precludes an evaluation of the contribution of conformation, inductive, and steric effects. Inductive effects at the carbon–carbon double bond are indeed important, as is shown in the linear free energy of log *k vs.* $\Sigma\sigma$ (Figure 4),[48,49] and the steric and conformation factors in **10** and **11** could be small, since the methyl groups are probably in the equatorial positions.[9,50] The lesser enhancing effect of the methyl group in the four position is also seen when the rates of oxidation for 1,3-dimethyl- and 1,4-dimethylcyclohexene are compared.

(46) B. Rickborn and S. Y. Lwo, *J. Org. Chem.*, **30**, 2212 (1965).
(47) H. Kwart and L. J. Miller, *J. Amer. Chem. Soc.*, **83**, 4552 (1961).
(48) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 556.
(49) The $\Sigma\sigma^*$ for the cycloalkenes was calculated as follows: in cyclohexene the C=C was considered as having two *n*-butyl groups (−0.26) and two hydrogens (0.98) = $\Sigma\sigma^*$ = 0.72. In this manner $\Sigma\sigma^*$ values of 0.23, 0.75, 0.26, and −0.23 were calculated for 1-methylcyclohexene, cyclopentene, and 1-methyl- and 1,2-dimethylcyclopentene, respectively. Perchance treating cycloalkenes as substituted ethenes is an oversimplication, since chromyl chloride oxidations presumbably proceed *via* a highly ordered activated complex and there may be small but significant variations in activation parameters owing to steric effects and *I* strain. However, it is also recognized that chromyl chloride oxidations are not particularly susceptible to steric effects.[9]
(50) A. I. Scott and A. D. Wrixon, *Tetrahedron*, **27**, 4787 (1971).

The relations between rate constants and substitution of methyl groups at the carbon–carbon double bonds of cyclopentene and cyclohexene are shown in Figure 4. A ρ^* of −2.04 is obtained from the two-point line for cyclohexene and 1-methylcyclohexene, and a ρ^* of −1.88 (r = 0.997, s = 0.093) is obtained for 1-methyl- and 1,2-dimethylcyclopentene.[49,50] These values are comparable to those reported for the chromyl chloride oxidation of alkenes (ρ^* = −2.63)[9] and styrenes (ρ^+ = −1.99),[20] and are compatible with activated complexes with a small degree of carbonium ion character.[20,51] Consequently, the observed ρ^* values for the chromyl chloride oxidation of cycloalkenes are not inconsistent with the formulation of unsymmetrical **3** or **4** as the activated complex.

A plot of ionization potential, which is a measure of electron availability, *vs.* log $k_{rel(1\text{-hexane})}$ (Figure 5 and Table VI) is also compatible with an electrophilic attack of chromyl chloride at the carbon–carbon double bond. In qualitative terms, cyclopentene, cyclohexene, and bicyclo[2.2.1]hept-2-ene might not be expected to give an excellent fit to the line owing to torsional strain, bond angle bending strain, and nonbonding interactions. However, it is seen that only the bicyclic system shows a large deviation from the line. Consequently, the possibility of a change in mechanism for the oxidation of bicyclo[2.2.1]hept-2-ene must also be considered.

In Table III it is noted that solvents which are empirically regarded as having higher polarity cause an increase in the rate of oxidation. This result is consistent with the development of a partially charged cyclic activated complex (**3** or **4**) in the transition state region from initially neutral cycloalkene and chromyl chloride.

Table IV shows the complex relation between strain energies and rate constants in the chromyl chloride oxidation of cycloalkenes. Since the heat of hydrogenation reflect strain energies in *both* the unsaturated and saturated compounds, interpretation of these data must be done with care. Garbisch and coworkers[52] have calculated that cyclopentene and bicyclo[2.2.1]-hept-2-ene are more strained than cyclohexene by approximately 3.7 and 9.7 kcal/mol, respectively. A considerable amount of this strain is relieved in reactions involving cyclic four-, five-, or six-membered activated complexes.[53] Therefore, the comparable rate constants for oxidation of cyclopentene and cyclohexene suggest that there is not a significant relief of strain and that the activated complex probably shows a close resemblance to **4**. Alternatively, the very small rate difference may be due to an activated complex which closely resembles the reactants.[54,55]

An examination of the relative rates and the ratios of reactivities in Table VII reveals that the chromyl chloride oxidation of cyclopentene and cyclohexene is remarkably similar to other reactions leading to cyclic three-membered activated complexes. In contrast, the bicyclo[2.2.1]hept-2-ene–cyclohexene ratio appears

(51) ρ^+ values larger than −3 are generally observed in reactions with a large degree of carbonium ion character in the activated complex.
(52) E. W. Garbisch, Jr., S. M. Schildcrout, D. B. Peterson, and C. M. Sprecher, *J. Amer. Chem. Soc.*, **87**, 2932 (1965).
(53) Table VII, ref e.
(54) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).
(55) R. E. Erickson and R. L. Clark, *Tetrahedron Lett.*, 3997 (1969).

to suggest a five-membered cyclic activated complex (3 or 6) for the bicyclic system.[53]

3, 4, 5, or 6 would require the large negative entropies of activation (−23.5 to −42.7 eu) tabulated in Table V. $\Delta S^{\pm}$ values of this magnitude have been observed for reactions, *e.g.*, epoxidation, 1,3-dipolar cycloadditions, with rigid orientation requirements in the activated complex.

We conclude from the kinetic studies and the comparative rate data that the activated complex for the chromyl chloride oxidation of cycloalkenes can be represented by the partially charged unsymmetrical structure 4.[56] 4 is consistent with the rapid rate of oxidation in solvents of low polarity and with the ρ^* of approximately −2.0. In this postulated mechanism, which is similar to the one proposed by Bartlett[57-59] for epoxidation, oxygen transfer from chromyl chloride occurs by a concerted process. That is, as the two new σ bonds are being formed, the oxygen–chromium bond is being broken.[60] After the rate-determining step, this mechanism could lead to a product-determining epoxide intermediate (Scheme II). Activated complexes similar to 4 and 5 have also been proposed for the chromic acid[44] and chromyl acetate[42] oxidation of carbon–carbon double bonds.[40,56]

The limited comparative rate data suggest that the activated complex for the chromyl chloride oxidation of bicyclo[2.2.1]hept-2-ene *probably* has a close resemblance to 3 or 6. Additional studies on more bicyclic systems are in process in order to fully elucidate the mechanism.

Registry No.—Chromyl chloride, 7791-14-2.

Acknowledgment.—We express our thanks to the donors of the Petroleum Research Fund administered by the American Chemical Society and the Long Beach California State College Foundation for support of this work.

(56) The symmetrical species 5 and 6 could have sufficient carbonium ion character to satisfy $\rho^* \cong -2.0$. It is also recognized that the oxidation is a process in which there is a net flow of electrons from the substrate through the oxidant. This results in the inevitable development of a partial positive charge either on the carbon atoms of the double bond or on the oxygen atom, and of a partial negative charge on the chromium atom undergoing a valency change or on its ligands.

(57) P. D. Bartelt, *Rec. Chem. Progr.*, **11**, 47 (1950).

(58) A $\rho = -1.20$ has been obtained for the epoxidation of stilbenes with peroxybenzoic acid: B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955); Y. Ogata and I. Tabushi, *J. Amer. Chem. Soc.*, **83**, 3440 (1961).

(59) D. Swern, "Organic Peroxides," Vol. II, Wiley, New York, N. Y., 1971, p 355.

(60) Concerted closure of the two incipient σ bonds does not necessarily mean that the development of the bonds has proceeded to the same degree in the activated complex. Any difference between the bond-making rates during the activation process would lead to a partial charge at the more substituted carbon atom.

Silation of Dichloromethyllithium in the Presence of Excess *n*-Butyllithium

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The silation of a −100° solution of 2 equiv of *n*-butyllithium and 1 equiv of methylene chloride in THF–hexane with trimethylchlorosilane leads to a complex product mixture of butyltrimethylsilane (3), dichloro(trimethylsilyl)methane (1), bis(trimethylsilyl)chloromethane (4), bis(trimethylsilyl)dichloromethane (2), tris(trimethylsilyl)methane (5), 1,1-di(trimethylsilyl)-1-chloropentane (6), and tris(trimethylsilyl)chlorosilane (7). Experimental evidence is presented that indicates that successive silation of monolithio intermediates is occurring rather than production of dilithiodichloromethane.

It has been reported[1] that additions of *n*-butyllithium to cold (−100°) solutions of methylene chloride and trimethylchlorosilane in tetrahydrofuran (THF) give respectable yields of dichloro(trimethylsilyl)-methane (1) and bis(trimethylsilyl)dichloromethane (2), depending on the quantity of reagents used (eq 1 and 2). In repeating this second reaction, we found it

$$1Me_3SiCl + 1CH_2Cl_2 + 1BuLi \xrightarrow[51\%]{THF,\ -100^\circ} \underset{1}{Me_3SiCHCl_2} \quad (1)$$

$$2Me_3SiCl + 1CH_2Cl_2 + 2BuLi \xrightarrow[40\%]{THF,\ -100^\circ} \underset{2}{Me_3SiCCl_2SiMe_3} \quad (2)$$

to be quite complex, regardless of whether the reaction was done *in situ* as Bamford and Pant describe or if the intermediate, dichloromethyllithium ($LiCHCl_2$), was preformed prior to addition of trimethylchlorosilane.

When trimethylchlorosilane was added last to a cold solution of 2 equiv of *n*-butyllithium to 1 equiv of methylene chloride in THF as the solvent, compound 2 was formed in approximately 50% yield (based on vpc). The other 50% of the reaction products was composed of compounds 1 and 3–7. The silated products were isolated by preparative gas chromatography and characterized by infrared, nmr, and mass spectra,[2] elemental analysis, and comparisons to previously reported properties[1,3-7] (see Experimental Section for details and relative amounts). Additional structure proof of compound 2 was provided by its hydride reduction to a mixture of 4 and bis(trimethylsilyl)methane (8).[3] (Compound 4, unlike 2, reduces only very slowly with lithium aluminum hydride.)

$\underset{3}{Me_3SiBu}$ $\underset{4}{(Me_3Si)_2CHCl}$ $\underset{5}{(Me_3Si)_3CH}$ $\underset{6}{(Me_3Si)_2CClBu}$

$\underset{7}{(Me_3Si)_3CCl}$ $\underset{8}{(Me_3Si)_2CH_2}$ $\underset{9}{(Me_3Si)_4C}$

(1) W. R. Bamford and B. C. Pant, *J. Chem. Soc. C*, 1470 (1967).

(2) D. R. Dimmel, C. A. Wilkie, and F. Ramon, *J. Org. Chem.*, **37**, 2665 (1972).

(3) R. L. Merker and M. J. Scott, *J. Organometal. Chem.*, **4**, 98 (1965).

(4) R. Müller and G. Seitz, *Chem. Ber.*, **91**, 22 (1958).

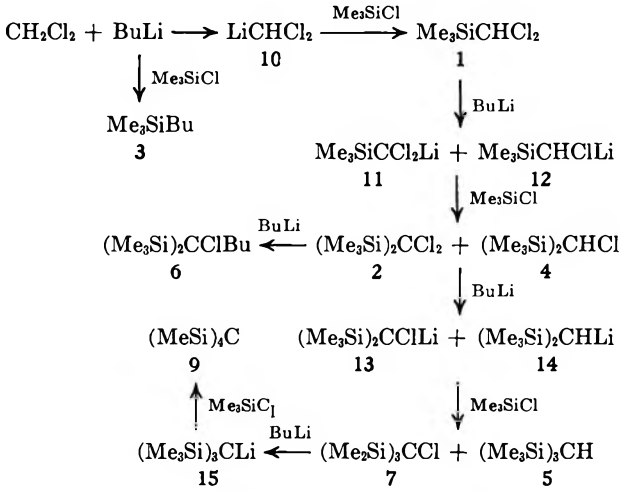
(5) R. Mueller and S. Reichel, *ibid.*, **99**, 793 (1966).

(6) G. Fritz and J. Grobe, *Z. Anorg. Allg. Chem.*, **309**, 77 (1961).

(7) V. F. Mironov and N. A. Pogonkina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 182 (1955); *Chem. Abstr.*, **50**, 1574*d* (1956).

A probable mechanism which might account for the variety of products found when methylene chloride is silated is presented in Scheme I. The evidence supporting Scheme I is the following.

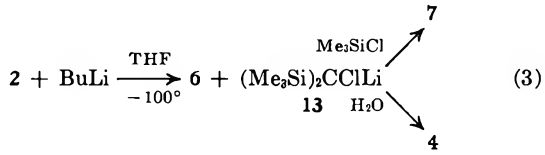
SCHEME I



(1) Silyl groups are known to enhance the reactivity of an α carbon toward further reactions with base[8] and, consequently, polysilation can occur. The reaction of methylene chloride with varying amounts of *n*-butyllithium supports this premise. With 1 equiv of *n*-butyllithium, the major product was the monosilated compound **1**, with 2 equiv it was **2**, with 3 equiv it was the trisilated compound **7**, and with 4.5 equiv it was the tetrasilated product **9**. The consecutive silations could be lessened to some extent by the inverse addition of the cold CH_2Cl_2/BuLi solutions to cold Me_3SiCl; here the product composition was 74% **2**, 14% **7**, 10% **4**, and 2% **6**.

(2) An equal molar mixture of bis(trimethylsilyl)-dichloromethane (**2**) and trimethylchlorosilane in THF was treated with 1 equiv of BuLi at −100° to afford products **7** and **3** in a 15:1 ratio. Thus, at these low temperatures, the reaction between *n*-butyllithium and trimethylchlorosilane is quite slow relative to reaction of the base with a silyl activated methylene, an observation also made by Bamford and Pant.[1]

(3) Verification that halogen exchange reactions,[9] such as **1** → **12**, **2** → **13**, etc., are plausible steps in these transformations was provided by the observation that a sample of **2** could be converted, *via* its lithium derivative **13**, to either **7** or **4** (eq 3). The results (eq 3) also



(3)

indicate that **2** is the likely precursor of **6** and that hydrolysis (or proton abstraction) of lithio intermediates **11**, **13**, and **15** could account for some or all of the observed products **1**, **4**, and **5**.

(4) If the reaction described by eq 2 was performed on a vacuum line, 1 equiv of butane was collected prior to silation and 0.5 equiv was collected after silation [in this case ineffective mixing led to more than the usual amount of butyltrimethylsilane (**3**)]. Butyl chloride was also detected as a by-product. In like manner, only 1 equiv of isobutane was collected when 2 equiv of *tert*-butyllithium was treated with 1 equiv of methylene chloride (eq 4). These results rule out di-

$$CH_2Cl_2 + 2\ t\text{-BuLi} \xrightarrow[-100^\circ]{\text{THF}} LiCHCl_2 + (CH_3)_3CH + t\text{-BuLi} \quad (4)$$

chloromethyllithium (Li_2CCl_2) as an intermediate in these reactions since its formation would lead to 2 equiv of butane prior to silation.

If the silations were done according to the procedure of Bamford and Pant,[2] namely, the *n*-butyllithium added last to a cold solution of trimethylchlorosilane and CH_2Cl_2 in solvent, a mixture of products was also obtained. Using an excess of Me_3SiCl and THF as the solvent, the predominant product was the trisilated compound **7** and not **2** (eq 5). With a solvent mixture

$$3Me_3SiCl + 1CH_2Cl_2 + 2BuLi \xrightarrow[-100^\circ]{\text{THF}} \underset{27\%}{2} + \underset{12\%}{4} + \underset{9\%}{6} + \underset{52\%}{7} \quad (5)$$

of 5 parts THF/5 parts hexane/1 part ether and a stoichiometric amount of Me_3SiCl, a 65% yield (vpc) of **2** was obtained (eq 6).

$$2Me_3SiCl + 1CH_2Cl_2 + 2BuLi \xrightarrow[-100^\circ]{\text{THF/hexane/ether}} \underset{65\%}{2} + \underset{19\%}{4} + \underset{9\%}{6} + \underset{7\%}{7} \quad (6)$$

To summarize, the silation of methylene chloride in the presence of excess *n*-butyllithium, no matter how the reaction is done, gives several products. These products apparently result because the reaction of trimethylchlorosilane with *n*-butyllithium is quite slow at −100° relative to *n*-butyllithium reacting with silyl-activated α protons or chlorines. The reaction does not appear to be a useful preparative reaction unless one has a very good fractionating column or preparative gas chromatograph. The exceptions to this generalized statement are **7** and **9**, which can be sublimed from the reaction mixtures and obtained in fairly pure states and decent quantities.

Experimental Section

All the *n*-butyllithium reactions were conducted in flame-dried 500-ml four-neck round-bottom flasks fitted with a dropping funnel, tru-bore stirrer, thermometer, and drying tube. The reactions were done under an atmosphere of nitrogen; temperature control was achieved using liquid nitrogen. The methylene chloride and THF were freshly distilled prior to use, the former from P_2O_5, the latter from sodium–potassium alloy. The *n*-butyllithium and *tert*-butyllithium in hexane solvent were purchased from Alfa Inorganics.

Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer, using TMS as the internal standard and CCl_4 as the solvent. Infrared spectra were recorded on a Beckman IR-12 spectrometer. Mass spectra were obtained using a CEC 21-104 mass spectrometer. Gas chromatographic analyses were performed on a 6 ft × 0.25 in. aluminum column packed with SE-30 on 60–80 mesh Chromosorb W using a F & M Model 700 gas chromatograph. Preparative work was done on 8 ft × 0.75 in. stainless steel columns packed with SE-30 on Chromosorb W using a F & M Model 770 preparative gas chromatograph.

(8) R. West and G. A. Gornowicz, *J. Organometal Chem.*, **28**, 25 (1971), and references cited therein.

(9) G. E. Coates, M. L. H. Green, P. Powell, and K. Wade, "Principles of Organometallic Chemistry," Methuen, London, 1968, p 47.

Boiling points were determined by the capillary method. All boiling points and melting points are uncorrected.

Silation of Methylene Chloride.—To a stirred solution of 8.85 g (0.104 mol) of methylene chloride in about 200 ml of THF, cooled to about −90°, was slowly added 90 ml (0.214 mol) of 2.37 *M* *n*-butyllithium in hexane. After complete addition and additional stirring for 3 hr, 24.7 g (0.229 mol) of trimethylchlorosilane in 50 ml of THF was added over a 2-hr period. The reaction was then allowed to gradually warm to room temperature. Much of the THF was distilled off; then water and ether were added to the residue. The organic layer was separated and the aqueous layer was extracted twice with fresh ether. The combined ether extracts were washed with water, dried ($MgSO_4$), and distilled. Four fractions ranging in boiling points of 35–145° were collected at atmospheric pressure using a Vigreux column. Another five fractions, bp 50–170° (15 mm), were collected using a short-path distillation column.

The various fractions were analyzed by gas chromatography (SE-30) and percentages of each component were calculated by the triangle method. From the percentages and quantities of each, the rough composition of product mixture was determined to be 20% **1**, 48% **2**, 12% **3**, 5% **4**, 9% **5**, 1% **6**, and 4% **7**. The various components were then separated by preparative gas chromatography (SE-30). The properties of the collected compounds (listed in increasing retention time) were the following.

Butyltrimethylsilane (**3**) was identical with a sample prepared by the reaction of *n*-butyllithium with trimethylchlorosilane, bp 115–116° (lit.[10] bp 116.0–116.5°).

Dichloro(trimethylsilyl)methane (**1**) had bp 134° (lit.[1] bp 132–134°); nmr (CCl_4) δ 0.22 (s, 9, Me_3Si) and 5.24 (s, 1, CH); ir (neat) 850 (s) and 1258 (s) (CSi), 633, 690, 717 (s), 763, 781, and 872 cm^{-1} (s); mass spectrum (70 eV) molecular ion at *m/e* 156, 158, and 160 (two chlorines).[11]

Anal. Calcd for $C_4H_{10}SiCl_2$: C, 30.58; H, 6.42. Found: C, 30.80; H, 6.31.

Bis(trimethylsilyl)chloromethane (**4**) had bp 175° [lit.[7] bp 177–8.5°]; nmr (CCl_4) δ 0.12 (s, 18, Me_3Si) and 2.35 (s, 1, CH); ir (neat) 850 (s) and 1260 (s) (CSi), 619, 632, 698, 713, 770, and 1145 cm^{-1} (s); mass spectrum (70 eV) molecular ion at *m/e* 194 and 196 (3:1 patterns, weak, monochloro).[11]

Anal. Calcd for $C_7H_{19}Si_2Cl$: C, 43.15; H, 9.83; Cl, 18.19. Found: C, 42.27; H, 9.59; Cl, 18.19.

Bis(trimethylsilyl)dichloromethane (**2**) had bp 204° [lit.[1] bp 125–127° (60 mm)]; nmr (CCl_4) δ 0.23 (s, Me_3Si); ir (neat) 851 (s) and 1266 (s) (CSi), 632, 649, 703 (s), 747, 768, 810 (s), and 878 cm^{-1} (s); mass spectrum (70 eV) molecular ion at *m/e* 228, 230, and 232 (weak, dichloro).[11]

Anal. Calcd for $C_7H_{18}Si_2Cl_2$: C, 36.67; H, 7.91; Cl, 30.92. Found: C, 36.82; H, 7.61; C, 30.79.

Tris(trimethylsilyl)methane (**5**) had nmr (CCl_4) δ 0.10 (s, 27, Me_3Si) and −0.78 (s, 1, CH) [lit.[11] nmr (CCl_4) δ 0.11 (Me_3Si–) and −0.79 (CH)]; ir (neat) 850 (s) and 1256 (s) (CSi), 680, 690, and 1010 cm^{-1} (s); mass spectrum (70 eV) no molecular ion, base peak at *m/e* 217 (M − 15).[11]

Anal. Calcd for $C_{10}H_{28}Si_3$: C, 51.64; H, 12.13. Found: C, 51.50; H, 12.08.

1,1-Di(trimethylsilyl)-1-chloropentane (**6**) had nmr (CCl_4) δ 0.13 (s, 18, Me_3Si), 0.95 (t, 3, CH_3), and 1.1–2.0 [m, 6, $-(CH_2)_3-$]; ir (neat) 850 (s) and 1254 (s) (CSi), 625, 695, and 765 cm^{-1}; mass spectrum (70 eV) no molecular ion, base peak at *m/e* 73 (Me_3Si^+).[11] A satisfactory analysis could not be obtained due to a small impurity of **7** which was difficult to remove. The primary basis of the structural assignment relied heavily on the nmr spectrum.

Tris(trimethylsilyl)chloromethane (**7**) had mp 125–126°; nmr (CCl_4) δ 0.19 (s, Me_3Si); ir (Nujol mull) 865 (s), 1259 (s) and 1267 (s) (CSi), 690 and 705 cm^{-1}; mass spectrum (70 eV), molecular ions at *m/e* 266 and 268 (3:1 ratio, weak, monochloro).[11]

Anal. Calcd for $C_{10}H_{27}Si_3Cl$: C, 44.98; H, 10.19; Cl, 13.28. Found: C, 44.83; H, 9.89; Cl, 13.23.

The experiment was repeated in the exact same manner except that trimethylchlorosilane was added to the reaction mixture very rapidly. The product distribution is this case was 2% **1**, 52% **2**, 9% **3**, 4% **4**, 0.5% **5**, 2% **6**, and 21% **7**.

The experiment was repeated a third time using 4.0 g (0.0486 mol) of methylene chloride and 100 ml (0.23 mol) of 2.3 *M* *n*-butyllithium and quenching with 40 ml (0.321 mol) of trimethylchlorosilane. Distillation removed the solvent and low-boiling products, leaving a solid mass. The latter was added to pentane and filtered to remove the inorganic salts. Removal of the pentane by distillation and sublimation of the residue gave 5.3 g (36%) of tetrakis(trimethylsilyl)methane (**9**): mp > 300° (lit.[12] mp 408–410°); nmr (CCl_4) δ 0.23 (s, Me_3Si) (lit.[3] single peak at δ 0.2]; ir (Nujol) 840 (s), 865 (s), and 1265 (s) (CSi), 330, 621, 678 (s), and 730 cm^{-1}; mass spectrum (70 eV), no molecular ion, base peak at *m/e* 289 (M − 15).[11]

Hydride Reduction of Bis(trimethylsilyl)dichloromethane (**2**). —To a stirred suspension of 0.6 g (16 mmol) of lithium aluminum hydride in about 40 ml of anhydrous ether was added, over a 10-min period, 2.3 g (10 mmol) of a sample containing (vpc) 80% **2**, 14% tris(trimethylsilyl)methane (**5**), 3% bis(trimethylsilyl)chloromethane (**4**), and 3% tris(trimethylsilyl)chloromethane (**7**) dissolved in 20 ml of ether. The reaction mixture was stirred at reflux for 3 hr and at room temperature for 21 hr. The reaction was quenched by adding 0.5 ml of saturated Na_2SO_4 solution. The salts were filtered and washed several times with ether. The combined ether washings were dried ($MgSO_4$) and distilled to remove the solvent. Analysis of the crude residue by vpc indicated incomplete reaction.

The residue was then placed in anhydrous ether, refluxed overnight with a large excess of lithium aluminum hydride, and worked up as before. Analysis of the crude product by vpc (SE-30, 120°) showed 20% **5**, 50% **4**, and 30% of a new low retention time component. The main starting material, **2**, was completely gone. The three components of the mixture were isolated by preparative vpc; compounds **4** and **5** were identical with previously characterized samples. The third, low retention time, component was bis(trimethylsilyl)methane (**8**): nmr (CCl_4) δ 0.02 (s, 18, Me_3Si) and −0.29 (s, 2, CH_2) [lit.[3] nmr (CCl_4) δ 0.02 (Me_3Si–) and −0.28 (CH_2)]; ir (neat) 845 (s) and 1257 (s) (CSi), 692 and 1058 cm^{-1} (lit.[13] identical match); mass spectrum (70 eV) molecular ion at *m/e* 160, base peak at *m/e* 145.[11]

Hydrolysis of Bis(trimethylsilyl)dichloromethane (**2**) ***via*** **Its Lithium Derivative.**—A sample (2.1 g, 9.2 mmol) which was known (by vpc) to contain 80% **2**, 14% tris(trimethylsilyl)-methane (**5**), 3% bis(trimethylsilyl)chloromethane (**4**), and 3% tris(trimethylsilyl)chloromethane (**7**) was dissolved in 20 ml of THF and cooled to −100°. To this stirred solution was slowly added 5 ml (11.5 mmol) of 2.3 *M* *n*-butyllithium in hexane. After the solution was stirred for 1 hr, 5 ml of water in 25 ml of THF was added and the solution was allowed to warm to room temperature. The reaction mixture was distilled to remove much of the THF. Ether was added, the water was separated, and the organic phase was dried ($MgSO_4$) and concentrated. Analysis of the crude product by vpc (SE-30, 150°) showed the following composition: 70% **4**, 13% **5**, and 17% 1,1-di(trimethylsilyl)-1-chloropentane (**6**). Besides vpc comparisons, the compounds were collected by preparative vpc and compared (ir and nmr) to previously characterized samples.

Silation of Bis(trimethylsilyl)dichloromethane (**2**) ***via*** **Its Lithium Derivative.**—A sample (1 g, 0.0436 mol) which was known (by vpc) to contain 80% **2**, 9% bis(trimethylsilyl)chloromethane (**4**), and 11% tris(trimethylsilyl)chloromethane (**7**), was dissolved in 40 ml of THF and cooled to −100°. To this stirred solution was slowly added 2 ml (0.046 mmol) of 2.3 *M* *n*-butyllithium. After the solution was stirred for 1 hr, 2 ml (excess) of trimethylchlorosilane was added and the solution was allowed to warm to room temperature. Water was added and the organic layer was separated. The aqueous phase was extracted with fresh ether and the combined organic extracts were dried over $MgSO_4$. Distillation at 1-atm pressure and under water aspirator pressure removed the low-boiling solvents and compounds, leaving a solid residue (0.3 g). Spectral and vpc analysis indicated that the solid mass was 77% **7**, 15% tetrakis(trimethylsilyl)methane (**9**), 3% 1,1-di(trimethylsilyl)-1-chloropentane (**6**), 2.5% tris(trimethylsilyl)methane (**5**), 2% **4**, and 0.5% **2**.

Inverse Silation of Methylene Chloride.—The procedure was as before except that the reaction mixture of CH_2Cl_2/BuLi in 200 ml at −100° was rapidly transferred under nitrogen to a tenfold excess of trimethylchlorosilane dissolved in THF cooled to −100°. Work-up as before and analysis by vpc (SE-30,

(10) D. Blake, G. E. Coates, and J. M. Tate, *J. Chem. Soc.*, 618 (1961).

(11) Refer to ref 2 for additional details.

(12) G. Köbrich and R. V. Nagel, *Tetrahedron Lett.*, 4693 (1970).

(13) C. C. Cerato, J. L. Lauer, and H. C. Beachell, *J. Chem. Phys.*, **22**, 1 (1954).

135°) gave a product composition of 74% **2**, 14% **7**, 10% **4**, and 2% **6**.

Competitive Silation of 2 and Trimethylchlorosilane.—To a cooled (−100°), stirred solution of 0.57 g (2.5 mmol) of bis(trimethylsilyl)dichloromethane (**2**) and 0.269 g (2.5 mmol) of trimethylchlorosilane in 40 ml of THF was slowly added 1 ml (2.3 mmol) of 2.3 *M* *n*-butyllithium in hexane. After stirring for 1 hr, the solution was allowed to warm to room temperature. Most of the solvent was then distilled off. The crude sample was then analyzed by vpc (SE-30, programmed from 60° to 135°), showing that most of the starting material, **2**, had reacted and that the ratio of tris(trimethylsilyl)chloromethane (**7**) to trimethylbutylsilane (**3**) was approximately 15:1. In the absence of **2**, the reaction between *n*-butyllithium and trimethylchlorosilane was shown to proceed cleanly at −100° to give **3**.

Vacuum Line Metalation of Methylene Chloride.—Five milliliters (11 mmol) of 2.3 *M* *n*-butyllithium was placed in a 100-ml round-bottom flask and pumped on to remove the hydrocarbon solvent. Methylene chloride (0.46 g, 5.5 mmol) and 20 ml of THF were condensed into the flask, and the solution was warmed to −100 (methanol slush) and allowed to stand for 3 hr in a closed system. Butane is volatile at −100° and was removed by pumping through a −100° bath to liquid nitrogen. After repeated pumping, 0.35 g of butane (1 equiv = 0.32 g) was collected in the liquid nitrogen trap; THF was in the −100° trap. These were both identified by infrared and mass spectral analysis. There was a trace of THF mixed with the butane.

While still cold, 10 ml of trimethylchlorosilane was distilled in the reaction flask. The mixture was allowed to slowly warm to room temperature overnight. Pumping through −78°, −100°, and liquid nitrogen, as before, afforded about 0.15 g (0.5 equiv) of butane. The black reaction mixture was worked up similarly to the other silation reactions. Analysis of the crude product by vpc (SE-30, 100°) showed the same products as previous silations of methylene chloride except that there was a larger amount of monosilated products; *i.e.*, trimethylsilyldichloromethane (**1**) and butyltrimethylsilane (**3**). The changes in product composition may be a result of changes in this particular reaction, namely less solvent, pure THF solvent, no mechanical mixing, and the apparent decomposition. The reaction was repeated to give the same overall results: 1 equiv of butane prior to silane, 0.5 equiv after silation and, relatively, the same product mixture.

The reaction as described was repeated except that 10 ml (23 mmol) of 2.3 *M* *tert*-butyllithium was combined with 0.8 g (10 mmol) of methylene chloride and 25 ml of THF. No silation was performed; however, 0.54 g (0.93 equiv) of isobutane was collected. The isobutane was analyzed by infrared spectroscopy. If the *tert*-butyllithium reaction was done as described except that no methylene chloride was present, isobutane was not observed in the 3-hr reaction time.

Registry No.—**1**, 5926-38-5; **2**, 15951-41-4; **4**, 5926-35-2; **5**, 1068-69-5; **6**, 27484-06-6; **7**, 27484-03-3; **9**, 1066-64-4; methylene chloride, 75-09-2; dichloromethyllithium, 2146-67-0.

Acknowledgment.—We wish to thank Research Corporation for their support of this research.

Mass Spectra of Silanes. Multiple Rearrangements and Bonding to Silicon[1]

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The mass spectra of mono-, bis-, tris-, and tetrakis(trimethylsilyl)methanes and chloromethanes have been compared. All of the major ions in the spectra, except possibly *m/e* 43, appear to be siliconium ions. The spectra of the silanes show little or no molecular ion and a base peak corresponding to loss of a methyl group. The α-chlorinated silanes all exhibit a base peak of the *m/e* 73 (Me_3Si), in addition to fragments which contain Cl–Si bonds. A rearrangement process involving a chlorine migration from carbon to silicon and a methyl migration from silicon to carbon is proposed. Three such rearrangements occur in the fragmentation of trichloro(trimethylsilyl)methane (**11**). Several allyl type siliconium ions appear to be present. Mechanisms are proposed for the various fragmentation reactions.

In connection with our studies on the silation of lithiodichloromethane,[2] we have had the opportunity to obtain the mass spectra of a variety of silanes and α-chlorosilanes. Molecular weight determination was our primary interest; however, many of the compounds did not display a molecular ion and, consequently, fragmentation ions had to be relied upon for structural information. Mass spectral studies on methylsilanes,[3] alkylsilanes,[4] bis(trimethylsilyl)methanes,[5] and other di- and trisilanes (alicyclic and cyclic)[5,6] have been reported, but the interpretations in most cases are either brief or ambiguous and, therefore, of little help. This paper reports our observations concerning the mass spectra of some selected silanes. The spectra of tris- and tetrakis(trimethylsilyl)methane and the α-chlorosilanes have not been previously described.

Interpretation of the elemental composition of fragment ions was generally quite simple since the compounds studied were composed of only C, H, Si, and possibly Cl. For example, the *m/e* 73 peak must be C_3H_9Si, since C_5H_{13} is an impossible composition. In some cases, the isotope pattern of chlorine was clearly evident.[7] It should be pointed out, however, that there is a certain element of risk involved with assigning compositions without high-resolution spectra to corroborate the findings. Unfortunately, we did not have a high-resolution instrument at our disposal. All our spectra were obtained with a CEC 21-103 mass spectrometer, at an ionizing voltage of 70 eV, with an inlet temperature of about 180° and a source temperature of 250°.

Compounds.—Most of the compounds studied were

(1) Taken in part from the Master's Thesis of F. Ramon, Marquette University, 1972.

(2) D. R. Dimmel, C. A. Wilkie, and F. Ramon, *J. Org. Chem.*, **37**, 2662 (1972).

(3) G. P. van der Kelen, O. Volders, H. van Onckelen, and Z. Eeckhaut, *Z. Anorg. Allg. Chem.*, **338**, 106 (1965).

(4) N. Ya. Chernyak, R. A. Khmelńitskii, T. V. Dyakova, and V. M. Vdovin, *Zh. Obshch. Khim.*, **36**, 89 (1966); *J. Gen. Chem. USSR*, **36**, 93 (1966).

(5) (a) G. Fritz, H. Buhl, J. Grobe, F. Aulinger, and W. Reering, *Z. Anorg. Allg. Chem.*, **312**, 201 (1961); (b) F. Aulinger and W. Reering, *Z. Anal. Chem.*, **197**, 24 (1963); (c) F. Aulinger and W. Reering, *Collog. Spectrosc. Int., 9th, 1961*, **3**, 556 (1962); (d) G. Fritz, J. Grobe, and D. Kummer, *Advan. Inorg. Chem. Radiochem.*, **7**, 348 (1965).

(6) N. Ya. Chernyah, R. A. Khmelńitskii, T. V. Dyakova, K. S. Pushchevaya, and V. M. Vdovin, *Zh. Obshch. Khim.*, **37**, 917 (1967); *J. Gen. Chem. USSR*, **37**, 867 (1967).

(7) The normal isotope ratio of ^{35}Cl to ^{37}Cl is 3:1 and, consequently, a monochloro fragment should show a 3:1 pattern, a dichloro fragment a 1:0.67:0.1 pattern, and a trichloro fragment a 1:1:0.33:0.03 pattern.

obtained from the reaction of methylene chloride with varying amounts of *n*-butyllithium (eq 1).[2] (The symbol Σ represents a trimethylsilyl group, Me_3Si–.)

$$CH_2Cl_2 + x\text{BuLi} \xrightarrow[-100°]{\text{THF/hexane}} \xrightarrow{Me_3SiCl} \underset{1}{\Sigma CHCl_2} + \underset{2}{\Sigma_2CHCl} + \underset{3}{\Sigma_2CCl_2} + \underset{4}{\Sigma_2CClBu} + \underset{5}{\Sigma_3CH} + \underset{6}{\Sigma_3CCl} + \underset{7}{\Sigma_4C} + \underset{8}{\Sigma Bu} \quad (1)$$

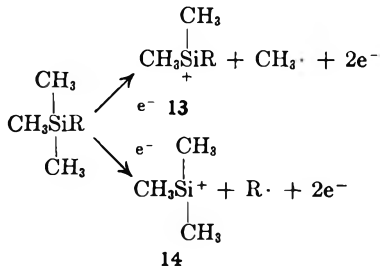
$x = 1$–4

Trimethylsilylchloromethane (**9**)[8] and tetramethylsilane (**10**) were commercially available. Trimethylsilyltrichloromethane (**11**) was synthesized by adding trimethylchlorosilane to a mixture of carbon tetrachloride and 1 equiv of *n*-butyllithium at −100°.[9] Bis(trimethylsilyl)methane (**12**) was obtained by hydride reduction of **3**.[2] All of the compounds gave suitable chemical analysis and were consistent with the properties already recorded in the literature.[2,9,10]

ΣCH_2Cl	ΣCH_3	ΣCCl_3	Σ_2CH_2
9	**10**	**11**	**12**

Results

The Silanes.—The unsubstituted silanes **5, 7, 8, 10,** and **12** are characterized by having no molecular ion, or at best a very weak one, and an intense M − 15 peak (see Table I). The weakness of the molecular ion was not unexpected, since, by analogy, branched hydrocarbons and groups possessing strong ion stabilizing powers, like alcohols, also show very weak molecular ions.[11] The loss of a methyl group results in the most intense peak in the spectra of all the simple silanes, except butyltrimethylsilane (**8**) which loses the butyl group in preference to the methyl by a factor of 5:1 (compare *m/e* 73 to *m/e* 115). In the bis-, tris-, and tetrakis(trimethylsilyl)methanes (**12**, **5**, and **7**), loss of the substituted methane fragment can also occur, producing a trimethylsilyl ion (**14**) (eq 2).



(2)

14

The exact origin of *m/e* 59, 45, and 31 (not shown in Table I but a weak peak in all spectra) is not clear. Zemany and Price,[12] in their study of the mass spectrum of tetramethylsilane, assigned the molecular formulas of Me_2SiH, $MeSiH_2$, and SiH_3 for peaks 59, 45, and 31. Metastable studies[3] have indicated that the *m/e* 45 peak arises by loss of ethylene (C_2H_4) by a rearrangement process from ion **14**. The *m/e* 59 fragment must also arise by a rearrangement process. Since the *m/e* 59 peak is virtually absent (<1%) in the spectra of the monosilated compounds **1**, **10**, and **11** and weak in **9**, it would appear that ion **13** is the precursor of *m/e* 59

(8) Peninsular ChemResearch (PCR), Inc., P. O. Box 1466, Gainesville, Fla. 32601.

(9) W. R. Bamford and B. C. Pant, *J. Chem. Soc. C*, 1470 (1967).

(10) R. L. Merker and M. J. Scott, *J. Organometal. Chem.*, **4**, 98 (1965).

(11) K. Biemann, "Mass Spectrometry: Organic Chemical Applications," McGraw-Hill, New York, N. Y., 1962, pp 51–52.

(12) P. D. Zemany and F. P. Price, *J. Amer. Chem. Soc.*, **70**, 4222 (1948).

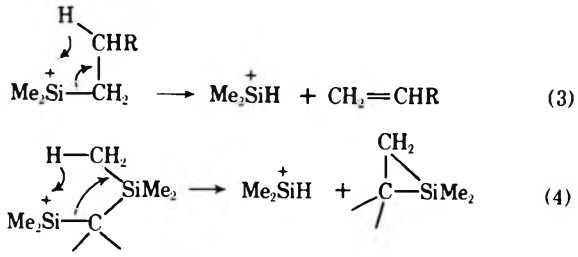
TABLE I

RELATIVE INTENSITIES[a] OF THE MAJOR PEAKS IN THE MASS SPECTRA OF SELECTED SILANES AND α-CHLOROSILANES

Compd	Mol wt	*m/e* (with proposed structures) 43 C_3H_7 or CH_3SiH	45 $MeSiH_2$	59 Me_2SiH	63 $MeCHCl$	65 H_2SiCl	73 Me_3Si	79 $MeSiHCl$	85 Me_3Si–CH=CH_2	93 Me_3SiCl	113 $MeSiCl_2$	Others (rel intensity)
10, ΣCH_3	88[b]	15	21				100					
8, ΣBu	130	16	13	46			100					115 (20)
12, Σ_2CH_2	160[b]	14	13	11		[c]	32		2			129 (5), 145 (100)
5, Σ_3CH	232	9	13	13			33		3			129 (22), 201 (4)
												217 (100)
7, Σ_4C	304	11	15	15			74		3			201 (29), 289 (100)
9, ΣCH_2Cl	122[b]	20	15	3	10	7	100	46		2		107 (8, Cl)
1, $\Sigma CHCl_2$	156[b]	20	19		16	10	100	4		14	33	155 (1, Cl_2)
11, ΣCCl_3	190	19	27		15	11	100	3		16	37	133 (2, Cl_3), 155 (1, Cl_2)
2, Σ_2CHCl	194[b]	15	12	23			100		37	6		106 (5, Cl), 129 (2), 179 (7, Cl)
3, Σ_2CCl_2	228[b]	22	16	26	8	10	100	9	42	43	2	105 (25, Cl),
												163, 178 (1, Cl)
4, $\Sigma CClBu$	250	28	20	32			100		20	20		99 (17), 127 (70)
6, Σ_3CCl	266[b]	14	20	25			100		29	6		83 (10), 143 (25),
												158 (8), 163 (6), 178 (17, Cl), 251 (9, Cl)

[a] Expressed as a percentage of the base peak. [b] Noticeable, but weak, molecular ion. [c] A peak of relative intensity 9% was observed at *m/e* 65; the structure of this ion is believed to be **15**.[5b]

and that R must be greater that one carbon in length. The strength of the *m/e* 59 ion in the spectra of butyltrimethylsilane (**8**) and ethyltrimethylsilane[4] suggests a process indicated by eq 3. The fact that bis and other higher silanes also display moderately intense *m/e* 59 peaks would seem to indicate that δ hydrogens can be transferred in the rearrangement which gives rise to this fragment (eq 4).

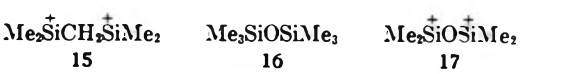


(3)

(4)

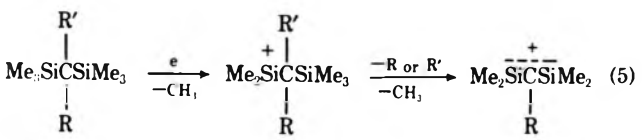
The *m/e* 43 peak, which could be C_3H_7 or CH_3Si or both, is present in all spectra. The appearance of a metastable peak at *m/e* 41.1 (45 → 43) indicates that at least some of the *m/e* 43 peak is due to a silicon fragment.[13]

The *m/e* 65 peak of bis(trimethylsilyl)methane (**12**) is probably due to the doubly charged species **15**.[5b] The mass spectrum of hexamethyldisiloxane (**16**) also shows a strong doubly charged ion at *m/e* 66 **17**.[14]



15 **16** **17**

Both bis- and tris(trimethylsilyl)methane (**12** and **5**) show a peak at *m/e* 129, which is attributed to the allyl ion **18**. Similarly, the allyl ion **19** is probably responsible for the peak at *m/e* 201 in the spectra of **5** and **7**. Equation 5 indicates a way in which these allyl



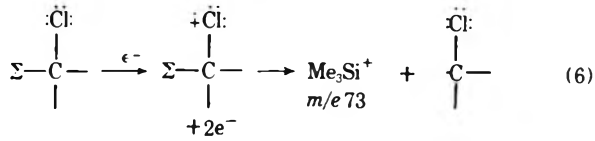
(5)

12, R = R′ = H
5, R = H; R′ = Σ
7, R = R′ = Σ

18, *m/e* 129, R = H
19, *m/e* 201, R = Σ

ions might arise. Another allyl ion, *m/e* 85, is present in the spectra of the unsubstituted silanes and will be discussed later. The mass spectrum of tris(trimethylsilyl)methane is shown in Figure 1.[15a]

The α-Chlorosilanes. –The base peak in the spectra of all the α-chlorosilanes is at *m/e* 73. Assuming that the initial ionization is predominantly the removal of a nonbonded electron of chlorine, then the strong production of the trimethylsiliconium ion can be explained by an α-cleavage mechanism (eq 6). The fact that

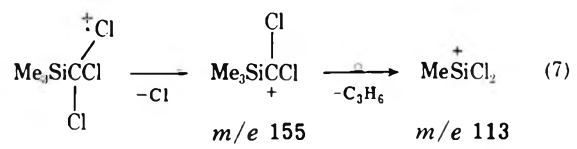


(6)

the M − 15 peak is relatively weak in the chlorosilanes spectra also supports the initial ionization being at chlorine and not at the C–Si bond.

Another characteristic feature of the chlorosilane spectra is the appearance of silicon–chlorine containing fragments that can be best explained as arising *via* a rearrangement process producing Si–Cl units. For example, dichloro(trimethylsilyl)methane[15a] exhibits a substantial peak at *m/e* 113, which on the basis of the accompanying peaks at *m/e* 115 and 117 (approximate rates of 1:0.67:0.1) is assigned the elemental composition and structure of CH_3SiCl_2. There are also significant peaks at *m/e* 93, 79, 65, and 63, which all contain one chlorine atom.[16] The rationale by which these chlorinated fragments arise is presented in Schemes I and II.

Two pathways are proposed in Scheme I to account for the formation of the *m/e* 113 ion. To decide which of the two pathways was correct, trichloro(trimethylsilyl)methane (**11**) was synthesized and its spectrum recorded. Examination of Table I shows that the spectrum of **11** is practically identical with that of **1**. Path A can accommodate these similarities, if it is assumed that **1** loses a hydrogen atom to give the *m/e* 155 fragment and **11** loses a chlorine atom to give the same fragment (eq 7). Both compounds exhibit a weak *m/e* 155 peak. The appearance of metastable peaks at *m/e* 82.4 (155 → 113) and 84.2 (157 → 115) in the spectrum of **11** further supports the proposed fragmentation given in eq 7.



(7)

m/e 155 *m/e* 113

In addition to the above evidence for pathway A, the ionic intermediates **20** and **21** would seem to be adequate presursors of the other chloro fragments (Scheme II). It is difficult to rationalize a reasonable process by which the *m/e* 93, 79, and 63 fragments could form from the ionic intermediates of path B, namely, **22** and **23**. In fact, a pathway similar to B may not even be responsible for the small amount of *m/e* 133 ion observed for compound **11**. Metastable ions in the regions of *m/e* 119.5 and 121.5 suggest that the precursor of the $SiCl_3$ fragment is CH_3SiCl_3 (*m/e* 148, 150, 152, and 154).

It is interesting that the spectrum of bis(trimethylsilyl)dichloromethane (**3**) is quite different from that of **1** and **11**. The primary fragmentation of **3** must not

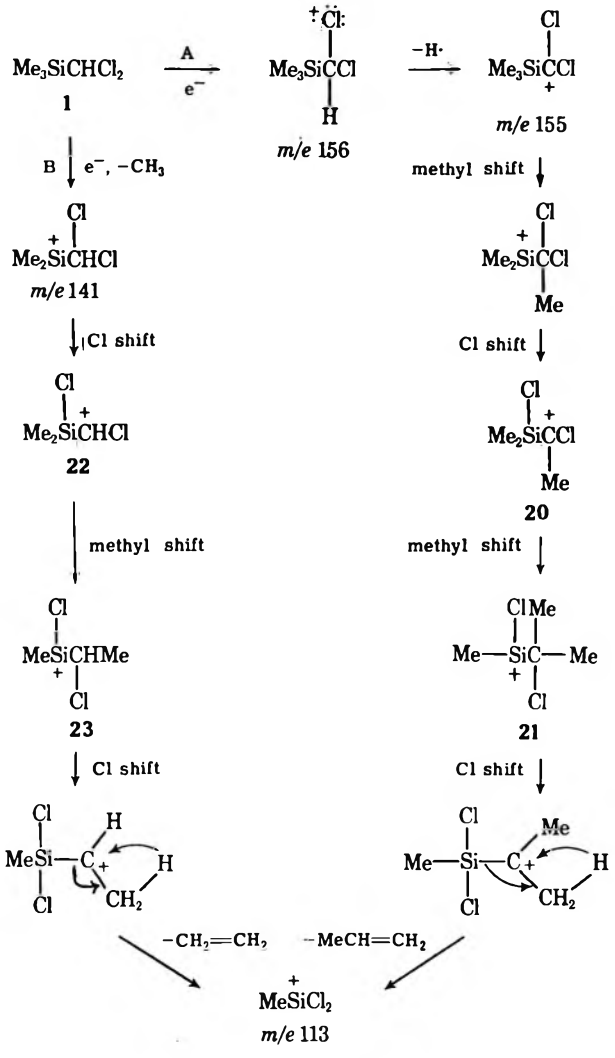
(13) In general there were few metastables in the various spectra to aid in the interpretation. The most frequent metastables were *m/e* 27.8 (73 → 45) and 41.1 (45 → 43).[2]

(14) V. H. Dibeler, F. L. Mohler, and R. M. Reese, *J. Chem. Phys.*, **21**, 180 (1953).

(15) (a) The bar graph representation of the mass spectrum of this compound will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-72-2665. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche. (b) In the supplementary data, available in the microfilm of this paper, a postulated breakdown of bis(trimethylsilyl)dichloromethane (**3**) is presented which tries to rationalize the formation of the allyl ions *m/e* 85 and 105. (c) In the supplementary data, available in the microfilm of this paper, a scheme is presented which attempts to depict reasonable structures for the fragments of **6**.

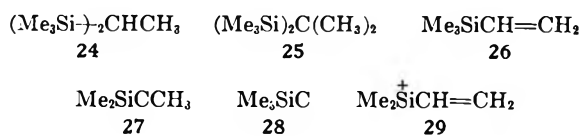
(16) The 3:1 pattern indicative of one chlorine atom is quite evident for the *m/e* 93/95 and 79/81 peaks. The *m/e* 63 and 65 fragments were assumed to be monochloro because (a) other elemental compositions do not make sense and (b) if 1/3 of the *m/e* 63 intensity is subtracted from the *m/e* 65 intensity, the remaining *m/e* 65 to 67 ratio is exactly 3:1. Other spectra containing *m/e* 63, 65, and 67 peaks also showed a similar pattern.

SCHEME I

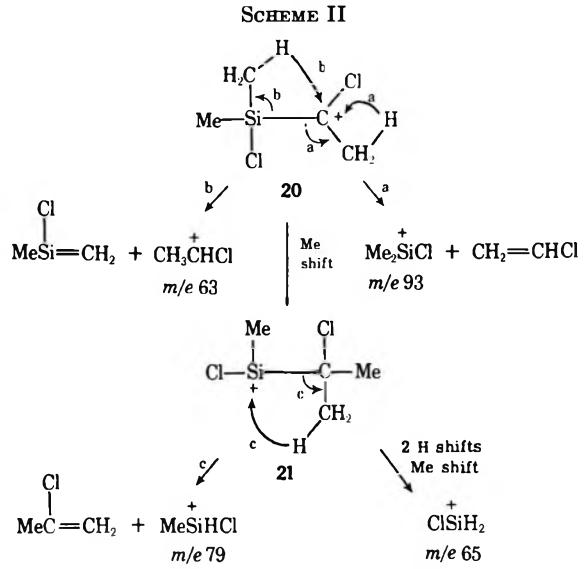


be loss of a trimethylsilyl group to give the *m/e* 155 fragment, but rather loss of a chlorine atom and eventual production of a monochloro fragment, *m/e* 93. Similarly, the differences in the spectra of **2** and **3** mean that they do not initially fragment to a common intermediate.

Allyl ions are also present in the α-chlorosilane spectra. The *m/e* 85 fragment would seem to be such an ion. Inspection of Table I reveals that the *m/e* 85 peak is absent in the spectra of the monosilated compounds, but present in all others. The fragment does not contain chlorine, as indicated by the lack of a substantial peak at *m/e* 87. Fritz, *et al.*,[5a] have proposed several structures to account for the *m/e* 85 peak. For example, they suggested structures **27** or **28** in the breakdown of **24**, **27** coming from **25** and **29** arising by loss of a methyl from **26**. Of these suggested structures, the last one seems the most reasonable (*m/e* 85 is the dominant peak in the spectrum of **26**). We are of the opinion that, regardless of the structures of the silanes, the *m/e* 85 fragment is best represented as **29**, even

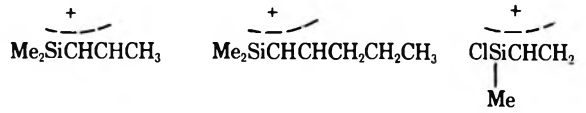


SCHEME II



though several rearrangements may have to be proposed to achieve this structure.

Besides the *m/e* 85 ion, there are other apparent allyl ions in the spectra. The butylated derivative **4** shows a pair of strong peaks, *m/e* 99 and 127, which appear to be homologs of *m/e* 85. Possible structures of these ions are **30** and **31**. Bis(trimethylsilyl)dichloromethane shows as a relatively strong peak at *m/e* 105, containing chlorine, which is probably due to the allyl ion **32**.[15b]



30, *m/e* 99 **31**, *m/e* 127 **32**, *m/e* 105

Finally, contrary to most of the spectra, tris(trimethylsilyl)chloromethane (**6**)[15a] shows several relatively abundant high molecular weight fragments, some of even mass, which lend support to the conclusion that carbon–silicon double bonds are present.[15c]

Conclusions

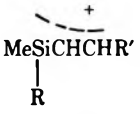
The major fragmentation site of the nonchlorinated silanes is at a C–Si bond, resulting in the formation of a tertiary siliconium ion. The direction of fragmentation by silicon can be explained by the low electronegativity of silicon; thus, silicon can accommodate a positive charge much better than carbon.[17] The presence of a trimethylsilyl group in a hydrocarbon is indicated by the homologous series of *m/e* 73, 59, 45, and 31 peaks in its mass spectrum.[4-6,14,18] The *m/e* 59 peak may, however, be very weak if there are no β, γ, ... hydrogens available for back donation to the siliconium ion as is the case for the four-carbon silanes **1** and **9**–**11**.

Both the polysilated hydrocarbons and alkyl chlo-

(17) J. Kleinberg, W. J. Argersinger, Jr., and E. Griswold, "Inorganic Chemistry," D. C. Heath, Boston, Mass., 1960, pp 104–105.

(18) R. A. Khmelńitzkii, A. A. Polyakova, and A. A. Petro, *Akad. Nauk Kirg. SSR*, 236 (1962); *Chem. Abstr.*, **62**, 2348*b* (1965).

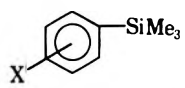
rides showed several peaks indicative of allyl ions of the following type.



R = Me; R′ = H *m/e* 85
R = R′ = Me *m/e* 99
R = Me; R′ = Pr *m/e* 127
R = Cl; R′ = H *m/e* 105, 103

R = H *m/e* 129
R = Σ *m/e* 201
R = Cl *m/e* 163, 161

Production of allyl ions was unexpected, since multiple bonding between carbon and silicon is rare.[19] Recently, Freeburger, *et al.*,[20] reported that the mass spectra of arylsilanes (**33**) and substituted benzylsilanes (**34**) displayed fragmentation patterns that were characteristic by lacking in the generation of carbon–silicon double bonds, like the one represented by structure **35**.



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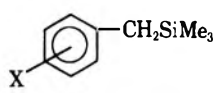

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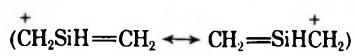
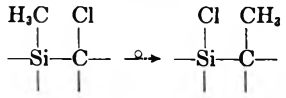


35

If it is assumed that the intensities of certain ions in a mass spectrum are related to their stabilities (and steric factors to formation), then it may be possible to explain the differences observed by Freeburger and ourselves. The aryl-substituted silanes may be able to fragment in such a way as to avoid –C=Si– situations and still give stable ions. However, allyl ions containing silicon may be moderately stable ions and reasonable postulates in the fragmentations of aliphatic silanes which have no strong cation-stabilizing groups other than silicon. Based on our results, these simple silanes are apparently good models for observing carbon–silicon multiple bonding.

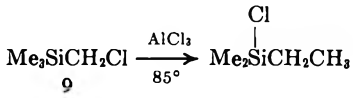
Besides displaying fragments similar to the hydrocarbon silanes, the α-chlorinated silanes show multiple rearrangements which eventually bring the silicon and chlorine together (*i.e.*, *m/e* 133, 113, 93, 79, and 65). The driving force of these rearrangements would appear to be the gain (approximately 18 kcal) in bond energies associated mainly with the strong Si–Cl bond (eq 8).[17] It is well known that chlorine can stabilize



(8)

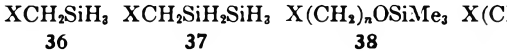
carbonium ions by 3p–2p orbital resonance; however, a chlorine should be able to stabilize a siliconium ion to even greater extent because of the more favorable 3p–3p orbital overlap. This latter fact may also account for the tendency to form chlorosiliconium ions.

Our proposal of chloro–methyl interchanges in the mass spectra of α-chlorosilanes is analogous to the ground state reaction of **9** with aluminum chloride as reported by Whitmore, Sommer, and Gould (eq 9).[21]



(9)

There have also been some recent reports of halogen rearrangements in the mass spectra of related silanes. Silicon–halogen fragments have been observed in the mass spectra of **33** and **34** (X = halogen),[20] halomethylsilanes (**36**) and disilanes (**37**),[22] and silated alcohols (**38**) and acids (**39**).[23] Besides halogen, phenyl[24] and



36 **37** **38** **39**

oxygen[21] rearrangements to silicon are known. It appears, however, that nitrogen and sulfur show little tendency to rearrange to silicon.[25] Our spectra are the first to show multiple rearrangements to silicon.

Registry No. –**1**, 5926-38-5; **2**, 5926-35-2; **3**, 15951-41-4; **4**, 27484-06-6; **5**, 1068-69-5; **6**, 27484-03-3; **7**, 1066-64-4; **8**, 1000-49-3; **9**, 2344-80-1; **10**, 75-76-3; **11**, 5936-98-1; **12**, 2117-28-4.

Acknowledgments. –We would like to thank Research Corporation for supplying funds to purchase the CEC 21-103C mass spectrometer used in this study. The assistance of Dr. T. C. Ehlert and Mr. J. Steskal was also greatly appreciated.

(19) V. G. Fritz and J. Grobe [*Z. Anorg. Allg. Chem.*, **311**, 325 (1961)] have reported the formation of $Me_2Si{=}CHSiMe_3$ in the pyrolysis of tetramethylsilane. The base peak in the mass spectrum of this compound is at *m/e* 129, which probably is best represented by the allyl ion **18**, although Fritz, *et al.*,[5a] propose the structure $MeSi{=}CHSiMe_3$.

(20) M. E. Freeburger, B. M. Hughes, G. R. Buell, T. O. Tiernan, and L. Spialter, *J. Org. Chem.*, **36**, 933 (1971).

(21) F. C. Whitmore, L. H. Sommer, and J. J. Gould, *J. Amer. Chem. Soc.*, **69**, 1976 (1947).

(22) J. M. Bellama and J. A. Morrison, Organosilicon Symposium, Carnegie-Mellon University, March 27, 1971.

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

(24) W. P. Weber, A. K. Willard, and H. G. Boettger, *ibid.*, **36**, 1620 (1971).

(25) (a) J. Diekman, J. B. Thomson, and C. Djerassi, *ibid.*, **34**, 3147 (1969); **33**, 2271 (1968).

Carbonylation of Amines with Carbon Monoxide and Silver Acetate[1]

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Facile and almost quantitative carbonylation of primary and secondary amines was performed at room temperature with a combination of carbon monoxide and silver acetate. The carbonylation product obtained depended upon the structure of the amine. Primary amines gave the corresponding *N,N'*-dialkylureas and secondary amines gave *N,N,N',N'*-tetraalkyloxamides. Carbamoylsilver derivatives, $AgC(=O)NR_1R_2$, resulting from carbon monoxide insertion into transiently formed silver–nitrogen bonds have been proposed as intermediates in the reaction.

Although the affinity of carbon monoxide to group Ib metal atoms (Cu, Ag, and Au) has been demonstrated by the formation of metal halide carbonyls, *e.g.*, $CuCl(CO)$,[2] little attention has been paid to the carbonylation of organic compound using group Ib metal compound. Recently, several interesting carbonylation reactions of copper compounds involving carbon monoxide insertion and subsequent ligand coupling have been reported by us. These include carbonate[3] and oxamide[4] formation by carbonylation of cupric alkoxides and cuprous amide, respectively. Symmetrical ketone formation by the carbonylation of organocopper complex is another example.[5] As for the carbonylation by silver compound, our previous communication[1] has reported *N,N,N',N'*-tetraethyloxamide formation by the carbonylation of diethylamine with carbon monoxide and silver acetate. However, the yield of oxamide was not high in this report. The present report is concerned with the facile and quantitative carbonylation of primary and secondary amines with a combination of carbon monoxide and silver acetate.

Results and Discussion

Primary and secondary amines underwent facile and quantitative carbonylation with a combination of carbon monoxide and silver acetate at room temperature (Table I). It is important to note that two carbonylation products were formed depending upon the structure of the amine.

$$RNH_2 \xrightarrow[CO]{AgOAc} RNHCNHR \quad (O)$$

$$R_2NH \xrightarrow[CO]{AgOAc} R_2NCCNR_2 \quad (O,O)$$

Primary amines gave predominantly the corresponding *N,N'*-dialkylureas, whereas secondary amines produced tetraalkyloxamides. Formamides were formed in small amounts; *e.g.*, in the carbonylation of diethylamine, *N,N*-diethylformamide was produced in a yield of 5% and *N*-butylformamide was detected in a yield of 3% in the case of *n*-butylamine.

Several variables of the reaction conditions were examined in the carbonylation of diethylamine. The results combined with the previous ones are summarized as follows.

(i) The amine/silver acetate ratio was important to the oxamide yield. Although the best yield of oxamide was only 40% in the ratio of 1:1,[1] an almost quantitative yield was obtained by increasing this ratio to 10:1.

(ii) Among the silver salts used (AgOAc, $AgNO_3$, AgCl, AgCN, and AgSCN), silver acetate was the most effective.[1]

(iii) Other metal acetates such as $Cu(OAc)_2$, $Zn(OAc)_2$, $Cd(OAc)_2$, $Co(OAc)_2$, and $Ni(OAc)_2$ were ineffective. $Pd(OAc)_2$ showed a slight activity.

(iv) High carbon monoxide pressure was not necessary. Carbonylation took place at a carbon monoxide pressure as low as 5 kg/cm^2.

(v) Lower reaction temperature (0° ~ room temperature) was favorable for the oxamide formation and higher reaction temperature (100–160°) diminished the yield of oxamide.[1]

(vi) Triethylamine, tetrahydrofuran, and 1,2-dimethoxyethane could be used as a reaction solvent, but pyridine and *N,N,N',N'*-tetramethylethylenediamine reduced the yield of oxamide remarkably.[1]

Examples of carbonylation reactions using transition metal compounds in which two carbonyl groups are coupled together are rare[6] and the transition metals used have been limited to group VIII. Thus, it is particularly interesting that oxamide is produced quantitatively by silver acetate under mild reaction conditions.

The determination of the stoichiometry of the reaction has provided insight into the mechanism. In the carbonylation of *n*-butylamine and diethylamine with carbon monoxide–silver acetate, metallic silver and acetic acid were formed together with the respective carbonylation products (Table II).

The yields of silver metal and acetic acid were in good agreement with those of the carbonylation products calculated on the basis of the following equations.

$$2AgOAc + 2n\text{-}BuNH_2 + CO \longrightarrow n\text{-}BuNHCNHBu\text{-}n + 2Ag + 2HOAc \quad (O)$$

$$2AgOAc + 2Et_2NH + 2CO \longrightarrow Et_2NCCNEt_2 + 2Ag + 2HOAc \quad (O,O)$$

(1) A preliminary report has appeared: T. Saegusa, T. Tsuda, K. Isayama, K. Nishijima, and Y. Isegawa, *Tetrahedron Lett.*, 1641 (1968).

(2) "Gmelins Handbuch der Anorganischen Chemie," Verlag Chemie GMBH, Weinheim/Bergstr., 1958, Kupfer, Teil B, Lieferung 1, p 240.

(3) T. Saegusa, T. Tsuda, and K. Isayama, *J. Org. Chem.*, **35**, 2976 (1970).

(4) T. Saegusa, T. Tsuda, K. Nishijima, and K. Isayama, *Tetrahedron Lett.*, 3379 (1968).

(5) T. Tsuda, K. Nishijima, and T. Saegusa, unpublished work.

(6) N. L. Bauld, *Tetrahedron Lett.*, 1841 (1963); G. Booth and J. Chatt, *J. Chem. Soc. A*, 634 (1966); J. Tsuji and N. Iwamoto, *Chem. Commun.*, 380 (1966); S. Fukuoka, M. Ryang, and S. Tsutsumi, *J. Org. Chem.*, **33**, 2973 (1968).

TABLE I

CARBONYLATION OF AMINES BY SILVER SALT AND CO[a]

Silver salt (mmol)	Registry no.	Amine (mmol)	Solvent (ml)	CO, kg/cm²	Time, hr	Yields of products, %[b] urea	oxamide
AgOAc (10)	109-73-9	n-$C_4H_9NH_2$ (50)	$N(C_2H_5)_3$ (7)	85	15.5	~100	
AgOAc (10)	107-11-9	CH_2=$CHCH_2NH_2$ (50)	$N(C_2H_5)_3$ (7)	85	15.5	73	
$AgNO_3$ (10)		n-$C_4H_9NH_2$ (100)		80	9.5	68	3
$AgNO_3$ (10)		CH_2=$CHCH_2NH_2$ (100)		80	6	60	Trace
AgOAc (10)	124-40-3	$(CH_3)_2NH$ (50)	$N(C_2H_5)_3$ (7)	80	33	Trace	~100
AgOAc (20)	109-89-7	$(C_2H_5)_2NH$ (200)	$N(C_2H_5)_3$ (20)	100	19.5		91
AgOAc (10)	111-92-2	$(n$-$C_4H_9)_2NH$ (50)		55	19.5	Trace	82

[a] The reaction was carried out at room temperature in a stainless steel tube with mechanical shaking. [b] The yield is based on silver salt. About the reaction stoichiometry; see the text.

TABLE II

STOICHIOMETRY OF CARBONYLATION OF AMINE[a]

AgOAc, mmol	Amine (mmol)	CO, kg/cm²	Time, hr	Yields of products, %[b] Oxamide	Urea	Acetic acid	Silver metal
10	n-$C_4H_9NH_2$ (100)	55	19.5		91	93	92
20	$(C_2H_5)_2NH$ (200)	100	5	90		Not determined	89
20	$(C_2H_5)_2NH$ (100)	90	7	74		72	Not determined

[a] The reaction was carried out at room temperature in a stainless steel tube with mechanical stirring. [b] The yield is based on silver acetate.

Although different carbonylation products were obtained from each, primary and secondary amines showed the same stoichiometry. This fact suggests that a commom intermediate is formed in these reactions.

It is significant to note here that mercuric acetate reacts with secondary amines in the presence of carbon monoxide to form stable carbamoylmercuric compounds with the release of acetic acid.[7]

$$2Et_2NH + Hg(OAc)_2 \xrightarrow{CO} Et_2NC(=O)HgC(=O)NEt_2 + 2HOAc$$

Carbamoylsilver may be the key reaction intermediate of the present study. In the carbonylation of secondary amines, the carbon monoxide insertion into a transient silver–nitrogen bond could give rise to a carbamoylsilver derivative with the liberation of acetic acid. In the N,N-dialkylcarbamoylsilver complexes, the nitrogen atom has no abstractable hydrogen and therefore the coupling of the two carbamoyl groups occurs to give oxamide and metallic silver.

$$2R_2NH + 2AgOAc \xrightarrow{2CO} 2\left[O{=}C(NR_2)\text{---}C(=O)OAg\right] \longrightarrow 2HOAc + 2[R_2NC(=O)Ag] \longrightarrow R_2NC(=O)C(=O)NR_2 + 2Ag$$

In the case of primary amines, the nitrogen atom of the carbamoylsilver species has one hydrogen atom. The abstraction of the hydrogen and the scission of the carbon–silver bond in carbamoylsilver may take place simultaneously to produce the corresponding alkyl isocyanate. Then the isocyanate would react rapidly with another molecule of primary amine to give the urea. In the carbonylation of primary amines with carbon monoxide–silver nitrate, a small amount of N,N'-dialkyloxamide was formed, which was probably derived from coupling of the carbamoylsilver species.

The carbonylation of an equimolar mixture of n-butylamine and diethylamine is compatible with an isocyanate intermediate.

$$AgOAc + n\text{-}C_4H_9NH_2 + (C_2H_5)_2NH \xrightarrow[\text{room temp, 25 hr}]{CO\ 55\ kg/cm^2}$$

$$n\text{-}C_4H_9NHC(=O)N(C_2H_5)_2 \quad (33\%) + n\text{-}C_4H_9NHC(=O)NHC_4H_9\text{-}n \quad (5\%)$$

$$(C_2H_5)_2NC(=O)N(C_2H_5)_2 \quad (0\%) + (C_2H_5)_2NC(=O)C(=O)N(C_2H_5)_2 \quad (3\%)$$

N,N'-Di-n-butylurea and N-n-butyl-N',N'-diethylurea were found, but N,N,N',N'-tetraethylurea could not be detected. These facts exclude the possibility of urea formation by the attack of amine on carbamoylsilver. n-Butylamine apparently reacts with silver acetate faster than it does with diethylamine to give n-butyl isocyanate, which then is attacked by the unreacted diethylamine to produce the unsymmetrical urea as the main product. The formation of N,N,N',N'-tetraethyloxamide indicates the intermediacy of diethylcarbamoylsilver. However, because of its inability to give an isocyanate intermediate, N,N,N',N'-tetraethylurea formation is impossible.

The carbonylation of an equimolar mixture of silver acetate, diethylamine, and organic halide such as ethyl bromide and allyl chloride did not change the yield of oxamide, and N,N-diethylpropionamide and N,N-diethylvinylacetamide were not detected. This result suggests that the carbonylation reaction may occur very rapidly in the silver acetate–amine complex.

Experimental Section

Reagents.—Silver acetate and other metal acetates were commercial reagents and were used without further purification. Commercial metal acetates which contain the water of hydration were dehydrated by heating *in vacuo*. Amines except dimethylamine were refluxed and distilled over KOH. Dimethylamine was generated by adding its aqueous solution to anhydrous

(7) U. Schoellkopf and F. Gerhart, *Angew. Chem.*, **78**, 675 (1966).

calcium carbonate, and was dried by passing through NaOH pellets and condensed at Dry Ice temperature. Carbon monoxide was obtained from a commercial cyclinder.

General Procedure of Carbonylation.—Silver salt, amine, and solvent, if used, were placed in a 50-ml stainless steel tube under nitrogen, into which carbon monoxide gas was compressed at room temperature. The tube was closed and heated. After reaction, carbon monoxide was released, and the organic layer was separated from the precipitated silver metal by centrifugation. The silver metal was washed several times with ether. The organic layer, combined with the ether washings, was concentrated and analyzed by glpc (9-ft column of Silicon DC 200 on Celite 545). Urea and oxamide were identified by comparison of ir spectra and glpc retention times with those of authentic samples. The authentic samples of oxamides were prepared from oxalyl chloride and amine. The authentic symmetrical ureas were obtained by the reaction of phosgene and amine. The authentic unsymmetrical ureas were synthesized from carbamoyl chloride and amine.

Stoichiometry of the Carbonylation Reaction. Determination of Silver Metal Deposited and Acetic Acid Liberated.—After reaction, the precipitated silver metal was separated by centrifugation and washed several times with the amine used in the reaction. Then silver metal was oxidized to silver nitrate by concentrated nitric acid and titrated with ammonium thiocyanate using ferric ammonium sulfate as an indicator. The acetic acid liberated in the reaction was determined by glpc analysis of the separated organic layer combined with the amine washings (9-ft column of PEG 20M on Celite 545).

Registry No.—CO, 630-08-0; AgOAc, 563-63-3; $AgNO_3$, 7761-88-8.

endo-7-Aminomethylbicyclo[3.3.1]nonan-3-ones from Rearrangement of 1-N-Substituted *N*-Haloadamantanamines by Aluminum Chloride[1]

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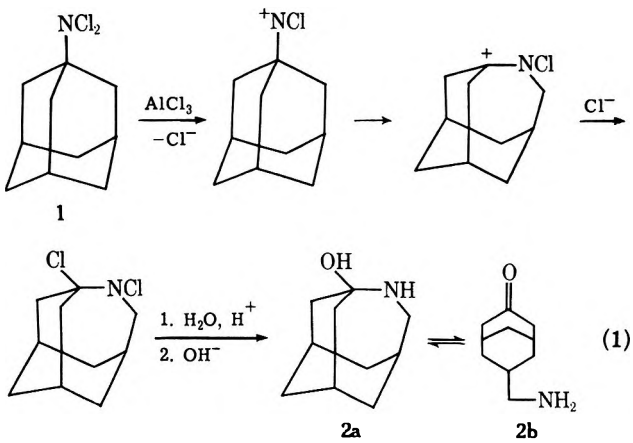
Received March 9, 1972

Treatment of *N*-chloro-*N*-ethyl-1-adamantanamine (**3**) with aluminum chloride afforded rearranged product which was isolated as *endo*-*N*-ethyl-7-aminomethylbicyclo[3.3.1]nonan-3-one (**4**) after acid hydrolysis. The configurational and conformational aspects of the isomeric alcohols obtained by hydride reduction are treated. The response of 3-methoxy-4-azahomoadamantanes to hydrolysis and hydride reduction was investigated. Rearrangement of *N*-chloro- and *N*,*N*-dibromo-1-adamantanamines yielded *endo*-7-aminomethylbicyclo[3.3.1]-nonan-3-one (**2**). Evidence is presented concerning the nature of the carbinolamine–amino ketone equilibrium for **2** and **4**.

Several rearrangements of *N*-haloamines have been characterized.[3] Most noted is the Hofmann–Löffler cyclization *via* an amminium radical.[4] α-Amino ketones are generated by the action of base on *N*,*N*-dichloro-*sec*-alkylamines, presumably by a pathway analogous to the Neber rearrangement.[5] Nitrenium ions have been proposed as intermediates in the Stieglitz rearrangement of *N*-halo- and *N*,*N*-dihalotritylamines.[6]

Evidence for the existence of a discrete electron-deficient nitrogen of this type was obtained[6] through studies of *N*-chloroalkylamine rearrangements in the presence of silver salts. Gassman's group,[6] as well as other investigators,[7] found that alkyl migration to nitrogen occurred with a strained ring system whose carbon analog is known to undergo carbonium ion rearrangement quite readily. Similar transformations of primary *N*-haloamines in the presence of aluminum chloride were observed when nitrogen was adjacent to a bicyclic[8] or tricyclic[9] ring system. For example, *N*,*N*-dichloro-1-adamantanamine (**1**) was converted to 7-aminomethylbicyclo[3.3.1]nonan-3-one (**2b**) by rearrangement followed by hydrolysis.[9] The postulated mechanism is depicted in eq 1. An analogous



(1)

rearrangement was recently reported for *N*-acetyl-*N*-chloro-1-adamantanamine.[10]

The objective of the present work was to determine the effect of variation in the substitutent on rearrangement of 1-N-substituted *N*-haloadamantanamines. The chemical behavior of various compounds obtained in this study was examined. In addition, carbinolamine–ketoamine equilibria and stereochemical aspects were investigated.

Results and Discussion

Most of our attention was devoted to the rearrangement of *N*-chloro-*N*-ethyl-1-adamantanamine (**3**). Synthesis of **3** was accomplished by hydride reduction of

(1) Paper V, "Adamantanes and Related Compounds;" for the preceding publication in the series see ref 9; presented at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972.

(2) Postdoctoral, 1970–1971.

(3) P. Kovacic, M. K. Lowery, and K. W. Field, *Chem. Rev.*, **70**, 639 (1970).

(4) M. E. Wolff, *ibid.*, **63**, 55 (1963).

(5) H. E. Baumgarten and F. A. Bower, *J. Amer. Chem. Soc.*, **76**, 4561 (1954).

(6) P. G. Gassman, *Accounts Chem. Res.*, **3**, 26 (1970).

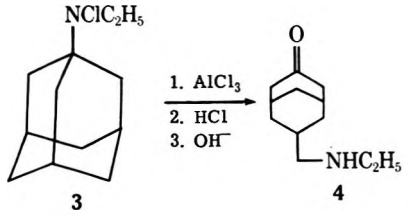
(7) H. H. Wasserman, H. W. Adickes, and O. E. de Ochoa, *J. Amer. Chem. Soc.*, **93**, 5586 (1971).

(8) P. Kovacic, M. K. Lowery, and P. D. Roskos, *Tetrahedron*, **26**, 529 (1970).

(9) P. Kovacic, J.-H. Liu, P. D. Roskos, and E. M. Levi, *Chem. Commun.*, 1034 (1970); *J. Amer. Chem. Soc.*, **93**, 5801 (1971).

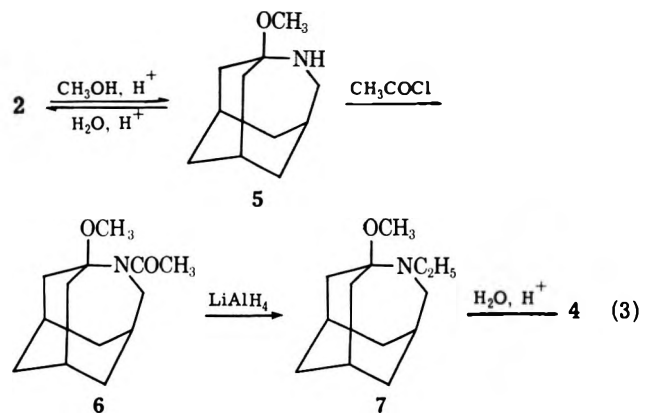
(10) T. Sasaki, S. Eguchi, T. Kiriyama, and H. Suzuki, *Syn. Commun.*, **1**, 267 (1971).

N-acetyl-1-adamantanamine followed by chlorination with calcium hypochlorite. Since the reduction process generated a minor amount of 1-adamantanamine, through a side reaction characteristic of hindered amides,[11] there was slight contamination (<5%) of **3** by **1**. When **3** was exposed to conditions similar to those used with **1**, *endo*-*N*-ethyl-7-aminomethylbicyclo[3.3.1]nonan-3-one (**4**) was isolated as the major product (65% yield), eq 2. The *N*-ethylamino ketone



3 4 (2)

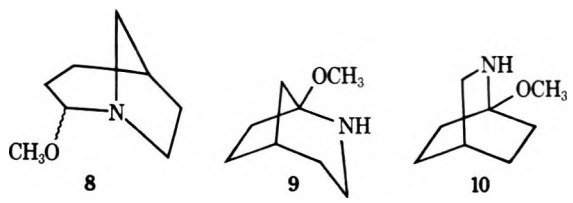
4 is apparently formed in a manner analogous to the conversion of **1** to **2**. The remainder of **3** was mostly accounted for by isolation of *N*-ethyl-1-adamantanamine which could possibly arise either from acid hydrolysis of unchanged **3** or from an intermediate nitrenium ion. Gassman has demonstrated[6] that electron-deficient singlet nitrogen is able to convert to the triplet state, which can abstract hydrogen as a competing process. Structure **4**, assigned by analogy to **2**, was supported by spectral data and elemental analysis. The ir spectrum clearly showed the presence of a keto group and a secondary amine. The amine functionality was also evident from the nmr spectrum in that one proton exchanged with D_2O; the triplet of the *N*-ethyl group was distinct. In addition, confirmation was obtained by independent synthesis, eq 3. The conversion of **2**



(3)

to 3-methoxy-4-azahomoadamantane (**5**) has been reported,[9] as well as the hydrolytic reverse. Acylation of **5** yielded acetamide **6**, which was then reduced with $LiAlH_4$ to the tertiary amine **7**. On acid hydrolysis, **7** readily underwent ring cleavage to afford **4**. In addition to acceptable elemental analyses, the intermediates displayed ir and nmr spectra in accord with the assigned structures.

Acid hydrolysis of α-amino ethers is reported[12] to proceed through formation of an iminium ion, $R_2N{=}CH_2{}^+$. However, for **5** and **7** delocalization in this manner would introduce double-bond character at the bridgehead position. Indeed, the resistance of 2-methoxy-1-azabicyclo[3.2.1]octane (**8**) to acid hydrolysis was rationalized[13] on this basis. In contrast, Reed and Lwowski[14] were able to effect hydrolysis of 1-methoxy-2-azabicyclo[3.2.1]octane (**9**) and 1-methoxy-2-azabicyclo[2.2.2]octane (**10**) by prolonged heating with acid. Although **9** could conceivably accommodate a strained double bond at the bridgehead,[14] as is also the case perhaps with **5** and **7**, compounds **8** and **10** are

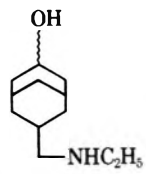


8 9 10

much less prone to do so because little, if any, overlap would occur between the π orbitals of C and N.[14]

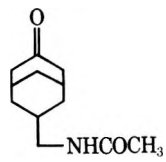
As previously discussed,[14] an alternate path appears to be available for hydrolysis of **9** and **10**, and possibly for **5** and **7**. Initial protonation on nitrogen and subsequent ring cleavage would give a resonance-stabilized, carbonium–oxonium ion which could serve as precursor of the amino ketone.

Various aspects of the chemical behavior of **4** were examined. $LiAlH_4$ reduction provided the isomeric *N*-ethylamino alcohols **11** and **12**.



11 (endo)
12 (exo)

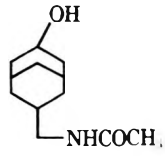
As predicted on the basis of steric factors, glpc analysis showed that the endo isomer predominated by a ratio of 4:1. Each of the isomeric alcohols gave satisfactory spectral and elemental analyses. In addition, similar reducing conditions applied to amide **13**[15]



13

yielded the same isomeric amino alcohols (**11** and **12**) with an endo:exo ratio of 3:2.

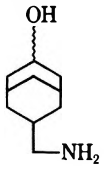
A high degree of stereoselectivity was obtained[15] when **13** was reduced with the less reactive sodium borohydride. The resulting amide alcohol **14** was



14

(11) P. A. S. Smith, "Open-Chain Nitrogen Compounds," Vol. I, W. A. Benjamin, New York, N. Y., 1965, pp 150–151.
(12) T. D. Steward and W. E. Bradley, *J. Amer. Chem. Soc.*, **54**, 4172 (1932); H. Meerwein in "Methoden der Organischen Chemie," Vol. VI, Part 3, E. Muller, Ed., Georg Thieme Verlag, Stuttgart, 1965, p 195.
(13) P. G. Gassman and B. L. Fox, *J. Amer. Chem. Soc.*, **89**, 338 (1967).
(14) J. O. Reed and W. Lwowski, *J. Org. Chem.*, **36**, 2864 (1971).
(15) J. A. Tonnis and T. A. Wnuk, unpublished work.

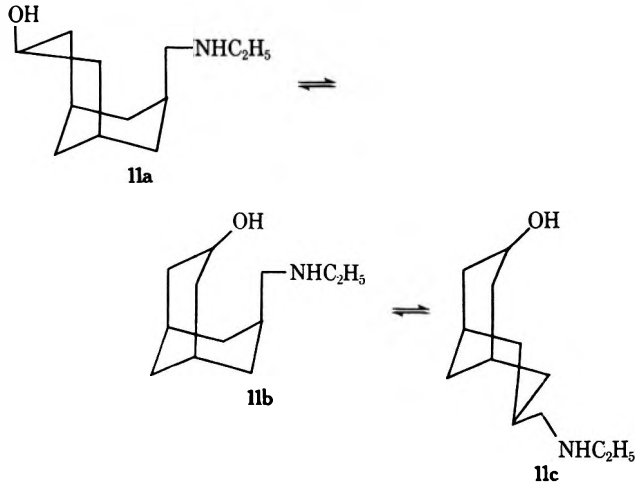
essentially the endo isomer, since subsequent conversion of the amide functionality with $LiAlH_4$ yielded *N*-ethylamino alcohol which was greater than 98% endo. Confirmation of the stereospecificity of the $NaBH_4$ reduction was provided by hydrolysis[15] of **14** to the endo amino alcohol **15**. None of the exo isomer **16** could be



15 (endo)
16 (exo)

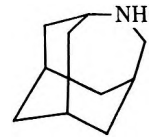
detected by glpc analysis. The $NaBH_4$ reduction of **2** in ethanol has been found[15] to afford **15** and **16** with an endo:exo ratio of 3:1. Analogous stereospecificity pertains in the hydride reduction of camphor.[16a]

Endo and exo assignment of isomers was based on spectral and chemical evidence. The parent hydrocarbon, bicyclo[3.3.1]nonane, is known to exist in the chair–chair conformation.[17] However, when an endo substituent is introduced at either C_3 or C_7, the substituted ring prefers the boat form.[17,18] An exo substituent maintains the chair–chair relationship. With the *N*-ethylamino alcohols, the aminomethyl group must be in the endo position. For both isomers, the most stable conformation will result when the aminomethyl-substituted ring is in the boat conformation, *e.g.*, **11c**. Distinction between isomeric alcohols can



11a **11b** **11c**

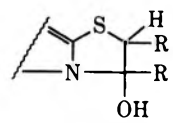
then be obtained from the vicinal splitting of the carbinyl proton in the nmr.[18b]. As expected, the minor isomer **12** showed a larger vicinal coupling constant than did the endo. Similar observations[15] were obtained for **15** and **16**. Amino alcohols **15** and **11** must have the same configurations since both are produced from **14**. In other studies mass spectral analysis has been used[19] to distinguish between the 3-*endo*- and 3-*exo*-bicyclo[3.3.1]nonanols, and oxidation is also reported[16b] as a means of differentiating between endo and exo isomers. In contrast to the $LiAlH_4$ reduction of the *N*-ethyl derivative **4**, parent **2** is known[9] to yield azahomoadamantane (**17**).



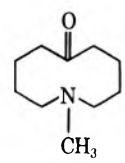
17

Attention was also devoted to the carbinolamine–ketoamine equilibrium situation for **2** and **4**. The ir spectrum of **2** in solution ($CHCl_3$) shows a carbonyl band of medium intensity at 1700 cm^{-1}, which is comparatively weak for this functional group. In the solid state (Nujol or KBr), the spectrum displays very weak absorption at 1650 cm^{-1}, indicating that the compound has little carbonyl characteristics in this physical form; the spectrum also shows strong absorption bands at 3300 and 3480 cm^{-1} which can be assigned either to NH_2 of **2b** or to the OH and NH of **2a**. However, from the weak carbonyl absorption observed, it is apparent that there is significant interaction between the carbonyl and amine functionalities, which can be described as an equilibrium between amino ketone **2b** and carbinolamine **2a** or as intimate complexing (hydrogen bonding or nucleophilic–electrophilic attraction) of the two groups. In any case, the interaction is carried to its full extent when **2** is converted to its hydrochloride salt. The ir spectrum of this derivative in the solid state is completely devoid of any carbonyl absorption.

Intramolecular interaction between amine and carbonyl groups has been noted by a number of prior investigators. In relation to the carbinolamine–amino ketone isomers, it is claimed[20] that when the ring is larger than five members the open-chain form is favored in certain heterocyclic series. Evidence indicates[21] that for compounds of type **18** some members



R = H, alkyl
18



19

assume this form both in the solid state and in solution, whereas others exist as the cyclic structure in the solid phase and as a tautomeric mixture in solution. Leonard and coworkers have studied[22] compounds such as **19** in which transannular interaction occurs between nitrogen and carbonyl carbon. Indeed, for the salt form a transannular covalent bond is apparently established.

In contrast, *N*-ethylamino ketone **4** shows strong carbonyl absorption in the ir for both the free amine and its hydrochloride salt, indicating little, if any, binding between amino and carbonyl. This situation can be ascribed to steric interference resulting from the ethyl group. Hence, the keto of **4** behaves typically in the $LiAlH_4$ reduction.

(16) (a) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 31; (b) p 83.

(17) G. L. Buchanan in "Topics in Carbocyclic Chemistry," Vol. 1, D. Lloyd, Ed., Plenum Press, New York, N. Y., 1969, p 199.

(18) (a) J. A. Peters, J. D. Remijnse, A. van der Wiele, and H. van Bekkum, *Tetrahedron Lett.*, 3065 (1971); (b) W. D. K. Macrosson, J. Martin, and W. Parker, *ibid.*, 2589 (1965).

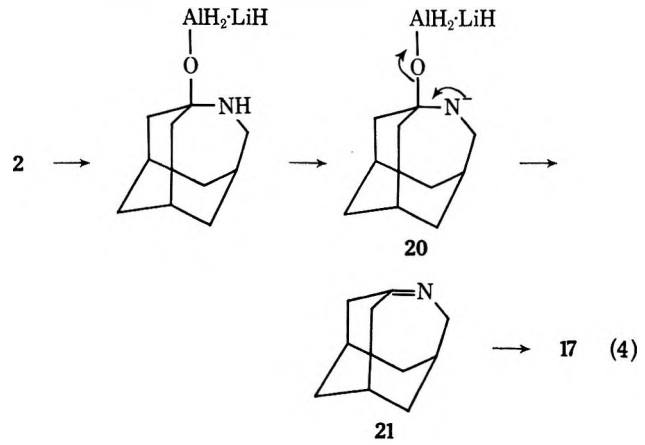
(19) J. K. MacLeod, M. Vegar, and R. J. Wells, *Recent Develop. Mass Spectrosc., Proc. Int. Conf. Mass Spectrosc.*, 1197 (1969); *Chem. Abstr.*, **75**, 97901 (1971).

(20) H. Singh and A. Singh, *Tetrahedron Lett.*, 585 (1970).

(21) A. E. Alper and A. Taurins, *Can. J. Chem.*, **45**, 2903 (1967).

(22) N. J. Leonard, *Rec. Chem. Progr.*, **17**, 243 (1956).

In the reaction[9] of **2** with $LiAlH_4$, the reducing agent may shift the equilibrium in favor of the carbinolamine structure by Lewis acid coordination[14] with carbonyl oxygen or by conversion of the primary amine to the more nucleophilic amide anion form.[9] Subsequent generation of anion **20** could result in displacement[9] of oxygen to form azahomoadamantene (**21**) which would be converted with ease to **17**, eq 4.



A related pathway has been postulated[14] in the $LiAlH_4$ reduction of **9**. The inertness[13,14] of **8** and **10** is presumably due to the reluctance of the bridgehead to assume double bond character. Reed and Lwowski suggested[14] that either the lone pair on nitrogen or the anion form could expel the adjacent oxygen. We believe, however, that involvement of the anion is necessary for formation of a bridgehead double bond. Although **2** and **5** were readily converted to **17**, the *tert*-amino ether **7** resisted reduction. Indeed, **7** was prepared in high yield by treating **6** with a large excess of $LiAlH_4$.

Since electron-deficient nitrogen appears to be involved in the rearrangement of **3** to **4**, we explored the behavior of **3** on exposure to silver salts according to the procedure of Gassman.[6] However, only a 5% yield of **4** was obtained with silver perchlorate. On prolonged heating with silver nitrate, the yield of **4** was increased to 22%. In both cases the majority of **3** was isolated as *N*-ethyl-1-adamantanamine. Similar reduced yields of **2** were noted when **1** was treated with silver salts. The reason for the greater effectiveness of aluminum chloride remains obscure.

N,*N*-Dibromo-1-adamantanamine (**22**) underwent facile rearrangement. With aluminum bromide catalyst, **2** was isolated in yields comparable to those obtained from **1**. *N*-Chloro-1-adamantanamine (**23**) afforded **2** in only 10% yield. The presence of an ethyl or halogen[23] substituent on the nitrenium ion would be expected to exert a favorable influence on ease of formation, and hence can rationalize the improved yields from rearrangements involving **1**, **3**, and **22**.

Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra were obtained with a Beckman IR-8 spectrophotometer (calibrated with the 1601-cm^{-1} band of polystyrene). Varian T-60 and HA-100 instruments were used to obtain nmr data, which are reported in parts per million relative to tetramethylsilane as internal standard. Gas chromatography was carried out with a Varian Aerograph instrument (A-90-P or 1700) with a 15 ft × 0.25 in. column of 15% Carbowax 20M and 10% sodium hydroxide on Chromosorb P (30/60).

Positive halogen in *N*-haloamines was determined by standard iodometric titration methods.[3] Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill., and by Mr. A. Gasiecki.

N-**Ethyl-1-adamantanamine.**—A sample of 19.33 g (0.1 mol) of *N*-acetyl-1-adamantanamine (Aldrich Chemical Co.) was placed in a Soxhlet apparatus and continuously extracted into a suspension of 10.32 g (0.272 mol) of lithium aluminum hydride in 800 ml of dry ether. After the extraction had continued for 72 hr, the mixture was cooled in an ice bath as 10 ml of water was slowly added, followed by 10 ml of 15% sodium hydroxide, and then by an additional 20 ml of water. The resulting mixture was filtered. The filtrate was dried over sodium sulfate and then evaporated to yield 18.2 g of the crude amine as a yellow oil. Distillation afforded 14.82 g (83%) of *N*-ethyl-1-adamantanamine, bp 57–59° (0.1 mm) [lit.[24] bp 101–102.5° (7 mm), lit.[25] mp 28°].

N-**Chloro-***N*-**ethyl-1-adamantanamine** (**3**).—To a mixture of 20.4 g of HTH [0.1 mol of $Ca(OCl)_2$] and 250 ml of water was added a solution of 11.01 g (0.0614 mol) of *N*-ethyl-1-adamantanamine in 100 ml of methylene chloride below 5°. After being stirred at 0–5° for 4.5 hr, the mixture was filtered and the layers were separated. The aqueous solution was extracted with four 100-ml portions of methylene chloride. The combined organic solution was dried over sodium sulfate and evaporated to yield 10.05 g (79%) of **3**, mp 45–51°, as a pale yellow solid; a sample of **3** titrated for the theoretical amount of chlorine.

Rearrangement of 3.—A solution of 35 mmol of **3** in 100 ml of methylene chloride was chilled to −30°. Aluminum chloride (11.1 g, 82 mmol) was added in one portion, and the mixture was then allowed to warm to 0°. After the mixture was stirred for 1.5 hr under a nitrogen sweep at 0°, 175 ml of concentrated hydrochloric acid was slowly added below 3°. The mixture was then stirred at room temperature for 2 hr and diluted with 200 ml of water, and the layers were separated. The methylene chloride phase was extracted with two 30-ml portions of concentrated hydrochloric acid and then with 60 ml of water. The aqueous solution was slowly added to 300 ml of 50% sodium hydroxide solution below 20°. The resulting suspension was extracted with two 200-ml portions of methylene chloride which was washed with 100 ml of water, dried over sodium sulfate, and then evaporated to yield 6.3 g of an orange oil. Glpc analysis showed that **4** was formed in 65% yield and *N*-ethyl-1-adamantanamine in 24% yield, in addition to several minor components. Distillation of the mixture afforded a pure sample of **4**, bp 83–85° (0.05 mm), which changed on standing to a white solid: mp 44–46°; ir (neat) 3320 (NH) and 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.87 (s, 1, NH, exchangeable), 1.06 (t, 3, CH_2CH_3) and 2.17 (m, 17, CH, CH_2).

Anal. Calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17. Found: C, 74.06; H, 10.73; N, 7.15.

N-**Acetyl-3-methoxy-4-azatricyclo[4.3.1.1^{3,8}]undecane** (**6**).—A solution of 2 ml (28 mmol) of acetyl chloride in 5 ml of benzene and 5 ml of pyridine was slowly added to a solution of 1.27 g (7 mmol) of **5**[9] in 10 ml of benzene and 10 ml of pyridine. After the mixture was stirred for 30 min at room temperature, it was poured into 100 ml of water. The benzene layer was separated and the aqueous layer was extracted with 25 ml of benzene. The combined benzene solution was washed with 25 ml of 5% sodium bicarbonate, dried (Na_2SO_4), and then evaporated to yield 1.21 g (78%) of **6**, mp 92–94°. Recrystallization from petroleum ether (bp 40–60°) gave prismatic plates: mp 97–99°; ir (CCl_4) 1620 (C=O), 1060 and 1080 cm^{-1} (COC); nmr ($CDCl_3$) δ 1.92 (m, 13, CH, CH_2), 2.28 [s, 3, (C=O)CH_3], 3.16 (s, 3, OCH_3), and 3.83 (d, 2, NCH_2).

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.20; H, 9.22; N, 6.23.

N-**Ethyl-3-methoxy-4-azatricyclo[4.3.1.1^{3,8}]undecane** (**7**).—A solution of 0.62 g (2.8 mmol) of **6** in 50 ml of ether was slowly added to a mixture of 0.5 g (13 mmol) of lithium aluminum hydride in 75 ml of ether so as to maintain a gentle reflux. After

(23) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 102.

(24) E. I. du Pont de Nemours and Co., Belgian Patent 646,581 (1964); *Chem. Abstr.*, **63**, 14726 (1965).

(25) E. Gottwald and H. Machoczek, German Patent 1,294,371 (1969); *Chem. Abstr.*, **71**, 38464 (1969).

being refluxed for 40 hr, the mixture was cooled in an ice bath while 0.5 ml of water was slowly added followed by 0.5 ml of 15% sodium hydroxide, and then by an additional 1 ml of water. The mixture was filtered and the filtrate was dried (Na_2SO_4) and evaporated to yield 0.51 g (88%) of **7** as a pale yellow oil: glpc indicated a purity greater than 98%; ir (neat) 1040 and 1070 cm^{-1} (COC); nmr ($CDCl_3$) δ 1.03 (t, 3, CH_2CH_3), 1.80 (m, 13, CH, CH_2), 2.76 (m, 4, NCH_2), and 3.13 (s, 3, OCH_3).

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.08; N, 6.69. Found: C, 74.72; H, 10.91; N, 6.80.

***N*-Ethyl-7-aminomethylbicyclo[3.3.1]nonan-3-one (4) from 7.**—A 0.913-g (0.924 mmol) sample of **7** was dissolved in 10 ml of 18% hydrochloric acid. After standing at room temperature for 16 hr, the solution was poured into 30 ml of 15% sodium hydroxide. The resulting suspension was extracted with two 25-ml portions of ether. The combined ether extract was dried (Na_2SO_4) and then evaporated to yield 0.172 g (95%) of **4**; ir and nmr spectra were identical with those of a sample of **4** prepared from **3**.

***N*,*N*-Dibromo-1-adamantanamine (22).**—To a solution of 9.6 g (0.24 mol) of sodium hydroxide in 75 ml of water, 6.8 ml (0.12 mol) of bromine was added below 0°. A solution of 5 g (0.033 mol) of 1-adamantanamine in 75 ml of methylene chloride was introduced below 0°. After the mixture was stirred at 0–5° for 6.5 hr, the layers were separated, and the aqueous portion was extracted with two 25-ml portions of methylene chloride. The combined organic solution was dried over sodium sulfate and evaporated to yield 8.16 g (80%) of **22**, mp 63–66° dec, which titrated for 89% of the theoretical amount of bromine. Sublimation afforded an analytical sample of **22**, mp 67–67.5°, which titrated for 99.8% of the theoretical amount of bromine.

Anal. Calcd for $C_{10}H_{15}NBr_2$: C, 38.86; H, 4.89; N, 4.53. Found: C, 39.01; H, 4.87; N, 4.58.

Rearrangement of 22.—A solution of 0.0262 mol of **22** in 230 ml of methylene chloride was chilled to −30°. Aluminum bromide (16 g, 0.06 mol) was then added in one portion, and the reaction temperature was allowed to rise to 0°. The mixture was stirred under a nitrogen sweep for 1.5 hr at 0°. Hydrochloric acid (18%) (200 ml) was slowly added below 3°. After the mixture was allowed to warm to room temperature, stirring was maintained for 2 hr. The layers were separated and the methylene chloride phase was extracted with two 50-ml portions of 18% hydrochloric acid. The combined acid solution was slowly added to 200 ml of 50% sodium hydroxide below 10°. The white solid which separated was collected, washed with water, and recrystallized from 95% ethanol to yield 3.15 g (72%) of **2**, mp 165–167° (lit.[9] mp 166.5–167.5°).

***N*-Chloro-1-adamantanamine (23).**—The preparation was according to the previously reported procedure.[26] Extension of the reaction time to 1 hr afforded a 74% yield.

Treatment of *N*-Chloro-1-adamantanamine (23) with Aluminum Chloride.—A solution of 3.01 g (16.4 mmol) of **23** in 150 ml of methylene chloride was chilled to −30°. After aluminum chloride (4.6 g, 34.6 mmol) was added in one portion, the mixture was allowed to warm to 0°. The mixture was stirred at 0° under a nitrogen sweep for 1.5 hr. Concentrated hydrochloric acid (35 ml) was slowly added below 3°. After the mixture was allowed to warm to room temperature, 40 ml of water was added to dissolve the suspended solid, the mixture was then stirred for 2 hr, and then the layers were separated. The organic layer was extracted with two 25-ml portions of concentrated hydrochloric acid. The combined acidic solution was slowly added to 125 ml of 50% sodium hydroxide below 5°. The white solid which separated was collected, washed with water, and recrystallized from 95% ethanol to yield 0.41 g (15%) of **2**, mp 166–167° (lit.[9] mp 166.5–167.5°).

$LiAlH_4$ Reduction. General Procedure.—An ethereal solution of the compound to be reduced was slowly added to a suspension of $LiAlH_4$ (x g) in ether. After the mixture had refluxed for 24 hr, it was cooled in an ice bath as x ml of water followed by x ml of 15% sodium hydroxide and an additional $2x$ ml of water were slowly added. The mixture was filtered; the filtrate was dried (Na_2SO_4) and evaporated to yield the designated products.

11 and 12 from 13.—A sample of 210 mg (1.0 mmol) of **13** was reduced with 130 mg (3.4 mmol) of $LiAlH_4$ to yield a mixture (174 mg, 88%) of **11** and **12**. Glpc analysis showed 62% of **11** and 38% of **12**.

Alcohol **11** had mp 110–111°; ir ($CHCl_3$) 3200 (NH, OH) and 1110 cm^{-1} (COH); nmr ($CDCl_3$) δ 4.09 (m, 1, $J_{AX} \cong J_{BX}$ = 3 Hz, CHOH), 2.58 (m, 4, $CH_2NHCH_2CH_3$), 1.90 (m, 15, CH, CH_2, NH, OH), 1.09 (t, 3, CH_2CH_3); mass spectrum m/e (rel intensity) 197 (49), 79 (12), 58 (100), 30 (31).

Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.78; H, 11.85; N, 7.02.

12 had mp 131.5–133°; ir ($CHCl_3$) 3200 (NH, OH) and 1100 cm^{-1} (COH); nmr ($CDCl_3$) δ 3.92 (m, 1, J_{AX} = 5, J_{BX} = 15 Hz, CHOH), 2.54 (m, 4, $CH_2NHCH_2CH_3$), 1.86 (m, 11, one exchangeable proton), 1.10 (m, 7, one exchangeable proton); mass spectrum m/e (rel intensity) 197 (20), 95 (29), 58 (100), 46 (50), 30 (25).

Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 73.18; H, 12.04; N, 6.97.

11 and 12 from 4.—**4** (195 mg, 1.0 mmol) was reduced with 100 mg (2.6 mmol) of $LiAlH_4$ to yield a mixture (160 mg, 82%) of **11** and **12**; glpc analysis showed 82% of **11** and 18% of **12**.

11 and 12 from 14.—**14** (214 mg, 1.0 mmol) was reduced with 110 mg (2.9 mmol) of $LiAlH_4$ to yield a mixture (149 mg, 76%) of **11** and **12**; glpc analysis showed 98% of **11** and 2% of **12**.

17 from 5.—A sample of 525 mg (2.9 mmol) of **5** was reduced with 300 mg (7.9 mmol) of $LiAlH_4$ to yield 390 mg (90%) of **17**, identified by comparison to an authentic sample.[9]

2 HCl and 4 HCl.—Hydrogen chloride gas was passed through an ethereal solution of the amine until precipitation ceased; **2** HCl had mp 192–193° dec.

Anal. Calcd for $C_{10}H_{18}NOCl$: C, 58.96; H, 8.91; N, 6.88. Found: C, 58.86; H, 8.69; N, 6.87.

4 HCl had mp 221–224° dec.

Anal. Calcd for $C_{12}H_{22}NOCl$: C, 62.18; H, 9.56; N, 6.04. Found: C, 61.89; H, 9.43; N, 6.15.

Registry No.—**2a** HCl, 34934-77-5; **2b**, 34650-78-7; **3**, 34913-37-6; **4**, 34913-38-7; **4** HCl, 34913-39-8; **6**, 34913-40-1; **7**, 34913-41-2; **11**, 34913-42-3; **12**, 34913-43-4; **22**, 34913-44-5.

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(26) P. Kovacic and P. D. Roskos, *J. Amer. Chem. Soc.*, **91**, 6457 (1969).

An Improved Synthesis of a 9-Oxo-6,7-benzomorphan and Its Homolog. A Novel Rearrangement of Heterocyclic Enamines *via* Bromination[1]

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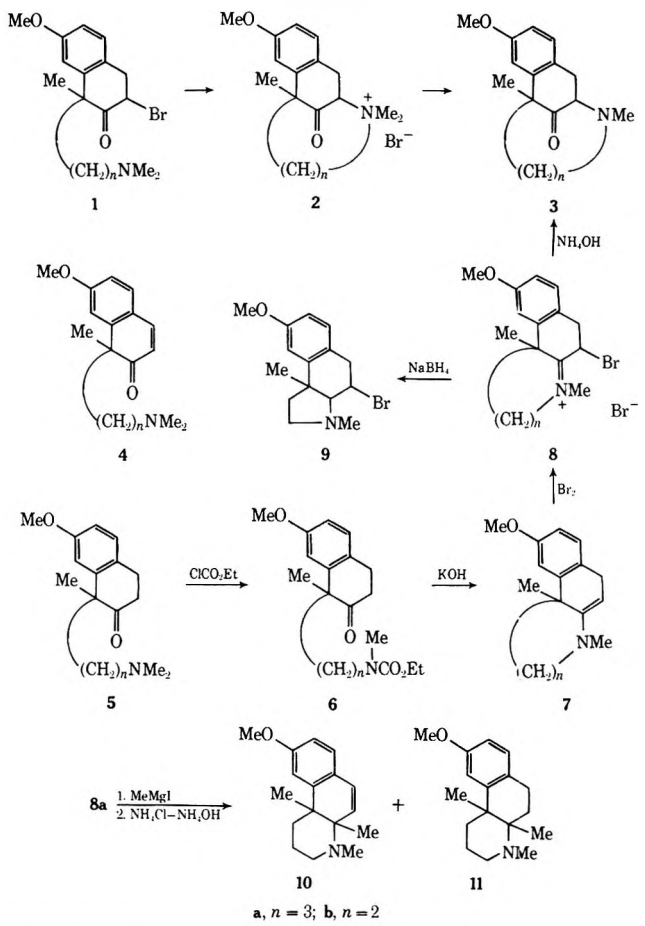
Received January 29, 1972

A new synthesis of 2′-methoxy-2,5-dimethyl-9-oxo-6,7-benzomorphan (**3b**) and its homolog (**3a**) is described. The key step involves bromination of 4,10b-dimethyl-9-methoxy-1,2,3,4,6,10b-hexahydrobenzo[*f*]quinoline (**7a**) and 3,9b-dimethyl-8-methoxy-5,9b-dihydrobenz[*e*]indoline (**7b**). Upon alkalinization with aqueous ammonium hydroxide, the bromination products (**8a,b**) easily underwent rearrangement to **3a,b**, respectively. A possible mechanism of this sequence of reactions is presented.

In our previous paper,[2] 2′-methoxy-2,6-dimethyl-10-oxo-7,8-homobenzomorphan[3] (**3a**), a key intermediate for the synthesis of homobenzomorphan analgesics, was prepared by cyclization of the bromo ketone **1a** followed by pyrolysis. Since the elimination product **4a** was concurrently formed in both steps, **3a** was obtained in rather low yield. A similar observation has been reported in the benzomorphan series[4] (**1b** → **3b**).

We now wish to report a more practical synthesis of **3a** as well as the benzomorphan analog **3b** by a novel rearrangement of the heterocyclic enamines **7a,b** *via* bromination (Scheme I).

SCHEME I



Treatment of 1-(3-dimethylaminopropyl)-7-methoxy-1-methyl-3,4-dihydro-2(1*H*)-naphthalenone (**5a**)[2] with ethyl chloroformate in benzene[5] yielded the *N*-carbethoxy derivative **6a** in 90% yield, which in turn was heated with potassium hydroxide in 1-butanol to afford the hexahydrobenzo[*f*]quinoline derivative **7a** in 58% yield. The presence of an unsaturated amine absorption at 1655 cm^{-1} and vinyl proton resonance at δ 4.75 (t, 1 H, J = 4 Hz) confirmed the heterocyclic enamine structure of **7a**.

When the enamine **7a** was brominated in methylene chloride[6] and the reaction mixture was treated with aqueous ammonium hydroxide at room temperature, the 10-oxohomobenzomorphan **3a** was obtained in 81% yield.

This new method appeared to be useful also for the synthesis of the benzomorphan analog **3b**. Thus, the dihydrobenz[*e*]indoline derivative **7b** was similarly prepared from **5b** in 48% overall yield. Conversion of **7b** into the 9-oxobenzomorphan **3b** proceeded in 60% yield, without isolation of the intermediate bromo iminium bromide. In another run, this intermediate was isolated in 83% yield; spectral data and elemental analysis (given in the Experimental Section) were compatible with the structure **8b**.

Treatment of **8b** with aqueous ammonium hydroxide gave **3b** in 65% yield. Substitution of anhydrous triethylamine for aqueous ammonium hydroxide in the reaction, however, did not give **3b**. This indicates that hydroxide is essential for the rearrangement.

Sodium borohydride reduction of **8b** gave the saturated bromo amine derivative **9**. Treatment of **9** with aqueous ammonium hydroxide resulted in a quantitative recovery of the material. Upon treating the bromination product **8a** with ethereal methylmagnesium iodide, followed by quenching the Grignard mixture with aqueous ammonium chloride–ammonium hydroxide, the elimination product **10** and the reduction product[7] **11** were obtained. Structural assignments for **10** and **11** were made from their nmr spectra.

Thus, no skeletal rearrangement could be observed by saturation of the iminium double bond in **8**.

Although extensive use of enamine halogenations has been reported in the synthesis of α-halo ketones,[8]

(1) Presented at the 3rd International Congress of Heterocyclic Chemistry, Aug 1971, Sendai, Japan.

(2) M. Takeda and H. Kugita, *J. Med. Chem.*, **13**, 630 (1970).

(3) *Chemical Abstracts* name: 3,7-dimethyl-9-methoxy-12-oxo-1,2,4,5,-6,7-hexahydro-2,7-methano-3*H*-3-benzazonine. The term "homobenzomorphan" has been given to this series of derivatives. See ref 2.

(4) J. G. Murphy, J. H. Ager, and E. L. May, *J. Org. Chem.*, **25**, 1386 (1960).

(5) V. Seidolová and M. Provita, *Collect. Czech. Chem. Commun.*, **32**, 2826 (1967).

(6) M. E. Kuehne, *J. Amer. Chem. Soc.*, **83**, 1492 (1961).

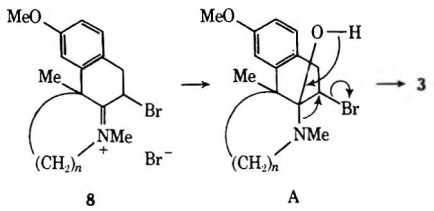
(7) The reductive removal of halogen has been reported in the addition of Grignard reagents to α-bromo iminium salts. See A. Kirrmann, E. Elkik, and P. Vaudescal, *C. R. Acad. Sci., Ser. C*, **262**, 1268 (1966).

(8) M. E. Kuehne in "Enamines; Synthesis, Structure and Reactions," A. G. Cook, Ed., Marcel Dekker, New York and London, 1969, p 415.

no reports have appeared on this sort of bromo enamine rearrangement.

A possible mechanism of the present reaction may be represented by the sequence of reactions shown in Scheme II.

SCHEME II



Attack of OH^- to the initially formed bromo iminium bromide **8** would give intermediate A, which may undergo, presumably in a concerted manner, rearrangement to **3**.[9]

Experimental Section[10]

1-[3-(*N*-Carbethoxy-*N*-methylamino)propyl]-7-methoxy-1-methyl-3,4-dihydro-2(1*H*)-naphthalenone (6a).—A solution of **5a**[2] (3.84 g) in benzene (20 ml) was added to a solution of ethyl chloroformate (4.55 g) in benzene (20 ml) at room temperature. The mixture was refluxed for 2 hr, washed with 5% HCl and then with water, dried, and evaporated. The residue was distilled to give 6a (4.2 g, 90%): bp 185° (0.5 mm); ir (liquid) 1700 cm^{-1}; nmr δ 1.38 (s, 3, CCH_3), 1.19 (t, 3, J = 7 Hz, CH_2CH_3), 2.72 (s, 3, NCH_3), 3.79 (s, 3, OCH_3), 4.16 (q, 2, J = 7 Hz, OCH_2).

Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.21; H, 7.89; N, 3.99.

1-[2-(*N*-Carbethoxy-*N*-methylamino)ethyl]-7-methoxy-1-methyl-3,4-dihydro-2-(1*H*)-naphthalenone (6b).—This compound was prepared in 83% yield from **5b**[4] in the same manner as that described above: bp 170° (0.2 mm); ir (liquid) 1700 cm^{-1}.

Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.41; H, 7.61; N, 4.28.

4,10b-Dimethyl-9-methoxy-1,2,3,4,6,10b-hexahydrobenzo[*f*]quinoline (7a) Picrate.—A mixture of 6a (1.67 g), KOH (2 g), and 1-butanol (28 ml) was refluxed for 18 hr and evaporated. The residue was taken up in ether and extracted with 10% HCl. The aqueous layer was made basic with NH_4OH and extracted with ether. Removal of solvent from the dried extracts gave an air-sensitive oil (**7a**), converted into its picrate. Recrystallization from ethanol–acetone gave yellow pillars (1.37 g, 58%), mp 158–160°.

Anal. Calcd for $C_{22}H_{24}N_4O_8$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.92; H, 5.03; N, 12.17.

The free base was regenerated from the picrate (lithium hydroxide–chloroform): ir (liquid) 1655 cm^{-1}; nmr δ 1.40 (s, 3, CCH_3), 2.54 (s, 3, NCH_3), 3.78 (s, 3, OCH_3), 4.75 (t, 1, J = 4 Hz, NC=CH). The perchlorate was crystallized from acetone–ether: mp 160–162°; ir 1685 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}NO_5Cl$: C, 55.89; H, 6.45; N, 4.08. Found: C, 56.02; H, 6.62; N, 4.11.

3,9b-Dimethyl-8-methoxy-5,9b-dihydrobenz[*e*]indoline (7b) Picrate.—This compound was prepared from **6b** in 56% yield by the method described above: mp 133–136° (from ethanol–acetone).

Anal. Calcd for $C_{21}H_{22}N_4O_8$: C, 55.02; H, 4.84; N, 12.22. Found: C, 55.14; H, 4.77; N, 12.31.

The free base was highly air-sensitive. The perchlorate was crystallized from ethanol–ether: mp 148–150° dec; ir 1683 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}NO_5Cl$: C, 54.62; H, 6.12; N, 4.25. Found: C, 54.58; H, 6.00; N, 4.16.

2′-Methoxy-2,6-dimethyl-10-oxo-7,8-homobenzomorphan (3a).—To a solution of **7a** (regenerated from 2.36 g of the picrate) in CH_2Cl_2 (20 ml) was added Br_2 (0.8 g) in CH_2Cl_2 (10 ml) at −30 to −35° and stirred at the same temperature for 30 min; then the bath was removed to raise the temperature to 0°. Water (10 ml) was added and the mixture was stirred at 5–10° for 2 hr, made basic with 3% aqueous NH_4OH (14 ml), stirred at 5–10° for 2 hr, and then allowed to stand at room temperature overnight. The organic layer was separated and the aqueous phase was extracted with chloroform. The combined organic phase was washed with water, dried, and evaporated to give **3a** (1.05 g, 81%), mp 79–83°. Recrystallization from ethanol gave plates, mp 82–84°, which proved to be identical with an authentic specimen.[2]

2′-Methoxy-2,5-dimethyl-9-oxo-6,7-benzomorphan (3b) Hydrochloride.—To a solution of **7b** (regenerated from 1.83 g of the picrate) in CH_2Cl_2 (20 ml) was added Br_2 (0.64 g) in CH_2Cl_2 (15 ml) at −30 to −35° and stirred at the same temperature for 1 hr.[11] Addition of water (10 ml) and stirring for 2 hr at 5–10° caused precipitation of a crystalline solid (**8b**, *vide infra*). A solution of 3% aqueous NH_4OH (12 ml) was added[12] and the mixture was stirred at 5–10° for 2 hr and then at room temperature overnight. Work-up as above gave an oil which was chromatographed on Al_2O_3 and eluted with benzene. Conversion of the eluate into the hydrochloride and recrystallization from ethanol–ether gave rods (0.675 g, 60%), mp 130–132° (lit.[4] mp 130–132°). The methobromide was crystallized from ethanol, mp 216–218°, identical with an authentic sample.[13]

In another run, the precipitated solid was collected from the brominated mixture and recrystallized from acetone–ethanol to give **4-bromo-9b-methyl-8-methoxy-2,4,5,9b-tetrahydro-1*H*-benz[*e*]indole methobromide (8b)**, 1.32 g, 83%): mp 124–125°; ir 1673, 3380 cm^{-1} (hydrate H_2O); nmr δ 1.75 (s, 3, CCH_3), 3.87 (s, 3, $=N^+CH_3$), 4.00 (s, 3, OCH_3); *m/e* 309, 307 (M^+), 213 (base).

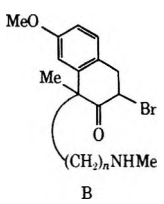
Anal. Calcd for $C_{15}H_{19}NOBr_2 \cdot 0.5H_2O$: C, 45.24; H, 5.06; N, 3.54; Br, 40.13. Found: C, 45.49; H, 4.80; N, 3.42; Br, 39.98.

Treatment of **8b** with 3% aqueous NH_4OH in CH_2Cl_2 gave **3b** in 65% yield.

4-Bromo-3,9b-dimethyl-8-methoxy-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indole (9) Perchlorate.—To a solution of **8b** (0.2 g) in methanol (13 ml) and water (3 ml) was added sodium borohydride (0.04 g) at 5–10°. The mixture was stirred at room temperature for 2 hr and evaporated. The residue was taken in ether, washed with water, dried, and evaporated. The residue was chromatographed on Al_2O_3 and eluted with benzene. The eluate was converted into the perchlorate and recrystallized from ethanol–ether to give needles (0.115 g, 56%): mp 144–146°; nmr (free base) 1.33 (s, 3, CCH_3), 2.61 (s, 3, NCH_3), 3.80 (s, 3, OCH_3), 4.65 (m, 1, CHBr).

Anal. Calcd for $C_{15}H_{21}NO_5ClBr$: C, 43.86; H, 5.15; N, 3.41. Found: C, 44.15; H, 5.21; N, 3.55.

(9) One of the referee of this journal suggests that **3** could also arise from the bromo amino ketone (B), which may be in equilibrium with A.



B

However, the reaction of α-halo ketones with a secondary amine has been recently reported to give β-halo enamines rather than α-amino ketones. See D. Cantacuzène and M. Torieux, *Tetrahedron Lett.*, 4807 (1971).

The higher yield of **3a** than that of **3b**, revealed in this rearrangement, may be also inconsistent with the mechanism involving an intermediate B. For instance, in cyclizing **1a,b** and the related compounds, six-membered amino ketone derivatives have been always obtained more readily than the corresponding seven-membered analogs. See E. L. May, *J. Org. Chem.*, **21**, 223 (1956), and ref 2.

(10) All melting points were determined in an open capillary tube and are uncorrected. Ir spectra were measured in Nujol and nmr spectra were taken in $CDCl_3$ (containing Me_4Si at δ 0.00 as internal standard) at 60 MHz, unless otherwise stated. The organic solutions were dried over sodium sulfate and all evaporations were carried out *in vacuo*.

(11) Treatment of this mixture with triethylamine (at 0° for 2 hr, then at room temperature overnight) gave a multicomponent mixture which did not include **3b** (by tlc).

(12) Direct addition of aqueous NH_4OH to the brominated mixture also gave **3b** in a comparable yield. Thus, it is unnecessary to add water prior to alkalinization.

(13) The authors thank Dr. Everette L. May, National Institutes of Health, for providing us with the sample of **3b** methobromide.

Treatment of **9** with 5% aqueous NH_4OH in CH_2Cl_2 at room temperature overnight resulted in a quantitative recovery of the material.

9-Methoxy-4,4a,10b-trimethyl-1,2,3,4,4a,10b-hexahydrobenzo[*f*]quinoline (10) Hydrobromide.—**7a** (regenerated from 2.92 g of the picrate) was brominated as described previously. Evaporation of CH_2Cl_2 at room temperature gave **8a** as an amorphous powder. Ethereal methylmagnesium iodide (100 ml of 0.43 *M*) was added to a suspension of **8a** in ether (70 ml) and refluxed for 15 hr. The cooled mixture was poured into ice–water containing NH_4Cl, basified with NH_4OH, and extracted with ether. Evaporation of the dried extracts gave the residue which was chromatographed over silica gel (80 g) and eluted with chloroform–methanol (95:5). Conversion of the eluate into the hydrobromide and recrystallization from acetone–methanol–ether gave **10** hydrobromide (0.38 g, 18%): mp 254–256° dec; uv max (MeOH) 282 mμ (ε 14,500); nmr (D_2O) 1.39 (s, 3, CCH_3), 1.44 (s, 3, CCH_3), 3.05 (s, 3, N^+CH_3), 3.95 (s, 3, OCH_3), 6.24 (d, 1, J = 10 Hz, C_5H), 6.75 (d, 1, J = 10 Hz, C_6H).

Anal. Calcd for $C_{17}H_{24}NOBr$: C, 60.36; H, 7.15; N, 4.15; Br, 23.66. Found: C, 60.15; H, 7.26; N, 4.09; Br, 23.52.

Elution with chloroform–methanol (9:1) and conversion of the eluate into the hydrochloride gave **9-methoxy-4,4a,10b-trimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (11) hydrochloride** (0.28 g, 13%): mp 227–230° dec; needles from acetone–methanol–ether; ir 3380, 3440 cm^{-1} (hydrate H_2O); nmr (D_2O) 1.37 (s, 3, CCH_3), 1.54 (s, 3, CCH_3), 3.08 (s, 3, N^+CH_3), 4.05 (s, 3, OCH_3).

Anal. Calcd for $C_{17}H_{26}NOCl \cdot H_2O$: C, 65.15; H, 8.99; N, 4.46. Found: C, 65.41; H, 8.95; N, 4.52.

Reaction of **7a** perchlorate with ethereal methylmagnesium iodide also gave **11** in 40% yield.

Registry No.—**3a**, 28360-42-1; **3b** hydrochloride, 34887-93-9; **6a**, 34887-94-0; **6b**, 34887-95-1; **7a**, 34887-96-2; **7a** picrate, 34887-97-3; **7a** perchlorate, 34917-95-8; **7b** picrate, 34887-98-4; **7b** perchlorate, 34887-99-5; **8b**, 34887-61-1; **9** perchlorate, 34887-62-2; **10** hydrobromide, 34887-63-3; **11** hydrochloride, 34887-64-4.

Acknowledgment.—The authors express their gratitude to Director Michio Yamazaki of this laboratory and Professor Emeritus S. Sugasawa of the Tokyo University for their interest and encouragement. Thanks are also extended to the staff of the analytical section presided over by Dr. K. Kotera for elemental and spectral analyses.

Studies on Heterocyclic Compounds. XI. 1,3-Dipolar Cycloaddition of Benzimidazolium Ylide with Acetylenic Compounds

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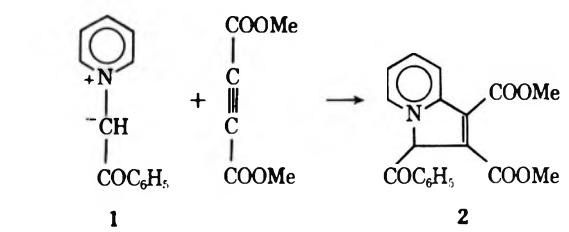
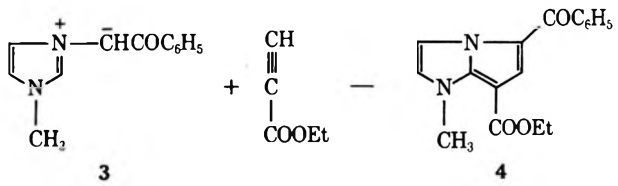
1,3-Dipolar cycloaddition of 3-substituted 1-alkylbenzimidazolium ylides with ethyl propiolate gave 3-substituted 9-alkyl-1-ethoxycarbonylpyrrolo[1,2-*a*]benzimidazoles. Reaction of 1-alkyl-3-phenacylbenzimidazolium ylides with dimethyl acetylenedicarboxylate afforded 4-alkyl-2,3-bis(methoxycarbonyl)-1-phenacylpyrrolo[1,2-*a*]-benzimidazole (**7**) and an open-chain compound (**8**). On the other hand, reaction of 1-alkyl-3-methoxycarbonylmethylbenzimidazolium ylides with dimethyl acetylenedicarboxylate gave 4-alkyl-1,2,3-tris(methoxycarbonyl)-pyrrolo[1,2-*a*]benzimidazole (**9**) and 5-alkyl-3,4-bis(methoxycarbonyl)-1-oxopyrido[1,2-*a*]benzimidazole (**10**).

For the purpose of obtaining potential physiologically active compounds, we synthesized compounds of the tricyclic azole system, such as thiazolo[3,2-*a*]benzimidazoles,[1] thiazolo[2,3-*b*]benzothiazoles,[2] imidazo[2,1-*b*]-benzothiazoles,[3] imidazo[2,1-*b*]benzoxazoles,[4] pyrimido-[1,2-*a*]benzazoles,[5] and imidazo[1,2-*a*]benzimidazoles.[6] In our previous report,[7] 9-alkylamino-2-arylimidazo-[1,2-*a*]benzimidazole showed a strong analgesic activity. We also suggested that pyrrolo[1,2-*a*]benzimidazole systems would have potential physiological activities.

Recently, Boekelheide and coworkers[8] prepared pyrrocoline (**2**) by the reaction of pyridinium ylide (**1**) and methyl acetylenedicarboxylate, and they found that 3-phenacylimidazolium ylide (**3**) reacted with ethyl propiolate to yield 4-benzoyl-6-ethoxycarbonyl-1-methyl-1,3a-diazapentalene[9] (**4**). These facts suggest



1 2



3 4

that the reaction of benzimidazolium ylide with acetylenic compounds might offer a useful synthesis for pyrrolo[1,2-*a*]benzimidazoles.[10]

Reaction of 3-substituted 1-alkylbenzimidazolium ylides, which were prepared from bromides **5**, with ethyl propiolate gave 1-substituted 4-alkyl-3-ethoxycarbonyl-4*H*-pyrrolo[1,2-*a*]benzimidazoles (**6**) (Chart I). Their structures were confirmed by the ir and nmr spectra. The chemical shift of the C-8 proton in **6a–f** is summarized in Table I, and the values show the para-

(1) H. Ogura, T. Itoh, and Y. Shimada, *Chem. Pharm. Bull.*, **16**, 2167 (1968); H. Ogura, T. Itoh, and K. Kikuchi, *J. Heterocycl. Chem.*, **6**, 797 (1969).

(2) H. Ogura, T. Itoh, M. Ogiwara, and T. Okamoto, *Yakugaku Zasshi*, **89**, 469 (1969).

(3) H. Ogura and T. Itoh, *Chem. Pharm. Bull.*, **18**, 1981 (1970).

(4) H. Ogura, T. Itoh, and S. Sugimoto, *ibid.*, **18**, 2204 (1970).

(5) H. Ogura and M. Kawano, Abstracts of Papers, 91st Annual Meeting of the Pharmaceutical Society of Japan, 1971, p 669.

(6) H. Ogura and T. Itoh, *Kitasato Arch. Exp. Med.*, **42**, 65 (1969).

(7) H. Ogura, M. Kawano, K. Kikuchi, and T. Itoh, Abstracts of Papers, 3rd International Congress of Heterocyclic Chemistry, 1971, p 506.

(8) V. Boekelheide and N. A. Fedoruk, *J. Org. Chem.*, **32**, 2062 (1967).

(9) V. Boekelheide and N. A. Fedoruk, *J. Amer. Chem. Soc.*, **90**, 3830 (1968).

(10) H. Ogura, T. Itoh, K. Kikuchi, and H. Sekine, Abstracts of Papers, 91st Annual Meeting of the Pharmaceutical Society of Japan, 1971, p 670.

CHART I

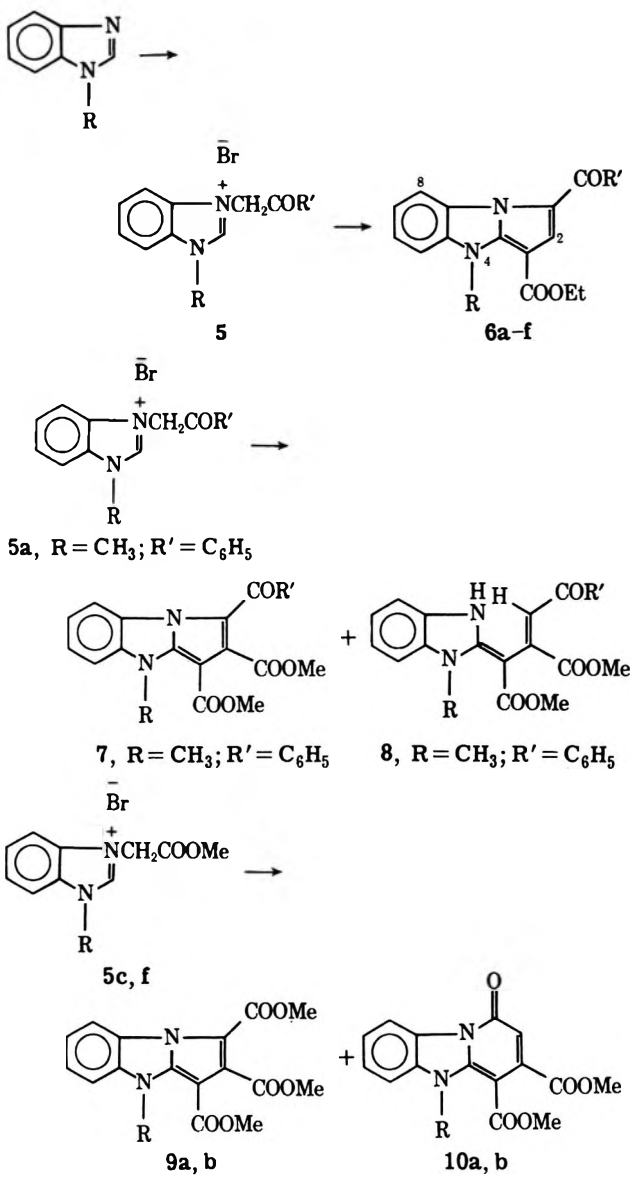


TABLE I

NMR DATA OF THE C-8 PROTON IN 6

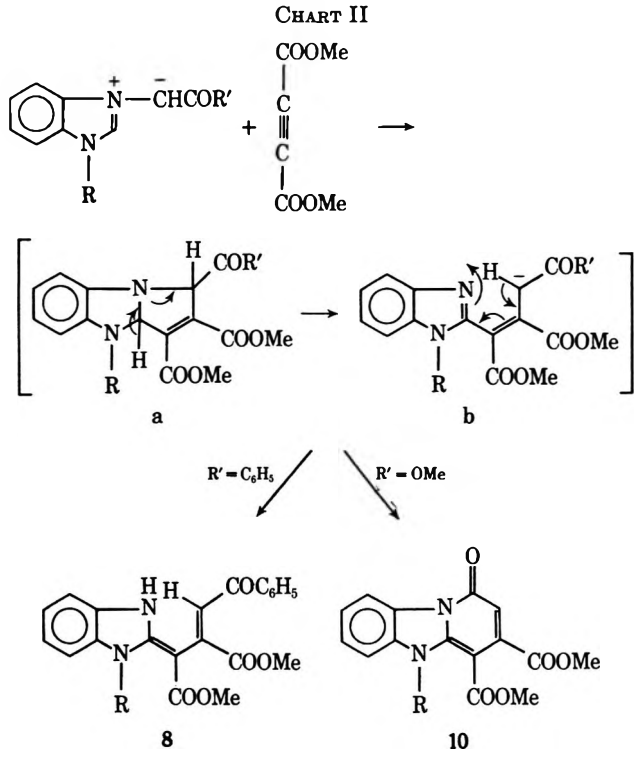
6	R	R'	δ, ppm (CDCl3)
a	Me	C_6H_5	8.90
b	Me	$C_6H_4Br(p)$	9.80
c	Me	OMe	8.13
d	Et	C_6H_5	8.90
e	Et	$C_6H_4Br(p)$	9.10
f	Et	OMe	8.21

magnetic anisotropic effect of the carbonyl group in the C-1 position. Moreover, there is no nuclear Overhauser effect between the N^4-methyl group and the proton at the C-2 position in **6a** (R = CH_3, R' = C_6H_5). Although there is a possibility of cyclization in another direction, the product in that case should have a nuclear Overhauser effect (*ca.* 15%), from the distance between protons in the N^4-methyl group and in the C-3 position (3).[11]

The reaction of dimethyl acetylenedicarboxylate with 1-methyl-3-phenacylbenzimidazolium ylide, prepared from the corresponding bromide (**5a**), gave a normal 1,3-dipolar cycloaddition product (**7**, 11%) and an open-chain 1-methyl-2-[1,2-bis(methoxycarbonyl)-3-benzoyl-2-propenylidene]benzimidazoline (**8a**, 6%). The reaction of 1-alkyl-3-methoxycarbonylmethylbenzimidazolium ylide (**5c,f**) and dimethyl acetylenedicarboxylate afforded 5-alkyl-3,4-bis(methoxycarbonyl)-1-oxo-1,5(2*H*)pyrido[1,2-*a*]benzimidazole (**10a,b**; both 6%) besides the normal product (**9a,b**; 7 and 2%, respectively). Structures of these compounds were determined by nmr, mass, and ir spectra. The ir spectrum of **8a** showed an NH band at 3432 cm^{-1} (10^{-4} mol in CCl_4), and the nmr spectrum of 3,4-bis(methoxycarbonyl)-5-methyl-1-oxo-1,5(2*H*)-pyrido-[1,2-*a*]benzimidazole (**10a**, R = CH_3) showed two ester methyl groups at 3.91 (s, 3 H) and 4.04 ppm (s, 3 H).

The mechanisms of these reaction may be represented by the sequence shown in Chart II. The initial 1,3-

CHART II



dipolar addition product a was oxidized by excess reagent to normal 1,3-addition products (**7**, **9**), but another possible route may proceed to a ring opening to yield the second intermediate b. In the compound **5c,f** with R' = OCH_3, cyclization occurred in a manner similar to the reaction of 2-aminobenzazole with acetylenic compounds.[5] In the case of R' = phenyl (**5a,b,d,e**), the second intermediate b was not cyclized. Further cyclization was not effected even on heating **8** in polyphosphoric acid. This result is similar to that of the reaction of dimethyl acetylenedicarboxylate and 1-methyl-3-imidazolium dicyanomethylide.[9]

Experimental Section

Temperatures are uncorrected. Nmr spectra were measured in $CDCl_3$ with a Varian T-60 spectrometer with Me_4Si as an internal standard. Mass spectra were measured with JEOL-01S spectrometer by a direct inlet system at 75 eV. Elemental analyses (C, H, N) of the compounds gave values corresponding to their formula within ±0.4%: Ed.

(11) R. A. Bell and J. K. Saunders, *Can. J. Chem.*, **48**, 1114 (1970).

TABLE II

1-SUBSTITUTED 3-ALKYLBENZIMIDAZOLIUM BROMIDES (5a–f)

Compd No.	R	R′	Solvent	Mp, °C form	Yield, %	Ir ν_{CO}^{KBr}, cm^{-1}
5a	CH_3	C_6H_5	Dichloromethane	205 white needles (EtOH)	78	1690
5b	CH_3	$C_6H_4Br(p)$	Me_2CO–MeOH	241 white needles (MeOH)	91	1685
5c	CH_3	OCH_3	Et_2O	109 white needles (EtOH)	88	1740
5d	C_2H_5	C_6H_5	Dichloromethane	119 white prisms (EtOH)	98	1685
5e	C_2H_5	$C_6H_4Br(p)$	Me_2CO	139 white needles (MeOH)	90	1685
5f	C_2H_5	OCH_3	Et_2O	129 white needles (EtOH)	84	1745

TABLE III

1-BENZOYL-3-ETHOXYCARBONYL-4-METHYL-4*H*-PYRROLO[1,2-*a*]BENZIMIDAZOLES (6a–f)

Compd No.	R	R′	Mp, °C	Yield, %	Ir ν_{CO}^{KBr}, cm^{-1}	Uv λ_{max}^{EtOH}, nm (log ϵ)	Mass *m/e* (M^+)
6a	CH_3	C_6H_5	164	4	1690, 1920		346
6b	CH_3	$C_6H_4Br(p)$	224	5	1685, 1610	227 (4.41) 333 (3.77)	425
6c	CH_3	OCH_3	185	5	1705, 1650	246 (4.73) 313 (4.07) 326 (4.02)	300
6d	C_2H_5	C_6H_5	155–157	4	1695, 1620		360
6e	C_2H_5	$C_6H_4Br(p)$	186	4	1680, 1610	228 (4.42) 332 (3.81)	439
6f	C_2H_5	OCH_3	160	2	1675, 1650	246 (4.63) 294 (4.18) 313 (4.10) 327 (4.17)	314

TABLE IV

1-ALKYL-2-[1,2-BIS(METHOXYCARBONYL)-3-BENZOYL-2-PROPENYLIDENE]BENZIMIDAZOLINES (8a,b,d,e)

Compd No.	R	R′	Mp, °C	Yield, %	Ir ν_{CO}^{KBr}, cm^{-1}	Uv λ_{max}^{EtOH}, nm (log ϵ)	Mass *m/e* (M^+)
8a	CH_3	C_6H_5	184 (white prisms)	6	1730, 1680	234 (4.63)	392
8b	CH_3	$C_6H_4Br(p)$	233 (white prisms)	9	1740, 1735, 1675	233 (4.59) 325 (3.87)	469
8d	C_2H_5	C_6H_5	229 (white prisms)	4	1720, 1690	235 (4.87) 332 (4.22)	406
8e	C_2H_5	$C_6H_4Br(p)$	199 (white needles)	12	1730, 1670	234 (4.60) 333 (3.89)	483

General Procedure for 1-Substituted 3-Alkylbenzimidazolium Bromides (5a–f) (Table II).—To a solution of 1-alkylbenzimidazole (0.03 mol) in a suitable organic solvent (50–100 ml), acyl bromide (0.04 mol) was added. After standing for 2–3 days at room temperature, the mixture deposited white crystals. Recrystallization from alcohol gave white needles.

Reaction of 1-Substituted 3-Alkylbenzimidazolium Bromide and Ethyl Propiolate (Table III).—To an orange-red solution of the ylide prepared from 1-substituted 3-alkylbenzimidazolium bromide (**5a–f**) (3 mmol) and K_2CO_3 (3 mmol) in dimethylformamide (40–50 ml), ethyl propiolate (6 mmol) was added at room temperature and the mixture stood for 2 days. After filtration, the organic solvent was removed under reduced pressure. Addition of EtOH gave **6a–f** as white needles after recrystallization from the same solvent.

Reaction of 3-Alkyl-1-phenacylbenzimidazolium Ylides and Dimethyl Acetylenedicarboxylate (Table IV).—To an orange-red solution of the ylide prepared from 3-alkyl-1-phenacylbenzimidazolium bromide (**5a,b,d,e**) (3 mmol) and K_2CO_3 (3 mmol) in dimethylformamide (40–50 ml), dimethyl acetylenedicarboxylate (6 mmol) was added at room temperature and the mixture was allowed to stand for 3 days. After filtration, the organic solvent was evaporated under reduced pressure. The residue was extracted with Me_2CO and the solvent was evaporated from the extract to obtain the open-chain compound **8** as white crystals after recrystallization from EtOH.

Chromatography of the Me_2CO-insoluble part of **8a** on silica gel afforded 1-benzoyl-2,3-bis(methoxycarbonyl)-4-methyl-4*H*-pyrrolo[1,2-*a*]benzimidazole (**7**) in 11% yield as white needles: mp 130–131°; ir (KBr) 1735 ($COOCH_3$), 1685 cm^{-1} (CO); uv λ_{max}^{EtOH} 234 nm (log ϵ 4.51), 330 (3.83); nmr δ 2.90 (singlet, NCH_3), 3.76, 3.83 [singlet, $(COOCH_3)_2$], 7.23 (multiplet, aromatic protons), 7.73 ppm (singlet, 5-H); mass spectrum *m/e* 390 (M^+). *Anal.* Calcd for $C_{22}H_{18}N_2O_5$: C, H, N.

Reaction of 1-Methoxycarbonylmethyl-3-methylbenzimidazolium Ylide with Dimethyl Acetylenedicarboxylate.—To a yellow

solution of the ylide prepared from 1-methoxycarbonylmethyl-3-methylbenzimidazolium bromide (**5c**) (3 mmol) and K_2CO_3 (3 mmol) in dimethylformamide (50 ml), dimethyl acetylenedicarboxylate (6 mmol) was added at room temperature and the mixture was stirred for 3 days. The black reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was extracted with acetone and the extract was evaporated to obtain 5-methyl-3,4-bis(methoxycarbonyl)-1-oxo-1,5(2*H*)-pyrido[1,2-*a*]benzimidazole (**10a**) in 6% yield as white prisms: mp 255° (EtOH); ir (KBr) 1740, 1710 ($COOCH_3$), 1655 cm^{-1} (CO); uv λ_{max}^{EtOH} 243 nm (log ϵ 4.23), 314 (3.71), 328 (3.62); nmr δ 3.64 (singlet, NCH_3), 3.91, 4.04 [singlet, ($COOCH_3$)$_2$], 7.42 (singlet, 3-H), 7.50 (multiplet, aromatic protons), 8.21 (doublet, 6-H); mass spectrum *m/e* 314 (M^+). *Anal.* Calcd for $C_{16}H_{14}N_2O_5$: C, H, N.

Chromatography of the acetone-insoluble part of **10a** on silica gel afforded 1,2,3-tris(methoxycarbonyl)-4-methyl-4*H*-pyrrolo[1,2-*a*]benzimidazole (**9a**) in 7% yield as white prisms: mp 177–178° (EtOH); ir (KBr) 1742, 1690, 1655 cm^{-1} ($COOCH_3$); uv λ_{max}^{EtOH} 247 nm (log ϵ 4 49), 292 (4.29), 331 (4.22); nmr δ 3.86, 3.93, 4.00 [singlet, ($COOCH_3$)$_3$], 4.23 (singlet, NCH_3), 7.36 (multiplet, aromatic protons), 3.40 (doublet, 8-H); mass spectrum *m/e* 344 (M^+). *Anal.* Calcd for $C_{17}H_{16}N_2O_6$: C, H, N.

Reaction of 3-Ethyl-1-methoxycarbonylmethylbenzimidazolium Ylide with Dimethyl Acetylenedicarboxylate.—A similar reaction occurred with the *N*-ethyl compound. 5-Methyl-3,4-bis(methoxycarbonyl)-1-oxo-1,5(2*H*)-pyrido[1,2-*a*]benzimidazole (**10b**) was obtained in 6% yield as white leaflets (EtOH): mp 202–203°; ir (KBr) 1740, 1710 ($COOCH_3$), 1655 cm^{-1} (CO); uv λ_{max}^{EtOH} 243 nm (log ϵ 4.72), 312 (4.09), 325 (3.99); nmr δ 1.31 (triplet, NCH_2CH_3), 3.88, 4.05 [singlet, ($COOCH_3$)$_2$], 4.36 (quartet, NCH_2CH_3), 7.36 (singlet, 3-H), 7.50 (multiplet, aromatic protons), 8.12 (doublet, 6-H); mass spectrum *m/e* 328 (M^+). *Anal.* Calcd for $C_{17}H_{16}N_2O_5$: C, H, N.

4-Ethyl-1,2,3-tris(methoxycarbonyl)-4*H*-pyrrolo[1,2-*a*]benzimidazole (**9b**) was obtained as white prisms (2% yield): mp 134–135° (EtOH); ir (KBr) 1740, 1710, 1690 cm^{-1} ($COOCH_3$); uv λ_{max}^{EtOH} 215 nm (log ϵ 4.43), 247 (4.48), 292 (4.38), 331 (4.31); nmr δ 1.43 (triplet, NCH_2CH_3), 3.90, 3.95, 4.02 [singlet, ($COOCH_3$)$_3$], 4.76 (quartet, NCH_2CH_3), 7.33 (multiplet, aromatic protons), 8.40 (doublet, 8-H); mass spectrum *m/e* 358 (M^+). *Anal.* Calcd for $C_{15}H_{18}N_2O_6$: C, H, N.

Registry No.—**5a**, 34910-61-7; **5b**, 34910-62-8; **5c**, 34910-63-9; **5d**, 34910-64-0; **5e**, 34910-65-1; **5f**, 34910-66-2; **6a**, 34910-67-3; **6b**, 34934-78-6; **6c**, 34910-68-4; **6d**, 34910-69-5; **6e**, 34910-70-8; **6f**, 34910-71-9; **7**, 34910-72-0; **8a**, 34910-73-1; **8b**, 34910-74-2; **8d**, 34910-75-3; **8e**, 34910-76-4; **9a**, 14882-70-3; **9b**, 34910-78-6; **10a**, 34910-79-7; **10b**, 34915-98-5.

The Cycloaddition of Vinyl Azides to Ketenes[1]

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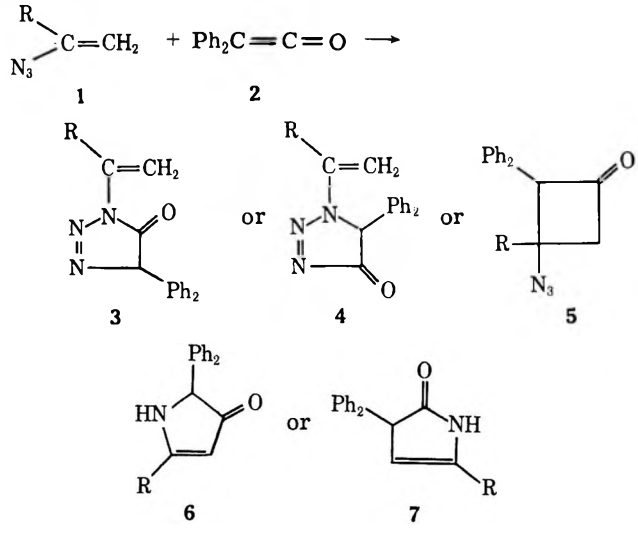
Vinyl azides undergo slow cycloaddition with diphenylketene (**2**) leading to five-membered ring enamino ketones **6** with loss of N_2. The reaction appears to involve nucleophilic attack of the β carbon from the vinyl azide upon the ketene. A substantial improvement in yield of **6** is achieved by generating **2** *in situ* from a diazo ketone in solution. Treatment of the enamino ketones with phosphorus pentachloride or chlorine leads to α chlorination. In the case of 2-azido-1-hexene, cycloaddition with **2** proceeds with formation of cyclobutanones.

The azide group represents a versatile function which can act as a nucleophile, electrophile, or 1,3 dipole.[2] An adjacent C=C, as in vinyl azides, accentuates or modifies the chemical behavior of this functional group.[3] Thus, vinyl azides exhibit a markedly greater reactivity than alkyl azides in cycloadditions with acetylenes.[4] Although the reaction of ketenes with olefins and imines has received a great deal of attention,[5] there appears to be no report of their interaction with azides.[6a] If one considers the cycloaddition of vinyl azides **1** to ketenes (*e.g.*, **2**) leading primarily to 1:1 adducts, one can envisage products of type **3**–**7** that might arise *via* a concerted or stepwise pathway.

Furthermore, in protonation and bromination of vinyl azides **1** it is difficult to distinguish whether the electrophile attacks one of the nitrogens or the β carbon of the unsaturated azide.[3] A product analysis of the reaction of **1** with ketenes offers the opportunity to establish any regiochemical preference in the cycloaddition (for instance preferential formation of **3** *vs.* **4** or **6** *vs.* **7**).



Results and Discussion

α-Azidostyrene (**1**, R = Ph) undergoes a slow reaction with diphenylketene (**2**) in ether at room temperature producing a 1:1 adduct with loss of N_2. Although the yield of this adduct was only 7% after a 3-day reaction, no other product was detected and a considerable amount of starting vinyl azide was present, together

(1) Cycloadditions. VIII. For previous paper in the series see ref 7.

(2) G. L'abbé, *Chem. Rev.*, **69**, 345 (1969).

(3) See, for instance, (a) A. Hassner, E. S. Ferdinandi, and R. J. Isbister, *J. Amer. Chem. Soc.*, **92**, 1672 (1970); (b) A. Hassner and A. B. Levy, *ibid.*, **93**, 5469 (1971).

(4) G. L'abbé, J. E. Galle, and A. Hassner, *Tetrahedron Lett.*, 303 (1970); G. L'abbé and A. Hassner, *Bull. Soc. Chim. Belg.*, **80**, 209 (1971).

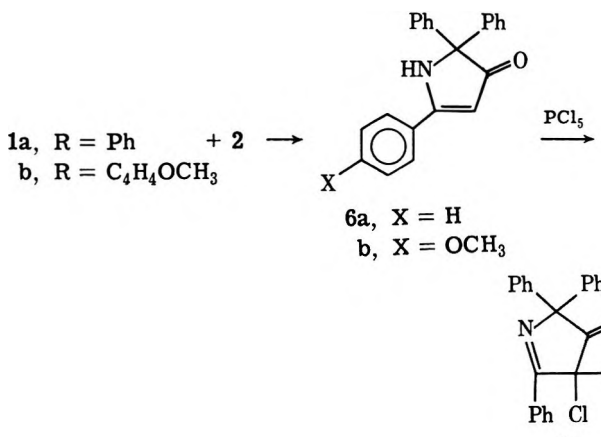
(5) See, for instance, (a) W. T. Brady, *Synthesis*, 415 (1971); R. Huisgen, B. A. Davis, and M. Morikan, *Angew. Chem., Int. Ed. Engl.*, **7**, 826 (1968); (b) J. C. Martin, K. C. Brannock, R. D. Burpitt, P. G. Gott, and V. A. Hoyle, Jr., *J. Org. Chem.*, **36**, 2211 (1971).

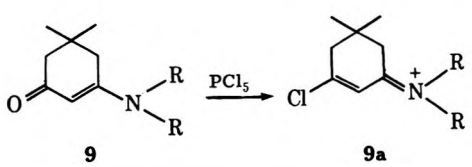
(6) (a) Only the intramolecular decomposition of azido ketenes has been described: A. Hassner, R. J. Isbister, R. B. Greenwald, J. T. Klug, and E. C. Taylor, *Tetrahedron*, **25**, 1637 (1969). (b) A. Hassner and F. W. Fowler, *J. Amer. Chem. Soc.*, **90**, 2869 (1968).

with some polymeric material. Heating of the reaction mixture did not lead to higher yields of cycloadduct but instead caused polymerization and conversion of the vinyl azide into 2-phenylazirine,[6b] which in turn reacted[7] with diphenylketene to produce a bicyclic aziridine (1:2 adduct). To avoid the presence of large amounts of diphenylketene (2), which undergoes polymerization, we generated 2 *in situ* by refluxing a solution of **1a** and α-diazo-α-phenylacetophenone in benzene. In this manner the yield of the adduct increased to 50%.

Structure **6a** was established for the 1:1 adduct, mp 300°, on the basis of the following spectral data and chemical reactions. The ir spectrum of **6a** contains NH absorptions at 3200 and 1580 cm^{-1} which shift on deuterium exchange, as well as a carbonyl band at 1620 cm^{-1}, typical of enamino ketones (vinylogous amides).[8] The compound exhibits a vinyl proton at τ 4.45 and NH (exchangeable with D_2O) at 0.77 in the nmr (in DMSO-d_6). The uv spectrum indicates extensive conjugation at 248 nm (ϵ 22,500) and 351 (8000). The molecular ion appears at *m/e* 311 in the mass spectrum with the base peak at *m/e* 282 ($M^+ - HCO$). The possibility that the adduct possessed structure **7** was dismissed on the basis of comparison with an authentic sample of **7**.[9]

As a vinylogous amide, **6a** did not form an oxime derivative on refluxing with $NH_2OH \cdot HCl$–pyridine. It was also unreactive toward $LiAlH_4$, apparently because of the resistance of the primarily formed anion to further attack by hydride. Whereas vinylogous amides of type **9** were reported to give **9a** on heating with PCl_5,[10] reaction of **6a** with PCl_5 in refluxing benzene led to the dichloro derivative **8** in 57% yield. In this



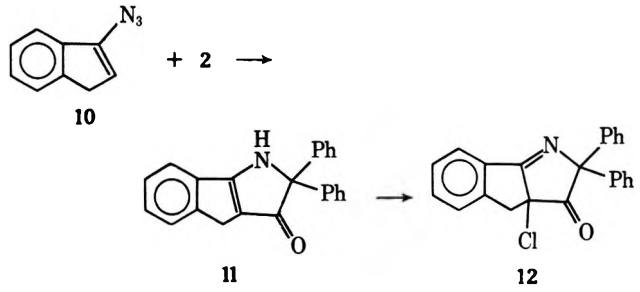


reaction, chlorination of the enamine carbon is favored over that of the carbonyl carbon[10] by two factors: (a) the steric effect imposed by the phenyl groups; (b) a possible higher nucleophilicity of the enamine carbon.

The same product **8** was obtained in quantitative yield on chlorination of **6a** in benzene. The ir spectrum of **8** shows carbonyl absorption, typical of a dichlorocyclopentanone, at 1780 cm^{-1} and conjugated C=N at 1605 cm^{-1}. NH absorptions were absent. The uv maximum at 254 nm (ϵ 14,500) is similar to that of benzalmethylamine at 247 nm (ϵ 15,900).

p-Methoxy-α-azidostyrene (**1b**) reacted with diphenylketene (2) to produce an analogous adduct **6b**. The cycloaddition proceeded faster than with **1a**, indicating a stabilizing effect in the transition state by virtue of the contribution of the *p*-methoxy group to the nucleophilicity of the β carbon in **1** (see 1 + 2 → **13** below). The spectral and chemical properties of enamino ketone **6b** were similar to those of **6a**.

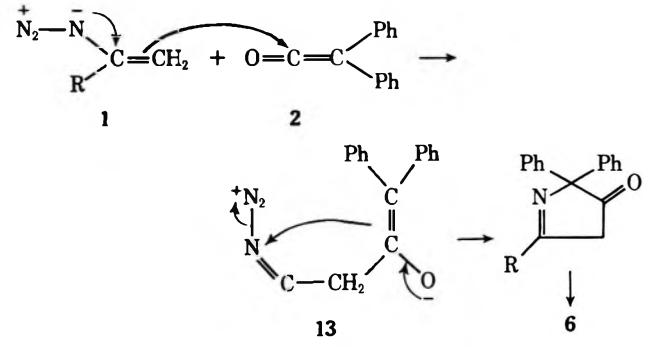
An analogous cycloadduct **11** was formed from 1-azidoindene (**10**) and 2. This vinyl azide was chosen because of its known reluctance to form an azirine on heating;[7] hence, heating of the reaction mixture is expected to lead to an improved yield of **11**. Indeed the



yield increased from 7% in ether and 11% in DMF at 25° to 35% in refluxing THF. The spectral properties of **11** [NH at 3250 and 1580 cm^{-1}, C=O at 1625 cm^{-1}, CH_2 singlet at τ 6.56, NH at τ 0.65, uv absorption at 248, 345, and 362 nm (ϵ 16,400, 5700, and 5800, respectively)] are consistent with its structure. Reaction of **11** with PCl_5 permits only monochlorination and led to 3-chloro-5,5-diphenylindeno[1,2-*b*]-1-pyrolin-4-one (**12**) in 34% yield.

1-Azidoindene (**10**) was the only β-substituted vinyl azide that was found to react with diphenylketene. 1-Azido-*cis*-1-phenylpropene, α-azido-*trans*-stilbene, and 1-azido-2-*tert*-butylethene gave no adducts with 2. In one case an azirine–ketene adduct[7] was isolated. These data indicate a steric effect at the β carbon of the vinyl azide during the cycloaddition and are reminiscent of the decrease in rate of dipolar cycloadditions observed upon increased hindrance in the olefin.[11]

The presented results can be rationalized by an ionic mechanism (1 → **13** → **6**) whereby a nucleophilic attack



(7) A. Hassner, A. S. Miller and M. J. Haddadin, *Tetrahedron Lett.*, 1353 (1972).

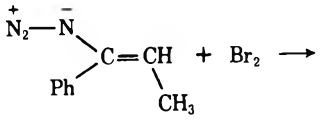
(8) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, *J. Amer. Chem. Soc.*, **71**, 3337 (1949); A. I. Meyers, A. H. Reine, and R. Gault, *J. Org. Chem.*, **34**, 698 (1969).

(9) F. R. Japp and F. Klingemann, *J. Chem. Soc.*, **57**, 662 (1890).

(10) G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **29**, 794 (1964).

(11) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 633 (1963).

by the β carbon of **1** upon the C=O of the ketene is facilitated by electron donation from nitrogen. Such a pathway is analogous to that of the reaction of enamines with ketene.[12] The process resembles the mechanism observed in bromination of vinyl azides (**14** → **15**),[3b] where nucleophilic attack through carbon



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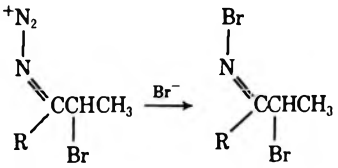

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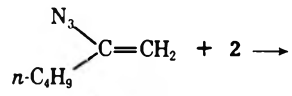
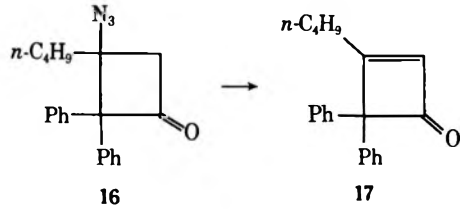
was postulated. In the reaction with ketene **2**, isolation of products **6** rather than of the regioisomeric **7** indicates that nucleophilic attack by C is preferred to attack by N. In the cases reported here ring closure with loss of N_2, as shown in **13**, is followed by tautomerization to the enamino ketone **6**.

The cycloaddition of diphenylketene (**2**) with vinyl azide **1c**, which contains an aliphatic substituent at the azido carbon, proceeded in a different manner. The major product (30% by nmr) was the azidocyclobutanone **16**. Cyclobutenone **17** and a 3:1 adduct



1c



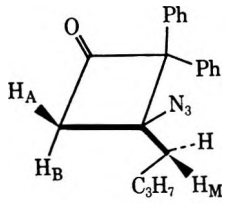
16 **17**

(not further characterized) were also formed.[13] The structure of **16** was apparent from its spectral and chemical properties. The ir absorption at 1780 cm^{-1} is characteristic of cyclobutanones and the bands at 2110 and 1200 cm^{-1} of an azide group. The methylene hydrogens in the cyclobutanone ring appear in the nmr as two doublets at τ 7.03 and 6.68 (J = 17.7 Hz), with the latter further split into a quartet (J = 0.9 Hz). This is attributable to long-range coupling (W effect) between H_M of the *n*-butyl group and the trans ring proton H_A (deshielded by the cis azide function) in the sterically preferred conformation **16a**. The reaction product is not likely to possess the regioisomeric structure **18**, since such a product would not be expected to eliminate HN_3 with ease. Moreover, structure **16** is consistent with the above behavior of vinyl azides **1** where the β carbon is the nucleophilic site in the reactant.[14]

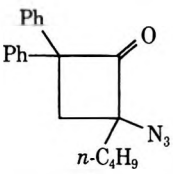
(12) R. H. Hasek and J. C. Martin, *J. Org. Chem.*, **28**, 1468 (1963).

(13) 3:1 adducts from the reaction of ketene with enamines have been reported (ref 12).

(14) The possibility that the reaction product of **1c** + **2** might be **18** was raised by one of the referees.



16a



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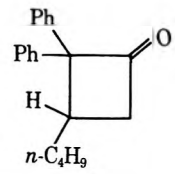

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Cyclobutenone **17** was shown to be a secondary product in the reaction, as evidenced by its formation from **16** on stirring with Merck alumina for 1.5 days. **17** shows absorption at 1750 (C=O) and 1580 cm^{-1} (C=C). In the nmr the vinyl proton absorption at τ 3.75 appears as a multiplet due to long-range coupling with the allylic hydrogens in the side chain. The latter absorb as a broad triplet at τ 7.35. Catalytic hydrogenation of **17** proceeds rapidly to furnish 3-*n*-butyl-2,2-diphenylcyclobutanone (**19**) (ir 1775 cm^{-1}) in 73% yield.

If one considers intermediate **13** as the first step in the reaction, the formation of a five-membered ring *vs.* a four-membered ring adduct from **1a** and **1b** can be rationalized on the basis of an inductive effect by the aryl group which promotes nucleophilic attack at N. It is unlikely that azidocyclobutanones are precursors of **6** and **11** because pyrolysis of **16** does not lead to any detectable amounts of **6** (R = *n*-C_4H_9). Whether the formation of cyclobutanone **16** proceeds by a concerted $_\pi2_s + _\pi2_a$ cycloaddition or by a stepwise process remains to be established.

Experimental Section[15]

2,5,5-Triphenyl-2-pyrrolin-4-one (6a).—To 0.55 g (3.8 mmol) of α-azidostyrene (**1a**) dissolved in 40 ml of anhydrous diethyl ether was added 0.80 g (4.1 mmol) of diphenylketene (**2**).[16] The reaction mixture was stirred for 3 days and the solid (0.13 g, 12%) was filtered, washed with cold ether, and recrystallized from benzene. The yield of pure **6a** was 0.08 g (7%): mp 300°; ir (KBr) 3200 (after exchange with D_2O, 2340), 1620, 1599, 1580, 1540 cm^{-1}; nmr (DMSO-d_6, 60°, HA-100) τ 4.45 (s, 1, C=CH), 1.85–3.19 (m, 15, phenyl hydrogens), −0.77 (s, broad, NH, exchangeable with D_2O); uv max (*p*-dioxane) 333 nm (ϵ 5900), 247 (17,700); uv (95% C_2H_5OH) 351 nm (ϵ 8000), 248 (22,500); mass spectrum (70 eV) *m/e* (rel intensity) 311 (54, M^+), 282 (100), 206 (26), 204 (30), 180 (22), 178 (30), 165 (26).

Anal. Calcd for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.50. Found: C, 85.06; H, 5.43; N, 4.34.

An nmr spectrum of the remaining reaction mixture shows the presence of a considerable amount of vinyl azide but no cyclobutanone.

In an alternate procedure a solution of 1.4 g of **1a** in 20 ml of benzene containing 2.2 g of α-diazo-α-phenylacetophenone[17] was heated on a steam bath for 1 hr. **6a** precipitated during the reaction. The slurry was cooled and **6a** was filtered off (1.6 g, 51% yield).

Enamino ketone **6a** was recovered unchanged (86–100%) upon exposure to $LiAlH_4$ in THF for 24 hr or upon heating with $NH_2OH \cdot HCl$ and pyridine for 19 hr.

3,3-Dichloro-2,5,5-triphenyl-1-pyrrolin-4-one (8).—To 0.5 g (1.6 mmol) of **6a** in 50 ml of dry benzene was added 1 g (4.8

(15) Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 457 grating spectrometer and nmr spectra on a Varian A-60A spectrometer. Mass spectra were taken on a Varian M.A.T. CH-5. All solvents were either reagent grade or distilled before use. All vinyl azides and azirines were prepared by the method of A. Hassner and F. W. Fowler, *J. Org. Chem.*, **33**, 2686 (1968), and ref 6.

(16) L. I. Smith and H. H. Hoehn, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 356.

(17) C. D. Nenitzescu and E. Solomonica, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 496.

mmol) of PCl_5. The solution was refluxed for 3 hr. After the solution had cooled, 5 ml of H_2O was added with stirring. The organic layer was separated and the solvent was evaporated. The residue (0.47 g, composed of 100% **8** as determined by nmr) was recrystallized from CH_3CN–H_2O (50:50) to give 0.38 g (57%) of **8**: mp 171–172°; ir (KBr) 1780, 1605, 1500 cm^{-1}; nmr ($DCCl_3$) τ 2.35–3.90 (m, 13, phenyl hydrogens), 1.45–1.90 (m, 2,2-phenyl ortho hydrogens); uv max (95% C_2H_5OH) 254 nm (ϵ 14,500); mass spectrum (70 eV) *m/e* (rel intensity) 383:381:379 (M^+) in a ratio of 1:5:7 (very weak), 317 (59), 165 (100).

Anal. Calcd for $C_{22}H_{15}Cl_2NO$: C, 69.48; H, 3.98. Found: C, 69.31; H, 4.13.

The same product **8** was obtained in quantitative yield by bubbling excess Cl_2 into a slurry of **6a** in benzene and subsequent evaporation of the benzene.

***p*-Methoxy-α-azidostyrene (1b).**—The synthesis of **1b** from *p*-methoxystyrene and iodine azide was modeled after that described for styrene.[13] DBN was used as the base in the elimination of HI from the iodine azide adduct. The vinyl azide **1b** was purified by dissolving the solid in a minimum amount of pentane and passing the solution through a disposable pipette filled with neutral alumina: mp 31–32°; ir (CCl_4) 2830, 2140, 2100, 1610 cm^{-1}; nmr (CCl_4) τ 2.65 (d, 2, J = 9 Hz, aromatic hydrogens), 3.32 (d, 2, J = 9 Hz, aromatic hydrogens), 4.33 (d, 1, J = 2 Hz, olefinic hydrogen), 5.30 (d, 1, J = 2 Hz, olefinic hydrogen), 6.38 (s, 3, OCH_3).

2-(*p*-Methoxyphenyl)-5,5-diphenyl-2-pyrrolin-4-one (6b).—From the reaction of 0.5 g (2.8 mmol) of *p*-methoxy-α-azidostyrene (**1b**) and 0.6 g (3.1 mmol) of diphenylketene (**2**) for 3 days as described for **6a**, there was obtained 0.3 g of a very insoluble compound. Purification was accomplished by absorbing 0.1 g of the solid on 2 g of silica gel and eluting the absorbed compound over 20 g of silica gel with benzene–ether (80:20). In this manner 0.66 g (16%) of **6b** was obtained: mp >300°; ir (KBr) 3200, 1625, 1600, 1580, 1560 cm^{-1}; nmr (DMSO-d_6, 100°, HA-100) τ 1.02 (s, 1, NH, exchangeable with D_2O), 2.02–3.34 (m, 14, phenyl hydrogens), 4.61 (s, 1, C=CH); uv max (95% C_2H_5OH) 282 nm (ϵ 20,000), 352 (12,000); mass spectrum (70 eV) *m/e* (rel intensity) 341 (82, M^+), 312 (100), 208 (26), 132 (26).

Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.91; H, 5.61. Found: C, 80.67; H, 5.58.

An nmr spectrum of the remaining reaction mixture shows the presence of 40% starting vinyl azide.

When the reaction was carried out by heating 0.85 g of **1b** with 1.1 g of α-diazo-α-phenylacetophenone in benzene at reflux for 15 min, **6b**, which precipitated during heating, was obtained in 45% yield (0.8 g).

5,5-Diphenylindeno[1.2-*b*]-2-pyrrolin-4-one (11).—From 8.1 g (52 mmol) of 1-azidoindene (**10**) in 100 ml of diethyl ether and 10 g (56 mmol) of diphenylketene (**2**) at 25° for 3 days there was obtained a powdery yellow solid. Recrystallization from benzene furnished 0.6 g of **11**: mp >300°; ir (KBr) 3260, 1625, 1605, 1540 cm^{-1}; nmr (DMSO-d_6, 100°, HA-100) τ 0.65 (s, 1, NH, exchangeable with D_2O), 2.14 (d, 1, hydrogen on indene), 2.48–2.18 (m, 13, phenyl hydrogens), 6.56 (s, 2, $-CH_2-$); uv max (dimethylformamide) 364 nm (ϵ 9100), 299 (3800), 285 (3500); uv (*p*-dioxane) 362 nm (ϵ 5800), 299 (4000), 289 (3900); mass spectrum (70 eV) *m/e* (rel intensity) 323 (56, M^+), 295 (32), 294 (100), 178 (32), 105 (50).

Anal. Calcd for $C_{23}H_{17}NO$: C, 85.42; H, 5.30. Found: C, 85.25; H, 5.31.

An nmr spectrum of the remaining reaction mixture shows mainly the presence of vinyl azide **10**.

When the reaction was carried out in DMF solution a tarry material coagulated on the side of the flask. It was dissolved in 50 ml of hot DMF, and the solution was filtered, cooled, and diluted with 50 ml of ether to precipitate 0.5 g (11%) of **11**.

From 10 g (64 mmol) of the vinyl azide **10** and 12.5 g (65 mmol) of the ketene **2** in 100 ml of THF under reflux for 3 days there was obtained 7.2 g (35%) of **11**.

3-Chloro-5,5-diphenylindeno[1,2-*b*]-1-pyrrolin-4-one (12).—A solution of 0.62 g (1.9 mmol) of **11** and 1.2 g (5.7 mmol) of PCl_5 in 50 ml of benzene was refluxed for 6 hr. Work-up as for **8** gave 0.57 g of crude **12**. Crystallization from CH_3CN–H_2O furnished 0.83 g (34%) of **12**: mp 128–129°; ir (KBr) 1770, 1640, 1500 cm^{-1}; nmr ($DCCl_3$) τ 6.65 (s, broad, 2, $-CH_2-$), 2.00–2.83 (m, 14, phenyl hydrogens); uv max (95% C_2H_5OH) 251 nm (ϵ 14,100).

Anal. Calcd for $C_{23}H_{16}ClNO$: C, 77.19; H, 4.51. Found: C, 76.98; H, 4.37.

3-Azido-2,2-diphenyl-3-*n*-butylcyclobutanone (16).—To 0.5 g (4 mmol) of 2-azido-1-hexene (**1c**) in 30 ml of anhydrous ether was added 1 g (5.1 mmol) of diphenylketene (**2**). The reaction mixture was stirred for 3 days. The precipitate, representing a 3:1 adduct, was filtered and weighed 0.06 g (4%), recrystallized from 95% C_2H_5OH: mp 218–218.5°; ir (KBr) 3260, 1740, 1640, 1130 cm^{-1}; nmr ($DCCl_3$) τ 2.73–3.12 (m, 30, phenyl hydrogens), 4.13 (broad, s, 1), 5.04 (s, 1), 7.50–7.90 (broad, s, 2), 8.67–9.50 (m, 9, aliphatic hydrogens); mass spectrum (70 eV) *m/e* (rel intensity) 681 (very weak), 439 (45), 318 (24), 212 (19), 167 (100), 166 (33), 165 (84).

The solvent was evaporated from the filtrate, yielding an oil (1.35 g). Chromatography on 50 g of silica gel with Skellysolve B as eluent afforded 0.27 g (21%) of **16** as an oil: ir (CCl_4) 2110, 1775, 1490, 1450, 1260 cm^{-1}; nmr (CCl_4) τ 2.32–3.03 (m, 10, phenyl hydrogens), 6.68 (d, 1, J = 17 Hz, OCCH trans to *n*-butyl), 7.03 (d, 1, J = 17 Hz, O=CCH cis to *n*-butyl), 7.91–9.50 (m, 9, $-C_4H_9$).

Anal. Calcd for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63. Found: C, 75.02; H, 6.78.

An nmr spectrum of the crude reaction mixture (before chromatography) showed it to consist of 30% cyclobutanone **16** and 70% vinyl azide **1c**.

When the reaction was allowed to proceed for a week, 2% of **17** was also found among the products.

3-*n*-Butyl-4,4-diphenyl-2-cyclobutenone (17).—Crude azido ketone **16** (2.89 g) was dissolved in 100 ml of ether and added to Merck alumina, and the mixture was stirred for 1.5 days. The ether was decanted and the alumina was washed several times with small portions of ether. The ether washes were combined and the ether was evaporated. The oil (1.2 g) was crystallized from 2 ml of ethyl acetate–pentane (40:60). The white needles of **17**, weighing 0.3 g (25%), were filtered and dried: mp 73–75°; ir (CCl_4) 1750, 1580, 1490, 1440 cm^{-1}; nmr ($DCCl_3$) τ 2.70 (s 10, phenyl hydrogens), 3.75 (t, 1, C=CHC=O), 7.45 (t, 2, $C_3H_7CH_2C$=C), 8.08–9.30 (m, 7, C_3H_7); uv (*p*-dioxane) shoulders on end absorption at 345 nm (ϵ 5800), 362 (5800).

Anal. Calcd for $C_{20}H_{20}O$: C, 86.92; H, 7.29. Found: C, 86.79; H, 7.33.

3-*n*-Butyl-2,2-diphenylcyclobutanone (19).—To 0.026 g (0.09 mmol) of the cyclobutanone **17** was added 0.053 g of Pd/C (5%) and 20 ml of thiophene-free benzene. After the solution was flushed with nitrogen, hydrogen was bubbled through for 25 min at a rate of approximately 0.1 cc/sec. Nitrogen was again bubbled through the solution and the catalyst was filtered. The product was purified by chromatography on a 2-mm silica gel plate using benzene–Skellysolve B (50:50) as eluent, yielding 0.019 g (73%) of **19** recrystallized from pentane: mp 46–49°; ir (KBr) 1770 cm^{-1}; nmr ($DCCl_3$) τ 2.53–3.08 (m, 10, phenyl hydrogens), 6.47–7.36 (m, 3, C_4CHCH_2C=O), 8.29–9.45 (m, 7, *n*-C_3H_7).

Anal. Calcd for $C_{20}H_{22}O$: C, 86.28; H, 7.97. Found: C, 86.52; H, 8.05.

Registry No.—**1a**, 16717-64-9; **1b**, 34910-42-4; **1c**, 34910-43-5; **2**, 525-06-4; **6a**, 34910-44-6; **6b**, 34910-45-7; **8**, 34910-46-8; **10**, 16719-57-6; **11**, 34910-48-0; **12**, 34910-49-1; **16**, 34910-50-4; **17**, 34910-51-5; **19**, 24242-42-0; 2-azido-1-hexene–diphenyl ketene adduct (1:3), 34910-53-7.

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The Reaction of α-Nitro Ketones with the Ketene-Generating Compounds, Isopropenyl Acetate and α-Acetoxystyrene. Synthesis of 3-Acetyl- and 3-Benzoyl-5-Substituted Isoxazoles[1a]

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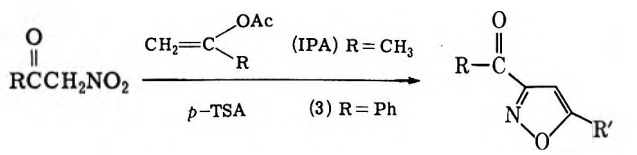
Reaction of α-nitroacetophenone (**1a**) with isopropenyl acetate (IPA) under acid-catalyzed conditions produced 3-benzoyl-5-methylisoxazole (**2a**) in 62% yield. A similar reaction with α-nitroacetone (**1b**) gave isoxazole **2b** although in much poorer yield (~5% by glc analysis). Reactions of **1a** and **1b** with α-acetoxystyrene (**3**) also produced the corresponding isoxazoles **4a** and **4b** in low but isolable yields (24 and 3%, respectively). A possible mechanism is suggested based on a study of the reaction of **1a** with IPA. Infrared, nmr, uv, and mass spectral data of the isoxazoles are reported.

As a possible facile entry into cyclopropyl analogs of the hormonal amines, epinephrine and norephrine, we envisaged a general route utilizing α-acetoxy-β-nitrostyrene as the key intermediate. Subsequent steps in the sequence were to involve formation of the cyclopropyl ring *via* condensation with dimethylsulfonium methylide[2] and reduction of the resultant nitrocyclopropane to the corresponding amine[3] followed by hydrolysis. In an attempt to prepare this intermediate by an acid-catalyzed enol acetate exchange reaction of α-nitroacetophenone (**1a**) with isopropenyl acetate (IPA), a solid product was obtained in reasonable yield which proved not to be the desired compound. This was demonstrated by the lack of asymmetric and symmetric ir stretching frequencies characteristic of a nitro group. The nmr spectrum showed the presence of five aromatic protons, a one-proton singlet at 6.42 ppm, and a three-proton singlet at 2.44 ppm. High-resolution mass measurement of the parent ion and combustion analysis showed that the compound had a molecular formula of $C_{11}H_9NO_2$. Analysis of the major peaks in the mass spectrum soon revealed that the compound was the isoxazole **2a**. Conclusive evidence for the proposed structure came from an independent synthesis of the isoxazole by the method of Ajello and Cusmano.[4]

Since the synthesis of isoxazoles by this method appeared to be novel, we decided to investigate whether the reaction was applicable to aliphatic nitro ketones. The reaction of α-nitroacetone (**1b**) and IPA did indeed produce the corresponding 3-acetyl-5-methylisoxazole (**2b**) (refer to Scheme I), although in very low yield and from consistently tarry reaction mixtures, an observation which will be discussed later in the text.

To further investigate the scope of the reaction the synthesis was extended by reacting the already prepared α-nitro ketones with an aromatic enol acetate, α-acetoxystyrene (**3**). As shown in Scheme I, the corresponding isoxazoles were isolated in both cases. Although the yields were poor, the isoxazoles formed were isomerically pure in contrast to the normal synthesis of

SCHEME I



1a, R = Ph
b, R = CH_3

2a, R = Ph; R′ = CH_3
b, R = CH_3; R′ = CH_3
4a, R = Ph; R′ = Ph
b, R = CH_3; R′ = Ph

3-keto 5-substituted isoxazoles using β diketones and nitric acid.[4a,b]

In recent years[5] 3-arylisoxazoles have been conveniently synthesized by a 1,3-dipolar cycloaddition of an aromatic nitrile oxide with some vinyl compound containing a leaving group. The reaction has been postulated[6] to proceed through a Δ^2-isoxazoline intermediate and recently Micetich[7] has in certain cases isolated such intermediates from the reactions between vinyl acetate or IPA and various nitrile oxides. The Δ^2-isoxazolines so obtained deacetylate to the corresponding isoxazoles upon heating or in the presence of acid.

Observation of a weak ir absorption[8] at 2260 cm^{-1} from a solution of 0.0003 mol of **1a** in 0.003 mol of IPA supports the postulated nitrile oxide intermediate. The intensity of this 2260-cm^{-1} peak increased when *p*-TSA was added to the solution, and an absorption at 1830 cm^{-1} also appeared suggesting the formation of acetic anhydride. This later observation was confirmed by isolation of acetic anhydride from the reaction mixture and is evidence for the formation of ketene under the reaction conditions.[9]

The formation of the nitrile oxide from the α-nitro ketone *via* Scheme II is consistent with these experimental data.

(1) (a) This investigation was supported by NIH Training Grant No. 5-T01-GM00728 and the University of California Academic Senate Grant 10, San Francisco Division; (b) NIH Trainee, 1970–1972; (c) NIH Trainee, 1969–1970; (d) Department of Pharmaceutical Chemistry, College of Pharmacy, University of Washington, Seattle, Washington 98195.

(2) J. Asunskis and H. Shechter, *J. Org. Chem.*, **33**, 1164 (1968).

(3) S. Matin and N. Castagnoli, Department of Pharmaceutical Chemistry, University of California at San Francisco, private communication.

(4) (a) T. Ajello and S. Cusmano, *Gazz. Chim. Ital.*, **68**, 792 (1938); (b) S. Cusmano, *ibid.*, **78**, 622 (1948).

(5) (a) N. K. Kochetkov and S. D. Solokov in "Advances in Heterocyclic Chemistry," Vol. 2, Academic Press, New York, N. Y., 1963, p 375; (b) R. Scarpati, C. Santocroce, and D. Sica, *Gazz. Chim. Ital.*, **93**, 1706 (1963); (c) P. Rajagopalan and C. N. Talaty, *Tetrahedron Lett.*, **No. 38**, 4537 (1966).

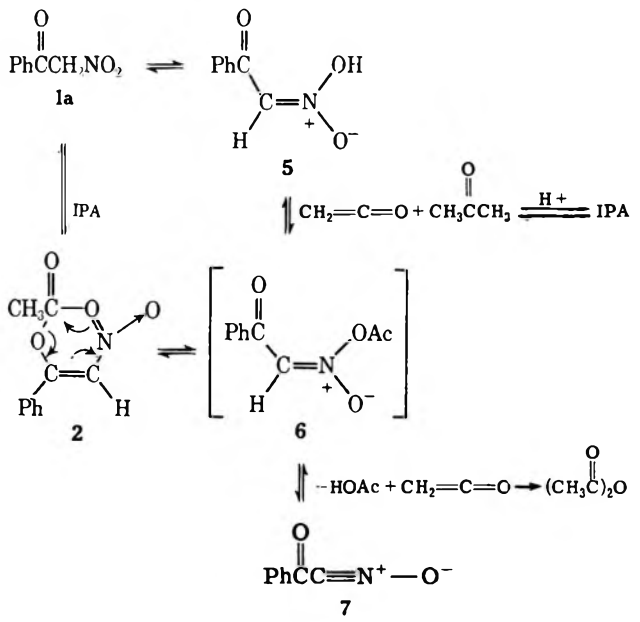
(6) P. Grunanger and S. Mangiapan, *Gazz. Chim. Ital.*, **88**, 149 (1958).

(7) (a) R. G. Micetich, *Can. J. Chem.*, **48**, 467 (1970); (b) *ibid.*, **48**, 3753 (1970).

(8) (a) S. Califano, R. Moccia, R. Scarpati, and G. Speroni, *J. Chem. Phys.*, **26**, 1777 (1957). (b) The C=N stretching of the α-ketonitrile oxide would be expected to occur at a lower frequency than the reported absorption at 2300 cm^{-1}.

(9) The production of ketene without the addition of *p*-TSA can be justified since **1a** itself is a fairly strong acid with a $pK_a^{nitro} \sim 5$ and $pK_a^{aci} \sim 2$. See "The Chemistry of Functional Groups—The Chemistry of Nitro and Nitroso Groups," Part 1, H. Feuer, Ed., Interscience, New York, N. Y., 1969, pp 374–376.

SCHEME II



Work by other groups would seem to support the mechanism outlined. Nenitzescu and Isacescu[10a] and Urbanski and Gurzynska[10b] have synthesized stable nitronic acid anhydrides from nitro compounds and ketene similar to the nitronic acid anhydride intermediate **6**. Work by Noland and coworkers[11a] and by Simmons and Kreuz[11b] has shown that certain nitrile oxides similar to intermediate **7** are formed from nitro compounds in acid solution, while synthesis of benzoylnitrile oxide (**7**) by another route has recently been proposed by two independent research groups.[12a,b]

Two pathways are presented in Scheme II for the formation of an intermediate nitronic anhydride **6**. One involves prior formation of α-acetoxy-β-nitrostyrene (**2**) followed by an acyl exchange reaction from the enol oxygen to the nitro group oxygen *via* a six-membered ring transition state. The second pathway involves prior tautomerization to the acinitro compound **5**, which reacts with ketene continuously being generated from IPA. The intermediate nitronic anhydride **6** could then eliminate acetic acid to form the nitrile oxide **7**. Although attempts were made to isolate and characterize the nitrile oxide, none were successful. Consequently, Scheme II can only be considered as a reasonable estimate of the reaction sequence.

Little change occurred in the reaction after 48 hr at room temperature; however, upon heating the solution for a few minutes the ir peak at 2260 cm^{-1} disappeared while two new singlets appeared in the nmr spectrum at 2.54 and 6.68 ppm. These singlets represent the methyl group hydrogens and the C-4 proton of the newly formed isoxazole **2a**, respectively. As expected, the two peaks integrated in a 3:1 ratio.

(10) (a) C. D. Nenitzescu and D. A. Isacescu, *Bull. Soc. Chim. Romania*, **14**, 53 (1932); (b) T. Urbanski and W. Gurzynska, *Rocz. Chem.*, **25**, 213 (1951).

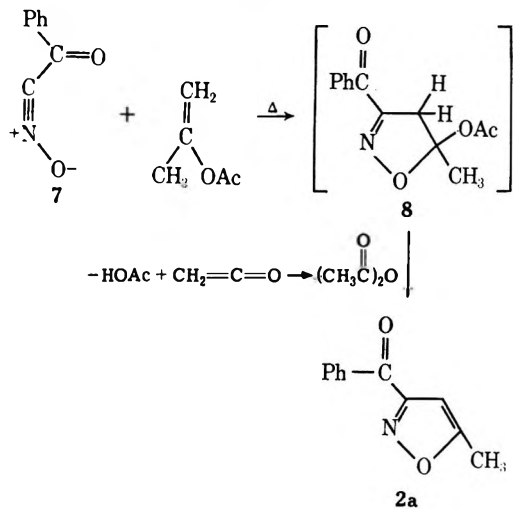
(11) (a) W. E. Noland, J. H. Colley, and P. A. McVeigh, *J. Amer. Chem. Soc.*, **81**, 1209 (1959); (b) T. Simmons and K. L. Kreuz, *J. Org. Chem.*, **33**, 836 (1968).

(12) (a) T. Sasaki, T. Yoshioka, and Y. Suzuki, *Bull. Chem. Soc. Jap.*, **44**, 185 (1971); (b) Y. Otsuji, Y. Tsujii, A. Yoshida, and E. Imoto, *ibid.*, **44**, 223 (1971).

The reaction mixture was then allowed to stand at room temperature for 24 hr. Once again the ir showed an intense absorption peak at 2260 cm^{-1}. The procedure of alternate heating and cooling was continued with the same results as noted before, that is, the loss of absorption in the ir at 2260 cm^{-1} upon heating, with a corresponding increase in formation of the isoxazole as noted by nmr.

Scheme III depicts the final steps of the reaction.

SCHEME III



The nitrile oxide **7** can undergo a 1,3-dipolar cycloaddition reaction with the enol acetate to form an intermediate Δ-2 isoxazoline **8** which can then eliminate acetic acid to form the product isoxazole **2a**.

However, no evidence could be found in the nmr spectrum for the Δ^2-isoxazoline intermediate **8**. Apparently, the slow step in the reaction sequence involves formation of the isoxazoline with a fast deacetylation to yield the isoxazole. The proposed sequence does help to explain why α-nitroacetone (**1b**) gives such poor yields, since it is well known that nonaromatic stabilized nitrile oxides spontaneously dimerize to furoxans,[13a] which may undergo further degradation or polymerization.[13b]

Experimental Section

General.—Melting points were taken by capillary using a Thomas-Hoover Uni-Melt instrument and are corrected. Boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer 457 spectrophotometer, uv spectra with a Cary II spectrophotometer, and nmr in deuteriochloroform on a Varian A-60A with tetramethylsilane as an internal standard. Vpc analyses were performed on a Varian Model 90-P with thermal detectors or Varian Model 2100-A with flame-ionization detectors. Mass spectra were obtained on an AEI Model MS-902 mass spectrometer. Elemental analyses were performed by Berkeley Microanalytical Laboratories.

α-Nitroacetophenone (**1a**).—This compound was prepared by the method of Bachman and Hokama[14] in 70% yield, mp 105–106°.

(13) (a) C. Grundman and J. M. Dean, *J. Org. Chem.*, **30**, 2809 (1965); (b) A. Quilico and G. Speroni in "Heterocyclic Compounds—Five- and Six-Membered Compounds with Nitrogen and Oxygen," R. H. Wiley, Ed., Interscience, New York, N. Y., 1962, p 295 ff.

(14) G. B. Bachman and T. Hokama, *J. Amer. Chem. Soc.*, **81**, 4882 (1959).

α-Nitroacetone (1b).—This ketone was prepared by oxidation of 1-nitro-2-propanol[15a] by the method of Brown and Garg,[15b] mp 48–50° (lit.[15c] mp 49–50°).

3-Benzoyl-5-methylisoxazole (2a).—A solution of 14.0 g (0.085 mol) of **1a** and *p*-TSA (140 mg) in IPA (60 ml) was refluxed in an atmosphere of dry nitrogen for 24 hr, during which period acetone was continuously distilled over and collected in a Dean–Stark trap. The clear, dark-brown reaction mixture was cooled and excess IPA was removed by rotary evaporation under reduced pressure. The black residue was taken up in ether (150 ml) and washed with 10% sodium carbonate solution followed by water, filtered through anhydrous sodium sulfate, and dried further over drierite.

Purification by distillation under reduced pressure, bp 102–110° (0.1 mm), followed by recrystallization yielded 9.86 g of white crystals from hexane: mp 43.0–44.5° (lit.[16] mp 50°); ir ν_{max} (KBr) 1665 (C=O), 1600 (C=N ring stretching), 1450 and 1425 (N–O ring stretch), 1270, 1215, and 895 cm^{-1}; nmr ($CDCl_3$) δ 8.2 (m, 2, *o*-aroyl), 7.48 (m, 3, *m*- and *p*-aroyl), 6.42 (s, 1, C-4), 2.44 (s, 3, C-5 Me); λ_{max}^{EtOH} 260 nm (log ε 4.40); mass spectrum *m/e* 187 (M^+), (base peak), 105, other major peaks 77, 58, 51, 43, 28; high resolution mass measurement of M^+, 187.0639 (calcd 187.0633).

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.55; H, 4.86; N, 7.47.

3-Acetyl-5-methylisoxazole (2b).—A solution of 1.03 g (0.01 mol) of **1b** and *p*-TSA (10 mg) in 20.0 g (0.10 mol) of IPA was refluxed under nitrogen for 15 hr, during which period acetone was collected in a Dean–Stark trap. The clear dark-brown reaction mixture was worked up as described for **2a**. Glc analysis of the partially purified reaction mixture on a 10 ft × 0.125 in. Versamid column operated at 100° in a Varian Aerograph Model 90-P showed the presence of a peak (~5% of the mixture) with a retention time of 7.1 min, identical with that of an authentic sample of **2a** synthesized by the method of Schmidt and Widmann.[17] The crude material was partially purified by distillation (10 mm), yield a few drops of a pale yellow liquid which contained ~50% of **2b** as determined by glc analysis. A small sample of the pure isoxazole was obtained by preparative glc and found to be identical with the known compound by comparative ir ν_{max}^{neat} 1701 (C=O), 1600 (C=N ring stretch), 1450 and 1425 (N–O ring stretch), 1355, 1260, 1180, and 950 cm^{-1}; nmr ($CDCl_3$) δ 6.40 (s, 1, C-4), 2.64 (s, 3, OC Me), 2.50 (s, 3, C-5 Me); λ_{max}^{EtOH} 249 nm (log ε 3.60); mass spectrum *m/e* 125 (M^+), 43 (base peak), other major peaks 110 (M − 15), 69, 58, 31, and 28.

α-Acetoxystyrene (or 1-Phenylethenol Acetate) (3).—A solution of 50.0 g (0.417 mol) of acetophenone and 4.0 g (0.021 mol) of *p*-TSA in IPA (200 ml) was stirred at reflux temperature under dry nitrogen for 16 hr. Acetone was collected in a Dean–Stark trap as the reaction proceeded. After the reflux period, the reddish-brown solution was poured into distilled water (250 ml) and extracted with three 100-ml portions of ether. The combined extracts were washed with 5% $NaHCO_3$, followed by water, filtered through anhydrous sodium sulfate, and dried further over Drierite. Evaporation of the solvent gave 105.2 g of a dark-brown, foul-smelling liquid which was purified by distillation: yield 47.5 g of clear liquid; bp 100–103° (10 mm); ir ν_{max}^{neat} 1780 (C=O), 1655 (C=C vinyl stretch), 1205 (C–O stretch of enol acetate), 955 and 880 cm^{-1}; nmr ($CDCl_3$) δ 7.31 (m, 5, aromatic), 5.39 (d, 1, J = 2 Hz, vinyl), 4.98 (d, 1, J = 2 Hz, vinyl), 2.19 (s, 3, Me); mass spectrum *m/e* 162 (M^+), 105 (base peak), other major peaks 134 (M − CO), 120 (M − ketene), 91, 77, 51, and 43; high resolution mass measurement of M^+, 162.0669 (calcd, 162.0681).

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: 73.78; H, 5.98.

3-Benzoyl-5-phenylisoxazole (4a).—A solution of 1.65 g (0.01 mol) of **1a**, *p*-TSA (10 mg), and 4.87 g (0.03 mol) of **3** was heated at 110° in a dry nitrogen atmosphere for 12 hr. The clear dark-brown reaction mixture was cooled, taken up in ether (75 ml), washed successively with 5% $NaHCO_3$ and water, and dried (Drierite). After rotary evaporation of the ether under reduced pressure, the residual liquid was distilled under reduced pressure, yielding 2.4 g of acetophenone as determined by comparative ir with an authentic sample.

Glc analysis of the black distillation residue on a 6 ft × 0.125 in. 3% OV-1 column operated at 130° using a Varian 2100 analyzer showed small amounts of acetophenone and **3** plus other minor impurities, as well as a relatively large peak with a retention time of 8.7 min. Tlc on Eastman silica gel GF chromograms developed in hexane–EtOAc–MeOH (2:2:1) and visualized with uv light showed a bright spot, R_f 0.64, running behind acetophenone, R_f 0.74, and **3**, R_f 0.68.

The residue was chromatographed on a 20-g silica gel column (E. Merck, 30–70 mesh) using hexane–EtOAc (9:1) as eluent. Fractions (10 ml) were collected using an ISCO Model 327 automatic collector. Glc analysis showed that fractions 7–16 were primarily the desired product. Two recrystallizations of the crude material from hexane gave 590 mg of white solid: mp 85.0–86.5° (lit.[18] mp 89°); ir ν_{max}^{KBr} 1665 (C=O), 1590 (C=N ring stretch), 1460 and 1430 (N–O ring stretch), 1240 and 895 cm^{-1}; nmr ($CDCl_3$) δ 8.49 (m, 2, ortho aroyl), 7.94 (m, 2, ortho aryl), 7.62 (m, 6, meta and para aroyl and aryl), and 7.15 (s, 1, C-4); λ_{max}^{EtOH} 264 nm (log ε 4.55); mass spectrum *m/e* 249 (M^+), 105 (base peak), other major peaks 189, 146, 116, 111, 89, 77, 63, 51, and 28.

3-Acetyl-5-phenylisoxazole (4b).—A solution of 1.03 g (0.01 mol) of **1b**, *p*-TSA (10 mg), and 4.87 g (0.03 mol) of **3** was heated at 70° in a dry nitrogen atmosphere for 4 hr. The resulting black, tarry reaction mixture was worked up and distilled to remove acetophenone as described for **4a**.

Glc analysis of the distillation residue on a 6 ft × 0.125 in. 3% OV-1 column operated at 125° using a Varian Aerograph Model 2100 with flame ionization detectors showed the residue to consist largely of unreacted **3**, approximately 10% of **4b** with a retention time of 8.3 min, and many minor unresolved products.

The isoxazole **4b** was isolated by column chromatography on a 15-g silica gel G column (E. Merck, 100 mesh) using hexane–ether (9:1) as eluent. Fractions (10 ml) were collected using an ISCO Model 327 automatic collector. Glc analysis showed that fractions 9–12 were primarily the desired product. Three recrystallizations of the crude material from hexane gave 56 mg of pure **4b**, mp 98–99° (lit.[19] mp 105° and 98–99°). Comparative ir, nmr, and a mixture melting point showed the product to be identical with that isolated by fractional recrystallization from the reaction mixture produced in the synthesis outlined by Ajello and Cusmano:[2a,b] ir ν_{max}^{KBr} 1701 (C=O), 1580 (C=N ring stretch), 1440 and 1430 (N–O ring stretch), 1355, 1220, and 940 cm^{-1}; nmr ($CDCl_3$) δ 7.71 (m, 2, ortho aryl), 7.40 (m, 3, meta and para aryl), 6.80 (s, 1, C-4), 2.65 (s, 3, O=C—CH_3); λ_{max}^{EtOH} 250 nm (log ε 4.18); mass spectrum *m/e* 187 (M^+), 43 (base peak), other major peaks 172 (M − 15), 145 (M − 42), 105, 77, 51, and 28.

Registry No.—**1a**, 614-21-1; **1b**, 10230-68-9; **2a**, 34671-15-3; **2b**, 24068-54-0; **3**, 2206-94-2; **4a**, 3672-49-9; **4b**, 7063-98-1; isopropenyl acetate, 108-22-5.

(15) (a) C. A. Sprang and E. F. Degering, *J. Amer. Chem. Soc.*, **64**, 1063 (1942); (b) H. C. Brown and C. P. Garg, *ibid.*, **83**, 2952 (1961); (c) C. Harries, *Justus Liebigs Ann. Chem.*, **319**, 251 (1901).

(16) The melting point reported by Ajello and Cusmano[4a,b] is in error.

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Pyridazines. L. Methylations and Methyl Group Migrations of Some Imidazo[1,2-b]pyridazines

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Methylation studies on different imidazo[1,2-b]pyridazines have been conducted and at elevated temperatures the methylated compounds undergo methyl group migrations. The methyl groups can be transposed from oxygen at C_6 to N_5 or N_1 and demethylation at N_1 or N_5 has been observed.

Our previous observation that quaternized *s*-triazolo[4,3-*b*]pyridazines may undergo methyl group transposition in the five-membered ring[1] prompted us to investigate this phenomenon in the imidazo[1,2-*b*]-pyridazine series.

It has been reported[2] that methylation of 2-phenylimidazo[1,2-*b*]pyridazin-6(5*H*)-one with methyl iodide afforded the corresponding 5-methyl derivative **3**. We have repeated this experiment and have found that the product is in fact a mixture of the 6-methoxy compound **2** (40%) and the 5-methyl compound **3** (52%) accompanied by a small amount of the starting material (8%).

On the other hand, 6-chloro-1-methyl-2-phenylimidazo[1,2-*b*]pyridazin-4-ium iodide (**4**), when treated with sodium methylate, afforded **5**. In a similar experiment with aqueous potassium hydroxide, however, the anhydro salt **6** was formed. Upon methylation, this anhydro salt was transformed into a mixture of the 1,5-dimethyl derivative **7** and the 6-methoxy compound **5** in a ratio of about 1:5. Moreover, compound **7** is formed also from **2** at 150–155° under pressure, and here again an almost equal amount of **5** was formed. Pure **7** could be obtained by thermal rearrangement of **5** when this compound was heated over its melting point (203°) or by quaternization of compound **3** with methyl iodide at about 160°. Although the 1,5-dimethyl derivative **7** on hand of these experiments appears to be the thermodynamically most stable compound, heating under high vacuum at 240° for 2 hr caused some demethylation to give **3** and a small amount of the anhydro salt **6** accompanying the unchanged starting material.

Migration of the methyl group from the methoxy compound **2** could be observed upon heating this compound at 240°, whereupon a mixture of three compounds could be separated by chromatography. There were present the starting compound, the *N*-methyl derivative **3**, and the anhydro salt **6** in the ratio of about 25:61:14. Evidently, this process involved migration not only to the neighboring N atom (N_5), but in considerable extent also to the nitrogen in the five-membered ring (N_1). In order to obtain evidence as to whether in the case of the above-mentioned transformation of **5** into **7** only methyl group migration from the methoxy group occurred or whether also the N_1-methyl group may participate in this process, the deuterated compound **8** was used as starting material. Nmr spectral evidence, which allowed distinction between the N_1-methyl and N_5-methyl groups in **7**, showed that the rearranged product **9** retained the CD_3 group at the N_5 atom and that no interchange of methyl groups was detected. As with other related systems, the migration of the methyl group is most probably intermolecular.[3] The driving force for these OMe → NMe rearrangements is certainly the greater stability of the amido structures, a feature which has been observed with several monocyclic heterocycles and which we have recently observed also in the *s*-triazolo[4,3-*a*]-1,3,5-triazine series.[4] On the other hand, it is well known that such rearrangements are promoted in the presence of small amounts of an alkyl halide.[3]

Except for an isolated example which we have described before,[5] the formation of anhydro salts of the type **6** represents the first case in this series. There are, however, several examples of anhydro salt formation with other heterocycles, in particular with cinnolines[6,7] and phthalazines.[8,9] The formation of **10** could be therefore accomplished similarly from 6-chloro-1-methylimidazo[1,2-*b*]pyridazin-4-ium iodide, and this undergoes also a smooth displacement of the chlorine atom with hydrazine hydrate to give **11**.

Experimental Section

Melting points were taken on a Kofler micro hot stage. Infrared spectra were recorded on a Perkin-Elmer 137 Infracord as KBr disks, nmr spectra were taken on a JEOL JNM-C-60HL spectrometer (tetramethylsilane as internal standard), and mass spectra were obtained on a CEC 21-110C instrument.

Methylation of 2-Phenylimidazo[1,2-*b*]pyridazin-6(5*H*)-one.—A solution of **1**,[2] 0.65 g, nmr (DMSO-d_6) τ 1.66 (s, H_3), 3.36 (d, H_7), 2.25 (d, H_8), 2.75, 2.20 (m, Ph), $J_{7,8}$ = 9.5 Hz, in methanolic KOH (0.21 g of KOH in 20 ml of MeOH) was treated with MeI (1.03 g) and the mixture was heated under reflux for 2 hr. The solvent was evaporated, the residue was treated with water (5 ml), and the precipitate was filtered off. Upon recrystallization from 65% EtOH the crystals (0.7 g) had mp 120–123°; 30 mg was separated by tlc (DC Fertigplatten Kieselgel F-254, Merck) with a mixture of $CHCl_3$ and MeOH (30:1). Each of the separated three spots was eluted with MeOH. There were obtained 10 mg of **2** [R_f 0.81; nmr (DMSO-d_6, 93°) τ 1.70 (d, H_3), 3.31 (d, H_7), 2.21 (dd, H_8), 2.75, 2.20 (m, Ph), 6.06 (s, OMe), $J_{3,8}$ = 0.6, $J_{7,8}$ = 9.5 Hz; mass spectrum *m/e* 225 (M^+). *Anal.* Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.64; H, 4.87; N, 18.32.], 13 mg of **3** [mp 153°; R_f 0.52; mass spectrum *m/e* 225 (M^+); nmr ($CDCl_3$) τ 2.40 (d, H_3), 3.42 (d, H_7), 2.24 (dd, H_8), 2.7, 2.3 (m, Ph), 6.20 (s, NMe), $J_{3,8}$ = 0.6, $J_{7,8}$ = 9.5 Hz; ir (KBr) 1656 cm^{-1} (CO). *Anal.* Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.54; H, 5.21; N, 19.00.], and the starting compound **1** (2 mg, R_f 0.23).

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(3) J. W. Schulenberg and S. Archer, *Org. React.*, **14**, 24 (1965).

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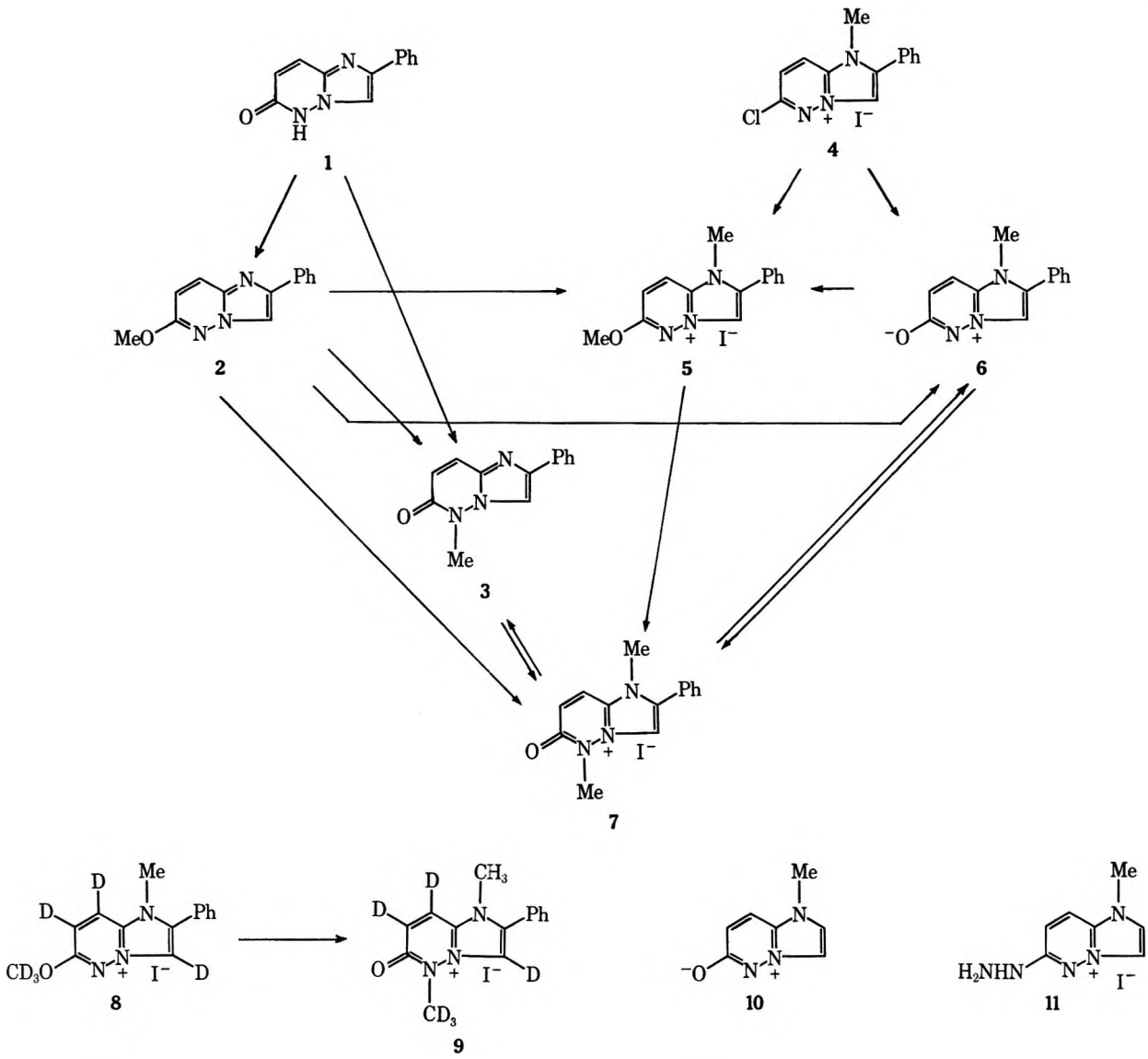

6-Chloro-1-methyl-2-phenylimidazo[1,2-*b*]pyridazin-4-ium Iodide (4).—A suspension of 6-chloro-2-phenylimidazo[1,2-*b*]-pyridazine[10] [2.30 g; nmr ($CDCl_3$) τ 1.92 (d, H_3), 3.11 (d, H_7), 2.25 (dd, H_8), 2.75, 2.20 (m, Ph), $J_{3,8}$ = 0.6, $J_{7,8}$ = 9.3 Hz] in EtOH (80 ml) was treated with MeI (2.84 g) and the mixture was heated in an autoclave at 160° for 5 hr. The separated product was filtered off (2.9 g, 78%) and upon recrystallization from EtOH it had mp 260–262°; nmr (DMSO-d_6) τ 1.10 (d, H_3), 1.96 (d, H_7), 1.12 (dd, H_8), 2.40 (m, Ph), 5.93 (s, Me), $J_{3,8}$ = 0.6, $J_{7,8}$ = 9.6 Hz.

Anal. Calcd for $C_{13}H_{11}ClIN_3$: C, 42.01; H, 2.98; N, 11.31. Found: C, 42.22; H, 3.44; N, 11.26.

6-Methoxy-1-methyl-2-phenylimidazo[1,2-*b*]pyridazin-4-ium Iodide (5).—A suspension of 4 (1.86 g) in a solution of sodium methylate in MeOH (prepared from 0.12 g of sodium in 20 ml of MeOH) was heated under reflux for 2 hr. The solvent was evaporated to dryness, ice water (5 ml) was added, and the residue was filtered off and crystallized from EtOH (1.1 g, 60%): the product melted at 203°; the melt solidified at about 205° and melted again at 249–250°; mass spectrum *m/e* 225 (M^+ − MeI); nmr ($CDCl_3$) τ 2.16 (d, H_3), 2.80 (d, H_7), 1.18 (dd, H_8), 5.98 (s, OMe), 5.85 (s, NMe), 2.53 (m, Ph), $J_{3,8}$ = 0.6, $J_{7,8}$ = 9.6 Hz.

Anal. Calcd for $C_{14}H_{14}IN_3O$: C, 45.80; H, 3.85; N, 11.45. Found: C, 45.60; H, 3.90; N, 11.46.

6-Trideuteriomethoxy-1-methyl-2-phenyl-3,7,8-trideuterioimidazo[1,2-*b*]pyridazin-4-ium iodide (8) was prepared in the same manner as 5, but using CD_3OD: mp 203°; mass spectrum 231 (M^+ − MeI); nmr ($CDCl_3$) τ 5.85 (s, NMe), 2.52 (m, Ph).

(10) B. Stanovnik and M. Tišler, *Tetrahedron*, **23**, 2739 (1967).

6-Hydroxy-1-methyl-2-phenylimidazo[1,2-*b*]pyridazin-4-ium Anhydro Salt (6).—A suspension of 4 (3.72 g) in aqueous KOH (20 ml of 10% solution) was heated under reflux for 10 min. Upon cooling the separated product was filtered off, washed with ice water until neutral, and crystallized from EtOH (1.77 g, 78%): mp 272–273°; mass spectrum *m/e* 225 (M^+); nmr (DMSO-d_6) τ 2.30 (s, H_3), 3.40 (d, H_7), 2.40 (d, H_8), 2.48 (m, Ph), 6.28 (s, NMe), $J_{7,8}$ = 9.6 Hz.

Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 68.99; H, 4.62; N, 18.58.

Methylation of 6-Hydroxy-1-methyl-2-phenylimidazo[1,2-*b*]-pyridazin-4-ium Anhydro Salt.—A solution of the anhydro salt 6 (0.9 g) in EtOH (10 ml) was treated with MeI (1 g) and the mixture was heated under reflux for 1 hr. Upon complete evaporation to dryness, $CHCl_3$ (5 ml) was added and after thorough mixing the solid was filtered off. The residue was crystallized from EtOH and had mp 249–250° (0.2 g). The compound was identified as 1,5-dimethyl-2-phenylimidazo[1,2-*b*]-pyridazin-6(5*H*)-on-4-ium iodide (7), mixture melting point undepressed with an authentic specimen prepared from 3. The filtrate was evaporated to dryness and crystallized from EtOH to give 6-methoxy-1-methyl-2-phenylimidazo[1,2-*b*]pyrid-azin-4-ium iodide (5, 1.0 g), mp 203° (after solidification of the melt, mp 249–250°) and mixture melting point with an authentic specimen undepressed.

Methylation of 6-Methoxy-2-phenylimidazo[1,2-*b*]pyridazine.—A mixture of 2 (1.12 g), MeI (2.0 g), and MeOH (80 ml) was heated in an autoclave at 150–155° for 3 hr. Upon evaporation to dryness, $CHCl_3$ (20 ml) was added and the residue was filtered off. Crystallization from EtOH gave the pure 7 (0.4 g), mp 249–250°. The filtrate was evaporated and the residue was crystallized from EtOH to give 5 (0.31 g), mp 203°.

1,5-Dimethyl-2-phenylimidazo[1,2-*b*]pyridazin-6(5*H*)-on-4-ium Iodide (7). A.—Compound **5** (50 mg) was heated just above its melting point in a sublimation tube for 5 min. Thereafter the tube was connected to vacuum (0.1 mm) and the temperature was raised to 240° to sublime off traces of the demethylated products. The residue (46 mg) was pure **7**: mp 249–250°; mass spectrum *m/e* 225 ($M^+ - MeI$); ir (KBr) 1672 cm^{-1} (CO); nmr (DMSO-d_6) τ 1.26 (s, H_3), 2.94 (d, H_7), 1.68 (d, H_8), 2.46 (m, Ph), 6.04 (s, 1-Me), 6.22 (s, 5-Me), $J_{7,8}$ = 9.9 Hz.

Anal. Calcd for $C_{14}H_{14}IN_3O$: C, 45.80; H, 3.85; N, 11.45. Found: C, 45.65; H, 3.81; N, 11.80.

B.—A mixture of **3** (0.45 g), MeOH (30 ml), and MeI (0.5 g) was heated in an autoclave at 160° for 3 hr. The solvent was evaporated and the residue was crystallized from EtOH (0.35 g, 48%), mp 249–250°. The compound was identical with the product obtained as described under A.

1-Methyl-2-phenyl-5-trideuteriomethyl-3,7,8-trideuteriomidazo[1,2-*b*]pyridazin-6(5*H*)-on-4-ium iodide (9) was obtained from **8** in the same manner as described for the nondeuterated compound **7** under A: mp 249–250°; mass spectrum *m/e* 231 ($M^+ - MeI$), 228 ($M^+ - CD_3I$); nmr (DMSO-d_6) τ 6.03 (s, 1-Me), 2.44 (m, Ph).

Demethylation of 1,5-Dimethyl-2-phenylimidazo[1,2-*b*]pyridazin-6(5*H*)-on-4-ium Iodide.—The compound **7** (183 mg) was heated in a sublimation tube at 240° (0.1 mm) for 2 hr. The sublimate (28 mg) was identified as 5-methyl-2-phenylimidazo-[1,2-*b*]pyridazin-6(5*H*)-one (**3**). The residue was composed of the starting material as the main component and a small amount of 6-hydroxy-1-methyl-2-phenylimidazo[1,2-*b*]pyridazin-4-ium anhydro salt (**6**) as shown by thin layer chromatography (DC Fertigplatten Kieselgel F-254, Merck, MeOH as solvent).

Rearrangement of 6-Methoxy-2-phenylimidazo[1,2-*b*]pyridazine.—The methoxy compound **2** (225 mg) was heated in a sealed tube at 240° for 2 hr. The dark residue was treated with MeOH (5 ml) and purified by column chromatography (column diameter 18 mm, length 10 cm, filled with alumina type 507 C Fluka, for elution MeOH was used). The purified solution was evaporated to dryness and the residue (150 mg) was a mixture of three compounds.

A solution of this mixture (30 mg) in MeOH (2 ml) was submitted to tlc (PSC Fertigplatten Kieselgel F-254, MeOH and $CHCl_3$, 1:30, as solvent) and the spots were separated and eluted with MeOH. Upon evaporation of each solution there were obtained the starting compound **2** (7 mg) and 5-methyl-2-phenylimidazo[1,2-*b*]pyridazin-6(5*H*)-one (**3**) (17 mg).

When the same tlc procedure was applied, but MeOH was used as solvent, the spot with R_f 0.48 afforded after elution with MeOH pure 6-hydroxy-1-methyl-2-phenylimidazo[1,2-*b*]pyridazin-4-ium anhydro salt (**6**) (4 mg), identified by its melting point and ir spectrum when they were compared with those of an authentic specimen.

6-Hydroxy-1-methylimidazo[1,2-*b*]pyridazin-4-ium Anhydro Salt (10).—A suspension of 6-chloro-1-methylimidazo[1,2-*b*]-pyridazin-4-ium iodide[1] [1.95 g; nmr (DMSO-d_6) τ 1.32 (d, H_2), 1.08 (dd, H_3), 1.73 (d, H_7), 0.92 (dd, H_8), 5.75 (s, NMe), $J_{2,3}$ = 2.1, $J_{3,8}$ = 0.6 $J_{7,8}$ = 9.6 Hz] in aqueous KOH (1.12 g of KOH in 7 ml of water) was heated under reflux for about 10 min until a complete dissolution was achieved. After cooling, neutralization with concentrated hydrochloric acid, and evaporation to dryness, the residue was sublimed at 220° (0.1 mm) (0.7 g, 47%): mp 125–127°; mass spectrum *m/e* 149 (M^+); nmr (DMSO-d_6) τ 2.25 (d, H_2), 2.06 (dd, H_3), 3.53 (d, H_7), 2.30 (dd, H_8), 6.30 (s, NMe), $J_{2,3}$ = 2.0, $J_{3,8}$ = 0.6, $J_{7,8}$ = 9.5 Hz.

Anal. Calcd for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.18. Found: C, 56.43; H, 4.85; N, 27.87.

6-Hydrazino-1-methylimidazo[1,2-*b*]pyridazin-4-ium Iodide (11).—A mixture of 6-chloro-1-methylimidazo[1,2-*b*]pyridazin-4-ium iodide[1] (1.48 g) and hydrazine hydrate (5 ml, 80%) was heated under reflux for 10 min. Upon cooling the separated product was filtered off, washed with water, and crystallized from EtOH (0.8 g, 54%), mp 260°.

Anal. Calcd for $C_7H_{10}IN_5$: C, 28.88; H, 3.46; N, 24.07. Found: C, 28.87; H, 3.70; N, 24.51.

Registry No.—**1**, 34876-76-1; **2**, 1844-61-7; **3**, 1845-04-1; **4**, 34876-79-4; **5**, 34876-80-7; **6**, 34876-81-8; **7**, 34876-82-9; **8**, 34876-83-0; **9**, 34876-84-1; **10**, 34876-85-2; **11**, 34876-86-3.

Acknowledgment.—We are indebted to Dr. V. Kramer and Dr. J. Marsel, Institute J. Stefan, for recording the mass spectra.

Ion Radicals. XXV. The Reactions of Thianthrene and Phenothiazine Perchlorates with Nitrite Ion, Pyridine, and Other Nucleophiles[1]

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Reaction of thianthrene perchlorate (**1**) with sodium nitrite in nitromethane solution gave thianthrene 5-oxide (**2**) and nitric oxide, each in greater than 90% yield. Reaction with ^{18}O-labeled nitrite ion showed that the oxygen in **2** came from the nitrite ion. Reaction of **1** with sodium nitrate gave **2** (92, 98%) and nitrogen dioxide (71, 75%). Reaction of **1** with pyridine in nitromethane solution gave 73% of *N*-(2-thianthrenyl)pyridinium perchlorate (**3**) and 90% of thianthrene (**4**), the yields being calculated after compensation for the reaction of **1** with residual water in the pyridine. Reaction of solid **1** with neat pyridine was violent and was accompanied by explosion and flame unless carried out with small amounts of **1**, in which case the products were again **3** and **4**. Attempts to prepare **3** directly by the oxidation of **4** with iodine and silver perchlorate in the presence of pyridine failed. Reaction of phenothiazine perchlorate (**5**) with nitrite ion gave 3-nitrophenothiazine (96%) and phenothiazine (**6**) (100%). Oxidation of **6** with iodine and silver nitrite in acetonitrile solution gave 3-nitrophenothiazine in 70% yield. Reaction of **5** with pyridine gave *N*-(3-phenothiazinyl)pyridinium perchlorate (**7**) (78, 84%), **6** (72, 80%), and 3,10′-biphenothiazine (**8**) (2.1, 9%). Attempts to prepare **7** directly by the oxidation of **6** with iodine and silver perchlorate in the presence of pyridine gave mixtures of **7** and unidentified green solids whose separation was too difficult to achieve. Reaction of **5** with chloride and bromide ion gave the 3- and 3,7-dihalogenophenothiazines in approximately 75 and 8% yields, respectively, and, in each case, **6** in 85–90% yield. Reaction of **5** with fluoride ion gave only **6** (38%), **8** (17%), and an unidentified green solid.

In earlier publications, we have described the reactions of thianthrene perchlorate (**1**) with water,[4] electron-rich aromatics,[5] and dry ammonia.[1a] In each of these reactions the nucleophile attacked the thianthrene ring at sulfur (the 5 position) to form a 5-sub-

(1) (a) Part XXIV: H. J. Shine and J. J. Silber, *J. Amer. Chem. Soc.*, **94**, 1026 (1972). (b) Part XXIII: C. V. Ristagno and H. J. Shine, *J. Org. Chem.*, **36**, 4050 (1971). Supported by the National Science Foundation, Grant No. GP-25989X.

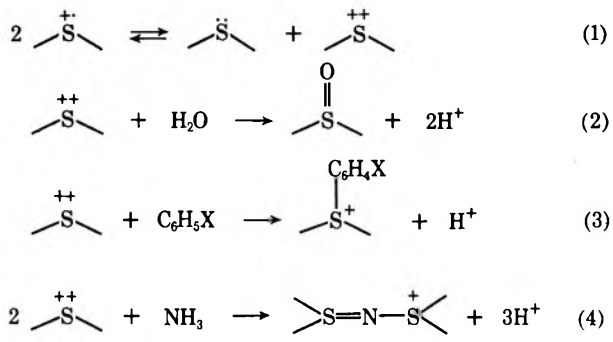
(2) Taken in part from the Ph.D. dissertation of Juana J. Silber, Texas Tech University, Jan 1972.

(3) Postdoctoral Fellow. We thank Texas Tech University for support of one of us (T. O.) under Grant No. 191-4719.

(4) Y. Murata and H. J. Shine, *J. Org. Chem.*, **34**, 3368 (1969).

(5) J. J. Silber and H. J. Shine, *ibid.*, **36**, 2923 (1971).

stituted thianthrene. In each case thianthrene was also formed. Kinetic data in two cases[4,5] allowed us to propose that the reactions involved the thianthrene dication which was formed by disproportionation of the cation radical when **1** was placed in solution. These reactions are illustrated with eq 1–3, in which only the 5 position of the thianthrene ring is shown.



Equation 4 illustrates the reaction with ammonia in which the heteroatom analog of the allylic cation is formed as part of the union of two thianthrene rings. The equations show that thianthrene is always an essential product of reaction.

The reaction of pyridine with aromatic hydrocarbons undergoing chemical[6] and anodic[7-10] oxidation has received quite a lot of attention. We have reported on the reaction between perylene perchlorate and pyridine,[1b] and have now studied the analogous reactions of **1** and phenothiazine perchlorate (**5**) with pyridine.

Reactions of cation radicals with nitrite and nitrate ions are not as well known. Oxidation of phenothiazine by ferric chloride in the presence of nitrite ion gave 3-nitrophenothiazine in good yield, and the reaction is thought to involve the phenazothionium ion.[11] Reaction of perylene perchlorate with nitrite ion gave good yields of 3-nitroperylene. The reaction can be carried out with *in situ* formation of the cation radical by using solutions of perylene, iodine, and silver nitrite.[12]

Anodic nitration, in which the involvement of cation radicals might be assumed, seems to have been confined to the oxidation of aromatics in nitric acid solution.[13,14]

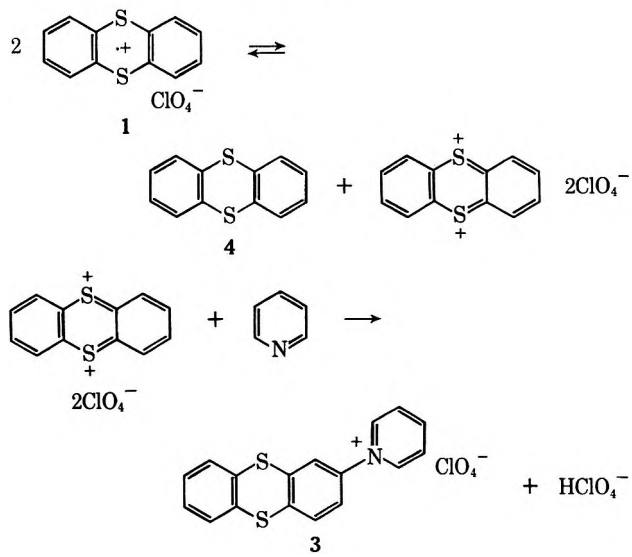
Since 2-nitrothianthrene is not readily prepared,[15] we thought that reaction of **1** with nitrite ion might be a convenient way of making that compound. We found this not to be the case, and our findings led also to a study of the reaction of **1** with nitrate ion. Reactions of phenothiazine perchlorate (**5**) with nitrite ion, halide ions, water, and hydroxide ion were also studied.

(6) J. Rochlitz, *Tetrahedron*, **23**, 3043 (1967).
(7) H. Lund, *Acta Chem. Scand.*, **11**, 1323 (1957).
(8) G. Manning, V. D. Parker, and R. N. Adams, *J. Amer. Chem. Soc.*, **91**, 4584 (1969).
(9) V. D. Parker and L. Eberson, *Tetrahedron Lett.*, 2839, 2843 (1969); *Acta Chem. Scand.*, **24**, 3542 (1970).
(10) L. Marcoux, *J. Amer. Chem. Soc.*, **93**, 537 (1971).
(11) J. Danecke and H.-W. Wanzlick, *Justus Liebigs Ann. Chem.*, **740**, 52 (1970).
(12) C. V. Ristagno and H. J. Shine, *J. Amer. Chem. Soc.*, **93**, 1811 (1971).
(13) M. J. Allen, "Organic Electrode Processes," Reinhold, New York, N. Y., 1958, p 162.
(14) F. Fichter, "Die Chemische Reaktion," herausgegeben von K. F. Bonhoeffer. Band VI. "Organische Elektrochemie," Theodor Steinkopf Verlag, Dresden and Leipzig, 1942, p 143.
(15) S. Krishna, *J. Chem. Soc.*, **123**, 156 (1923).

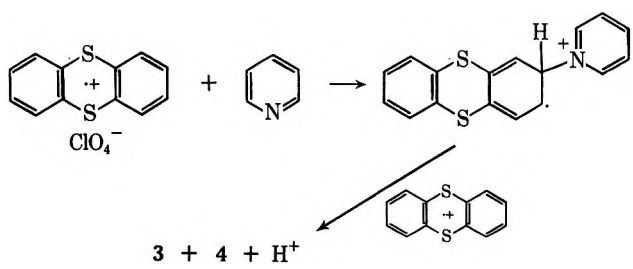
Results and Discussion

Reactions of Thianthrene Perchlorate (1).—Reaction of pyridine with **1** was very rapid. When carried out in solution (nitromethane) the color of **1** was discharged within seconds. Reaction of **1** with neat pyridine was violent and accompanied on one occasion by flame and explosion. Controlled reaction of **1** with neat pyridine was achieved by adding small amounts of **1** to swirling pyridine, and led, as with reaction in solution, to essentially equimolar amounts of *N*-(2-thianthrenyl)pyridinium perchlorate (**3**) and thianthrene (**4**). We do not have kinetic evidence on which to base a mechanism for this reaction, since reaction was too fast to be adapted to kinetic study by the spectrophotometric technique used earlier.[4,5] By analogy with the earlier work we would recognize reaction as occurring with the dication formed by disproportionation of the cation radical (Scheme I), although we cannot rule out the stepwise sequence of Scheme II.

SCHEME I



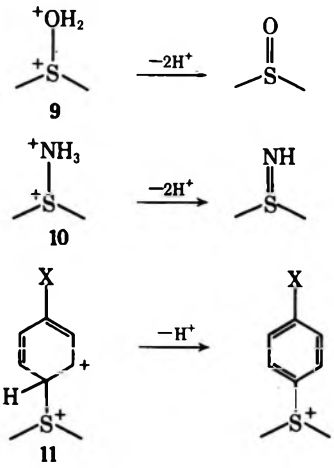
SCHEME II



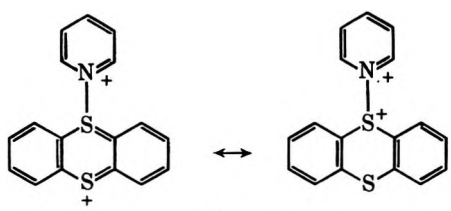
Marcoux has shown recently that anodic pyridination of 9,10-diphenylanthracene *via* the disproportionation route is not unreasonable.[10]

The identity of **3** was established by analysis and Zincke degradation to known 2-aminothianthrene. Substitution at nitrogen rather than at ring carbon of pyridine is consistent with our findings of the electrophilic nature of the earlier reactions, which, in fact, involve the thianthrene dication.[4,5] One would anticipate therefore that in the pyridination reaction the dication would not readily attack the 3 position of pyridine. The reaction we observe is very fast. There-

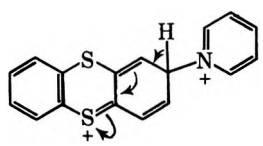
fore, we can understand that a pyridinyl carbon atom is not involved in bonding with the thianthrene ring. It is necessary to stress also that *N*-pyridinyl bonding occurs at the 2 and not the 5 position of the thianthrene ring. In all of our earlier reactions with other nucleophiles the contrary occurred.[4,5] The reason, we believe, is that in the earlier reactions the dicationic intermediate (depicted as **9**–**11**), formed in the first step of



reaction of the nucleophile with the thianthrene dication, can easily lose either one or two protons and form a stable product. This is not the case if pyridination occurs at the 5 position. The product (**12**) would re-



main dicationic and for this reason its formation is likely to be reversible. In contrast, attack of pyridine at the 2 position of the thianthrene dication would be followed by proton loss (eq 5) and give the monocationic product, **3**.

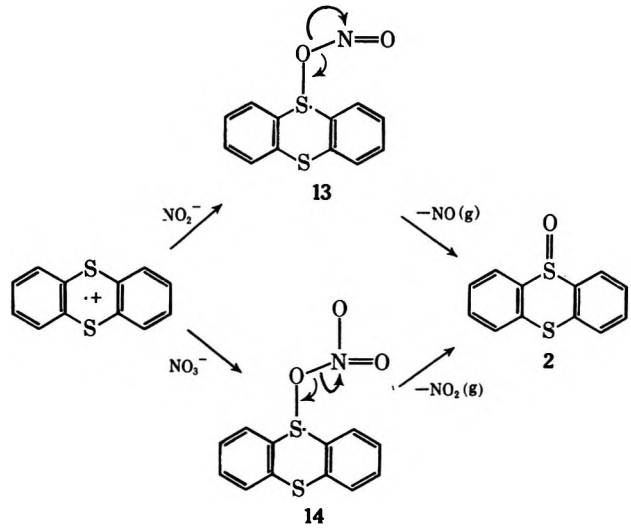


$$\longrightarrow 3 + H^+ \qquad (5)$$

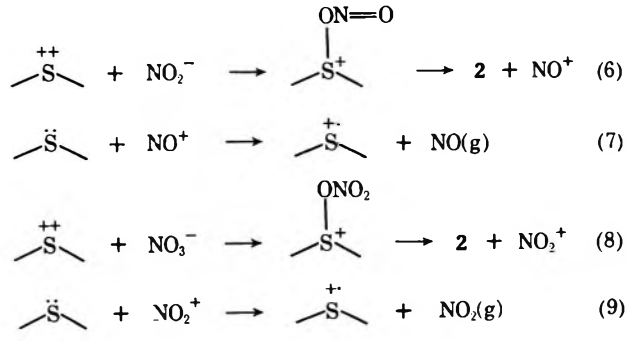
Attempts to prepare **3** by oxidation of thianthrene (**4**) with iodine and silver perchlorate in the presence of pyridine failed. Iodine–silver perchlorate in nitromethane in the absence of pyridine oxidized **4** only slowly. Purple solutions were obtained, characteristic of the cation radical, and these gave, finally, thianthrene 5-oxide (**2**) as product, apparently from reaction with the residual water in the solvent.[4] Although oxidation was slow, silver iodide precipitated early in reaction, presumably from reaction of iodine with silver perchlorate.[16] If carried on long enough, reaction led to almost total oxidation of **4** to **2**. On the other hand, only **4** was recovered from reactions of **4** with iodine–silver perchlorate in the presence of pyridine. We believe that the iodine becomes complexed by pyridine[17] and is no longer available for oxidation of thianthrene. These reactions were not pursued further.

Reaction of nitrite ion with **1** is quite unlike the analogous reactions with perylene[12] and phenothiazine (see later) perchlorates. These lead to ring nitration. In contrast, **1** is converted into thianthrene 5-oxide (**2**). The same occurs in reaction of **1** with nitrate ion. Furthermore, reaction of **1** with ^{18}O-labeled nitrite ion (1.6 atom %) gave **2** with an ^{18}O content (1.3 atom %) that could have come only from the nitrite ion. We propose that these reactions involve the cation radical (Scheme III). Our reasons for so doing are

SCHEME III



deductive because once again reactions were too fast for kinetic study by our spectrophotometric technique.[4,5] Scheme III designates reaction *via* the negatively charged oxygen of the ambident nitrite ion at a position of high positive charge density, which is in accord with the way in which this nucleophile is understood to react. An intermediate radical (**13**) is formed, which can decompose into a stable product (**2**) and a stable radical (nitric oxide). The intermediate **14** in the nitrate reaction is shown to decompose analogously, the stable radical being nitrogen dioxide. If the reaction were to involve the dication rather than the cation radical (see eq 1) the nitrosonium ion (eq 6) and nitro-



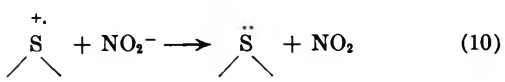
nium ion (eq 8) would be formed, and these would have to undergo subsequent reduction by thianthrene (eq 7 and 9) to account for the products. The cation

(16) N. W. Alcock and T. C. Waddington, *J. Chem. Soc.*, 2510 (1962).

(17) R. Foster, "Organic Charge-Transfer Complexes," Academic Press, New York, N. Y., 1969, p 276.

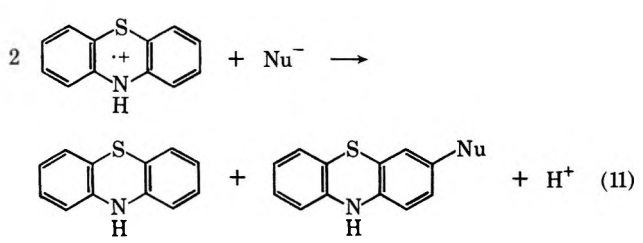
radical formed also (eq 7 and 9) would have to reenter into disproportionation (eq 1). While we cannot rule out these sequences (eq 1, 6, and 7; eq 1, 8, and 9), we feel that the two electrophiles, NO^+ and NO_2^+, would not be limited to the oxidation reactions of eq 7 and 9, but would also attack the thianthrene ring. However, no ring-substituted products were obtained, the only organic product detected by tlc being **2**.

Yet another route to product formation needs to be considered. Thianthrene (**4**)[18] and other organic sulfides[19,20] are oxidized to sulfoxides by dinitrogen tetroxide. If electron exchange between the cation radical and nitrite ion were to occur (eq 10) the two



products (**4** and nitrogen dioxide) would be available for whatever oxidation pathway dinitrogen tetroxide and **4** engage in. We do not believe that this (eq 10) is the way in which nitrite ion and **1** react, however. In none of our work have we been able to detect the formation of **4**. If reaction were to occur according to eq 10 we might expect some **4** to survive. Further, when nitrogen was bubbled through a solution while **1** reacted with nitrite ion there was no fall in yields of **2** and nitric oxide, and again no sign of formation of **4**. If electron exchange (eq 10) preceded oxidation we would anticipate that some nitrogen dioxide would be carried out of solution by the nitrogen-gas carrier. Thianthrene was not detected (tlc) in reactions of **1** with nitrate ion and, in analogy with the reasoning given above, we feel that electron exchange between cation radical and nitrate ion (to give **4** and NO_3) does not take place either. Thus, we feel that Scheme III best describes our results.

Reactions of Phenothiazine Perchlorate (5).—In contrast with **1**, phenothiazine perchlorate does not undergo nucleophilic reactions at sulfur.[11] Reaction with nitrite ion, pyridine, chloride, and bromide ion led to phenothiazine and a 3-substituted phenothiazine according to the following stoichiometry (eq 11).



In the case of pyridine, of course, appropriate changes in eq 11 are necessary. We do not know yet the mechanisms of these reactions. The possibilities of either direct reaction with the cation radical or reaction with the dication formed in disproportionation need to be considered and solved by kinetic work. Reaction of **5** with chloride and bromide ion may involve electron exchange first, followed by halogenation by molecular halogen. Chlorination and bromination of phenothiazine occur very readily,[21] although ordinarily polyhalogenated phenothiazines are formed. Preparation of monochloro- and monobromophenothiazine is usually achieved by reductive halogenation of the 5-oxide (see Experimental Section). In the reaction of **5** with bromide ion, the yields of products were not affected much when nitrogen was bubbled through the solution while reaction was occurring. The formation of both 3,7-dichloro- and 3,7-dibromophenothiazine in our reactions suggests that the reactions are not simple nucleophilic substitutions and mechanistic exploration of the reactions is needed.

Iodide ion, if used in excess, reduces **5** completely. Iodine will oxidize phenothiazine and, depending on the conditions, phenazothionium periodide[21] or 3,10′-biphenothiazine (**8**)[22] are obtained. We have used iodine as the oxidant in the direct "nitration" of phenothiazine by nitrite ion. Obviously, therefore, phenothiazine and iodine form an easily reversible redox system, and it is understandable that reduction of the cation radical by iodide ion could be achieved only by using an excess of iodide ion. We encounter also the same experience with iodide ion and **5** as with iodide and **1**[4] and perylene perchlorate,[1b] namely, that, although iodide ion is a good nucleophile, it is too easily oxidized by the cation radical to permit nucleophilic substitution in the ring.

Nucleophilic substitution by fluoride ion did not occur even though oxidation of fluoride ion by the cation radical is not possible. Apparently, fluoride ion is not sufficiently nucleophilic, as was discovered in the perylene perchlorate case.[1b] Fluorination of aromatics by xenon fluoride was once thought to involve reaction between the aromatic cation radical and fluoride ion, but this is now believed not to be the case.[23]

Reaction of **5** with fluoride ion systems gave phenothiazine (**6**), 3,10′-biphenothiazine (**8**), and an unidentified green solid (or solids).[24] The same behavior was observed in reactions of **5** with water and hydroxide ion solutions. These are not unexpected results. The dimer **8** appears to be formed from the phenothiazine cation radical in basic or weakly acidic solutions. Tsujino has reported that the dimer is a major product of reaction of phenothiazine in 90% sulfuric acid, and represents the cation radical as undergoing deprotonation in that medium.[25] We feel that this cannot be correct since the esr spectrum of the cation radical is so well established, not only in acid solutions.[26,27] but also in acetonitrile,[26,28] and the cation radical is stable even in acetic acid solution.[27] Furthermore, we have found that solutions of **5** in acetonitrile obey Beer's law at the maxima 437 and 515 nm over the concentrations tested, namely 1.6–15.2 × 10^{-4} M. Deprotonation and dimerization would certainly be encouraged in these circumstances (acetic acid and acetonitrile) as com-

(18) R. D. Whitaker and C. L. Bennett, *Quart. J. Fla. Acad. Sci.*, **28**, 329 (1965).
(19) R. D. Whitaker and C. L. Bennett, *ibid.*, **28**, 137 (1965).
(20) R. D. Whitaker and H. H. Sisler, *J. Org. Chem.*, **25**, 1038 (1960).
(21) C. Bodea and I. Silberg, *Advan. Heterocycl. Chem.*, **9**, 321 (1968).
(22) (a) Y. Tsujino, *Tetrahedron Lett.*, 2545 (1968); (b) *Nippon Kagaku Zasshi*, **90**, 490 (1969).
(23) M. J. Shaw, H. H. Hyman, and R. Filler, *J. Org. Chem.*, **36**, 2917 (1971).
(24) The nature of green solid(s) from phenothiazine reactions is discussed by Bodea and Silberg, ref 21, p 377.
(25) Y. Tsujino, *Nippon Kagaku Zasshi*, **90**, 809 (1969). We thank Professor Kimio Ohno for translating this article.
(26) J.-P. Billon, G. Cauquis, and J. Combrisson, *J. Chim. Phys.*, **61**, 374 (1964).
(27) H. J. Shine and E. E. Mach, *J. Org. Chem.*, **30**, 2130 (1965).
(28) S. Odiot and F. Tonnard, *J. Chim. Phys.*, **61**, 382 (1964).

pared with solution in 90% sulfuric acid. Therefore, we feel that dimerization occurs when **5** reacts with bases, and this is what has complicated the reactions with most of the nucleophiles used by us, *i.e.*, pyridine, fluoride ion, water, and hydroxide ion. These reactions may be complicated further because the dimer **8** is easily oxidized[22,25] giving rise to the so-called green products.

Deprotonation, dimerization, and oxidation of the dimer are undoubtedly the cause of the complexity of the reaction of phenothiazine with iodine, silver perchlorate, and pyridine. Instead of the pyridinium compound (**7**) a mixture of colored solids was obtained in which **7** was present but could not be separated cleanly. Phenothiazine, its dimer **8**, and **7** have now been found to undergo anodic oxidation in acetonitrile at closely similar potentials, and both oxidized **8** and oxidized **7** appear to react with pyridine.[23] It is not surprising, therefore that our attempt at the pyridination of **6** in the presence of excess of iodine–silver perchlorate should have given a mixture of products.

Reaction of **5** with nitrite ion was clean and gave an excellent yield of 3-nitrophenothiazine. Until recently this compound was not easily made. Direct reaction either by the ferric chloride–nitrite ion[11] or our iodine–silver nitrite method now gives 3-nitrophenothiazine in good yield. Reaction of **6** with nitrite ion in acidic media is described as giving colored products[30] while reaction in acetic acid–chloroform gave pure 3,7-dinitrophenothiazine.[31]

Experimental Section

Acetonitrile was Eastman anhydrous grade (<0.01% water). Nitromethane and methylene chloride were Eastman Spectro Grade and were redistilled over phosphorous pentoxide. Each solvent was stored over molecular sieve in a septum-capped bottle and removed by syringe when needed.

Phenothiazine was crystallized from butanol, phenothiazine 5-oxide from ethanol, and thianthrene from acetone.

Thianthrene perchlorate (**1**) was prepared by the oxidation of thianthrene with perchloric acid.[4] Iodimetric assay gave 98–100% cation radical content consistently.

Phenothiazine perchlorate (**5**) was prepared either from disproportionation of an equimolar mixture of phenothiazine and phenothiazine 5-oxide in 70% perchloric acid (Billon's methods[32]) or by the oxidation of phenothiazine with iodine, as follows. A solution of 420 mg (2 mmol) of silver perchlorate in 3 ml of acetonitrile was added to a solution of 400 mg (2 mmol) of phenothiazine and 270 mg (1 mmol) of iodine in 40 ml of methylene chloride. After 30 min of stirring the precipitate was filtered off and the filtrate was poured into 180 ml of dry ether. The green-black crystalline precipitate was filtered on glass paper and dried under vacuum, and gave 210 mg (35%) of **5**.

A sample of **5** prepared by Billon's method was analyzed.[33]

Anal. Calcd for $C_{12}H_9NO_4SCl$: C, 48.48; H, 3.17; N, 4.70; S, 10.94; Cl, 12.02. Found: C, 48.24; H, 3.04; N, 4.69; S, 10.73; Cl, 11.87.

Thereafter, **5** samples were assayed iodimetrically. A weighed amount of **5** was dissolved in a solution of tetrabutylammonium iodide (TBAI) in acetonitrile. The liberated iodine was titrated potentiometrically with sodium thiosulfate after adding a small amount of water.[1b] Phenothiazine is oxidized by iodine. Therefore, iodimetric assay was successful only if a severalfold excess of TBAI was used. Analyses were consistently in the range of 95–98% cation radical content. After titration, the solution was extracted with benzene, placed on a column of silica, and eluted with benzene to give phenothiazine in 90% and better yield.

Solutions of **5**, prepared in a sealed apparatus under vacuum in acetonitrile which had been degassed by the freeze–thaw technique, obeyed Beer's law over the range of concentrations used, namely $1.6–15.2 \times 10^{-4}$ *M*, at 437 nm (ϵ 6020) and 515 (10,300), the two maxima in the visible spectrum of the phenothiazine cation radical.[27]

Halogenophenothiazines.—Authentic samples were prepared for spectroscopic characterization by reductive halogenation of phenothiazine 5-oxide.[34] Each pair of mono- and dihalogenophenthiazines was separated by column chromatography [silica gel, petroleum ether (bp 30–60°)–ethyl ether, 2:1]. 3-Chlorophenothiazine, mp 200–202° (benzene) (lit.[35] mp 201–201.5°), had λ_{max} (methylene chloride) at 320 nm (ϵ 4.13×10^3) and 258 (3.85×10^4). 3,7-Dichlorophenothiazine, mp 220–221° (benzene) (lit.[22b] mp 219–220°), had λ_{max} (methylene chloride) at 322 nm (ϵ 5.45×10^3) and 260 (4.6×10^4). 3-Bromophenothiazine, mp 182–183° (benzene) (lit.[36] mp 181.5°), had λ_{max} (methylene chloride) at 320 nm (ϵ 5.0×10^3) and 258.5 (4.7×10^4). 3,7-Dibromophenothiazine, mp 199–200° dec (lit.[37] mp 206–207° dec), had λ_{max} (methylene chloride) at 324 nm (ϵ 6.7×10^3) and 261 (5.9×10^4).

Reaction of 1 with Nitrite Ion.—To stirred solution of 33.9 mg (0.107 mmol) of **1** in 20 ml of dry nitromethane was added an excess (500 mg, 6.6 mmol) of solid, dry sodium nitrite. Some sodium nitrite remained undissolved. The purple color of the solution turned a yellowish-brown immediately, and slowly became colorless. (When a similar reaction was carried out under nitrogen the yellow-brown color was not observed, indicating that it was caused by the air oxidation of nitric oxide to nitrogen dioxide.) Tlc of the filtered colorless solution gave only one spot identified as thianthrene 5-oxide (**2**). Column chromatography (10% ether in benzene on a silica column) gave **2**, mp 143° (ethanol). Spectroscopic assay in acetonitrile at 242 nm (ϵ 1.67×10^4) gave a yield of 88%. Similar experiments gave yields of 95 and 100%.

Quantitative Assay of Nitric Oxide.—Reaction of **1** with nitrite ion gave nitric oxide as the second product. This was assayed twice in separate experiments. The experiments were carried out under a stream of nitrogen in an apparatus and gas-bottle chain which had been flushed with dry nitrogen for 4 hr previously. The nitric oxide formed in the reaction was carried into a series of two bottles, each containing 100 ml of sulfuric acid and 2 ml of nitric acid. At the end of the reaction the nitrosylsulfuric acid in the absorption bottles was determined by the permanganate–ferrous ammonium sulfate method.[38] The two experiments beginning with 85.2 and 78.3 mg of **1**, respectively, gave 96 and 90% of theoretical nitric oxide and 91 and 89% of theoretical **2**.

Reaction of 1 with ^{18}O-Nitrite Ion.—Labeled nitrite ion was prepared with the use of 1.6% enriched ^{18}O water.[39] Reaction with **1** was carried out, and mass spectrometry showed that the ^{18}O content of the isolated **2** was 1.3 atom %.

Reaction of 1 with Nitrate Ion.—Sodium nitrate was used as described for sodium nitrite. The purple color of the solution of **1** changed to brown even under a nitrogen atmosphere, indicating the formation of nitrogen dioxide. Thianthrene 5-oxide was determined as described above. Nitrogen dioxide was determined by absorption in sulfuric acid and titration by the permanganate–ferrous ammonium sulfate method.[38] Two experiments beginning with 70.9 and 74.6 mg of **1** gave 73 and 84% of nitrogen dioxide and 92 and 98% of **2**.

Reaction of 5 with Nitrite Ion.—A solution of 90 mg (0.301 mmol) of **5** in 10 ml of acetonitrile was added dropwise to a suspension of 1 g of sodium nitrite in 10 ml of acetonitrile. The

(29) Private communication from Dr. L. S. Marcoux.
(30) Reference 21, p 408.
(31) Reference 21, p 350.
(32) J.-P. Billon, *Bull. Soc. Chim. Fr.*, 1923 (1961).
(33) Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.
(34) H. Gilman and J. Eisch, *J. Amer. Chem. Soc.*, **77**, 3862 (1955).
(35) E. A. Nodiff and M. Hausmann, *J. Org. Chem.*, **29**, 2453 (1964).
(36) J. Cymerman-Craig, W. P. Rogers, and G. P. Warwick, *Aust. J. Chem.*, **8**, 252 (1955).
(37) S. Bodea and M. Raileanu, *Justus Liebigs Ann. Chem.*, **631**, 194 (1960).
(38) G. C. Whitmarck, C. J. Holdord, E. St. Clair Gantz, and G. B. L. Smith, *Anal. Chem.*, **23**, 464 (1951).
(39) C. A. Bunton, D. R. Llewellyn, and G. Stedman, *J. Chem. Soc.*, 568 (1959).

orange solution was diluted with 20 ml of benzene, washed with 0.1 *M* sodium hydroxide and water, and evaporated to dryness under vacuum. The residue, 65 mg, was chromatographed on a silica column. Elution with benzene gave 31 mg (0.155 mmol, 100%) of phenothiazine, mp 181–183°; elution with benzene–ether gave 35 mg (0.143 mmol, 96%) of deep violet 3-nitrophenothiazine, mp 210–211° (lit.[11] mp 212°), λ_{max} (ethanol) 454, 309, and 246 nm. Continued elution with ether gave 2 mg of unidentified orange solid.

Elemental analysis[33] of the 3-nitrophenothiazine was in excellent agreement with required values.

Reaction of Phenothiazine with Iodine and Silver Nitrite.—To a solution of 1.0 g (5 mmol) of phenothiazine and 635 mg (2.5 mmol) of iodine in 100 ml of acetonitrile was added 770 mg (5 mmol) of silver nitrite in 20 ml of acetonitrile. Silver iodide was filtered off and the solvent was removed under vacuum, giving 1.16 g of black residue. Chromatography on a silica column gave 854 mg (3.5 mmol, 70%) of crude 3-nitrophenothiazine, mp 198–199°. Crystallization from benzene gave mp 210°.

Reaction of 1 with Pyridine.—Reaction was carried out either in neat pyridine or in nitromethane solution. *Reaction in neat pyridine is violent and may be hazardous. On one occasion the mixture burst into flames.* No trouble was encountered with the use of small amounts of 1 and rapid swirling of the mixture. Addition of pyridine to a solution of 1 in nitromethane caused rapid change from a purple to a yellow solution. When nitromethane was used pyridinium perchlorate precipitated and was filtered off before proceeding further. The disadvantage to using nitromethane was that, although the solvent was dried, residual water reacted with the 1 and gave more thianthrene 5-oxide than was obtained with the use of dry, neat pyridine. When 1 reacts with water, both thianthrene 5-oxide and thianthrene are formed.[4] When 1 reacts with pyridine, both *N*-(2-thianthrenyl)-pyridinium perchlorate (**3**) and thianthrene are formed. Therefore, all reactions gave four products: thianthrene, thianthrene 5-oxide, **3**, and pyridinium perchlorate. These were separated and assayed as follows. The solution (whether in pyridine alone or in nitromethane–pyridine) was evaporated to dryness under vacuum to remove excess pyridine. Solid pyridinium perchlorate, if present, was filtered off before evaporation. The dry residue was dissolved in nitromethane and extracted with small amounts of cyclohexane until tlc of the nitromethane solution showed absence of thianthrene and its 5-oxide. The cyclohexane portions were combined and evaporated to dryness. The residue was dissolved in acetonitrile and analyzed spectroscopically for thianthrene and the 5-oxide.

The nitromethane solution, containing **3** and pyridinium perchlorate, was evaporated to dryness. The residue was washed with water to remove pyridinium perchlorate, and repeatedly with benzene or cyclohexane to remove traces of thianthrene and thianthrene 5-oxide. Crystallization from aqueous methanol gave yellow **3**, mp 206–207°, λ_{max} (acetonitrile) 255 nm (ϵ 2.3 $\times$ 10^4).

Anal. Calcd for $C_{17}H_{12}NO_4S_2Cl$: C, 51.84; H, 3.04; N, 3.60; S, 16.28; Cl, 9.00. Found: C, 51.94; H, 2.86; N, 3.84; S, 16.31; Cl, 8.87.

Quantitative assay of **3**, before the washed and dried solid residue was crystallized, was made spectroscopically in acetonitrile at 255 nm. A typical reaction of 1 (53.7 mg, 0.170 mmol) with Eastman Spectro Grade pyridine (not dried further) gave 19.4 mg (0.089 mmol) of thianthrene, 11.2 mg (0.048 mmol) of thianthrene 5-oxide, and 12.5 mg (0.032 mmol) of **3**. A typical reaction of 1 (90.8 mg, 0.287 mmol) in nitromethane solution gave 30.3 mg (0.140 mmol) of thianthrene, 25.2 mg (0.108 mmol) of thianthrene 5-oxide, and 10.3 mg (0.026 mmol) of **3**. After compensating for reaction with water these results correspond with 87 and 73% yields of **3**, respectively.

Degradation of 3 into 2-Aminothianthrene.—Aqueous sodium hydroxide (15%, 5 ml) was added to a solution of 27.5 mg of **3** in 30 ml of methanol under a nitrogen atmosphere. A red precipitate and solution formed during 3 hr of stirring. These were extracted with benzene, the benzene was removed under vacuum, and the red residue was dissolved in 5 ml of methanol. To this was added 15 ml of concentrated hydrochloric acid, and the mixture was stirred for 15 hr. The yellow solution was made alkaline and extracted with benzene. Tlc showed 2-aminothianthrene and one other spot (R_f 0) only. Column chromatography (benzene on silica gel) gave 43% of 2-aminothianthrene, mp 255–256° (ethanol), shown to be identical with an authentic sample.[40]

Reaction of 5 with Pyridine.—To a stirred solution of 1.21 g (4.05 mmol) of **5** in acetonitrile was added 0.4 ml (4.9 mmol) of pyridine. The solution became green immediately but turned orange-red over a period of 5 hr. Evaporation of the solvent and extraction of the residue with benzene left a dark residue. The benzene-soluble portion was evaporated, giving 467 mg of a green solid. Chromatography of this solid on a silica column gave 290 mg (72%, based on the stoichiometry of the reaction) of phenothiazine, mp 185–186°, and 50 mg (0.126 mmol, 2.1%) of 3,10′-biphenothiazine (**8**), mp 196–198° (acetonitrile) (lit.[22] mp 199–200°), nmr spectrum in agreement with nmr of authentic compound, λ_{max} (methylene chloride) 319 nm (ϵ 0.95 $\times$ 10^4) and 259 (1.04 $\times$ 10^5). Crystallization of the dark residue gave 600 mg (1.59 mmol, 78%) of brick-red *N*-(3-phenothiazinyl)-pyridinium perchlorate (**7**), mp 260–261° (aqueous ethanol).

Anal. Calcd for $C_{17}H_{13}N_2O_4SCl$: C, 54.2; H, 3.48; N, 7.43; S, 8.51; Cl, 9.41. Found: C, 54.1; H, 3.73; N, 7.98; S, 8.58; Cl, 9.80.

Compound **7** had λ_{max} (acetonitrile) at 412 nm (ϵ 4.4 $\times$ 10^3), 282 (1.07 $\times$ 10^4), and 252 (3.75 $\times$ 10^4).

In a similar experiment employing 154 mg of **5** and 50 μl of pyridine, the products were separated by tlc, removed from the tlc plate, and assayed spectroscopically, giving 80% of phenothiazine, 84% of **7**, and 9% of **8**.

Reaction of 5 with Chloride Ion.—A solution of 400 mg (1.44 mmol) of tetrabutylammonium chloride in 10 ml of acetonitrile was added to a stirred solution of 362 mg (1.21 mmol) of **5** in acetonitrile. After 3 hr the green solution was evaporated and the residue was extracted with benzene. The washed and dried benzene solution was evaporated to give 265 mg of brown residue. This was placed on a silica column and eluted with benzene to give 261 mg of yellow solid. Weighed samples of the solid were streaked on a silica gel tlc plate and developed with 2:1 petroleum ether–ether. The three tlc bands were removed and assayed spectrophotometrically, giving, in two separate assays, 42 and 43% of phenothiazine, 35 and 32% of 3-chlorophenothiazine, and 4.8 and 4.3% of 3,7-dichlorophenothiazine.

Reaction of 5 with Bromide Ion. A.—The procedure was the same as above, with the use of 446 mg of **5** and 1.0 g of potassium bromide. Two separate assays of tlc bands gave 46 and 48% of phenothiazine, 40 and 37% of 3-bromophenothiazine, and 4.2 and 4.1% of 3,7-dibromophenothiazine.

B.—A sample of 65 mg of **5** was treated with potassium bromide as above while a stream of nitrogen passed through the solution. Assay of products gave 50% of phenothiazine, 37% of 3-bromophenothiazine, and 4.1% of 3,7-dibromophenothiazine.

Reaction of 5 with Fluoride Ion.—Potassium fluoride and **5** (157 mg) were used as above. A green benzene solution was obtained, portions of which, by tlc separation (2:1 petroleum ether–ether) and spectroscopic analysis (methylene chloride) gave 38% of phenothiazine and 17% of 3,10′-biphenothiazine. A green band remained at the base of the tlc plate. On the upper edge of the green band was another, small band, light pink in color. These were not identified. They did not correspond with phenothiazine 5-oxide. The pink band may have been 3-phenothiazone.

Treatment of the green benzene solution with 1% aqueous sodium hydroxide caused the green color to disappear. The light brown solution was streaked on a silica plate and developed as earlier. The phenothiazine (19%) and 3,10′-biphenothiazine (35%) bands were followed by a series of three or four overlapping bands, and no attempt was made to separate and identify them.

Reaction of 5 with Water.—Water (2 ml) was added to a stirred solution of 157 mg (0.503 mmol) of **5** in 20 ml of acetonitrile. The solution became green. Work-up as in the fluoride ion reaction gave 33% of phenothiazine and 25% of 3,10′-biphenothiazine. The base of the tlc plate contained the green and pink bands observed in the fluoride ion reaction. Treatment of the benzene solution with 1% aqueous sodium hydroxide and work-up as in the fluoride ion case gave an identical chromatogram, consisting of the phenothiazine (19%) and 3,10′-biphenothiazine (45%) bands followed by the overlapping group of three or four bands.

(40) Prepared by Dr. C. F. Dais. See H. J. Shine, C. F. Dais, and R. J. Small, *J. Org. Chem.*, **29**, 21 (1964).

Reaction of 5 with Hydroxide Ion.—Aqueous sodium hydroxide (1%, 50 ml) was added to a solution of 2.62 g (8.78 mmol) of **5** in 100 ml of acetonitrile. The solution became green and a green solid precipitated. Extraction with chloroform and repeated chromatography of the chloroform soluble material on silica columns gave 300 mg (1.5 mmol, 17%) of phenothiazine, 210 mg (0.53 mmol, 6%) of 3,10′-biphenothiazine, and 24 mg (0.11 mmol, 1.3%) of 3-phenothiazone. At least four other products were present but were not identified.

Registry No.—**1**, 21299-20-7; **2**, 2362-50-7; **3**, 34874-72-1; **5**, 34874-73-2; **7**, 34874-74-3; phenothiazine, 92-84-2.

7,8,9-Trimethoxy-1,2,3,4,4a,5,6,10b-octahydro- and 7,8,9-Trimethoxy-1,2,3,4,4a,10b-hexahydrophenanthridines. Synthesis and Stereochemistry of Certain 6-Substituted and 5,6-Disubstituted Derivatives[1]

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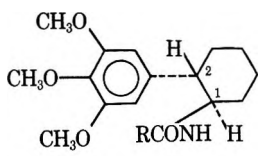
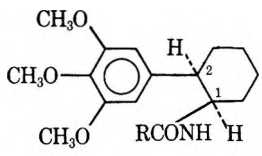
The diastereomers of 6-methyl and of 6-*o*-hydroxyphenyl derivatives of 7,8,9-trimethoxy-4a,10b-*trans*-1,2,3,4,-4a,5,6,10b-octahydrophenanthridine, obtained by the Pictet–Spengler reaction, were characterized by nmr. 7,8,9-Trimethoxy-4a,10b-*trans*-1,2,3,4,4a,10b-hexahydrophenanthridine (**7**), its 6-methyl derivative **9**, and the 4a,10b-cis isomer **8** and its methyl derivative **10** were prepared by the Bischler–Napieralski reaction from the appropriate amides **3**–**6**. Conformations of **8** and **10** were established by nmr in deuteriochloroform and rotational isomerism of the amides is discussed. Catalytic hydrogenation of **9** and **10** yielded only the isomer having the methyl group trans to H-4a in each case, compounds **11** and **15**, respectively. The conformation of the cis compound **15** was established by nmr. Epimerization studies of the hydrochloride salts of the *N*-methyl derivatives of **11** and **12** (compounds **16** and **17**, respectively) in formic acid showed that for **16** the equilibrium is essentially in the direction of a single epimer having the two methyl groups trans to each other, while at equilibrium **17** shows a mixture with at least 75% of the epimer having the methyl groups trans.

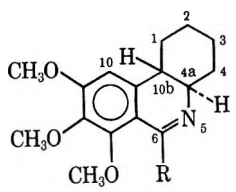
In a preceding paper[2] we have discussed the stereochemistry and epimerization of salts of N-substituted 7,8,9-trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,3,4,-4a,5,6,10b-octahydrophenanthridines prepared from *trans*- (**1**) and *cis*-2-(3,4,5-trimethoxyphenyl)cyclohexylamine[3] (**2**) *via* the Pictet–Spengler reaction. The present paper deals with the stereochemistry of 6-substituted and 5,6-disubstituted derivatives and their preparation by the same route and by the Bischler–Napieralski cyclodehydration of the appropriate amides of **1** and **2**. The 7,8,9-trimethoxy-1,2,3,4,4a,10b-hexahydrophenanthridine intermediates of the Bischler–Napieralski reaction were of interest from a pharmacological standpoint in addition to being potential sources of specific stereoisomers of the 6-substituted octahydro series because of probable stereoselectivity in the catalytic hydrogenation step, as was actually shown to be the case (*vide infra*).



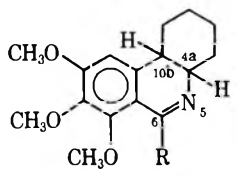
3, R = H
5, R = CH_3



4, R = H
6, R = CH_3



7, R = H
9, R = CH_3



8, R = H
10, R = CH_3

Results and Discussion

7,8,9-Trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,-3,4,4a,10b-hexahydrophenanthridines and 6-Methyl Derivatives.—A wide variety of condensing agents and solvents have been used in the Bischler–Napieralski reaction.[4] In the present study yields of better than 90% of the hydrochloride salts of **7**, **8**, **9**, and **10** were obtained by use of phosphorus oxychloride in chlorobenzene with the appropriate amides **3**–**6**.

The nmr spectra of amides **3**, **4**, and **6** show the presence of amide C–N bond rotational isomers, but no evidence of two isomers was found in **5**. The ratio of isomers, estimated from the integration of the signals of the aromatic hydrogens which give a singlet for each isomer, was found to be about 6:1 for **3**, 5:4 for **4**, and 7:1, or more, for **6**. Published data on isomerism of secondary amides[5] indicate a usual predominance of the isomer having a trans orientation of the N substituents and the R or H on the carbonyl carbon. Our results are in agreement with this. In the formamides **3** and **4** the signal of the formyl hydrogen of the major isomer in each case gives a doublet with a coupling constant of 2 Hz between the formyl and NH protons, while the doublet for the minor isomer has a coupling constant of 12 Hz, consistent with a trans orientation of the coupled hydrogens in the minor isomer. This assignment is also supported by the fact that the signal of the formyl hydrogen, or the acyl methyl group, of the minor isomer is at higher field than that of the major isomer in each case. Molecular models in-

(1) This investigation was supported by Grant MH 12204 from the National Institute of Mental Health, U. S. Public Health Service. The compounds were submitted to Eli Lilly and Company for pharmacological evaluation.

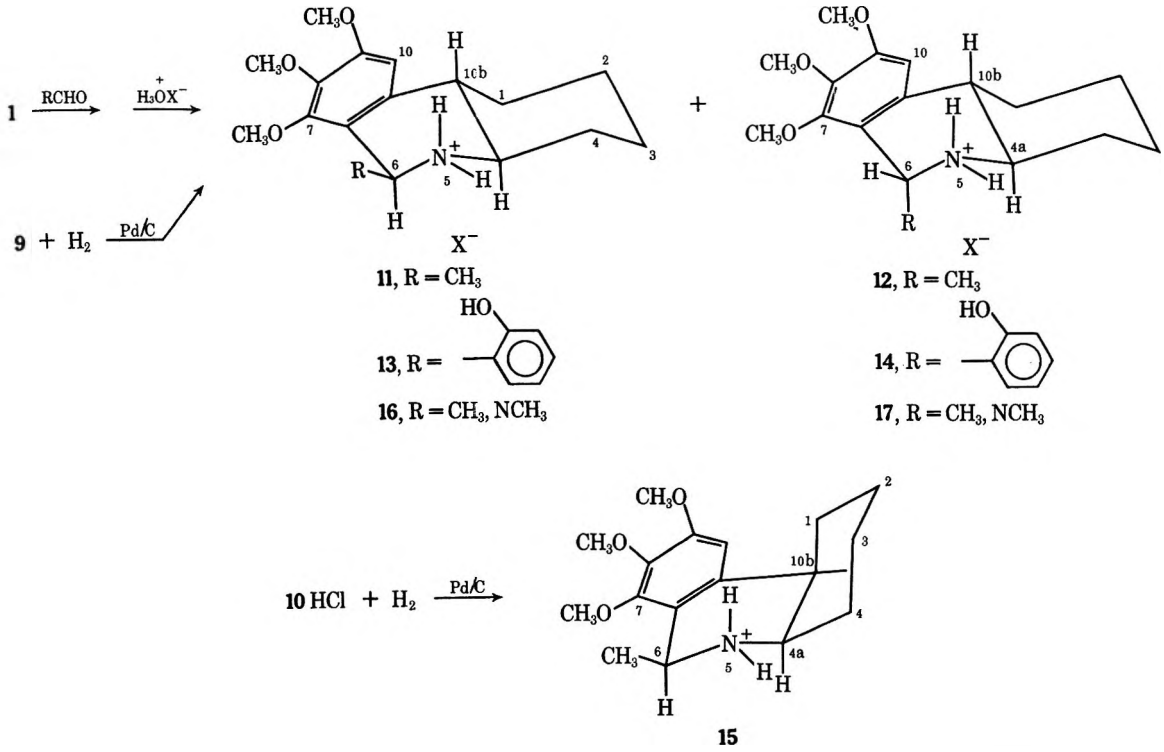
(2) B. R. Lowry and A. C. Huitric, *J. Org. Chem.*, submitted for publication.

(3) W. F. Trager and A. C. Huitric, *J. Pharm. Sci.*, **54**, 1552 (1965).

(4) W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 74 (1951).

(5) W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **70**, 517 (1971).

SCHEME I



dicate that these groups should experience a greater shielding effect from the magnetic anisotropy of the aromatic ring when the groups have a cis orientation to the N substituent.

There is more conformational mobility in the *cis*-hexahydrophenanthridines **8** and **10**, where inversion of the cyclohexane ring is possible, than in the trans isomers **7** and **9** where only one chair form of the cyclohexane ring is possible. The nmr data indicate that in deuteriochloroform the cis compounds **8** and **10**, as well as their hydrochloride salts, have a predominance of that chair conformation of the cyclohexane ring in which H-4a has an axial orientation and H-10b is equatorial. This conclusion is based on a comparison of the spectra of the cis compounds with those of the corresponding trans isomers. For any of the cis compounds in the conformation where H-4a is axial and H-10b is equatorial the hydrogen H-10b has the asme relative position to the aromatic ring as in the trans isomer, but H-4a lies essentially in the plane, and in the deshielding region, of the imine double bond and the aromatic ring. In the inverted chair conformation it is H-4a that has the same relative position to the imine and aromatic groups as in the trans isomer while H-10b now lies in the deshielding region of the aromatic ring. For every cis compound the chemical shift of H-4a is from 0.6 to 0.7 ppm downfield from the position for the corresponding trans isomer, while the chemical shift of H-10b is downfield by about 0.1 to 0.3 ppm compared to the trans isomer. The patterns of the signals of the methylene hydrogens of the cyclohexane ring for the cis compounds are also consistent with a predominance of the conformation having H-4a axial and H-10b equatorial. The signals of these hydrogens give a fairly narrow envelope ($W_{1/2} \cong$ 15–19 Hz) accounting for seven protons which is centered at τ 8.5 for the free bases **8** and **10** and at τ 8.3 for their hydrochloride salts, and in each case there is a downfield signal accounting for one hydrogen in the region of τ 7.8–7.9 for the free bases and slightly lower for the salts. This downfield signal is attributed to the equatorial proton on C-1, which in the proposed conformation falls in the deshielding region of the aromatic ring. In the trans isomers both protons on C-1 experience a deshielding effect from the aromatic ring and the signal of the remaining six methylene protons give a broad envelope spread over a region of about 50 Hz.

Allylic coupling of about 3 Hz occurs between H-6 and H-4a in **7** and **8**, and of about 2 Hz in their hydrochloride salts. Homoallylic coupling[6] of about 2 Hz is seen between H-4a and the C-6 methyl protons in **9** and **10**, and of about 1.8 Hz in the salts following deuterium exchange with D_2O.

7,8,9-Trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,3,-4,4a,5,6,10b-octahydrophenanthridines and Derivatives. —In the preparation of 7,8,9-trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridines, good yields were obtained by refluxing the hydrochloride salts of **1** and **2** with formaldehyde in ethanol.[2] This method was not so successful with other aldehydes. The best yields of the cyclization product of **1** with acetaldehyde, and salicylaldehyde, were obtained by preformation of the imines followed by treatment with acid. With acetaldehyde the ratio of H-6,4a-cis and H-6,4a-trans isomers varied with temperature. Treatment of the imine with 20% aqueous sulfuric acid at room temperature yielded **11** and **12** in ratio of about 2:1, while at 80° about equal amount of the two isomers was obtained (Scheme I). With salicylaldehyde, heating the imine to reflux in 10% sulfuric acid in 50% aqueous methanol gave **13** and **14** in a ratio of about 17:2. The ratio of **11** and **12** was estimated from the intensities of the nmr C-6 methyl

(6) L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, pp 326, 327.

signals of the free bases which, in pyridine in the presence of slight amount of D_2O, appear as doublets at τ 8.40 for **11** and τ 8.46 for **12**. In the absence of D_2O the two signals overlap at τ 8.46. Since the signals appear in the region of the cyclohexane envelope absorption, only an estimate of the ratio of isomers is possible.

Separation of **11** and **12** was accomplished by fractional crystallization of the *p*-toluenesulfonate salts from methanol. Progress of the separation was followed by melting points and by nmr in 1:1 formic acid–deuterium oxide solution. The head fraction (**12**) was characterized by higher melting point and higher field 6-CH_3 doublet, τ 8.30 compared to τ 8.27 for isomer **11** enriched in the mother liquors.

The assignment of configurations to **11** and **12** is based on the nmr spectra of the hydrochloride salts in deuteriochloroform and supported by the fact that catalytic hydrogenation of **9** yielded almost exclusively **11**. The nmr spectra of the hydrochloride salts of **11** and **12** differ mostly in the chemical shifts of the C-6 methyl signals and the ammonium protons. The chemical shift of H-6 is essentially the same in both isomers. The chemical shift of 6-CH_3 is at lower field (τ 8.10) for **11** than for **12** (τ 8.24). In view of the long-range effects of the magnetic anisotropy of the aromatic ring,[7] and assuming that the half-chair is the predominant conformation of the heterocyclic ring, the data are consistent with a pseudoequatorial orientation of the methyl group in **11** and a pseudoaxial orientation in **12**. This assignment is supported by the chemical shifts of the ammonium protons which are equivalent at τ 0.00 in the hydrochloride salt **12** but are at τ −0.50 and +0.63 in the hydrochloride **11**. The chemical shifts of the ammonium protons in **12** remained equivalent upon addition of trifluoroacetic acid, showing that the equivalence in **12** is not the result of a more rapid proton exchange than in **11**. The effect of a methyl group on C-6 will be to shield the H-5 proton cis to the methyl,[2] causing an upfield shift of the axial H-5 in **11** and thus causing an increase in the difference between the chemical shifts of these two protons. In **12** the effect is to shield the equatorial ammonium proton and thus decrease the difference between the chemical shifts of the two protons.

Separation of **13** and **14** was accomplished by taking advantage of a significant solubility of the hydrochloride salt of **14** in benzene. The assignment of configuration is based on the difference of the nmr signals of the methoxy groups in the two isomers. The spectrum of the free base of the minor isomer **14** in deuteriochloroform shows the overlapping of the signals of two methoxy groups at τ 6.11 and the signal of the third group at τ 6.20. Under the same conditions there is a considerable upfield shift of the signal of one of the methoxy groups in the spectrum of the major isomer **13**, where the chemical shifts of the methoxy groups are τ 6.16, 6.20, and 6.62. In the parent compound,[2] unsubstituted at C-6, two of the signals overlap at τ 6.15 and the third is at τ 6.17. Infrared studies of chloroform and carbon tetrachloride solutions showed intramolecular hydrogen bonding of the phenolic hydrogen in both isomers. Molecular models indicate that for intramolecularly hydrogen bonded conformations, a greater shielding of the C-7 methoxy group by the phenolic atomatic ring is expected in isomer **13** than in isomer **14**.

Catalytic reductive alkylation[2] of **11** with formaldehyde yielded 5,6-dimethyl-7,8,9-trimethoxy-H6,4a-*cis*-4a,10b-*trans*-1,2,3,4,4a,5,6-10b-octahydrophenanthridine (**16**), and, correspondingly, **12** gave 5,6-dimethyl-7,8,9-trimethoxy-H6,4a-*trans*-4a,10b-*trans*-1,2,3,4,4a,5,-6,10b-octahydrophenanthridine (**17**), both in good yields. It was of interest to compare the epimerization of the salts of the tertiary amines **16** and **17** with the results obtained by nmr with the 6-nor analogs[2] under conditions of slow proton exchange. The results indicate that the hydrochloride salts of **16** and **17**, obtained from crystallization from a mixture of ethyl acetate and 2-propanol, each had crystallized in a single epimeric form.

The nmr spectrum of the hydrochloride salt of **16** in formic acid exhibits a single NCH_3 signal which appears as a doublet (J_{NHCH_3} = 5 Hz) at τ 6.83, and a single C-6 methyl signal which appears as a doublet (J_{CHCH_3} = 6.6 Hz) at τ 8.22. Addition of sodium formate to catalyze the equilibration of N epimers did not cause the appearance of either a second NCH_3 doublet, as was the case with the 6-nor analog,[2] nor a second 6-CH_3 signal. This indicates that in formic acid the thermodynamic equilibrium for protonated **16** is far in the direction of a single epimer. From steric consideration this is expected to be the isomer with the methyl groups trans to each other (structure **11** with an equatorial NCH_3 group). In this epimer the NCH_3 group is gauche to only two groups, the C-6 methyl and C-4 methylene groups, while in the other epimer it is gauche to four groups and experiences 1,3-diaxial repulsion from the C-4 and C-10b hydrogens. This assignment is substantiated by the chemical shift of the NCH_3 signal, which is identical with that of the NCH_3 group of the epimer of the 6-nor analog having the equatorial NCH_3 in formic acid.[2] The coupling between H-6 and NH, as measured from the signal of H-6, is only about 4 Hz, while a value of at least 8 Hz is expected between the pseudoaxial CH and adjacent axial NH protons. This suggests a reduction of the dihedral angle which could result from a deformation of the half-chair conformation due to repulsion of the adjacent methyl groups, or it could result from an equilibrium between the half-chair and a boat conformation.

The nmr spectrum of the hydrochloride salt of **17** in formic acid exhibits a single NCH_3 signal as a doublet ($J_{NHCH_3} \cong 5$ Hz) at τ 7.02, and a single C-6 methyl signal as a doublet (J_{CHCH_3} = 6.6 Hz) at τ 8.18. There was no sign of epimerization after standing for 2 days, but the addition of sodium formate caused the gradual appearance of a second NCH_3 doublet at τ 6.91 and a second C-6 methyl doublet at τ 8.33. Equilibration appeared complete within 6 hr. An accurate estimate of the ratio of epimers was not possible because the doublets overlap other signals, but at equilibrium there appeared to be at least 75% of the original epimer. Prior to equilibration the signal of H-6 appears as a quartet (J_{CHCH_3} = 6.6 Hz). There is no evidence of coupling between H-6 and the adjacent NH. This implies a dihedral angle of about 90° between H-6 and NH. This is approximately what is expected for a structure with the hetero ring in a half-chair confor-

(7) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

mation and with the C-6 methyl in a pseudoaxial orientation and the NCH_3 group in an axial orientation. The downfield position of the NCH_3 signal of the minor epimer implies an isomerization from an axial to an equatorial position. The upfield position of the 6-CH_3 signal in the minor epimer could result from repulsion between the cis methyl groups causing the 6-CH_3 group to be further out of the plane of the aromatic ring.

Catalytic hydrogenation of the hydrochloride salt of **10** yielded only one product. Cis addition to the imine double bond is expected to give the H-6,4a-cis isomer **15**. This structure is supported by nmr data of the hydrochloride salt in deuteriochloroform. The chemical shift of the C-6 methyl group and the nonequivalence and patterns of the signals of the ammonium protons are consistent with the half-chair, chair conformation shown by structure **15** where the C-6 methyl group has a pseudoequatorial orientation. In this conformation H-4a and H-10b have equatorial and axial orientations, respectively, in relation to the cyclohexane ring. The 6-CH_3 signal appears as a doublet at τ 7.92. The chemical shift implies a similar orientation of the methyl group to the aromatic ring as in **11**. The signal of one of the ammonium protons is at τ −1.10 and the other at τ 1.47. This large difference in chemical shifts supports structure **15** where the effect of the C-6 methyl group is to shield the axial H-5 proton cis to the methyl, thus increasing the difference in chemical shifts between the equatorial and axial NH protons. The upper field signal is considerably broader than the signal at τ −1.10, and this is consistent with the signal at τ 1.47 belonging to axial H-5 coupled with axial H-4a and pseudoaxial H-6. In the spectrum of the free base in deuteriochloroform the signal of H-4a occurs as a fairly narrow, unresolved multiplet, $W_{1/2}$ = 8 Hz, at τ 6.99 and the signal of H-10b occurs at τ 7.62 as a much broader signal. This implies an equatorial orientation of H-4a and an axial orientation of H-10b in relationship to the cyclohexane ring, and the same predominant conformation in chloroform as for the hydrochloride salt.

Experimental Section

Microanalyses were performed by Alfred Berhardt, Mulheim, Germany, and Huffman Laboratories, Wheatridge, Colo. Melting points were determined on a Kofler hot stage unless otherwise indicated. Heat sensitivity of most of the salts necessitated placement of samples on the hot stage within about 5–10° of the melting point for most consistent results.

Nuclear magnetic resonance spectra were recorded in the presence of an internal tetramethylsilane standard on Varian A-60 or T-60 spectrometers operating at temperatures of about 33–35°. Infrared spectra of solids and neat liquids were determined on a Beckman IR-5a spectrophotometer and solution spectra were recorded on a Beckman IR-20 spectrophotometer. Matched cells (0.1 and 1 mm) were used for solution spectra in chloroform. The dilute sample of **13** in carbon tetrachloride was determined using a Beckman variable path cell at 3 mm, without reference cell. Spectral grade solvents were used.

trans-2-(**3,4,5-Trimethoxyphenyl**)**cyclohexylformamide** (**3**).—A mixture of 531 mg (2.0 mmol) of **1**, 1.00 g (*ca.* 22 mmol) of 99% formic acid, and 35 ml of benzene was heated under gentle reflux for 21 hr. Water azeotrope was collected as formed in a water separator. After cooling, an additional 20 ml of benzene was added and the unreacted amine was removed by extraction with 5% HCl (15 ml in two portions). Upon work-up, these acid extracts produced 60 mg (11%). The benzene solution was washed neutral with 5% $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated under reduced pressure. The viscous crude product, 0.50 g, was chromatographed on 15 g of silica gel using dry column technique starting with ethyl ether and progressing to a 3:1 ether–acetone mixture. Product fractions were combined and crystallized from ethyl ether with gradual addition of hexane at room temperature, yielding 432 mg (74%) of formamide **3** as colorless cubes: mp 101–102°; ir (solid, KBr) 3360 (NH), 1660 cm^{-1} (C=O); nmr ($CDCl_3$) τ 2.10 (d, <1, J = 2 Hz, CHO, major), 2.33 (d, <1, J = 12 Hz, CHO, minor), 3.55 (s, <2, ArH, major), 3.61 (s, <2, ArH, minor), 4.33 (m, <1, NH, major), ~6.2 (m, <1, H-1, major), ~7.7 (m, ~1, H-2).

Anal. Calcd for $C_{16}H_{23}O_4N$: C, 65.51; H, 7.90; N, 4.78. Found: C, 65.40; H, 7.75; N, 4.74.

cis-2-(**3,4,5-Trimethoxyphenyl**)**cyclohexylformamide** (**4**).—Application of the above formylation procedure to **2** regenerated from 2.11 g (7.00 mmol) of the hydrochloride, with the reflux period extended to 60 hr, gave crude crystalline product directly upon evaporation of the benzene solution. Recrystallization from benzene yielded 1.833 g (89%) of **4** as colorless crystals, mp 177.5–180.5°. A sample recrystallized from acetone for analysis gave colorless cubes: mp 176.5–179°; ir (KBr, solid) 3240 (NH), 1680 cm^{-1} (C=O); nmr ($CDCl_3$) τ 2.00 (d, <1, J = 2 Hz, CHO, major), 2.60 (d, <1, J = 12 Hz, CHO, major), 3.53 (s, <2, ArH, major), 3.60 (s, <2, ArH, minor), ~2.9 (m, <1, NH, minor), 3.86 (m, <1, NH, major), 5.5 (m, <1, H-1), 6.3 (m, <1, H-1), 7.2 (m, ~1, H-2).

Anal. Calcd for $C_{16}H_{23}O_4N$: C, 65.51; H, 7.90; N, 4.78. Found: C, 65.58; H, 8.00; N, 5.12.

trans-2-(**3,4,5-Trimethoxyphenyl**)**cyclohexylacetamide** (**5**).—A cold solution of 1.061 g (4.00 mmol) of **1** in 20 ml of pyridine was treated with 1.0 g (10 mmol) of acetic anhydride with stirring, and then the reaction flask was protected with a drying tube and left at room temperature for 91 hr. After the reaction mixture was rechilled and treated with 5 ml of methanol to destroy excess acetic anhydride, it was evaporated under reduced pressure. The residue was dissolved in 100 ml of benzene and the resulting solution was washed successively with 5% HCl, water, 5% $NaHCO_3$ solution, and water to neutrality, then dried (Na_2SO_4) and evaporated. Crystallization of the residue from benzene afforded 1.213 g (98%) of **5** as fine, colorless needles: mp 141–141.5°; ir (KBr, solid) 3320 (NH), 1640 cm^{-1} (C=O); nmr ($CDCl_3$) τ 3.57 (s, 2, ArH), 4.37 (d, 1, J = 8 Hz, NH), 6.0 (m, 1, H-1), 7.6 (m, 1, H-2), 8.28 (s, 3, $COCH_3$).

Anal. Calcd for $C_{17}H_{25}O_4N$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.18; H, 8.10; N, 4.71.

cis-2-(**3,4,5-Trimethoxyphenyl**)**cyclohexylacetamide** (**6**).—N-Acetylation of **2**, as described above, followed by crystallization from benzene, gave 94% of acetamide **6**: mp 157.5–159.5°; ir (solid, KBr) 3320 (NH), 1630 cm^{-1} (C=O); nmr ($CDCl_3$) τ 3.51 (s, <2, ArH, major), 3.58 (s, <2, ArH, minor), 3.85 (d, <1, J = 8 Hz, NH, major), 5.65 (m, <1, H-1, major), ~7.2 (m, ~1, H-2), 8.17 (s, <3, $COCH_3$, major), 8.53 (s, <3, $COCH_3$, minor).

Anal. Calcd for $C_{17}H_{25}O_4N$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.15; H, 8.13; N, 4.60.

Bischler–Napieralski Cyclization of *cis*- **and** *trans*-**2-(3,4,5-Trimethoxyphenyl)cyclohexylamides.**—Reagent grade chlorobenzene and phosphorus oxychloride were used without purification. Removal of traces of moisture from the apparatus, solvent, and starting amide was accomplished simultaneously by distillation of a few milliliters of the chlorobenzene. The resulting dry amide–chlorobenzene solution was then cooled prior to $POCl_3$ addition. The operations described below for **7** are typical of procedures applied in all cases. In cognate preparations, reaction times of 2–3 hr were allowed, although the vigorous HCl evolution during the initial heating period suggested that cyclization is quite rapid. A large excess (7–9 equiv) of $POCl_3$ was used in all instances.

7,8,9-Trimethoxy-4a,10b-*trans*-**1,2,3,4,4a-10b-hexahydrophenanthridine** (**7**) **Hydrochloride.**—With stirring at room temperature, 3.0 ml (*ca.* 33 mmol) of $POCl_3$ was added to a dry solution of 1.027 g (3.50 mmol) of **3** in 40 ml of chlorobenzene. The stirred mixture was slowly heated to gentle reflux for 3 hr. After cooling, the mixture was treated dropwise with 10 ml of water at a rate slow enough to prevent vigorous exothermic reaction with excess $POCl_3$. The resulting warm two-phase system was cooled, the aqueous layer was separated, and the chlorobenzene solution was extracted with two 5-ml portions of 5% HCl solution. The combined aqueous acid extracts were washed with three 10-ml portions of carbon tetrachloride and cooled in an ice bath. With stirring, the solution was made basic with KOH and the

hexahydrophenanthridine was extracted with a total of 125 ml of benzene. The benzene solution was dried (Na_2SO_4) and concentrated to about 25 ml, diluted with 100 ml of petroleum ether (bp 30–60°), and saturated with HCl gas. Removal of solvents under reduced pressure and crystallization of the residue from 2-propanol–ethyl acetate gave 987 mg (90%) of the hydrochloride of **7** as nearly colorless crystals: mp 184–185° dec (with gas evolution); ir (solid, KBr) 2670, broad (NH^+), 1640 cm^{-1} (C=N); nmr ($CDCl_3$), **7** HCl, τ −4.5 (1, NH), 1.18 (dd, 1, H-6, $J \cong 8.5$ and 2 Hz), 3.22 (s, 1, H-10), 5.87 (s, 6, OCH_3), 6.11 (s, 3, OCH_3), ~6.4 (m, 1, H-4a), ~7.2–7.3 (m, 3, H-10b and H-1); free base **7**, τ 1.48 (d, 1, H-6, $J \cong 3$ Hz), 3.38 (s, 1, H-10), 6.03 (s, 3, OCH_3), 6.08 (s, 3, OCH_3), 6.13 (s, 3, OCH_3), ~7.0 (m, 1, H-4a), ~7.6 (m, 3, H-10b and H-1).

Anal. Calcd for $C_{16}H_{22}O_3NCl$: C, 61.63; H, 7.11; N, 4.49. Found: C, 61.58; H, 7.23; N, 4.55.

7,8,9-Trimethoxy-4a,10b-*cis*-1,2,3,4,4a,10b-hexahydrophenanthridine (8) Hydrochloride.—The hydrochloride of **8** was obtained in 95.1% yield as long plates, mp 177.5–178° dec (with gas evolution), after crystallization from 2-propanol–ethyl acetate: ir (solid, KBr), 2670, broad (NH^+), 1640 cm^{-1} (C=N); nmr ($CDCl_3$), **8** HCl, τ −4.4 (1, NH), 1.13 (dd, 1, H-6, $J \cong 7.5$ and 2 Hz), 3.15 (s, 1, H-10), 5.85 (s, 3, OCH_3), 5.88 (s, 3, OCH_3), 6.10 (s, 3, OCH_3), ~5.85 (m, 1, H-4a), ~6.9 (m, 1, H-10b), ~7.5 (m, 1, H-1); free base **8**, τ 1.33 (d, 1, H-6, $J \cong 3$ Hz), 3.53 (s, 1, H-10), 6.03 (s, 3, OCH_3), 6.10 (s, 3, OCH_3), 6.14 (s, 3, OCH_3), ~6.3 (m, 1, H-4a), ~7.4 (m, 1, H-10b), ~7.8 (m, 1, H-1).

Anal. Calcd for $C_{16}H_{22}O_3NCl$: C, 61.63; H, 7.11; N, 4.49. Found: C, 61.39; H, 7.08; N, 4.76.

6-Methyl-7,8,9-trimethoxy-4a,10b-*trans*-1,2,3,4,4a,10b-hexahydrophenanthridine (9) Hydrochloride.—2-Propanol–ethyl acetate crystallization of the Bischler–Napieralski cyclization product of **5** gave the hydrochloride of **9** in 94% yield: mp 182.5–183.5° dec; ir (KBr, solid) 2680, broad (NH^+), 1630 cm^{-1} (C=N); nmr ($CDCl_3$), τ −4.13 (1, NH), 3.22 (s, 1, H-10), 5.95 (s, 6, OCH_3), 6.15 (s, 3, OCH_3), ~6.7 (m, 1, H-4a), 6.97 (b s, 3, 6-CH_3), ~7.3 (m, 3, H-10b and H-1).

Anal. Calcd for $C_{17}H_{24}O_3NCl$: C, 62.66 H, 7.42 N, 4.30. Found: C, 62.47; H, 7.44; N, 4.40.

The free amine **9**, obtained from base treatment of the hydrochloride salt, was crystallized from hexane: mp 113–115° ir (solid, KBr) 1610 cm^{-1} (C=N); nmr ($CDCl_3$), τ 3.38 (s, 1, H-10), 6.10 (s, 6, OCH_3), 6.15 (s, 3, OCH_3), 7.55 (d, 3, 6-CH_3, $J \cong 1.7$ Hz), 7.3 (m, 1, H-4a), ~7.6 (m, 3, H-10b and H-1).

6-Methyl-7,8,9-trimethoxy-4a,10b-*cis*-1,2,3,4,4a,10b-hexahydrophenanthridine (10) Hydrochloride.—Bischler–Napieralski cyclization of **6** produced the hydrochloride of **10**, mp 173–175° (Fisher-Johns), in 94% yield upon crystallization from 2-propanol–benzene. Recrystallization from 2-propanol–ethyl acetate gave small cubes: mp 171–172° dec (with gas evolution); ir (solid, KBr) 2720, broad (NH^+), 1630 cm^{-1} (C=N); nmr ($CDCl_3$), τ −4.4, (1, NH), 3.22 (s, 1, H-10), 5.93 (s, 6, OCH_3), 6.13 (s, 3, OCH_3), ~6.0 (m, 1, H-4a), 6.92 (d, 3, 6-CH_3, $J \sim 1.8$ Hz), ~7.2 (m, 2, H-10b and H-1).

Anal. Calcd for $C_{17}H_{24}O_3NCl$: C, 62.66 H, 7.42; N, 4.30. Found: C, 62.64; H, 7.52; N, 4.58.

A sample of the amine **10**, prepared by base treatment of its hydrochloride salt, and recrystallization from hexane, had mp 97–98°; ir (solid, KBr) 1610 cm^{-1} (C=N); nmr ($CDCl_3$), τ 3.50 (s, 1, H-10), 6.10 (s, 6, OCH_3), 6.17 (s, 3, OCH_3), 6.65 (m, 1, H-4a), 7.52 (d, 3, 6-CH_3, $J \cong 2.2$ Hz), ~7.6 (m, 1, H-10b), ~7.9 (m, 1, H-1).

6-Methyl-7,8,9-trimethoxy-4a-6*H*-*cis*- and -4a,6*H*-*trans*-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridines (11 and 12).—Excess acetaldehyde was bubbled through a stirred solution of 5.31 g (20.0 mmol) of **1** in 100 ml of benzene under nitrogen. The solution became turbid, then water separated. When no turbidity remained, the benzene solution was dried (Na_2SO_4) and evaporated under reduced pressure. The azomethine produced was a nearly colorless oil. This intermediate was cooled in an ice bath and dissolved in 50 ml of 20% H_2SO_4. After 4 days at room temperature partial crystallization occurred from the aqueous mixture. The sulfate salts were extracted with chloroform (200 ml in three portions), and the chloroform extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was redissolved in 25 ml of water and washed with CCl_4 and benzene to remove any nonbasic impurities. The free base mixture was regenerated by treatment of the cold, stirred aqueous solution with excess KOH, and was extracted with benzene (175 ml in four portions). Drying (Na_2SO_4) and evaporation to constant weight gave 5.56 g (95%) of a crude liquid mixture of **11** and **12**. This material, upon examination by nmr in pyridine containing a small amount of D_2O, exhibited two doublets at τ 8.40 and 8.46 (6-methyl) in a ratio of about 2:1.

Separation of 11 and 12 *via* *p*-Toluenesulfonic Acid Salts.—A cooled solution of the crude mixture of **11** and **12** free bases was treated with a methanolic solution of 3.80 g (20 mmol) of *p*-toluenesulfonic acid hydrate. The resulting acidic solution was evaporated under reduced pressure. Crystallization of the residue from methanol and water, followed by filtration, washing of the crystals with water to remove excess *p*-toluenesulfonic acid, and drying, afforded a quantitative yield of impure salts. The nmr of this mixture in 1:1 formic acid–deuterium oxide exhibited two 6-methyl doublets at τ 8.27 and 8.30 in an approximate ratio of 2:1. Recrystallization from methanol gave 6.7 g of a mixture of crystalline **11** and **12** *p*-toluenesulfonates, a 73% yield based on **1**. Extensive fractional crystallization from methanol with periodic recovery of the more soluble isomer from mother liquors with ethyl acetate afforded 1.76 g of **12** *p*-toluenesulfonate as head fractions, mp >260° (Fisher-Johns), 1.41 g of **11** *p*-toluenesulfonate as tail fraction, mp >204°–206° (Fisher-Johns), and 1.94 g of intermediate crystalline fractions in various stages of separation. Crystallization was continued to constant melting point for each isomer. Examination of separated *p*-toluenesulfonates of **11** and **12** by nmr in 1:1 formic acid–deuterium oxide in the τ 8.3 region indicated no contamination. By this separation procedure, the **11** isomer predominating in the Pictet–Spengler reaction was isolated in smaller amounts than **12** due to losses resulting from its markedly greater solubility in crystallization solvents.

6-Methyl-7,8,9-trimethoxy-4a,6*H*-*trans*-4a,10b-*trans*-1,2,3,4,-4a,5,6,10b-octahydrophenanthridine (12).—An analytical sample of **12** *p*-toluenesulfonate crystallized from methanol gave rocklike crystals, mp 264.5–266.5° dec.

Anal. Calcd for $C_{24}H_{33}O_6NS$: C, 62.18; H, 7.18; N, 3.20. Found: C, 62.04; H, 7.12; N, 3.17.

Amines were recovered from the respective *p*-toluenesulfonates by passage over a base-treated ion exchange column. A large excess of Amberlite IRA-401 was placed in a column with methanol. Excess methanolic KOH was passed over the resin, which was then washed with methanol until no longer basic to phenolphthalein.

A methanolic solution of **12** *p*-toluenesulfonate was passed over a column prepared as described above followed by methanol until no more product eluted. Evaporation, resolubilization in benzene, drying (Na_2SO_4), and reevaporation gave a quantitative yield of the liquid amine **12**: ir (liquid, neat) 3310 cm^{-1} (NH); nmr (pyridine + D_2O) τ 8.46 (d, 3, 6-CH_3, $J = 6.5$ Hz).

The hydrochloride of **12** was prepared in 93% yield by passage of a methanolic solution of **12** *p*-toluenesulfonate over a large excess of Amberlite IRA-401 ion exchange resin. The column was washed with methanol until no more material eluted. Addition of a small amount of HCl to the methanol solution improved the yield. Evaporation of the methanol solution and crystallization of the residue from methanol and ethyl acetate afforded **12** hydrochloride which was identical with a sample prepared from the amine **12**: mp 281–282.5° dec; ir (solid, KBr) *ca.* 2745 cm^{-1} (NH_2^+); nmr ($CDCl_3$) τ 0.0 (2, NH_2^+), 3.43 (s, 1, H-10), 5.25 (m, 1, H-6), 6.03 (s, 3, OCH_3), 6.17 (s, 6, OCH_3), 8.24 (d, 3, 6-CH_3, $J = 6.8$ Hz).

6-Methyl-7,8,9-trimethoxy-4a,6*H*-*cis*-4a,10b-*trans*-1,2,3,4,4a,-5,6,10b-octahydrophenanthridine (11).—Pure **11** *p*-toluenesulfonate crystallized from methanol as plates: mp 204–205.5° dec; ir (solid, KBr) *ca.* 2800 cm^{-1} (broad, NH_2^+).

Anal. Calcd for $C_{24}H_{33}O_6NS$: C, 62.18; H, 7.18; N, 3.02. Found: C, 62.34; H, 7.25; N, 2.95.

Passage of **11** *p*-toluenesulfonate over basic ion exchange resin as described for **12** also afforded **11** in high yield by the ion-exchange method described for **12** hydrochloride. This product and a sample prepared from the amine gave identical nmr spectra and melting points upon crystallization from methanol and ethyl acetate: mp 257–258.5° dec; ir (solid, KBr) *ca.* 2780 cm^{-1} (broad, NH_2^+); nmr ($CDCl_3$), τ −0.50 (1, 5-H_e), 0.63 (1, 5-H_a), 3.40 (s, 1, H-10), 5.25 (m, 1, H-6), 6.10 (s, 3, OCH_3), 6.15 (s, 6, OCH_3), 8.10 (d, 3, 6-CH_3, $J = 6.6$ Hz).

5,6-Dimethyl-7,8,9-trimethoxy-4a,6*H*-*trans*-4a,10b-*trans*-1,2,3,-4,4a,5,6,10b-octahydrophenanthridine (17).—A solution of **12** prepared from 1.39 g (3.00 mmol) of **12** *p*-toluenesulfonate by ion exchange was dissolved in 75 ml of ethanol and treated with a

large excess (*ca.* 35 mmol) of 37% formaldehyde. This solution was hydrogenated at room temperature in the presence of 300 mg of 10% palladium on carbon at an initial hydrogen pressure of 30 psi. Hydrogen uptake was rapid for about 15 min, and no uptake was observed after 3 hr. The filtrate was acidified with glacial acetic acid and evaporated under reduced pressure. The residue was dissolved in 5 ml of water and the crude amine **17** was regenerated with excess KOH with cooling and stirring. Extraction with benzene, drying (Na_2SO_4), and evaporation gave crude **17** as a nearly colorless oil. Preparation of the hydrochloride and crystallization from ethyl acetate and 2-propanol yielded 929 mg (90%) of **17** hydrochloride, mp 245–256° dec with rapid sublimation. A sample recrystallized from 2-propanol gave mp 236–238° dec; ir (solid, KBr) 2480 cm^{-1} (broad, NH^+); nmr (HCOOH) τ 3.16 (s, 1, H-10), 5.27 (q, 1, H-6, J = 6.6 Hz), 6.00 (s, 3, OCH_3), 6.08 (s, 3, OCH_3), 6.10 (s, 3, OCH_3), 7.02 (d, 3, NCH_3, J = 5.2 Hz), 8.18 (d, 3, 6-CH_3, J = 6.6 Hz). After equilibration, doublets of the minor epimer appeared at τ 6.91 and 8.33 for the NCH_3 and 6-CH_3 groups, respectively.

Anal. Calcd for $C_{18}H_{28}O_3NCl$: C, 63.24; H, 8.26; N, 4.10. Found: C, 63.24; H, 8.13; N, 4.08.

5,6-Dimethyl-7,8,9-trimethoxy-4a,6*H*-*cis*-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (**16**).—Compound **11** prepared from 1.39 g (3.00 mmol) of **11** *p*-toluenesulfonate by ion exchange was methylated according to the catalytic reductive alkylation procedure described for **17**. Conversion of the crude **16** product to the hydrochloride and crystallization from ethyl acetate and 2-propanol gave 830 mg (81%) of **16** hydrochloride: mp 191–193.5° dec with sublimation; ir (solid, KBr) 2610 cm^{-1} (NH^+); nmr (HCOOH) τ 3.17 (s, 1, H-10), 5.23 (dq, 1, H-6, J = 6.6 and 4.0 Hz), 6.02 (s, 3, OCH_3), 6.08 (s, 3, OCH_3), 6.10 (s, 3, OCH_3), 6.83 (d, 3, NCH_3, J = 5.0 Hz), 8.22 (d, 3, 6-CH_3, J = 6.6 Hz).

Anal. Calcd for $C_{18}H_{28}O_3NCl$: C, 63.24; H, 8.26; N, 4.10. Found: C, 63.27; H, 8.23; N, 4.06.

Catalytic Hydrogenation of 6-Methyl-7,8,9-trimethoxy-4a,10b-*trans*-1,2,3,4,4a,10b-hexahydrophenanthridine (**9**).—A solution of 200 mg (0.691 mmol) of **9**, mp 113–115°, in 30 ml of ethanol was hydrogenated in the presence of 100 mg of 10% palladium on carbon at an initial pressure of 25 psi at room temperature. Hydrogen uptake slowed after about 20 min. After 1.5 hr, catalyst was filtered and washed with methanol. Evaporation of the filtrate under reduced pressure, addition of toluene, and reevaporation gave 189 mg of a slightly discolored oil. The nmr of this material in pyridine was identical with that of **11** and indicated the presence essentially of only one isomer, *p*-toluenesulfonate salt, mp 200–204°.

6-Methyl-7,8,9-trimethoxy-4a,6*H*-*cis*-4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (**15**).—A solution of 180 mg of the hydrochloride salt of **10** in 20 ml of ethanol was hydrogenated in the presence of 60 mg of 5% palladium on carbon for 45 min at an initial pressure of 25 psi at room temperature. The product was crystallized from absolute ethanol acidified with HCl gas, and then from absolute ethanol: mp 235–238° dec; nmr ($CDCl_3$) τ −1.10 (1, 5-H_e), 1.47 (1, 5-H_a), 3.57 (s, 1, H-10), 5.23 (m, 1, H-6), 6.11 (s, 3, OCH_3), 6.17 (s, 6, OCH_3), 7.92 (d, 3, 6-CH_3, J = 6.7 Hz).

Anal. Calcd for $C_{17}H_{26}O_3NCl$: C, 62.28; H, 8.00; N, 4.27. Found: C, 62.11; H, 8.12; N, 4.29.

6-(*o*-Hydroxyphenyl)-7,8,9-trimethoxy-4a,6*H*-*cis*- and -4a,6*H*-*trans*-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridines.—A nitrogen atmosphere was maintained throughout the preparation of **13** and **14**. A mixture of 1.061 g (4.00 mmol) of **1** and 0.743 g (6.08 mmol) of redistilled salicylaldehyde was stirred and heated without solvent for 30 min, then 5 ml of benzene was added and distilled to azeotrope the water and drive the azomethine formation to completion. The resulting bright yellow residue was diluted with methanol (20 ml) and treated with 30 ml of 20% sulfuric acid. Addition of acid caused a rapid loss of the characteristic color. After 1 hr at reflux, the mixture had become essentially colorless. Heating was continued for a total of 24 hr. The reaction mixture was evaporated under reduced pressure until excess salicylaldehyde azeotroped. The concentrated solution partially crystallized on cooling, and was extracted with 60 ml of 5:1 chloroform and methanol, diluted with water (20 ml), and reextracted with chloroform. The crude salt of **1** (95 mg) was recovered from the aqueous phase. The combined chloroform extracts were dried (Na_2SO_4) and evaporated. The residue was redissolved in 30 ml of hot water, filtered, cooled, and washed with petroleum ether. The resulting aqueous solution was saturated with sodium carbonate, then extracted with benzene. Drying and evaporation gave 1.251 g of a cream-colored crystalline residue. A homogeneous sample of this material in deuteriochloroform was examined by nmr. After D_2O exchange, integration of signals for H-6 (**13**, **14**), total methoxy protons (**1**, **13**, **14**), and shielded methoxy (**13**) protons indicated 87% of cyclized products **13** and **14** in a ratio of 17:2. The proportion of cyclized products to **1** in the mixture, estimated from H-6 and the total aromatic proton signals, was in good agreement (86%) with that above, as was the estimation (85%) based on integrals for aromatic protons of **1** which are shielded with respect to all aromatic protons in **13** and **14**.

Crystallization of the mixture from benzene removed the more soluble starting material **1** and yielded 1.02 g (69%) of a mixture of **13** and **14**. The hydrochloride salts were prepared by bubbling HCl gas in a solution of the amines in benzene. The higher solubility of the hydrochloride of **14** in benzene allowed good separation of the two isomers.

The free base **13** was obtained from the hydrochloride salt and recrystallized from methanol and from a benzene–hexane mixture, to yield long, fine, colorless needles: mp 172–174°; ir ($CHCl_3$, 0.03 *M*) 3320 (NH), ~3100 cm^{-1} (broad) (bonded OH); ir (CCl_4, 0.01 *M*) 3320 (NH), ~3040 cm^{-1} (broad) (bonded OH); nmr ($CDCl_3$) τ 4.38 (s, 1, H-6), 6.16 (s, 3, OCH_3), 6.20 (s, 3, OCH_3), 6.62 (s, 3, OCH_3).

Anal. Calcd for $C_{22}H_{27}O_4N$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.46; H, 7.38; N, 3.99.

The hydrochloride of **13**, crystallized from a 2-propanol–benzene mixture, had mp 244–246° dec, and *p*-toluenesulfonate, crystallized from a methanol–water mixture, had mp 230–232° dec.

The free base of **14**, crystallized from benzene, gave colorless, dense crystals: mp 231–233°; ir ($CHCl_3$, 0.015–0.03 *M*), 3300 (NH), ~3080 cm^{-1} (bonded OH); nmr ($CDCl_3$) τ 4.41 (s, 1, H-6), 6.11 (s, 6, OCH_3), 6.20 (s, 3, OCH_3).

Anal. Calcd for $C_{22}H_{27}O_4N$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.40; H, 7.36; N, 3.76.

The *p*-toluenesulfonate of **14**, crystallized from a benzene–hexane mixture, had mp 234–236° dec.

Registry No.—**3**, 34913-46-7; **4**, 34913-47-8; **5**, 34913-48-9; **6**, 34913-49-0; **7** HCl, 34910-03-7; **8** HCl, 34910-04-8; **9**, 34910-05-9; **9** HCl, 34910-06-0; **10**, 34910-07-1; **10** HCl, 34910-08-2; **11**, 34910-09-3; **11** *p*-toluenesulfonate, 34910-10-6; **12**, 34910-11-7; **12** HCl, 34910-12-8; **12** *p*-toluenesulfonate, 34910-13-9; **13**, 34910-14-0; **13** HCl, 34910-15-1; **13** *p*-toluenesulfonate, 34910-16-2; **14**, 34910-17-3; **14** *p*-toluenesulfonate, 34910-18-4; **15** HCl, 34910-19-5; **16** HCl, 34910-20-8; **17** HCl, 34910-21-9; 7,8,9-trimethoxy-1,2,3,4,4a,5,6,10b-octahydrophenanthridine, 34910-22-0; 7,8,9-trimethoxy-1,2,3,4,4a,10b-hexahydrophenanthridine, 34910-23-1.

Nonbenzenoid Aromatic Systems. VI.[1a] pK_a Values of Azuloic Acids

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The thermodynamic pK_a values of 1-, 2-, 5-, and 6-azuloic acids, 1-, 4-, and 6-azulylacetic acids, and azulene-1,2-dicarboxylic acid were determined in 50% aqueous ethanol (v/v) at 25°. The relative acidities of the azuloic acids (1 < 2 < 5 < 6) were consistent with decreasing π-electron density at these positions in the order of 1 > 2 > 5 > 6.

While experimental and theoretical results agree that the 1 position of azulene is the site of largest π-electron density and the site of ready electrophilic substitution, there is disagreement in both types of results as to whether the 2 or 5 position is the second most electron-rich ring site. Experimentally, Vilsmier formylation of 1,3-dimethylazulene reportedly gave the 2-carboxaldehyde while 1,3-di-*tert*-butylazulene produced only the corresponding 5-carboxaldehyde probably due to steric control in the substitution.[2] However, acylation and halogenation of 1,3-dihaloazulenes (X = Cl, Br) and 1,3-dibenzoyloxyazulene produced only the products of 5 substitution.[3] The molecular orbital π-electron density calculations commonly referred to in this chemistry[4-6] likewise disagree in the ordering of these two positions.

The above experimental results involve 1,3-disubstituted azulenes which offer electronic perturbations and steric effects in the reactions examined. Further, these electrophilic substitution reactions would not necessarily reflect the ground state of the unperturbed azulene molecule.

Our approach to this question was to determine the thermodynamic pK_a's of the azuloic acids where steric factors should not be important and the electronic perturbation caused by the carboxylic acid and its conjugate base should be reduced compared to electrophilic substitution and be more constant at each of the nonequivalent ring positions. The pK_a's for four of the possible five azuloic acids are given in Table I. The previous nonthermodynamic pK_a value for 1-azuloic acid is in good agreement with the present result, but reported values for 5- and 6-azuloic acids are shown to be incorrect.[7]

Of significance is the increasing acidity order of these four acids, 1- < 2- < 5- < 6-azuloic acid. While it is recognized that the carboxylic acid and carboxylate anion groups surely perturb the electron densities at these nonequivalent azulene ring positions, we suggest that such perturbations are not sufficient to cause reversal of the relative electron densities at these positions (1 > 2 > 5 > 6) and that the above acidity order gives a truer reflection of these relative electron densities than previous experimental results.[7a]

TABLE I

pK_a's OF AZULOIC ACIDS IN 50% AQUEOUS ETHANOL (v/v) AT 25.0°

Acid	pK_a	Lit. pK_a[a]
1-Azuloic	6.992 ± 0.004[b]	7.01
2-Azuloic	5.855 ± 0.016	
5-Azuloic	5.682 ± 0.017	6.25
6-Azuloic	5.206 ± 0.013	6.09

[a] These literature values are corrected by adjusting the pK_a given for benzoic acid to 5.80; lit. pK_a +0.34.[7] [b] Standard deviations.

It is interesting that plotting these pK_a's *vs.* the charge densities of azulene listed by Streitwieser,[4] the results of the HMO, with or without ω technique, and the VESCF methods give reasonably linear correlations while the correlations from the nonempirical SCF and Pariser–Parr values are poorer. The VESCF correlation predicts that 4-azuloic acid would have a pK_a of about 4.8 in this medium. The acidity of 4-azuloic acid may decrease somewhat if hydrogen bonding to the electron-rich 3 position occurs in the acid which we believe accounts for the observed order of the pK_a's of 1- (pK_a = 5.987 ± 0.006), 4- (pK_a = 5.596 ± 0.010), and 6-azulylacetic acid (pK_a = 5.508 ± 0.032), the latter two being inverted from the order expected. It is our hope that these pK_a results will be helpful to those applying these and more advanced MO methods to azulene.

We have also determined the pK_a's of azulene-1,2-dicarboxylic acid (**1**); pK_a^1 = 3.352 ± 0.015, pK_a^2 = 10.459 ± 0.008. The K_1/K_2 ratio of $10^{7.1}$ is very large compared to that of phthalic acid in water, K_1/K_2 = 288.[8a] This shows that there is a larger distance separating the carboxylic acid groups on the five-membered ring of **1** approaching an optimum distance for hydrogen bonding in the half-neutralized **1** compared to the acid groups in phthalic acid (six-membered ring attachments).[8b,9] We were unable to determine the pK_a's of azulene-5,6-dicarboxylic acid (**2**)[10] because of

(1) (a) For paper V see R. N. McDonald, D. L. Morris, H. E. Petty, and T. L. Hoskins, *Chem. Commun.*, 743 (1971). (b) NDEA Fellow, 1968–1970; NSF Trainee, 1970–1971.

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(5) See footnotes 7–9 in ref 3.

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(7a) NOTE ADDED IN PROOF.—Using ^{13}C chemical shifts for azulene, the relative π-electron densities would be 1 > 5 > 2 > 6: P. C. Lauterbur, *J. Amer. Chem. Soc.*, **83**, 1838 (1961).

(8) (a) H. C. Brown, D. H. McDaniel, and O. Hafliger in "Determination of Organic Structures by Physical Methods," Vol. 1, E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, N. Y., 1955, Chapter 14. (b) J. A. Richards and T. J. Curphey, *Chem. Ind. (London)*, 1456 (1956), reported pK_a^1 = 3.64 and $pK_a^2 \geq 12$ for ferrocene-1,2-dicarboxylic acid in 2:1 ethanol–water.

(9) L. L. McCoy, *J. Amer. Chem. Soc.*, **89**, 1673 (1967).

(10) (a) We wish to thank Professor K. Hafner for a generous sample of the dimethyl ester of **2**. (b) The pK_a's of azulene-1,3-dicarboxylic acid could not be measured in 50% ethanol due to insolubility of this diacid.

ready anhydride formation; this requires the acid functions to be quite close, probably closer than those in phthalic acid. These findings agree with the expectation that groups on adjacent carbons of the five-membered ring of azulene are more distant from one another than those on the seven-membered ring.

Experimental Section

1-Azuloic Acid.—Methyl 1-azuloate[11] (110 mg, 0.68 mmol) [mp 59–60°; λ_{max} (c-C_6H_{12}) 544 nm (lit.[12] mp 56–57°); λ_{max} 544 nm)] was hydrolyzed with 0.3 g of potassium hydroxide in 50% methanol. Chromatography of the acid product on silica gel and recrystallization from ether–hexane gave 60 mg of lavender crystals of 1-azuloic acid, mp 183–184° (lit.[13] mp 181–182°).

2-Azuloic Acid.—Methyl 2-azuloate[11] (90 mg, 0.56 mmol) [mp 109–110°; λ_{max} (c-C_6H_{12}) 654 nm (lit.[14] mp 110–111°; λ_{max} 656 nm)] was hydrolyzed and purified as above giving 50 mg of green crystals of 2-azuloic acid, mp 205–210° dec [lit.[14,15] mp 200–203° dec; 218–220° dec].

5- and 6-Azuloic Acids.—A slightly modified procedure described by Plattner, *et al.*,[16] for the ethyl diazoacetate ring enlargement of indan was employed.[11a] After dehydrogenation with chloranil in refluxing benzene, the resulting blue oil was dissolved in a small quantity of hexane and extracted with 70% sulfuric acid which was again washed with hexane. Careful dilution of the acid layer with water and extraction with hexane gave a mixture (460 mg) of ethyl 5- and 6-azuloates in a 3:1 ratio (nmr), respectively, contaminated with only trace amounts of benzenoids. Separation of these isomers was achieved by saponifying this mixture in 100 ml of 1% methanolic potassium hydroxide. After standing for 48 hr, water was added and the mixture was extracted with ether. The aqueous layer was acidified with 5% hydrochloric acid and extracted with ether. The ether solution was dried (Na_2SO_4) and evaporated to give a green residue which when sublimed at 75° (0.25 mm) yielded a dark gray-black sublimate. When the temperature was raised to 125°, a green solid sublimed.

Each of these sublimates was treated with ethereal diazomethane and chromatographed on basic, activity I alumina. The first sublimate, after recrystallization from hexane at −25°, yielded 70 mg of green needles of methyl 6-azuloate, mp 112–113°, λ_{max} (c-C_6H_{12}) 634 nm (lit.[16] mp 112.5–113°, λ_{max} 635 nm). The second sublimate, after similar recrystallization, gave 270 mg of deep blue plates of methyl 5-azuloate, mp 38–40°, λ_{max} (c-C_6H_{12}) 567 nm (lit.[16] mp 40–41°, λ_{max} 565 nm).

A sample of methyl 5-azuloate was hydrolyzed as above for the other acids. Silica gel chromatography and recrystallization from ether–hexane gave the bluish-gray solid acid, mp 203–205° (lit.[16] mp 206–207°).

Similar hydrolysis of methyl 6-azuloate and purification of the resulting acid gave 6-azuloic acid as green crystals, mp 208–212° dec (lit.[16] mp 225–227° dec). While we presently do not understand this discrepancy in melting points, we hasten to add that we have obtained 6-azuloic acid from a completely different route and find its decomposition point to again be as we have recorded it.

4- and 6-Azulylacetic Acids.—Both acids were prepared by the procedure of Hafner, *et al.*,[17] for the synthesis of 6-azulylacetic acid. Chromatography on silica gel and recrystallization from ether–hexane gave blue crystals of 4-azulylacetic acid: mp 123–125° dec; ir (KBr) 3000–2820 (OH) and 1690 cm^{-1} (C=O); nmr (DMSO-d_6, internal TMS) τ −2–0 (s, OH, 1), 1.2–3.0 (m, Az H's, 7), and 5.74 (s, CH_2, 2); visible–uv (CH_2Cl_2) 677 nm (log ϵ 2.08), 617 (2.52), 575 (2.60), 356 (3.14), 343 (3.68), 329 (3.54), 286 (4.67), and 280 (4.68); mass spectrum (70 eV, direct insertion) *m/e* (rel intensity) 186 (M^+, 100) and 142 (19).

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.15; H, 5.33.

Similarly, 6-methylazulene gave blue-green crystals of 6-azulylacetic acid, mp 130–131° dec (lit.[17] mp 126–127° dec).

1-Azulylacetic Acid.—This was prepared according to the procedure of Anderson, *et al.*[18] Chromatography on silica gel and recrystallization from ether–hexane gave blue needles of 1-azulylacetic acid, mp 91–92° (lit.[18] mp 92–93°).

Azulene-1,2-dicarboxylic Acid.—Dimethyl azulene-1,2-dicarboxylate [mp 46.5–47.5°, λ_{max} (c-C_6H_{12}) 578 nm][11,19,20] was hydrolyzed as above to give the diacid which was recrystallized from aqueous ethanol: mp 205–215° dec; λ_{max} (95% EtOH) 573 nm (log ϵ 2.87), 368 (3.86), 346 (3.98), 308 (4.72), and 298 (4.71).

Anal. Calcd for $C_{12}H_8O_4$: C, 66.67; H, 3.73. Found: C, 66.95; H, 3.91.

Determination of Dissociation Constants.—A 25-ml, jacketed, round-bottomed titration cell was maintained at 25.00 ± 0.01°. The cell stopper was fitted with glass (half of a Metrohm EA 147X combination electrode) and calomel (Radiometer K 100) electrodes, and the tip of a microburet. Solutions of the acids (0.003 *M*) were stirred magnetically using a micromagnetic stirring bar encased in Teflon and were titrated with 0.03 *N* NaOH in 50% aqueous ethanol (v/v).

The microburet (Koch type) was constructed from a three-way Teflon stopcock, a 1-ml pipet calibrated in 0.01-ml divisions, and a 25-ml reservoir. The buret was connected to the cell by means of Teflon microtubing fitted at the end with a capillary glass tube constricted halfway closed at its tip. The tip was placed 0.5 cm below the surface of the solution during titrations.[21]

The pH of the cell was determined with a Metrohm Herisau E 436 recording potentiograph. Scale expansion in this instrument allowed pH readings to ±0.001.

Standardization of the pH scale was based on the thermodynamic pK_a of benzoic acid, 5.80 ± 0.01, in 50% ethanol.[22] A 0.003 *M* solution of zone-refined benzoic acid (Fisher Certified Reagent Zone Refined) in 50% ethanol was titrated to half-neutralization with 0.03 *N* NaOH in 50% ethanol. The pH of the cell was adjusted to read 5.750, which is the theoretical, "apparent" pH of benzoic acid at half-neutralization under these concentration and solvent conditions.[22] The calculated pK_a of benzoic acid was then found to be 5.799 ± 0.009. The pH of 0.02 *M* potassium hydrogen phthalate in 50% ethanol was then 5.415 and was used as a secondary reference buffer. Before and after each titration the pH of the secondary reference was determined; any run that gave readings differing by 0.005 pH units was rejected.

The solution of acid was transferred to the cell by means of a 10-ml pipet. The stopper holding the electrodes, which were rinsed with 50% ethanol, was set in place in the cell. The titrant inlet glass capillary tube was inserted through a hole in the stopper and placed with its tip below the solution's surface. The pH values were recorded on the chart paper at 9–10 stages between 25 and 75% neutralization of the acid. After each addition of a volume of base titrant, magnetic stirring was continued for *ca.* 1 min and then the stirrer was shut off to record the pH. Complete neutralization was assumed at pH *ca.* 10 in this solvent system and was used to verify the original acid concentration.

(11) The esters used to obtain the acids in this investigation resulted from the studies of (a) H. E. Petty and (b) N. L. Wolfe. Their contribution to the present results is gratefully acknowledged.

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(20) W. v. E. Doering and D. W. Wilye, *Tetrahedron*, **11**, 183 (1960), reported the preparation of what appears to be impure dimethyl azulene-1,2-dicarboxylate.

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The pK_a values for these monocarboxylic acids were calculated using the computer program of Leung.[21,23,24]

The water used was distilled water which was passed slowly through a Barnstead Mixed Bed Demineralizer Cartridge (#8902) and redistilled. The ethanol was twice distilled 95% ethanol.

(23) C. Leung, Ph.D. Thesis, Cornell University, Ithaca, N. Y., 1967.
(24) R. R. Reitz, Ph.D. Thesis, Kansas State University, Manhattan, Kans., 1971.

Registry No.—4-Azulylacetic acid, 26157-13-1; azulene-1,2-dicarboxylic acid, 34906-10-0.

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Intermolecular Aromatic Substitution by Aryl Nitrenes

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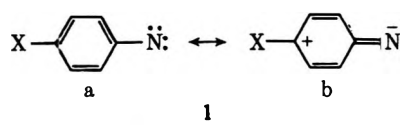
Thermally generated aryl nitrenes have been shown to undergo intermolecular aromatic substitutions provided that the nitrene is made sufficiently electrophilic by the introduction of an electron-withdrawing substituent in the aromatic nucleus and the aromatic substrate is sufficiently nucleophilic. The nitrenes were generated both by the thermolysis of aryl azides and from monomeric nitrosobenzenes and triethyl phosphite. The rate of first-order decomposition of *p*-cyanophenyl azide was found to be independent of the presence of *N*,*N*-dimethylaniline or of its concentration. The formation of a number of by-products is discussed.

The intermediacy of nitrenes in the thermolysis and photolysis of aryl azides is well documented.[1-3] Evidence for the involvement of nitrenes in deoxygenation reactions of nitro and nitroso compounds[4] is good in some cases but more tenuous in others, and depends largely upon analogy of the products of these reactions with those of the corresponding azide reactions. In particular, aryl nitrenes (or their rearrangement products) generated by thermolysis or photolysis of aryl azides or by deoxygenation of nitroso compounds have been trapped by nucleophiles, such as aniline,[5] diethylamine,[6] and carbon monoxide.[7]

Singlet aryl nitrenes generated thermally drop readily to the triplet ground state, so that these species can exhibit reactions typical of both singlet (intramolecular substitution[1] and rearrangement[2]) and triplet states (C–H insertion and hydrogen abstraction[8]). Intramolecular electrophilic aromatic substitution has been extensively studied; the thermal[1] and photolytic[2,9] conversion of *o*-azidobiphenyls to carbazoles involves free nitrenes except in those cases where there is a phenylazo, nitro, acetyl, or benzoyl group ortho to the azido function. Kinetic studies have indicated that there is a concerted loss of nitrogen and cyclization in these cases.[10] Cadogan and Todd[11] have cyclized a number of substituted *o*-nitrobiphenyls to carbazoles with phosphorus reagents. Nitrenes appeared to be involved, but the possibility of a concerted loss of phosphate could not be ruled out, though easy cyclization onto both electron-rich and electron-poor rings make this last rather unlikely. Products of intramolecular aromatic substitution have also been observed from the thermolysis of *o*-azidodiphenyl sulfides,[12] and the deoxygenation of *o*-nitro-*N*-acetyldiphenylamines.[13]

In contrast to the ready intramolecular aromatic substitutions by aryl nitrenes, the corresponding intermolecular reactions are relatively unknown. The decomposition of phenyl azide in aromatic solvents did not yield any diphenylamines. In benzene, only azobenzene and aniline were formed[14] even when 1000-fold excess of benzene was present.[15] On the other hand, intermolecular attack of an aromatic nucleus by ethoxycarbonyl-,[16] cyano-,[17] and sulfonylnitrenes[18] is well known. The absence of intermolecular aromatic substitution by aryl nitrenes could be attributed to rapid decay of the thermally generated singlet nitrene to the triplet[8] before substitution could take place, but could also be due to the possibility that, unlike the above nitrenes, phenylnitrene was insufficiently electrophilic to substitute into benzene. If the latter is true, then it should be possible to increase the electrophilic character of the aryl nitrene by the introduction of electron-withdrawing substituents into the aromatic ring, which would have the effect of decreasing the contribution of **1b** to the structure of the singlet



a b

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(18) R. A. Abramovitch and R. G. Sutherland, *Fortschr. Chem. Forsch.*, **16** (1), 1 (1970).

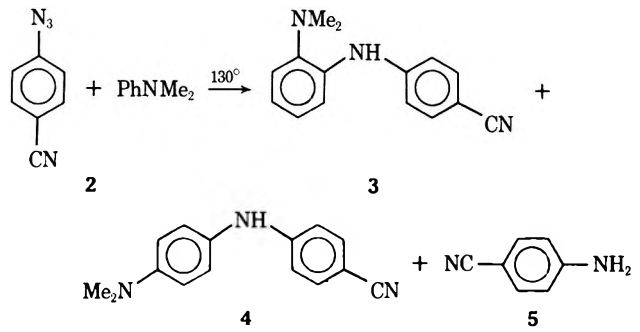
TABLE I
THERMOLYSIS OF ARYL AZIDES IN AROMATIC SOLVENTS

Azide	Registry no.	Solvent	Products, % Ortho substitution	Para substitution	Azo	Amine	Other
p-CN		Benzene			25.2	4.9	
p-CN		Anisole			2.4	18.1	
p-CN		*p*-Dimethoxybenzene			3.4	41.0	
p-CN		1,3,5-Trimethoxybenzene	19.2		2.0	13.6	
p-CN		*N,N*-Dimethylaniline	25.1	3.4		20.3	
p-CN		Mesitylene	13.2			16.4	23.0[a]
p-NO_2	1516-60-5	*N,N*-Dimethylaniline	13.5	Trace	1.0	18.3	23.7[b]
p-NO_2		1,3,5-Trimethoxybenzene	18.9			16.8	3.4[c]
p-CF_3	5586-13-0	*N,N*-Dimethylaniline	13.4			Trace	9.0[b]
o-CN	31656-77-6	1,3,5-Trimethoxybenzene	38.6			4.0	
m-CN	31656-78-7	1,3,5-Trimethoxybenzene	8.4			7.3	

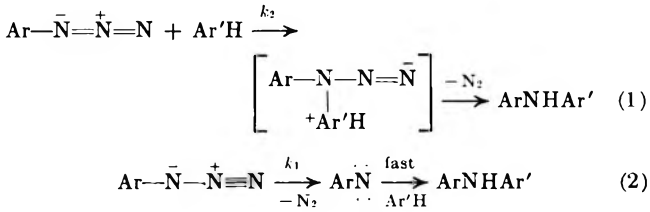
[a] 3,3′5,5′-Tetramethylbibenzyl. [b] 4,4′-Methylenebis(*N,N*-dimethylaniline). [c] 2,4,6-Trimethoxy-4′-nitrobiphenyl.

nitrene **1**. This, indeed, has now been found to be the case.

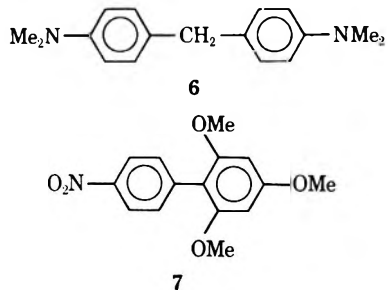
Thermolysis of *p*-cyano-, *p*-nitro-, or *p*-trifluoromethylphenyl azide in benzene at 140° gave no products of intermolecular aromatic substitution, the only compounds isolated being the azo compound and the primary amine, both probably arising from the triplet aryl nitrene. Similarly, no diphenylamines were obtained by the triethyl phosphite deoxygenation of the corresponding nitrosobenzenes in benzene. Thermolysis of *p*-cyanophenyl azide (**2**) in the more nucleophilic anisole and *p*-dimethoxybenzene also failed to reveal any aromatic substitution products. On the other hand, when **2** was decomposed in *N,N*-dimethylaniline, mesitylene, or *sym*-trimethoxybenzene the desired diphenylamines were obtained. Thus, **2** and *N,N*-dimethylaniline yielded a mixture of 4-cyano-2′- (**3**) (25.1%) and 4-cyano-4′-(*N,N*-dimethylamino)diphenylamine (**4**) (3.4%), together with the hydrogen-abstraction product **5** (20.3%). The orientation of the diphenylamines was assigned on the basis of their infrared and nmr spectra and confirmed by unambiguous synthesis from *N,N*-dimethyl-*o*- and -*p*-phenylenediamine and the appropriate aryl halide. The decomposition of *p*-nitrophenyl and *p*-trifluoromethylphenyl azide in dimethylaniline and *sym*-trimethoxybenzene also gave the products of intermolecular aromatic substitution. The results are summarized in Table I.



The possibility had to be considered that, since aromatic substitution was only observed between highly nucleophilic substrate and an aryl azide bearing an electron-attracting group, a change of mechanism—from the stepwise nitrene intermediate mechanism (eq 2) to a concerted nucleophilic attack (say by the tertiary amine nitrogen) on the azide followed by nitrogen elimination (eq 1)—had occurred to account for the formation of the substitution products. This was discounted readily by studying the kinetics of the decomposition of *p*-cyanophenyl azide in chlorobenzene solution at 132° in the presence of varying amounts of *N,N*-dimethylaniline (from none to a fivefold excess over azide concentration) which showed that the rate of the first-order decomposition of the azide was unaffected by the presence of the amine, thus confirming the partial mechanism given in eq 2.



From the decomposition of **2** in mesitylene (as in all other cases as well) the hydrogen-abstraction product **5** was isolated. In addition 3,3′,5,5′-tetramethylbibenzyl was obtained in 23% yield. This undoubtedly arises by hydrogen abstraction by the triplet aryl nitrene to give a benzyl radical which dimerizes. In both the decompositions of *p*-nitrophenyl azide and *p*-trifluoromethylphenyl azide in *N,N*-dimethylaniline, 4,4′-methylenebis(*N,N*-dimethylaniline) (**6**) was obtained. The same product has been obtained from the decomposition of benzenesulfonyl azide in dimethylaniline,[19] and it has been suggested that it arises from formaldehyde (formed during aqueous work-up) and the aniline.[20]



(19) T. Curtius and J. Rissoni, *J. Prakt. Chem.*, **125**, 311 (1930).
(20) D. S. Breslow in "Nitrenes," W. Lwowski, Ed., Interscience, New York, N. Y., 1970, p 276.

TABLE II

DEOXYGENATION OF NITROSOBENZENES IN AROMATIC SOLVENTS

Registry no.	Nitrosobenzene	Solvent	Products, %: Ortho substitution	Para substitution	Azoxy	Amine	Other
31125-07-2	p-CN	*N*,*N*-Dimethylaniline	17.5	7.6	16.8	6.9	2.4[a]
		Anisole			26.6	7.6	
		Mesitylene			40.0	2.6	
		1,3,5-Trimethoxybenzene	2.5		40.0	4.2	
4485-08-9	p-NO_2	*N*,*N*-Dimethylaniline	19.7	6.1	2.8	5.7	
		Mesitylene			51.0	13.4	
34913-26-3	p-CF_3	*N*,*N*-Dimethylaniline	6.2	4.3	16.0		1.5[b]
		Mesitylene			30.6		

[a] 4,4'-Dicyanoazobenzene. [b] 4,4'-Ditrifluoromethylazobenzene.

$$PhSO_2N_3 + Me_2NPh \longrightarrow PhSO_2NHCH_2N(CH_3)Ph \xrightarrow{H_2O} PhSO_2NH_2 + HCHO + PhNHMe$$

$$2PhNMe_2 + HCHO \longrightarrow \mathbf{6}$$

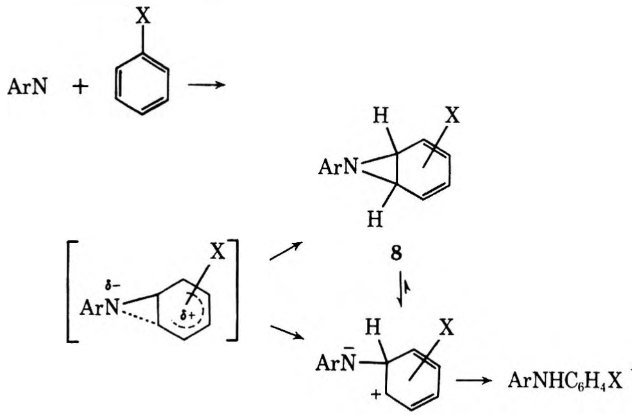
In the present case no aqueous work-up was used so that either formaldehyde was formed by the accidental intrusion of atmospheric moisture or a formaldehyde precursor, *e.g.*, $PhN(Me)CH_2\cdot$, was the active condensing agent.

The decomposition of p-nitrophenyl azide in 1,3,5-trimethoxybenzene gave, in addition to substitution and hydrogen-abstraction products, a small amount (3.4%) of 2,4,6-trimethoxy-4'-nitrobiphenyl (**7**). It seems likely that **7** arises from the homolytic cleavage of $p\text{-}NO_2C_6H_4N_3 \rightarrow p\text{-}NO_2C_6H_4\cdot + N_3\cdot$, followed by arylation of the *sym*-trimethoxybenzene by the p-nitrophenyl radical. There is some precedent for the homolysis of C–N_3 bonds. Thus, thermolysis of ferrocenyl azide in benzene gave ferrocene and phenylferrocene together with nitrene products.[21] Similarly, cleavage of the C–N bond in tertiary alkyl azides has been reported on photolysis[22] and thermolysis.[23]

Similar results have been obtained by generation of the aryl nitrene from the corresponding nitrosobenzene and triethyl phosphite in nucleophilic aromatic solvents (Table II). In dimethylaniline and 1,3,5-trimethoxybenzene the nitrosobenzene appears to be mainly monomeric, but in mesitylene the solutions are a light yellow, indicating that the nitroso dimer is present. This would account for the fact that, unlike the thermolysis of **2** in mesitylene, deoxygenation of p-cyanonitrosobenzene (and of the other nitroso compounds) in that solvent does not give any diphenylamine derivative, the major product being the azoxy compound. The latter probably arises from the deoxygenation of the nitroso dimer in these cases, though in those examples where the monomeric nitroso compound exists in solution it can arise by a trapping of the aryl nitrene by the nitrosobenzene.[24] Some azo compound is also formed in some of the reactions in which substitution is observed, while the primary amine hydrogen abstraction product is obtained in most cases, except with p-trifluoromethylnitrosobenzene. As expected, the nitroso function in p-nitronitrosobenzene is deoxygenated much more readily than is the nitro group.

The main question remaining to be answered is that of the mechanism of formation of the substitution products. Two pathways appear possible for the intermolecular attack of an aromatic nucleus by an aryl nitrene.

Reaction *via* the benzaziridine intermediate **8** would



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be analogous to the behavior of sulfonyl-,[18] ethoxycarbonyl-,[16] and cyanonitrene,[17] and would readily account for the preferred ortho/para orientation observed. On the other hand, no *N*-arylazepines, which could arise by an electrocyclic ring opening of **8**, were observed in this work, but this could be due to thermodynamic control obtaining and favoring ring opening to **9** with irreversible formation of the diarylamine. It is not possible to decide between the alternative pathways on the basis of the present results.

A comment may be appropriate concerning the predominant (if not exclusive) ortho substitution in the reactions of the aryl nitrenes (generated from the azides) and dimethylaniline. This could either be due to the reaction proceeding by one of the above routes, with attack at C_2 (or upon the C_1–C_2 or C_2–C_3 double bond) being favored over attack at C_4 (or at the C_3–C_4 double bond), as is the case, say with phenylsulfonylnitrene and anisole,[25] or the nitrene once formed could attack the tertiary nitrogen atom to form an ylide **10**

$$Ar\ddot{N} + PhNMe_2 \longrightarrow Ar\bar{N}\text{—}\overset{+}{N}(Me)_2Ph\ (\mathbf{10}) \longrightarrow o\text{-} + p\text{-}ArNHC_6H_4NMe_2$$

(21) R. A. Abramovitch, C. I. Azogu, and R. G. Sutherland, *Chem. Commun.*, 134 (1971).

(22) F. D. Lewis and W. H. Saunders, *J. Amer. Chem. Soc.*, **90**, 3828 (1968).

(23) R. A. Abramovitch and E. P. Kyba, *Chem. Commun.*, 265 (1969).

(24) J. H. Boyer and G. J. Mikol, *ibid.*, 734 (1969); R. A. Abramovitch and S. R. Challand, unpublished results.

(25) J. F. Heacock and M. T. Edmison, *J. Amer. Chem. Soc.*, **82**, 3460 (1960).

which could then rearrange thermally to give mainly the ortho-substituted aminodiphenylamine.

Such an attack by a nitrene at an aniline nitrogen atom has been observed with carbethoxynitrene[26] and cyanonitrene,[27] and at a pyridine nitrogen atom by a sulfonylnitrene.[28] The isomer ratio observed with aryl nitrene generated by deoxygenation of the nitrosobenzene at low temperatures is appreciably different, with much more para isomer being formed (Table II). This could be accommodated in an addition–ring-opening pathway in which the azepine (formed under kinetic control) leading (under thermodynamic control) to the *p*-phenylenediamine was less stable at higher temperatures than that leading to the ortho isomer, and went to by-product more readily. On the other hand, the ratio of products observed could just be a reflection of the effect of temperature upon the relative rates of the two substitution processes.

A comparison of the percentage of substitution of 1,3,5-trimethoxybenzene as a function of the position of the nitrile group in the three cyanophenylnitrenes indicated (Table I) that, as expected, the most electrophilic species, *o*-CNC_6H_4N, gives most substitution, while the meta isomer gives the least.

After our work on the aryl azide decomposition was completed, Huisgen and von Fraunberg[29] reported intramolecular aromatic substitutions by 2-pyridyl- and 4,6-dimethyl-2-pyrimidylnitrene into activated substrates. Their results fit well with the concept of the electrophilicity requirement for aryl nitrenes to undergo such reaction.

Experimental Section

General.—Melting points are uncorrected. Infrared spectra were determined on a Perkin-Elmer 257 spectrophotometer. Nmr spectra were measured on a Varian HA-100 spectrometer, and mass spectra were determined at 70 eV on a CEC 21-104 mass spectrometer. For column chromatography, Alcoa chromatographic alumina F-20 was used, and Merck silica gel PF_{254} was used for thin layer chromatography. Light petroleum ether refers to the fraction of bp 30–60°.

Starting Materials.—Azides were synthesized from the corresponding amine by diazotization, followed by treatment of the diazonium salt with sodium azide. Thus prepared were *p*-azidobenzonitrile, mp 70° (lit.[30] mp 70°), *m*-azidobenzonitrile, mp 57–58° (lit.[31] mp 57°), *o*-azidobenzonitrile, mp 55° (lit.[32] mp 58°), *p*-nitrophenylazide, mp 71–72° (lit.[33] mp 74°), and *p*-trifluoromethylphenyl azide, bp 66° (15 mm), n_D 1.4850 (lit.[34] n_D 1.4870). *p*-Nitrosobenzonitrile, mp 136–137°, was prepared by Caro's acid oxidation of *p*-aminobenzonitrile according to the method of Ashley and Berg.[35] Similarly prepared were *p*-nitrosonitrobenzene, mp 119–120° (lit.[36] mp 118–119°), and ***p*-trifluoromethylnitrosobenzene**, mp 51–53° (sublimed *in vacuo*).

Anal. Calcd for $C_7H_4F_3NO$: C, 48.00; H, 3.28. Found: C, 47.85; H, 2.34.

4-Cyano-2′-*N*,*N*-dimethylaminodiphenylamine.—*N*,*N*-Dimethyl-*o*-phenylenediamine (0.61 g), *p*-bromobenzonitrile (1.82 g), potassium carbonate (1.38 g), and powdered copper (100 mg) were intimately mixed and heated at 140° for 36 hr. The cooled residue was extracted with chloroform and purified by chromatography on alumina and elution with benzene. The product (0.20 g, 19%), mp 123°, was recrystallized from light petroleum ether–chloroform: ir (KBr) 3355 (NH), 2200 (C≡N), 760 cm^{-1}; nmr ($CDCl_3$) δ 7.48 (d, J = 8 Hz, 2 H), 7.11 (d, J = 8 Hz, 2 H), 7.44–6.96 (m, 4 H), 6.78 (b s, 1 H, exchanges with D_2O), 2.47 (s, 6 H); mass spectrum *m/e* (rel intensity) 237 (100), 222 (47), 206 (24), 205 (64), 133 (17), 121 (18), 119 (25), 94 (15), 92 (20), 91 (17), 77 (22), 69 (17), 65 (23).

Anal. Calcd for $C_{15}H_{15}N_3$: C, 75.95; H, 6.34. Found: C, 75.82; H, 6.52.

The following diphenylamines were prepared similarly.

4-Cyano-4′-*N*,*N*-dimethylaminodiphenylamine (6%) had mp 164–165° (from light petroleum ether–chloroform); ir (KBr) 3313 (NH), 2216 (C≡N), 818, 803 cm^{-1}; nmr ($CDCl_3$) δ 7.40 (d, J = 9 Hz, 2 H), 7.10 (d, J = 9 Hz, 2 H), 6.76 (d, J = 9 Hz, 4 H), 5.93 (b s, 1 H, exchanges with D_2O), 3.98 (s, 6 H); mass spectrum *m/e* (rel intensity) 237 (100), 236 (23), 222 (43), 221 (18), 192 (17), 118 (39), 65 (16).

Anal. Calcd for $C_{15}H_{15}N_3$: C, 75.95; H, 6.34. Found: C, 75.93; H, 6.64.

2-(*N*,*N*-Dimethylamino)-4′-trifluoromethyldiphenylamine (7%) had mp 48–49° (from hexane); ir (KBr) 3350 (NH), 1325 (CF), 840, 765 cm^{-1}; nmr ($CDCl_3$) δ 7.43 (d, J = 9 Hz, 2 H), 7.08 (d, J = 9 Hz, 2 H), 7.35–6.85 (m, 4 H), 6.65 (b s, 1 H, exchanges with D_2O), 2.61 (s, 6 H); mass spectrum *m/e* (rel intensity) 280 (100), 265 (28), 248 (40), 196 (20), 180 (22), 133 (14), 119 (19), 92 (13), 91 (14), 77 (20). 65 (17), 44 (22), 42 (18).

Anal. Calcd for $C_{15}H_{15}F_3N_2$: C, 64.28; H, 5.36. Found: C, 63.95; H, 5.51.

4-(*N*,*N*-Dimethylamino)-4′-trifluoromethyldiphenylamine (5%) had mp 112–114° (from light petroleum ether); ir (KBr) 3400 (NH), 1324 (CF), 830 cm^{-1}; mass spectrum *m/e* (rel intensity) 280 (62), 279 (12), 265 (20), 235 (4), 140 (5), 125 (5), 87 (12), 85 (73), 83 (100), 47 (37).

Anal. Calcd for $C_{15}H_{15}F_3N_2$: C, 64.28; H, 5.36. Found: C, 64.54; H, 5.48.

4,4′-Bis(trifluoromethyl)azobenzene.—4,4′-Bis(trifluoromethyl)azoxybenzene (1.0 g) (from the performic acid oxidation of *p*-$CF_3C_6H_4NH_2$) and triethyl phosphite (0.5 g) were heated at 160–170° for 18 hr, after which the mixture was cooled and chromatographed on silica gel (10 × 4 cm). Elution with benzene–light petroleum ether (3:1, v/v) gave **4,4′-bis(trifluoromethyl)azobenzene** (0.79 g, 83%): mp 101–102° (light petroleum ether); ir (KBr) 1609, 1320, 1170–1100, 1061, 852 cm^{-1}; mass spectrum *m/e* (rel intensity)) 318 (19), 299 (8), 173 (20), 145 (100).

Anal. Calcd for $C_{14}H_8F_6N$: C, 52.84; H, 2.52. Found: C, 52.84; H, 2.57.

Thermolysis of *p*-Azidobenzonitrile in *N*,*N*-Dimethylaniline.—*p*-Azidobenzonitrile (0.5 g) was heated in *N*,*N*-dimethylaniline (10 ml) at 130° for 48 hr under nitrogen. The reaction mixture was chromatographed on alumina (30 × 3 cm). Elution with light petroleum ether gave *N*,*N*-dimethylaniline. Elution with benzene gave *p*-azidobenzonitrile (80 mg, 15%), mp 67° (from water) (lit.[29] mp 70°). Elution with ether–benzene (1:3, v/v) gave 4-cyano-2′-(*N*,*N*-dimethylamino)diphenylamine (180 mg, 25.1%), mp 123° (from light petroleum ether), ir (KBr) 3355 (NH), 2200 (C≡N), 760 cm^{-1}, identical with an authentic sample. Elution with ether–benzene (3:1, v/v) gave 4-cyano-4′-(*N*,*N*-dimethylamino)diphenylamine (24 mg, 3.4%), mp 163–164° (from EtOH), ir (KBr) 3325 (NH), 2200 (C≡N), 810, 800 cm^{-1}, identical with an authentic sample. Elution with ether gave *p*-aminobenzonitrile (144 mg, 20.3%), mp 86–87° (from water) (lit.[37] mp 86°).

Thermolysis of *p*-Azidobenzonitrile in *sym*-Trimethoxybenzene.—*p*-Azidobenzonitrile (0.5 g) was heated in *sym*-trimethoxybenzene (3 g) at 130° for 50 hr under nitrogen. The reaction mixture was chromatographed on alumina (30 × 3 cm). Light petroleum ether–benzene (1:3, v/v) gave *sym*-trimethoxybenzene. Elution with benzene gave *p*-azidobenzonitrile (43 mg, 8.5%), mp 67–70° (from water). Elution with ether–benzene (1:3, v/v) gave 4,4′-dicyanoazobenzene (7 mg, 2.3%), mp 272° (from EtOH) (lit.[38] mp 270°). Elution with ether–benzene

(26) K. Hafner, D. Zinser, and K. L. Moritz, *Tetrahedron Lett.*, 1733 (1964).
(27) A. G. Anastassiou, H. E. Simmons, and F. D. Marsh in "Nitrenes," W. Lwowski, Ed., Interscience, New York, N. Y., 1970, p 343.
(28) J. N. Ashley, G. L. Buchanan, and A. P. T. Eason, *J. Chem. Soc.*, 60 (1947); P. K. Datta, *J. Indian Chem. Soc.*, **24**, 109 (1947); R. A. Abramovitch and T. Takaya, *J. Org. Chem.*, **37**, 2022 (1972).
(29) R. Huisgen and K. von Fraunberg, *Tetrahedron Lett.*, 2595 (1969).
(30) H. Rupe and K. v. Majewski, *Ber.*, **33**, 3406 (1900).
(31) P. Griess, *ibid.*, **2**, 370 (1869).
(32) M. O. Forster and H. M. Judd, *J. Chem. Soc.*, 252 (1910).
(33) E. Noelting and O. Michel, *Ber.*, **26**, 86 (1893).
(34) A. V. Kirsanov, *Zh. Obshch. Khim.*, **36**, 1248 (1966).
(35) J. N. Ashley and S. S. Berg, *J. Chem. Soc.*, 3089 (1957).
(36) E. Bamberger and R. Hübner, *Ber.*, **36**, 3803 (1903).
(37) M. T. Bogert and E. Wise, *J. Amer. Chem. Soc.*, **34**, 693 (1912).
(38) J. N. Ashley, H. J. Barber, A. J. Ewins, G. Newberry, and A. P. H. Self, *J. Chem. Soc.*, 103 (1942).

(3:1, v/v) gave **4-cyano-2',4',6'-trimethoxydiphenylamine** (176 mg, 19.2%): mp 159° (from EtOH); ir (KBr) 3325 (NH), 2205 (C≡N), 840 cm^{-1}; nmr ($CDCl_3$) δ 7.38 (d, J = 8 Hz, 2 H), 6.57 (d, J = 8 Hz, 2 H), 6.22 (s, 2 H), 3.84 (s, 3 H), 3.79 (s, 6 H); mass spectrum m/e (rel intensity) 284 (100), 269 (54), 241 (32), 226 (15), 142 (20), 69 (12).

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.60; H, 5.63. Found: C, 67.65; H, 5.87.

Further elution with ether gave *p*-aminobenzonitrile (56 mg, 13.6%), mp 86°.

Similar reaction conditions were used in the thermolyses of *p*-$N_3C_6H_4CN$ in *p*-dimethoxybenzene and in mesitylene (see below).

Thermolysis of *p*-Azidobenzonitrile in *p*-Dimethoxybenzene.—Chromatography of the reaction mixture gave 4,4'-dicyanoazobenzene (5.4%), mp 265° (from EtOH), and *p*-aminobenzonitrile (41%), mp 84°.

Thermolysis of *p*-Azidobenzonitrile in Mesitylene.—Chromatography of the reaction mixture over alumina gave 3,3'5,5'-tetramethylbibenzyl (23%), mp 70° (from EtOH) (lit.[39] mp 72°), and **4-cyano-2',4',6'-trimethyldiphenylamine** (13.2%): bp 175–180° (0.5 mm); ir (film) 3360 (NH), 2215 (C≡N), 830 cm^{-1}; nmr (CCl_4) δ 7.34 (d, J = 8 Hz, 2 H), 6.80 (b s, 2 H), 6.46 (d, J = 8 Hz, 2 H), 4.19 (b s, 1 H, exchanges with D_2O), 2.24 (s, 6 H), 2.09 (s, 3 H); mass spectrum m/e (rel intensity) 236 (1.1), 152 (3.3), 148 (2.9), 133 (4.1), 119 (26), 118 (100), 113 (12), 91 (63), 90 (13), 81 (21), 65 (17), 63 (17), 55 (17), 43 (50).

Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.26; H, 6.79. Found: C, 81.15; H, 6.96.

Further elution gave *p*-aminobenzonitrile (25.2%), mp 86°.

Thermolysis of *p*-Azidobenzonitrile in Benzene.—*p*-Azidobenzonitrile (0.5 g) was heated in a bomb in benzene (10 ml) at 140° for 45 hr. Only 4,4'-dicyanoazobenzene (75 mg, 25.2%), mp 268–270°, and *p*-aminobenzonitrile (20 mg, 4.9%), mp 85–87°, were detected.

Deoxygenation of *p*-Nitrosobenzonitrile in *N,N*-Dimethylaniline.—Triethyl phosphite (435 mg) in *N,N*-dimethylaniline (5 ml) was added dropwise at 0° to a stirred solution of *p*-nitrosobenzonitrile (346 mg) in *N,N*-dimethylaniline (15 ml). After 30 min the mixture was diluted with light petroleum ether and chromatographed on alumina (20 × 5 cm). Elution with light petroleum ether gave *N,N*-dimethylaniline. Benzene–light petroleum ether (3:1, v/v) eluted 4-cyano-2'-(*N,N*-dimethylamino)diphenylamine (104 mg, 17.5%), mp 121° (from light petroleum ether). Elution with benzene gave 4,4'-dicyanoazobenzene (7 mg, 2.4%), mp 271–274°. Further elution with benzene gave 4,4'-dicyanoazoxybenzene (53 mg, 16.8%), mp 226–228° (from $CHCl_3$) (lit.[35] mp 228°), and 4-cyano-4'-(*N,N*-dimethylaminodiphenylamine (46 mg, 7.6%), mp 159–162°. Elution with ether–benzene (1:4, v/v) gave *p*-aminobenzonitrile (21 mg, 6.9%).

Similar reaction conditions were used in the deoxygenation of *p*-nitrosonitrobenzene and *p*-nitrosotrifluoromethylbenzene in dimethylaniline (see below).

Thermolysis of *p*-Azidonitrobenzene in *N,N*-Dimethylaniline.—The following were isolated by chromatography of the reaction mixture: *p*-azidonitrobenzene (2.5%), mp 71–73°; 4,4'-bis(*N,N*-dimethylamino)diphenylmethane (23.7%), mp 90° (from light petroleum ether, bp 60–110°) (lit.[40] mp 90°); 4,4'-dinitroazobenzene (1.0%), mp 223–225° (from light petroleum ether, bp 60–110°) (lit.[35] mp 222–223°); **2-(*N,N*-dimethylamino)-4'-nitrodiphenylamine** (13.5%): mp 121° (from $CHCl_3$); ir (KBr) 3315 (NH), 752 cm^{-1}; nmr ($CDCl_3$) δ 8.04 (d, J = 9 Hz, 2 H), 7.30 (m, 1 H), 6.97 (m, 6 H), 2.59 (s, 6 H); mass spectrum m/e (rel intensity) 257 (100), 242 (20), 196 (23), 195 (29), 181 (17), 180 (23), 179 (20), 133 (15), 77 (16).

Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.37; H, 5.84. Found: C, 65.47; H, 5.86.

Elution with ether–benzene (3:1, v/v) gave *p*-nitroaniline (18.3%), mp 145–147°.

Thermolysis of *p*-Azidonitrobenzene in *sym*-Trimethoxybenzene.—*p*-Azidonitrobenzene (1.0 g) in *sym*-trimethoxybenzene (6.0 g) was heated at 130° for 50 hr under nitrogen. The reaction mixture was chromatographed on alumina. Elution with benzene gave *sym*-trimethoxybenzene. Elution with ether–benzene (1:3, v/v) gave **4-nitro-2',4',6'-trimethoxybiphenyl** (60 mg, 3.4%): mp 170° (from EtOH); ir (KBr) 1590, 1490, 1320, 850 cm^{-1}; nmr ($CDCl_3$) δ 8.27 (d, J = 9 Hz, 2 H), 7.56 (d, J = 9 Hz, 2 H), 6.29 (s, 2 H), 3.93 (s, 3 H), 3.80 (s, 6 H); mass spectrum m/e (rel intensity) 288 (15), 287 (100), 227 (13), 212 (8), 113 (7).

Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.19. Found: C, 62.37; H, 5.38.

Elution with ether–benzene (3:1, v/v) gave **4-nitro-2,'4',6'-trimethoxydiphenylamine** (350 mg, 18.9%): mp 145° (from light petroleum ether); ir 3380 (NH), 1580, 1490, 1375, 835 cm^{-1}; nmr ($CDCl_3$) δ 7.97 (d, J = 9 Hz, 2 H), 6.47 (d, J = 9 Hz, 2 H), 6.18 (s, 2 H), 5.87 (b s, 1 H, exchanges with D_2O), 3.81 (s, 3 H), 3.75 (s, 6 H); mass spectrum m/e (rel intensity) 305 (19), 304 (100), 288 (32), 261 (18), 243 (22).

Anal. Calcd for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.26. Found: C, 59.28; H, 5.36.

Elution with ether gave *p*-nitroaniline (50 mg, 16.8%).

Deoxygenation of *p*-Nitrosonitrobenzene in *N,N*-Dimethylaniline.—Chromatography of the reaction mixture gave 4,4'-dinitroazoxybenzene (2.8%), mp 190–191° (lit.[41] mp 193°); 2-(*N,N*-dimethylamino)-4'-nitrodiphenylamine (19.7%), mp 119° (from $CHCl_3$) undepressed on admixture with an authentic sample; 4-(*N,N*-dimethylamino)-4'-nitrodiphenylamine (6.1%), mp 148–150° (from $CHCl_3$) (lit.[42] 152°); and *p*-nitroaniline (5.7%).

Deoxygenation of *p*-Nitrosotrifluoromethylbenzene in *N,N*-Dimethylaniline.—The reaction mixture was chromatographed over silica gel (25 × 5 cm). Elution with light petroleum ether gave *N,N*-dimethylaniline and three other compounds as an unresolved mixture. The *N,N*-dimethylaniline was evaporated under reduced pressure and the residue was subjected to preparative tlc. Elution with benzene–light petroleum ether (1:3, v/v) gave 4,4'-bis(trifluoromethyl)azobenzene (1.5%), mp 101–102° (light petroleum ether), identical with an authentic sample; and **4,4'-bis(trifluoromethyl)azoxybenzene** (16.0%): mp 106–108° (from light petroleum); ir (KBr) 1611, 1320, 1160–1100, 849 cm^{-1}; mass spectrum m/e (rel intensity) 334 (25), 318 (13), 299 (5), 173 (19), 145 (100).

Anal. Calcd for $C_{14}H_8F_6N_2O$: C, 50.30; H, 2.40. Found: C, 50.62; H, 2.55.

Further elution gave 2-(*N,N*-dimethylamino)-4'-trifluoromethyldiphenylamine (6.2%), mp 46–48°, ir (NaCl) 3358, 1328, 760 cm^{-1}, identical with an authentic sample.

Thermolysis of *o*-Azidobenzonitrile in *sym*-Trimethoxybenzene.—*o*-Azidobenzonitrile (0.5 g) in *sym*-trimethoxybenzene (3 g) was heated at 130° for 60 hr under nitrogen. The reaction mixture was chromatographed on alumina (3 × 35 cm). Elution with benzene gave *sym*-trimethoxybenzene. Elution with ether–benzene (1:3, v/v) gave **2-cyano-2',4',6'-trimethoxydiphenylamine** (380 mg, 38.6%): mp 125–126° (from light petroleum ether); ir (KBr) 3330 (NH), 2215 (C≡N), 1290, 1230, 1210, 1160, 1130, 810, 770, 760 cm^{-1}; nmr ($CDCl_3$), δ 7.74–7.40 (m, 2 H), 6.92 (t, J = 8 Hz, 1 H), 6.62 (d, J = 8 Hz, 1 H), 6.06 (b s, 1 H, exchanges with D_2O), 3.93 (s, 3 H), 3.86 (s, 6 H); mass spectrum m/e (rel intensity) 284 (100), 268 (36), 241 (46), 226 (12), 198 (12), 155 (15), 142 (21), 141 (16), 129 (19), 102 (24), 76 (14), 75 (13), 69 (37), 66 (12), 59 (15), 55 (18), 39 (32).

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.60; H, 5.63. Found: C, 67.67; H, 5.80.

Elution with ether gave *o*-aminobenzonitrile (10 mg, 4.0%), mp 49–50° (lit.[43] mp 51°).

Thermolysis of *m*-Azidobenzonitrile in *sym*-Trimethoxybenzene.—The reaction was carried out as for the ortho isomer to give **3-cyano-2',4',6'-trimethoxydiphenylamine** (8.4%): mp 78–80° (from EtOH); ir (KBr) 3360 (NH), 2230 (C≡N), 1330, 1300, 1230, 1210, 1160, 1130, 790 cm^{-1}; nmr ($CDCl_3$) δ 7.24–6.70 (m, 4 H), 6.19 (s, 2 H), 5.38 (b s, 1 H, exchanges with D_2O), 3.80 (s, 3 H), 3.76 (s, 6 H); mass spectrum m/e (rel intensity) 284 (29), 269 (22), 147 (13), 142 (14), 129 (64), 125 (16), 118 (40), 112 (23), 102 (20), 97 (21), 91 (20), 83 (34), 71 (63), 69

(39) E. Matwui, *J. Soc. Chem. Ind., Jap.*, **45**, 300 (1942); *Chem. Abstr.*, **44**, 7580*d* (1942).

(40) B. R. Brown and A. M. S. White, *J. Chem. Soc.*, 3755 (1957).

(41) E. Bamberger and R. Hübner, *Ber.*, **36**, 3808, 3810 (1903).

(42) G. Modena, *Boll. Sci. Fac. Ind. Bologna*, **17**, 45 (1959); *Chem. Abstr.*, **54**, 12773 (1960).

(43) A. Reissert and F. Grube, *Ber.*, **42**, 3710 (1909).

(55), 57 (100), 55 (71), 43 (79). *m*-Aminobenzonitrile (7.3%), mp 52–54°, mmp 52–54° (lit.[44] mp 53–54°), was also obtained.

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.60; H, 5.63. Found: C, 67.39; H, 5.68.

Kinetics of the Thermal Decomposition of *p*-Azidobenzonitrile in the Presence of *N*,*N*-Dimethylaniline.—*p*-Azidobenzonitrile was thermolyzed in chlorobenzene solution at 132° in the presence of varying amounts of *N*,*N*-dimethylaniline. During the thermolyses, portions were removed at regular intervals with a syringe, diluted fourfold with chlorobenzene, and assayed by measuring the area of the asymmetric azide stretching band in the infrared (2160 and 2110 cm^{-1}). Concentrations of azide were obtained from a previously prepared calibration curve,[45] and rate constants for the disappearance of azide were obtained from the slopes of plots of log [azide] *vs.* time. The results are summarized below.

[*p*-Cyanophenyl azide], *M*	[*N*,*N*-dimethylaniline], *M*	Rate constant ($\times 10^4$), sec^{-1}
0.02		1.47
0.02	0.02	1.47
0.02	0.06	1.70
0.02	0.10	1.48

(44) A. Fricke, *Ber.*, **7**, 1321 (1874).

(45) The variation of the area of this band with concentration deviated from linearity above 0.05 *M*, suggesting possible association of the azide in solution.

Registry No.—**2**, 18523-41-6; **3**, 29547-82-8; **4**, 29547-83-9; **7**, 34915-93-0; 2-(*N*,*N*-dimethylamino)-4′-trifluoromethyldiphenylamine, 29547-88-4; 4-(*N*,*N*-dimethylamino)-4′-trifluoromethyldiphenylamine, 34913-28-5; 4,4′-bis(trifluoromethyl)azobenzene, 34913-29-6; 4-cyano-2′,4′,6′-trimethoxydiphenylamine, 29547-84-0; 4-cyano-2′,4′,6′-trimethyldiphenylamine, 29547-85-1; 2-(*N*,*N*-dimethylamino)-4′-nitrodiphenylamine, 29547-86-2; 4-nitro-2′,4′,6′-trimethoxydiphenylamine, 29547-87-3; 4,4′-bis(trifluoromethyl)azoxybenzene, 34913-34-3; 2-cyano-2′,4′,6′-trimethoxydiphenylamine, 34913-35-4; 3-cyano-2′,4′,6′-trimethoxydiphenylamine, 34913-36-5.

Organic Disulfides and Related Substances. 34. Synthesis and Reactions of Some Substituted Cyclic Disulfides and Corresponding *S*-Oxides[1]

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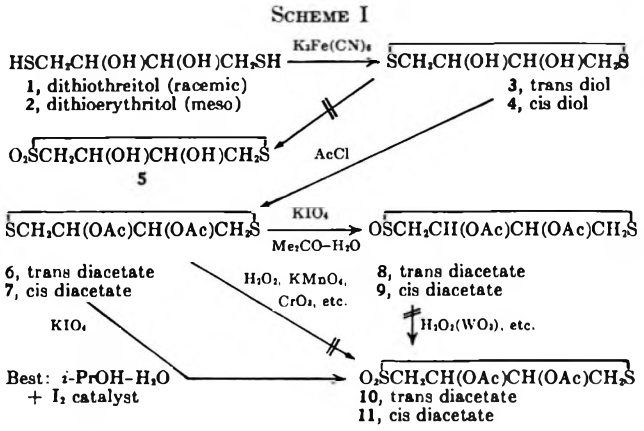
Functionally substituted 1,2-dithianes, 1,2-dithiolanes, and *S*-oxides were sought for study of their properties and reactions and for testing as antiradiation drugs. Oxidation of *trans*- and *cis*-1,2-dithiane-4,5-diol diacetate (**6** and **7**) gave the 1-monoxides **8** and **9**. Oxidation of **6** and **7** to the trans and cis 1,1-dioxides **10** and **11** failed with numerous agents but finally was accomplished using potassium metaperiodate in aqueous 2-propanol with iodine as an effective catalyst as the best means. A thiolate ion cleaved the 1,1-dioxide **10**, giving a disulfide sulfinate (**14**), but amines did not cleave 1,2-dithiane 1,1-dioxide (**12**). Procedures are compared for the synthesis of 1,2-dithiolane-4-carboxylic acid (**16**), and syntheses of some other dithiolanes are discussed.

This paper reports some syntheses and reactions of substituted five- and six-membered cyclic disulfides and of the corresponding *S*-oxides. There were two motivations for the work. One was to permit testing of representative compounds as antiradiation drugs, since *trans*-1,2-dithiane-4,5-diol (**3**) has been said to be active in this respect;[2] such activity would be of considerable interest because most antiradiation drugs contain nitrogen functions that may have much to do with their toxicity. A second motivation was to begin an extension to substituted systems of earlier studies of unsubstituted cyclic disulfides and their *S*-oxides.[3]

In Scheme I, conversion of dithiothreitol (**1**) to *trans*-1,2-dithiane-4,5-diol (**3**) and of dithioerythritol (**2**) to the cis isomer **4** proceeded by standard methods (70–75% yield); recrystallization provided a convenient purification. Although 1,2-dithiane can be oxidized to the 1,1-dioxide by hydrogen peroxide or potassium metaperiodate (KIO_4) in 66–68% yield,[3a] the dihydroxydithiane **3** gave only intractable oil with no indication of the dioxide **5** (ir); cleavage of **3** to sulfonic acids evidently predominated, since the products were strongly acidic, probably complicated by cleavage at the glycol moiety.

SCHEME I



It seemed likely that adverse reactions of the glycol moiety could be prevented by prior acetylation. Both of the diols **3** and **4** have been acetylated by means of acetic anhydride and pyridine but, since the diacetates **6** and **7** were desired for nmr studies, few other details were given.[4] Acetyl chloride gave the trans diacetate **6** and cis diacetate **7** in yields of 74–82% (Scheme I).

Oxidation of the diacetates **6** and **7** to the 1-monoxides **8** and **9** occurred, but oxidation to the 1,1-dioxides

(1) (a) Paper 33: L. Field and Y. H. Khim, *J. Med. Chem.*, **15**, 312 (1972). (b) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DADA17-69-C-9128. (c) We are indebted to Professor H. E. Smith of Vanderbilt University for helpful discussion.

(2) C. Falconi, P. Scotto, and P. De Franciscis, *Boll. Soc. Ital. Biol. Sper.*, **44**, 326 (1968); *Chem. Abstr.*, **69**, 16658 (1968).

(3) (a) L. Field and R. B. Barbee, *J. Org. Chem.*, **34**, 36 (1969); (b) L. Field and R. B. Barbee, *ibid.*, **34**, 1792 (1969).

(4) A. Lüttringhaus, S. Kabuss, W. Maier, and H. Friebolin, *Z. Naturforsch. B*, **16**, 761 (1961).

10 and 11 proved far more difficult than had been anticipated from studies with 1,2-dithiane under similar or less vigorous conditions (*cf.* ref 3a). Thus with the trans diacetate 6, hydrogen peroxide at 25° gave the monoxide 8 (64%), not the expected dioxide 10, and longer times or higher temperatures led only to cleavage into presumed sulfonic acids (the pH dropped to 1–2). Similarly, a large excess of KIO_4 in aqueous acetone gave only 8 (85% yield). Other agents with 6 also gave only cleavage or monoxide 8, with no indication through ir spectra of the dioxide 10; these agents included potassium permanganate in acetone (38% of 8), chromium trioxide in acetone (low yield of 8), *m*-chloroperbenzoic acid, and ceric ammonium nitrate. The monoxide 8 itself was submitted to oxidation but was equally refractory. For example, under conditions that finally were made vigorous enough to destroy most of the 8 (*e.g.*, 5 days at 60°), aqueous KIO_4 led only to cleavage of 8. Use of hydrogen peroxide–tungsten trioxide–sulfuric acid in dioxane–acetic acid, a combination useful for oxidizing another refractory disulfide to a dioxide,[5] also led mainly to cleavage (10% recovery of 8 after 48 hr at 25°, with no indication of 10). With the cis diacetate 7, fewer experiments were done because of the greater expense of 2 but, again, resistance to oxidation seemed marked. With KIO_4, the monoxide 9 was obtained in 80% yield from 7, but various efforts to prepare the dioxide 11 were largely unavailing. On one occasion, KIO_4 in aqueous acetone did convert 7 to the dioxide 11 in 66% yield. The 11 thus could be characterized, but this preparation could not be repeated (see Experimental Section). The conditions required for the one successful preparation of 11 (40°, 50 hr), and particularly the failure of other efforts, seem to contrast sufficiently with those for oxidation of 1,2-dithiane to the dioxide (~25°, 4 days)[3a] to suggest that the cis diacetate 7 parallels the trans diacetate 6 in intransigence.

It is noteworthy that neither the monoxide 8 nor 9 seems to be particularly unstable (the melting point of 8 was unchanged after 20 months). In stability 8 and 9 resemble 2,4,6-triisopropylphenyl 2,4,6-triisopropylbenzenethiolsulfinate, which seems considerably more stable than is usual for thiolsulfinates and which could not be oxidized to the dioxide; the corresponding 2,4,6-triisopropylphenyl disulfide resembled 6 and 7 in resisting oxidation (*cf.* ref 5). These characteristics in the triisopropylphenyl series were attributed to steric factors. The resistance of 6–9 toward oxidation to 1,1-dioxides probably has its explanation in steric or conformational factors also (perhaps, for example, to resistance to a necessary ring inversion of conformers during the two-stage oxidation).

A report that sodium metaperiodate in *methanol* will oxidize a sulfide to a sulfone ultimately proved the key to successful preparation of the 1,1-dioxide 10,[6] and in initial studies 10 was obtained in fairly good yield (60%) by using aqueous 2-propanol as solvent for the reaction of 6 with potassium metaperiodate (80°, 49 hr; the ir peak for –SO– persisted at 30 hr). With aqueous methanol, 6 was oxidized to 10 but in only 28% yield (40 hr); with a short reaction time (3 hr), the yield of 10 was 48%. Potassium metaperiodate rather than the sodium salt was used because it had given better results with 1,2-dithiane.[3a] Nmr, ir, and mass spectra and elemental analyses met expectation for 10.

During the successful oxidation of 6 to 10 in aqueous 2-propanol, the mixture slowly became brown. Loss of the color when the product was washed with aqueous sulfite suggested that iodine was responsible for the color and led to the suspicion that the reaction might have been autocatalytic, with the iodine generated serving as a catalyst. This suspicion was confirmed by estimating the amounts of monoxide 8 and dioxide 10 present as a function of time when increasing amounts of iodine were used (see Experimental Section). The time required for complete loss of ir absorption attributable to the –SO– moiety (and for appearance of that of the $-SO_2-$ moiety) varied with the molar proportion of iodine (in parentheses) as follows: 33 (0), 16 (0.02), 9 (0.04), and 6.5 hr (0.08). Hence I_2 is indeed quite effective as a catalyst. This usefulness of alcohols and iodine under vigorous conditions in a periodate oxidation appears to be an exciting lead. Further exploration of the combination KIO_4–*i*-PrOH–H_2O–I_2 as a tool for oxidizing –S– moieties of both sulfides and disulfides to $-SO_2-$ moieties seems called for, and it seems likely that studies of the mechanism also would lead to rewarding results. When iodine catalysis was used preparatively with potassium metaperiodate to oxidize 6 in *i*-PrOH–MeOH–H_2O, 10 was obtained in a yield of 67% after 7 hr of reflux (0.02 mol of I_2/mol of 6).

Earlier work on the cleavage of 1,2-dithiane 1,1-dioxide (12) by nucleophiles revealed that such "oxodisulfide" cleavages can lead to useful syntheses of disulfides terminated with the moieties $-SO_2^-$, $-SO_3^-$, $-SO_2R$, and $-SO_2SR$.[3b] In further studies of the generality of cleavage, hydride and halide ion cleavages were found to be unpromising in the solvents tried.[1a] Similarly, we have now been unable to see that morpholine or piperidine effect any useful degree of cleavage, even though amines are known to cleave certain acyclic thiolsulfonates.[7] Thus when 12 was heated under reflux in benzene, methylene chloride, or tetrahydrofuran with these amines for 21–24 hr it was recovered quantitatively in each instance; presumably, under the conditions used, the equilibrium constant for cleavage was quite unfavorable (*cf.* ref 7). On the other hand, the sodium salt of 2-acetamidoethanethiol (13) smoothly cleaved the dioxide 10 to give the disulfide sulfinate 14 in 73% yield (eq 1). Nmr and ir spectra are consistent

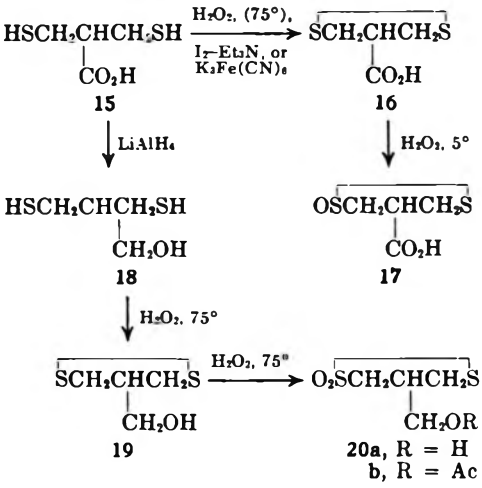
$$\underset{\mathbf{13}}{AcNH(CH_2)_2SH} \xrightarrow{NaOEt} AcNH(CH_2)_2SNa \xrightarrow[-10°]{EtOH\text{-}Me_2CO,\ \mathbf{10}} AcNH(CH_2)_2SSCH_2CH(OAc)CH(OAc)CH_2SO_2Na \quad (1)$$
$$\mathbf{14}$$

with the formulation of product as 14, as is the analogy of a similar reaction with 1,2-dithiane 1,1-dioxide (12).[1a,3b]

Scheme II shows the results of studies with 1,2-dithiolanes. The dithiol 15 was oxidized previously to 1,2-dithiolane-4-carboxylic acid (16) by use of oxygen and ferric chloride (overall yield from β,β′-diiodoiso-

(5) L. Field and T. F. Parsons, *J. Org. Chem.*, **30**, 657 (1965).
(6) L. L. Replogle and J. R. Maynard, *J. Org. Chem.*, **32**, 1909 (1967).
(7) J. E. Dunbar and J. H. Rogers, *J. Org. Chem.*, **31**, 2842 (1966).

SCHEME II



butyric acid, 17%).[8] 1,2-Dithiolane itself has been synthesized in good yield by adding the thiol and hydrogen peroxide simultaneously but separately to acetic acid containing a little KI at 75°,[3a] and use of this procedure with **15** gave **16** in yields of 57–85%. Use of I_2–Et_3N, which often gives good results in cyclization of α,ω-dithiols,[3a,9] led to **16** in 40% yield, and use of potassium ferricyanide, which was effective for synthesis of the dithianes **3** and **4**,[10] gave **16** in 32% yield. We were able to confirm the experience of Lindberg and Bergson in being able to convert the dithiolane **16** to the monoxide **17** (72% yield; 63% reported).[11] Unfortunately, we also confirmed their experience in being unable to obtain the 1,1-dioxide of **16**; the hydrogen peroxide–tungsten trioxide procedure,[5] as well as KIO_4 in H_2O or aqueous 2-propanol (with **16** or its sodium salt), seemed to lead only to cleavage to sulfonic acids (pH ~1–2) and to polymerization.

Lindberg and Bergson succeeded in oxidizing 4,4-bis(hydroxymethyl)-1,2-dithiolane to the 1,1-dioxide by the use of hydrogen peroxide.[11] Although the *gem*-methylol moieties may well have stabilized this dioxide, in common with frequently observed effects of groups on otherwise unstable ring systems, we considered the sequence of **18** → **19** → **20a** worth exploration (Scheme II). The acid **15** therefore was reduced to the carbinol **18** (70% yield), which was oxidized to a liquid that polymerized readily but was presumed from spectra to be largely **19** (~70% yield). Oxidation of a sample of **19** without delay did seem to give a dioxide, but spectra indicated that the product was the acetate **20b** rather than the carbinol **20a** (see Experimental Section); if the assignment of structure **20b** to the product is correct, esterification of **20a** to **20b** is understandable, since reaction of acetic acid used as solvent with the carbinol **20a** could have been catalyzed by sulfonic acids produced by cleavage of the ring. This reaction was not investigated further because it was not very clean and because the yield was low.

Results available thus far for compounds tested as antiradiation drugs are unpromising.[12] Compounds, LD_{50} (mg/kg), doses (mg/kg), per cent of survival of mice after 30 days, and antiradiation ratings, respectively, were as follows: **3**, 450, 250, 0, inactive; **6**, 750, 200, 13 (17-day survival), slight; **8**, 120, 25–50, 7–13, slight.

Experimental Section[13]

Starting Materials.—Commercial dithiothreitol (**1**) and dithioerythritol (**2**) (N. B. C. Research Biochemicals) were used after checking them by ir and nmr, and 2-mercaptomethyl-3-mercaptopropionic acid (**15**) was kindly supplied by Dr. D. L. Klayman of the Walter Reed Army Institute of Research, Washington, D. C. 2-Acetamidoethanethiol (**13**) was prepared as reported.[14]

1,2-Dithiane-4,5-diols, *trans*- (3) and *cis*- (4), were prepared by oxidizing **1** and **2**, respectively, with $K_3Fe(CN)_6$[10] and recrystallizing the products from EtOAc; yield of **3**, 75%, mp 133–134° (lit.[10] mp 132°); yield of **4**, 70%, mp 132–133° (lit.[10] mp 132°).

1,2-Dithiane-4,5-diol Diacetate, *trans*- (6) and *cis*- (7).—Well dried and powdered trans diol **3** (15.0 g, 0.0987 mol) was added slowly to acetyl chloride (23.4 g, 0.298 mol) with good stirring at 0–5°. The mixture boiled spontaneously during the first part of the reaction. After stirring had been continued for 3 hr at ~25°, clear liquid resulted. $CHCl_3$ (200 ml) then was added, and the solution was poured into 100 ml of water containing 200 g of ice. The organic layer was well shaken with 100 ml of iced saturated aqueous Na_2CO_3 solution and then with cold H_2O until it was neutral. It was dried and concentrated to 22.0 g (94%) of oil, which gradually solidified at 0°. Recrystallization by dissolution in Et_2O at 25°, addition of *n*-hexane to incipient turbidity, and chilling at 0° gave 19.0 g (82%) of **6**, mp 43–49°. Further recrystallization from Et_2O gave **6** as white plates: mp 52–53° (lit.[4] mp 54–55°); nmr ($CDCl_3$) δ 2.07 (s, CH_3CO), 3.19–3.03 (m, CH_2), 5.15–4.90 (m, OCH).

Anal. Calcd for $C_8H_{12}O_4S_2$: C, 40.70; H, 5.09; S, 27.18. Found: C, 40.92; H, 5.10; S, 27.35.

Essentially by the same procedure, *cis*-1,2-dithiane-4,5-diol (**4**, 0.65 g, 4.27 mmol) and AcCl (1.00 g, 12.80 mmol) gave the cis diacetate **7** (0.75 g, 74%): mp 73–74° (lit.[4] mp 74–75°); nmr ($CDCl_3$) δ 2.03 (s, CH_3CO), 3.22–2.95 (m, $-CH_2-$), 5.15–4.96 (m, OCH).

***trans*-1,2-Dithiane-4,5-diol Diacetate 1-Monoxide (8). A. *Via* Potassium Metaperiodate (KIO_4).**—The diacetate **6** (10.0 g, 42.4 mmol) in 100 ml of Me_2CO was added to a solution of KIO_4 (40.0 g, 174.0 mmol) in 300 ml of H_2O. After this heterogeneous reaction mixture had been stirred for 5 days, it was heated at 60° for 4 hr and was filtered to remove KIO_4.

The filtrate was concentrated to 100 ml and then extracted with $CHCl_3$ three times. The $CHCl_3$ extract was washed with cold H_2O and concentrated to give 9.1 g (85%) of crude **8**, mp 110–145°. Recrystallization by dissolution in benzene at ~40°, addition of *n*-hexane to incipient turbidity, and standing at 25° overnight, and then further recrystallization from benzene, gave **8** as white plates of constant mp 150–151°: nmr ($CDCl_3$) δ 2.04 (s, CH_3CO), 2.11 (s, CH_3CO), 3.98–2.80 (m, CH_2), 6.02–5.03 (m, CH); ir 1750, 1375, 1250, 1240, 1060 and 1030 cm^{-1}; mass spectrum *m/e* (rel intensity) 43 (100), 70 (45), 84 (45), 112 (35), 132 (8), 150 (4), 172 (6), 252 (3).

(8) L. Schotte and H. Ström, *Acta Chem. Scand.*, **10**, 687 (1956). A referee kindly pointed out a recent modification that affords **16** from **15** in ~90% yield [J. P. Danehy and V. J. Elia, *J. Org. Chem.*, **37**, 369 (1972)].

(9) D. N. Harpp and J. G. Gleason, *J. Org. Chem.*, **35**, 3259 (1970).

(10) W. W. Cleland, *Biochemistry*, **3**, 480 (1964).

(11) B. Lindberg and G. Bergson, *Ark. Kemi*, **23**, 319 (1965).

(12) We are indebted for these results to T. R. Sweeney, D. L. Klayman, and (especially) M. M. Grenan of the Walter Reed Army Institute of Research, Washington, D. C. For details of procedures, see ref 1a and other papers cited therein.

NOTE ADDED IN PROOF.—The two enantiomers of **3** were recently reported to have LD_{50} = 410 and 435 mg/kg and not to be protective at doses of 200–300 mg/kg against 625–750 R of radiation [M. Carmack, C. J. Kelley, S. D. Harrison, Jr., and K. P. DuBois, *J. Med. Chem.*, **15**, 600 (1972)].

(13) Melting points are corrected, and boiling points are uncorrected. Mass spectra were obtained with an LKB Model 9000 instrument operated at 70 eV with a source temperature of 250° and an accelerating potential of 3.5 kV, using the direct-probe inlet; this instrument was obtained through Science Development Program Grant GU-2057 from the National Science Foundation; we are indebted to C. T. Wetter for these spectra. Moist extracts ordinarily were dried over anhydrous $MgSO_4$, and solvent then was removed using a rotating-flask evaporator. The ratios of nmr integrals met expectation and therefore are not reported. Other details were as given in footnote 6 of ref 1a.

(14) R. Kuhn and G. Quadbeck, *Chem. Ber.*, **84**, 844 (1951).

Anal. Calcd for $C_8H_{12}O_5S_2$: C, 38.08; H, 4.77; S, 25.41; mol wt, 252. Found: C, 38.38; H, 4.84; S, 24.98; mol wt, 252 (mass spectrum).

B. *Via* **Hydrogen Peroxide.**—A solution of ~30% H_2O_2 (2.5 mmol) in glacial AcOH (2 ml) was added to **6** (0.44 g, 1.87 mmol) in glacial AcOH (2 ml) with stirring at 25°. Stirring was continued for 3 hr at 25°. After removal of solvent, addition of cold H_2O resulted in white crystals. Filtration gave 0.30 g of **8** (64%), mp 150–151°; the nmr and ir spectra corresponded to those of **8** from **A**.

C. *Via* **Potassium Permanganate.**—A solution of $KMnO_4$ (0.20 g, 1.27 mmol) in Me_2CO (10 ml) was added to **6** (0.100 g, 0.43 mmol) in Me_2CO (5 ml). The mixture was heated under reflux for 5 hr and then was allowed to stand for 10 hr at ~25°. Removal of solvent and extraction of the residue with $CHCl_3$ gave 0.04 g (38%) of **8**, mp 150–151°.

D. *Via* **Chromium Trioxide.**—A solution of CrO_3 (2.1 mmol) in ~8 *N* H_2SO_4 was added to **6** (0.11 g, 0.47 mmol) in Me_2CO (10 ml). The heterogeneous mixture was stirred for 18 hr at ~25° and then was diluted with $CHCl_3$. Insoluble solid was removed, and the $CHCl_3$ layer was washed with cold H_2O, dried, and concentrated, leaving a mixture (0.08 g) of disulfide **6** and monoxide **8**.

cis-**1,2-Dithiane-4,5-diol Diacetate 1-Monoxide** (**9**).—The cis diacetate **7** (0.70 g, 2.96 mmol) in Me_2CO (60 ml) was added to a solution of KIO_4 (3.10 g, 13.5 mmol) in H_2O (120 ml). After this heterogeneous mixture had been stirred for 68 hr at ~25°, the volume was reduced to about 10 ml, and the mixture was extracted with benzene. The extract was dried and evaporated to give **9**, 0.60 g (80%), mp 112–114°. Recrystallization from *n*-hexane and then from benzene gave **9** as white crystals of constant mp 113–114°: nmr ($CDCl_3$) δ 2.11 (s, CH_3CO), 2.21 (s, $-CH_3CO$), 4.20–3.26 (m, $-CH_2-$), 5.93–5.41 (m, OCH); ir 1745, 1370, 1240, 1200, 1065, 1045, 1030 cm^{-1}; mass spectrum *m/e* (rel intensity) 43 (100), 70 (45), 84 (35), 112 (40), 132 (4), 150 (4), 172 (7), 252 (3).

Anal. Calcd for $C_8H_{12}O_5S_2$: C, 38.08; H, 4.77; S, 25.41; mol wt, 252. Found: C, 37.90; H, 4.75; S, 25.80; mol wt, 252 (mass spectrum).

trans-**1,2-Dithiane-4,5-diol Diacetate 1,1-Dioxide** (**10**). **A.** *Via* KIO_4 **in** *i*-**PrOH.**—A solution of the trans diacetate **6** (6.4 g, 27.1 mmol) in *i*-PrOH (500 ml) was added to KIO_4 (18.57 g, 80.6 mmol) in H_2O (140 mmol). After the heterogeneous reaction mixture has been heated at 80–82° for 30 hr with good stirring, a small portion of solution was withdrawn to check for complete oxidation to the dioxide **10** by ir; the monoxide peak at 1060 cm^{-1} still remained. After 49 hr, the mixture had become brown and showed only strong dioxide-peak absorption at 1310 and 1110 cm^{-1}, with no peak at 1060 cm^{-1}. After removal of the *i*-PrOH and H_2O, the residue was extracted with $CHCl_3$ three times. The extract then was washed with 10% aqueous Na_2SO_3 solution to remove I_2. The extract was washed again with H_2O, dried, and evaporated to give **10**, yield 4.4 g (60%), mp 133–139°. Recrystallization from benzene gave **10** as white needles having a constant mp of 140–142°; nmr ($CDCl_3$) δ 2.18 (s, CH_3CO), 2.22 (s, CH_3CO), 3.90–3.51 (m, $-CH_2$), 5.60–5.08 (m, OCH); ir 2980, 1740, 1720, 1360, 1310, 1220, 1110, 1030, 860, 760 cm^{-1}; mass spectrum *m/e* (rel intensity) 43 (100), 84 (33), 101 (8), 148 (3), 208 (1).

Anal. Calcd for $C_8H_{12}O_6S_2$: C, 35.82; H, 4.48; S, 23.85. Found: C, 35.79; H, 4.52; S, 23.68. In another experiment, a 24-hr reflux period led to **10** in 69% yield.

B. *Via* KIO_4 **in MeOH.**—From the reaction of **6** (0.128 g, 0.54 mmol) in 10 ml of MeOH with KIO_4 (0.36 g, 1.56 mmol) in H_2O (3 ml) at 80° for 40 hr, **10** was obtained (after recrystallization from benzene) as white needles, 0.040 g (28%), mp 140–142°. Experiments like those described in **C** with *i*-PrOH showed that only 3 hr actually was necessary for complete loss of the –SO– peak, and a shorter reaction period of 3 hr gave **10** in 48% yield.

C. *Via* KIO_4 **in** *i*-**PrOH–H_2O Containing I_2.**—In order to learn whether I_2 was an effective catalyst, experiments were done using the different amounts of I_2 shown in Table I. For example, a mixture of **6** (177 mg, 0.75 mmol) in *i*-PrOH (16 ml) with KIO_4 (540 mg, 2.34 mmol) in H_2O (5 ml) was heated at 80–82° with good stirring. From time to time, ~1.5 ml of solution was withdrawn and was concentrated and extracted with $CHCl_3$. After the extract had been dried and the $CHCl_3$ removed, the residue was used directly as an ir sample. The percentages of the dioxide **10** and monoxide **8** were approximated by comparing intensities at 1110 and 1060 cm^{-1}, respectively, with those of authentic samples (by use of a plot for **8** and another for **10** in which intensity had been normalized to a constant value for –CHO– at 1030 cm^{-1} and then plotted *vs.* per cent of **8** and **10**). The results are shown in Table I; concentrations and amounts were the same in all experiments as those given above, except for I_2.

TABLE I

OXIDATION OF *trans*-1,2-DITHIANE-4,5-DIOL DIACETATE (**6**) WITH KIO_4 IN AQUEOUS *i*-PrOH AT ~80°

Mol of I_2 / Mol of **6**	Time, hr	Estimated composition of products, %: **8**	**10**
0	12	95	5
	16	80	20
	21	55	45
	26	25	75
	33	0	100
0.02	5	90	10
	6	60	40
	8	50	50
	11	10	90
	16	0	100
0.04	3	90	10
	5	60	40
	8	10	90
	9	0	100
0.08	1	75	25
	3	55	45
	5	5	95
	6.5	0	100

In a preparative experiment, a mixture of 18.0 g of **6**, 52.6 g of KIO_4, 0.386 g of I_2, 200 ml of *i*-PrOH, 100 ml of MeOH, and 300 ml of H_2O was heated at 80° with good stirring for 7 hr. The yield of **10**, isolated as a white solid of mp 133–139°, was 13.6 g (67%).

cis-**1,2-Dithiane-4,5-diol Diacetate 1,1-Dioxide** (**11**).[15]—A mixture of the dithiane **7** (0.20 g, 0.85 mmol) in Me_2CO (20 ml) and of KIO_4 (0.80 g, 3.48 mmol) in H_2O (40 ml) was kept at 40° for 50 hr and then was let stand at ~25° for 24 hr. A $CHCl_3$ extract gave 0.15 g (66%) of **11**, mp 145–150°. Recrystallization from benzene gave **11** of constant mp 153–154°: nmr ($CDCl_3$) δ 2.11 (s, CH_3CO), 2.21 (s, CH_3CO), 3.86–3.48 (m, CH_2), 5.35–5.66 (m, OCH); ir 1750, 1370, 1320, 1220, 1200, 1120, 1040, 955, and 775 cm^{-1}; mass spectrum *m/e* (rel intensity) 43 (100), 84 (55), 101 (15), 148 (5), 208 (2).

Anal. Calcd for $C_8H_{12}O_6S_2$: C, 35.82; H, 4.48; S, 23.85. Found: C, 35.72; H, 4.49; S, 24.00.

Sodium 4-(2-Acetamidoethyldithio)butane-2,3-diol-1-sulfinate Diacetate (**14**).[16]—A 0.5 *N* solution of NaOEt (40.0 ml, 20.0 mmol) was added to the thiol **13** (2.44 g, 20.5 mmol) in EtOH (20 ml) at 0° (the pH then was ~8). This solution of the thiolate was added during ~1 hr to a solution of **10** (5.36 g, 20 mmol) in a mixture of Me_2CO (50 ml) and EtOH (20 ml) at ~−10° with stirring (pH ~6.5). Dry Et_2O (700 ml) then was added until no more precipitate appeared, and the mixture was kept at 0° for 5 hr. Most of the solvent was decanted, and the precipitate was dried at 25° (0.1 mm). The dry white **14** was dissolved in Me_2CO. A small amount of insoluble solid was removed by centrifugation, and Et_2O was added to precipitate **14**. Et_2O was decanted, and residue was dried at 25° (0.1 mm) for 10 hr; yield of **14**, 6.0 g (73%), mp ~99° dec. Similarly prepared **14** (identical ir spectrum) was characterized: nmr (D_2O) δ 2.15–2.31 (CH_3CO), 2.60–3.66 (m, CH_2), 5.33–5.65 (m, OCH); ir 3260 (broad) 1730, 1640, 1540, 1430, 1375, 1220, 1020, 950 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}NNaO_7S_3$: C, 35.20; H, 4.91; N,

(15) This reaction succeeded only once. Use of the same conditions twice more resulted in no **11**. It seems likely, however, that one of the procedures that later gave the trans isomer (**10**) will succeed. Synthesis of the trans dioxide **10** sufficed at present for chemical and biological studies and, unless biological results warrant, we plan no further studies with the cis isomer **11**.

(16) This procedure was based on one for the reaction of the salt of **13** with 1,2-dithiane 1,1-dioxide (**12**),[3b] but it includes important modifications discussed in ref 1a.

3.42; S, 23.48. Found: C, 35.37; H, 5.40; N, 3.25; S, 23.28.

Compounds Related to 1,2-Dithiolane-4-carboxylic Acid (16).[17] **A. 16 *via* H_2O_2.**—The acid **15** (15.2 g, 0.10 mol) in AcOH (150 ml) and H_2O_2 (11.5 g of 30%, 0.1 mol) in AcOH (150 ml) were added simultaneously from two dropping funnels to AcOH (100 ml) containing KI (0.418 g, 0.00251 mol; as a catalyst) at 75° during 3 hr. After 10 min at 25° (starch–KI test negative), most of the AcOH and H_2O were removed at 40° (20 mm). The residue was extracted with Et_2O and benzene. The extracts were combined, dried, and evaporated to a greasy solid, yield 10.2 g (68%), mp 63–70°. This solid was extracted carefully with benzene at 25°. Removal of benzene gave yellow, crystalline **16**: yield 8.5 g (57%; yields up to 85% were obtained on a smaller scale); mp 75–76° (lit.[8] mp 76.5–77.5°); nmr ($CDCl_3$) δ 3.5 (m, CH_2 and CH), 12.3 (s, CO_2H).

B. 16 *via* I_2–Et_3N.—A solution of **15** (0.76 g, 5.0 mmol) and Et_3N (1.04 g, 10.3 mmol) in MeOH (15 ml) was added to one of I_2 (1.28 g, 5.0 mmol) in MeOH (30 ml) at 25° during 10 min. Benzene (180 ml) then was added immediately. The organic layer was washed with 10% aqueous Na_2SO_3 solution to remove I_2, then with a little cold H_2O, and was dried. Removal of benzene left 0.30 g (40%) of yellow **16**, mp 76–78°.

C. 16 *via* $K_3Fe(CN)_6$.—Aqueous solutions of $K_3Fe(CN)_6$ (16.6 ml of 1 *N*) and of KOH (6.5 ml of 2 *N*) were added to the sodium salt of **15** (1.0 g, 6.58 mmol) in H_2O (5 ml); the pH was kept at ~7 (*cf.* ref 10). The mixture then was acidified with 2% aqueous HCl and was extracted with benzene. Removal of benzene left 0.32 g (32%) of yellow **16**, mp 73–75°.

D. 1-Monoxide (17) of 16.—A solution of H_2O_2 (0.113 g of 30% H_2O_2, 1.0 mmol) in 1 ml of H_2O was added slowly to **16** (0.15 g, 1.0 mmol) in H_2O (30 ml) at 5°, and the mixture was kept at 25° for 16 hr; a starch–KI test then was negative. Removal of H_2O by freeze drying left white **17**: yield 0.12 g (72%); mp 100–102° (lit.[11] mp 104–110°); ir 1020 (SO) and 1725 cm^{-1} (CO).

E. Study of the Carbinol (19) Corresponding to Acid 16. 2-Mercaptomethyl-3-mercaptopropanol (18) first was prepared by heating a mixture of the acid **15** (7.6 g, 50.0 mmol) in THF (700 ml) with $LiAlH_4$ (7.6 g, 200 mmol) in THF (100 ml) under reflux for 26 hr and then carefully hydrolyzing with H_2O (40 ml) by heating for 2 hr. The mixture then was acidified with 5% aqueous HCl, and **18** was extracted with Et_2O. Drying and removal of solvent gave liquid **18**. Distillation gave 4.8 g (70%) of **18**: bp 90–91° (0.6 mm); $n^{25}D$ 1.5606; nmr ($CDCl_3$) δ 1.43 (t, SH), 1.89 (m, CH), 2.70 (m, CH_2SH), 3.04 (s, OH), 3.72 (d, OCH_2); ir (neat) 3360, 2900, 2520, 1430, 1015 cm^{-1}.

Anal. Calcd for $C_4H_{10}OS_2$: C, 34.75; H, 7.25; S, 46.35. Found: C, 35.00, H, 7.17 S, 46.19.

For conversion of **18** to **4-hydroxymethyl-1,2-dithiolane (19)**, solutions of **18** (0.55 g, 4.0 mmol) and of H_2O_2 (0.45 g, 30%, 4.0 mmol) in AcOH (14 ml) were added simultaneously from separate dropping funnels to AcOH (8 ml)–H_2O (12 ml) containing KI (17 mg) at 75° during 10 min with stirring (a starch–KI test then was negative). A benzene extract of the concentrated mixture was washed with 5% aqueous Na_2CO_3 solution and then with H_2O, dried, and concentrated; yield of presumed (impure) liquid **19**, 0.38 g (70%). Ir spectra were consistent with the assignment of structure **19** (the pale yellow benzene-soluble product polymerized to a gum, insoluble in benzene, in ~10 hr and began to polymerize even in ~2–3 hr at 25°): ir (neat) 3480, 2920, 1470, 1410, 1250, 1035, and 670 cm^{-1} [no SH absorption at 2520 cm^{-1}; the ir spectrum of **19** resembled that of **18** and did not have the flattened-out appearance expected of a polymer (*cf.* ref 11)].

Since **19** polymerized so readily, in the attempt to convert it to 1,2-dithiolanyl-4-carbinol 1,1-dioxide (**20a**), 0.38 g (2.80 mmol) of **19** immediately after its preparation was allowed to react with H_2O_2 (0.77 g, 30%, 6.8 mmol) in aqueous AcOH (H_2O, 10 ml; AcOH, 10 ml) at 75° for 20 hr with stirring. The mixture was concentrated and then extracted with $CHCl_3$. The removal of $CHCl_3$ after drying gave 0.10 g (16%, for **20b** not **20a**): ir 1740 (ester C=O),[18] 1430 (CH_3 of CH_3CO),[18] 1300 ($-SO_2-$), 1230 (AcO),[18] 1125 ($-SO_2-$), and 1050 cm^{-1} (–CO–) (slight absorption, relative to **19**, at 3450 cm^{-1} was attributed to an ester overtone and suggested little if any –OH);[18] nmr ($CDCl_3$) δ 2.12 [s, $CH_3C(O)$],[18] 3.7–2.7 (m, $-CH_2-$ and –CH–), 4.4–4.2 (m, $-CH_2-$) (no OH peak was observed).[18]

Registry No.—**6**, 34910-57-1; **7**, 34910-58-2; **8**, 34910-59-3; **9**, 34910-60-6; **10**, 34915-74-7; **11**, 34915-75-8; **14**, 34915-76-9; **16**, 2224-02-4; **17**, 3083-96-3; **18**, 34915-79-2; **20b**, 34934-76-4.

(17) Wherever feasible, protection from light was effected using Al foil.

(18) These observations support the formulation of the product isolated as **20b** but are inconsistent with formulation as **20a**. The ir spectrum of the product impressed us as the type expected for a monomer, rather than the flattened-out type expected for a polymer (*cf.* ref 11).

Organic Disulfides and Related Substances. 35. Preparation of Unsymmetrical Disulfides Containing Carboxylate Moieties and Neighboring-Group Effects of Sulfinate and Carboxylate Moieties on Disproportionation[1a,b]

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The sulfinate salt $AcNH(CH_2)_2SS(CH_2)_4SO_2Na$ (**2**), upon disproportionation, reaches equilibrium with the two possible symmetrical disulfide products in ~0.5 hr in water at 61° ($K \cong 3$–6). The sulfone analog [$AcNH(CH_2)_2SS(CH_2)_4SO_2CH_2Ph$ (**5**)] and sulfonate analog [$AcNH(CH_2)_2SS(CH_2)_4SO_3Na$ (**6**)] do not disproportionate under these conditions. The marked acceleration with **2** *vis-à-vis* **5** and **6** is attributed to a neighboring-group effect of the $-SO_2^-$ moiety, which was further indicated by slower reaction of **2** in methanol (attributed to a tight ion pair) and by isolation of 1,2-dithiane 1,1-dioxide (**8**, 39% yield) in the presence of a thiol trap. Carboxylate analogs, $AcNH(CH_2)_2SS(CH_2)_nCO_2H$ (**11–14**, n = 1–4), were best prepared by thioalkylating ω-mercapto acids with a thiolsulfonate (these analogs proved to be only slightly protective against ionizing radiation). The acids **11–14** resisted disproportionation. The salts **11′–14′** disproportionated fairly readily, but (n = 4) less readily than **2** by a factor of ~300. Neighboring-group acceleration of disproportionation in the carboxylate series is indicated by the difference in behavior of the salts **11′–14′** and the acids **11–14**, by a marked dependence of rapidity on the pH near neutrality, and by variations in rapidity from n = 1 (fastest) to n = 2, 3, or 4 (slower and comparable).

Earlier work showed that the aminosulfone salt **1** was among the most stable disulfides we have studied in resistance to disproportionation to two symmetrical disulfides (79% disproportionation at 100° in water after 72 hr.[2] To our surprise, sodium 4-(2-acetamidoethyldithio)butanesulfinate (**2**) disproportionated far

(1) (a) Paper 34: L. Field and Y. H. Khim, *J. Org. Chem.*, **37**, 2710 (1972). (b) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DADA17-69-C-9128.

(2) L. Field and R. B. Barbee, *J. Org. Chem.*, **34**, 1792 (1969).

$$\underset{1}{Cl^-H_3N^+(CH_2)_2SS(CH_2)_4SO_2CH_2Ph}$$

more rapidly (~50%, 61°, water, 0.5 hr); the reaction appeared to reach equilibrium after ~55% disproportionation.[3] It seems likely that a neighboring-group effect of the sulfinate moiety ($-SO_2^-$) is responsible for this marked acceleration. This paper considers this matter and related ones. Similar increases with other disulfides have been attributed to neighboring-group participation of amino, acetamido, *o*-carboxylate, and perhaps to some extent other functional groups.[4]

Equation 1 shows the disproportionation of the sul-

$$\underset{2}{2AcNH(CH_2)_2SS(CH_2)_4SO_2Na} \xrightleftharpoons{H_2O \text{ or } MeOH} \underset{3}{[AcNH(CH_2)_2S]_2} + \underset{4}{[NaO_2S(CH_2)_4S]_2} \quad (1)$$

finate **2** to form the two symmetrical disulfides, 2-acetamidoethyl disulfide (**3**) and disodium 4,4′-dithiobis(butanesulfinate) (**4**). After the disproportionation of **2** in methanol, **3** was isolated in 50% yield; as previously reported,[3] several equilibrations with removal of **3** each time forced the reaction, giving what could only be **4** (consistent spectra); **4** could not be obtained entirely free of **3**, but elemental analyses nevertheless were satisfactory (C, H, S, and Na).[3]

In much of our earlier work, disproportionation of unsymmetrical disulfides has been nearly complete (for reasons such as virtual insolubility of one product) instead of reaching the usual equilibrium.[5] Since **2**, **3**, and **4** are soluble in water or methanol, however, it is not surprising that eq 1 represents an equilibrium.

Figure 1 shows that the per cent of disproportionation of **2** in water or methanol rises to ~50–55% and then remains constant. If ~53% is assumed to be the equilibrium value, the usual reverse sense of **3** + **4** ⇄ 2(**2**) would give $K \cong 3$ for eq 1, a value close to the statistical one of 4.[6] The reversibility of eq 1 was confirmed by equilibrating **3** and **4** and determining the amount of **2** by tlc. Table I shows that an equilibrium value of 50–55% of **2** resulted after ~0.5 hr in water or ~7 hr in methanol and was unchanged thereafter. The assumption that 55% of **2** is present at equilibrium results in $K \cong 6$.

Table I
Formation of the Unsymmetrical Disulfide 2 by Equilibration of the Symmetrical Disulfides 3 and 4 (61°)

In H_2O		In MeOH	
Time, hr	Formation of 2, %	Time, hr	Formation of 2, %
0.5[a]	~50	0.5	~0
7	~55	7[a]	~50
19	~50	19	~55
28	~55	28	~55

[a] Equilibration time first reached. At this time, the tlc spot for **2** had an area which did not increase significantly thereafter and which corresponded to a yield of ~50–55% for **2**.

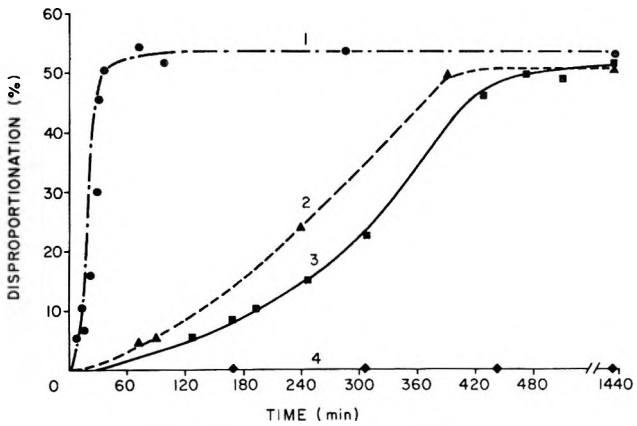


Figure 1.—Disproportionation of **2** under various conditions (61°): curve 1, ●, in H_2O; curve 2, ▲, in MeOH containing NaOMe equal to mol of **2**; curve 3, ■, in MeOH; curve 4, ◆, dry solid.

Comparison of the rapidity with which equilibrium was achieved under various circumstances was desirable in order to assess better the importance of $-SO_2^-$ in accelerating disproportionation. Fortunately, **2**, **3**, and **4** could be separated cleanly by tlc, and good calibration curves were possible by correlating spot areas with known amounts of **2**, **3**, and **4**. Since this method is not highly precise, it is appropriate to discuss results in terms of the more cautious word "rapidity" rather than of "rates." Nevertheless, use of the tlc correlations for analysis of test mixtures showed the results to be within about ±5% (this method was used in determining the data for Table I and Figure 1).

If disproportionation of **2** is in fact accelerated by a neighboring-group effect of $-SO_2^-$ on the disulfide linkage, the rapidity would be expected to be significantly greater for **2** than for **1**, the amide of **1** (**5**), or the sulfonate analog of **2** (**6**), since **1**, **5**, and **6** contain no $-SO_2^-$ moiety; solvent effects also might be anticipated with **2**, corresponding to variable tightness of ion pairs. The results of experiments that bear on these points are summarized in Figure 1 and Table II.

Further assurance as to the reliability of the conclusions from tlc was provided by a check isolation of **3** from the disproportionation of **2** at a point where the results indicated equilibrium had been reached; the two results agreed well (50% of **3** isolated after 8 hr for **2** in methanol; curve 3 of Figure 1 predicts 50%).

When the relative rapidity of the disproportionation of **2** in water and methanol are compared, disproportionation in water is seen to be about 21 times faster from Table II and clearly more rapid from Figure 1 (curve 1 *vs.* curve 3). It seems likely that $-SO_2Na$ is a much tighter ion pair in methanol than in water, so that $-SO_2^-$ is less able to assist cleavage of the S–S bond. The fact that the rapidity of disproportionation was negligibly affected by a tenfold increase in concentration seems more consistent with an intra- than an intermolecular effect (Table II, 0.4 *vs.* 0.5 hr). There is little increase of rapidity in going from methanol to a methanol–methoxide mixture (curve 2, Figure 1; relative rapidity of ~1.4 from Table II). Hence the possibility that the $-SO_2^-$ functions significantly as a weak base can be disregarded, and the slight acceleration seen can be attributed to attack of methoxide ion on the –SS– bond (or on a proton α to it) to generate

(3) L. Field and Y. H. Khim, *J. Med. Chem.*, **15**, 312 (1972).
(4) (a) For leading references, see ref 4b; (b) L. Field, W. S. Hanley, and I. McVeigh *J. Org. Chem.*, **36**, 2735 (1971).
(5) For leading references, see L. Field and H. K. Kim, *J. Med. Chem.*, **9**, 397 (1966), especially footnote 7.
(6) H. Haraldson, C. J. Olander, S. Sunner, and E. Varde, *Acta Chem. Scand.*, **14**, 1509 (1960).

TABLE II

DISPROPORTIONATIONS OF UNSYMMETRICAL DISULFIDES 1, 2, 5, AND 6 AT 61°

Compd	Solvent	Time of reaction, hr	Disproportionation, %	k_{approx},[a] sec^{-1}	Relative rapidity
2	MeOH	8[b]	~50[b]	1.5×10^{-6} [b]	1
2	H_2O	0.5[c]	~50–55[c]	3.1×10^{-4} [c]	21
2	H_2O	~0.4[d]	~55[d]		
2	MeOH–NaOMe	6.5[e]	~50[e]	2.1×10^{-5}	1.4
2	None	72[f]	Trace		
1	MeOH	8	0		
1	H_2O[g]	72[g]	79[g]		*h*
1	H_2O	8	Trace		
5	MeOH	8	0		
6	H_2O	1.5	0		
6	H_2O	96	Trace		

[a] Apparently first order, as seen with several other disproportionations (*cf.* ref 9, especially footnotes 6 and 7). [b] *Cf.* Figure 1, curve 3. [c] *Cf.* Figure 1, curve 1. [d] The concentration of 2 was ten times that for Figure 1, curve 1; ~0.4 and 0.5 are considered essentially the same, within experimental error, but because small amounts of 2 had to be used, calculation of k_{approx} was not justified. [e] *Cf.* Figure 1, curve 2. The reaction was done as it was in MeOH but with a molar amount present of NaOMe equal to that of 2. [f] *Cf.* Figure 1, curve 4. [g] Done at 100° (see ref 2). [h] Relative rapidity unknown but clearly *much* less than for 2.

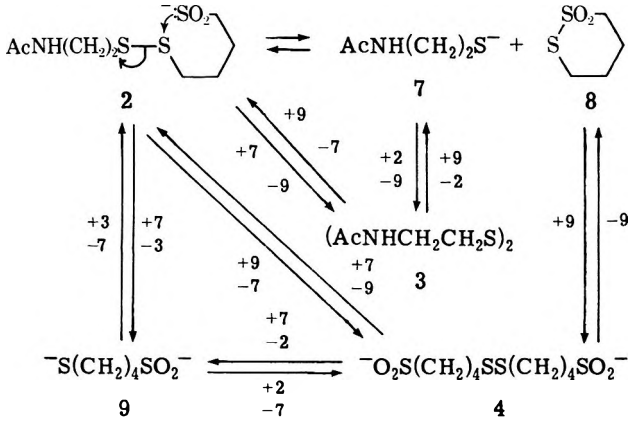
thiolate ion as a catalyst. The sulfinate 2 resists disproportionation as a solid. When it was heated dry at 61° for 25 hr it was stable; even after 72 hr, tlc indicated only slight disproportionation. The results of Table II are *highly* significant in that 1, 5, and 6, which contain no $-SO_2^-$ moiety but otherwise are close counterparts of 2, are stable under conditions that result in disproportionation of 2 (*cf.* eq 2 *vs.* eq 1).[7]

$$2X(CH_2)_2SS(CH_2)_4Y \xrightarrow{\text{very slow}} [X(CH_2)_2S]_2 + [S(CH_2)_4Y]_2 \quad (2)$$

1, X = $H_3N^+Cl^-$; Y = SO_2CH_2Ph
5, X = AcNH; Y = SO_2CH_2Ph
6, X = AcNH; Y = SO_3Na

The facts above thus support the probability that the disproportionation of 2 is initiated by a neighboring-group attack of $-SO_2^-$ on the –SS– bond, probably with 2-acetamidoethanethiolate ion (7) as a leaving group, as shown in Scheme I. Thiolate ion 7 then could catalyze the disproportionation of 2.[8a] Scheme I illustrates reactions in which the thiolate 7 and 1,2-dithiane 1,1-dioxide (8) could be engendered and in which the other possible sulfinate ion 9 then could be formed to serve as a catalyst like 7. Such equilibria could lead to the mixture of 2, 3, and 4 summarized at the outset by eq 1. Scheme I has much in common with similar ones that are believed to involve neighboring-group effects of amino[8b] or *o*-carboxylate moieties,[9] although the earlier ones were less complex since they went essentially to completion and could not be significantly reversed.

SCHEME I



It was possible in the *o*-carboxylate series to show that a cyclic intermediate like 8 was feasible.[9] It was satisfying to be able to confirm neighboring-group attack directly in the present instance by isolating the stable dioxide 8 (39% yield) after heating an aqueous solution of 2 in the presence of *N*-ethylmaleimide as a trap for the thiolate 7 and of benzene to remove the dioxide 8 from the sphere of the reaction. The isolation of 8 has the further important implication that $-SO_2^-$ exerts its effect through the proposed *intra*- rather than an *inter*molecular attack, since formation of 8 in the presence of a thiol trap is hard to envision by an intermolecular process.

One wonders whether the ambident $-SO_2^-$ ion exerts its effect by attack of an unshared pair of electrons of the oxygen atom, or of the sulfur atom as in Scheme I. The formation of the dioxide 8 strongly supports the view of attack by an electron pair of the sulfur atom; so, too, does failure of the sulfonate 6 to disproportionate nearly so readily as the sulfinate 2. Also consistent is the finding of Meek and Fowler that the ambident sulfinate ion gives sulfones (*cf.* 8) with "soft" alkylating agents (*cf.* the soft sulfur atom at which attack is suggested in Scheme I) but sulfinate esters preferentially with "hard" alkylating agents.[10] It should be noted that neighboring-group participation by sulfinyl oxygen in solvolysis of chloroalkyl sulfoxides greatly exceeds any such effect by sulfides (or

(7) When the amino sulfone hydrochloride 1 was heated at 61° in methanol for 8 hr, 1 was quantitatively recovered. Since disproportionation of 1 at 100° in water for 72 hr gave one of the symmetrical disulfides in 79% yield,[2] however, disproportionation of 1 *can* occur. When 5 was heated at 61° in MeOH for 8 hr, it was recovered quantitatively, and in water (same conditions) only a trace of one of the symmetrical disulfides was obtained. The aqueous solution of 6 after 1.5 hr at 61° showed only the one spot for recovered 6 (R_f 0 on alumina, 0.69 on silica gel) with none whatever for 3 (R_f 0.45 on alumina); evaporation gave pure 6; even after 96 hr at 61°, tlc showed only slight traces of disproportionation (small spot for 3 on alumina). Identifications of recovered 1, 5, and 6 were performed by comparing ir absorptions and melting points.

(8) (a) For further discussion of the catalytic effect of thiolate ion on disproportionation, see ref 8b; (b) M. Bellas, D. L. Tuleen, and L. Field, *J. Org. Chem.*, **32**, 2591 (1967).

(9) L. Field, P. M. Giles, Jr., and D. L. Tuleen, *J. Org. Chem.*, **36**, 623 (1971).

(10) J. S. Meek and J. S. Fowler, *ibid.*, **33**, 3422 (1968).

sulfones),[11a] and that it can be involved also in other reactions at electrophilic carbon atoms.[11b] However, this difference of the functioning of oxygen rather than sulfur is not surprising, since a carbon center should be much harder than a sulfur center (solvation also may be a factor; *cf.* ref 11a). The six-membered ring of **8** no doubt favors lone-pair participation of sulfur in **2**, however, so that in homologs of **2** lone-pair participation of oxygen conceivably might become important.

In summary, the main points that support neighboring-group assistance of $-SO_2^-$ to disproportionation are these. (1) The $-SO_2^-$ moiety is far more effective than $-SO_2R$ or $-SO_3^-$. (2) Reaction is faster in water than in methanol, and the reaction seems to be first order. (3) A tenfold increase in concentration had little effect on the rapidity of disproportionation. (4) **8** was isolated.

It was of considerable interest to compare neighboring-group participation of carboxylate ion with that of sulfinate (carboxylate groups were the first used in studying neighboring-group participation).[12] Two other features of carboxylates also were attractive. (1) For a study of variable effects in homologs, $RSS(CH_2)_nX$, synthesis promised to be easier with X = CO_2^- than with X = SO_2^- (a study of homologs with R = Ac and X = CO_2^- failed because of the lability of Ac to agents used to convert the carboxylic acids to the salts).[4b] (2) Although **2** is a promising antiradiation drug,[2,3] quite possibly because of the anchimeric effect of $-SO_2^-$, its ease of disproportionation in solution and its redox properties might present problems in its practical use. Carboxylates offered a prospective compromise in ease of handling and stability with neighboring-group induced activity as antiradiation drugs.

Three methods to prepare **12** were examined. Only from the reaction of the thiolsulfonate **10** with 3-mercaptopropionic acid in alkaline media could **12** be obtained successfully in good yield (eq 3). The method

$$\underset{\mathbf{10}}{AcNH(CH_2)_2SSO_2(CH_2)_2NHAc} + HS(CH_2)_nCO_2H \xrightarrow{\text{NaOH, 0–10°}} AcNH(CH_2)_2SS(CH_2)_nCO_2H + AcNH(CH_2)_2SO_2Na \quad (3)$$

11, $n = 1$ **13**, $n = 3$
12, $n = 2$ **14**, $n = 4$

of eq 3 then was used also to prepare the homologs **11**, **13**, and **14**. The buffering action of the carboxylate ion doubtless led to sufficient thiolate ion to provide a rapid reaction. (2-Acetamido)ethanesulfinic acid, the strongest acid species present, formed as the salt (presumably), leaving **11–14** as extractable free acids (yields, 77–97%). Nmr, ir, and mass spectra and elemental analyses met expectation. The activity of **11–14** as antiradiation drugs proved to be minimal (ALD_{50} ~175–480 mg/kg; 13–27% survival 30 days after irradiation of mice dosed with ~1/2 the ALD_{50}).[13]

(11) (a) M. Cinquini, S. Colonna, and F. Montanari, *Tetrahedron Lett.*, 3181 (1966); (b) M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc. C*, 572 (1970).

(12) For a review, see E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Reinhart and Winston, New York, N. Y., 1959, p 561 ff.

(13) For details on methods, see ref 3. We are indebted for these results to T. R. Sweeney, D. L. Klayman, and (especially) M. M. Grenan of the Walter Reed Army Institute of Research, Washington, D. C.

The reaction of diethyl azodicarboxylate with two different thiols,[14] as appropriate for **11** and **12**, was unsuccessful; the main products were the symmetrical disulfides. An effort also failed to prepare **11** by conversion of either thiol to its sulfenyl chloride at −20°, for reaction with the other thiol; only polymers were obtained.

The acids **11–14** resisted disproportionation at 61° in methanol or water. Tlc showed no change after 3 days, and no acetamidoethyl disulfide (**3**) was detected in confirming experiments; each acid also was isolated quantitatively after 3 days.

On the other hand, the salts of the acids disproportionated fairly readily in water. Similar observations were made for 2-(phenyldithio)benzoic acid (**15**) and its salt **15′**; the more rapid disproportionation of **15′** was attributed to anchimeric assistance by the ortho CO_2^- moiety in a scheme resembling Scheme I.[9] Such observations are not surprising, since "when the carboxylate group is converted by protonation to the carboxyl group, −COOH, it becomes very much less nucleophilic and loses a great deal of its effectiveness as a participant."[12]

As with **2**, disproportionation of **11–14** as the salts (**11′–14′**; from **11–14** using NaOH at pH ~7–8) gave the symmetrical disulfide **3**. The yields of **3** isolated appear to represent near-equilibrium values, since Table III shows that disproportionation of **13′** and

TABLE III
EQUILIBRIUM IN THE DISPROPORTIONATION OF SALTS 13′ AND 14′

	Time, hr[a]				
	2	3	4	5	9
13′, disproportionation, %	37	41	45	43	44
14′, disproportionation, %	38	44	42	43	46

[a] Determined after heating **13** or **14** in the presence of ~1 equiv of NaOH in H_2O (pH 8) at 61° and isolating **3** (see Experimental Section).

14′ reached values of ~44% in ~2–3 hr at latest and then remained constant. Since the disproportionation thus appears to be reversible, the equilibria of eq 4 seem to be the best way to represent the reactions.

$$2AcNH(CH_2)_2SS(CH_2)_nCO_2H \underset{}{\overset{2NaOH}{\rightleftharpoons}} \underset{\mathbf{11'\text{–}14'}}{2AcNH(CH_2)_2SS(CH_2)_nCO_2Na} + 2H_2O \quad (4)$$

11, $n = 1$ **13**, $n = 3$
12, $n = 2$ **14**, $n = 4$

$$[AcNH(CH_2)_2S]_2 + \underset{\mathbf{3}}{[S(CH_2)_nCO_2Na]_2}$$

The fact that both **13′** and **14′** required about the same length of time to reach equilibrium (Tables III and IV), even though the presumed anchimeric effect of oxygen on the nearest sulfur atom would involve a six- and a (less favorable) seven-membered ring, respectively, is surprising; this similarity may even argue against an anchimeric effect as the sole accelerating factor. Perhaps this apparent similarity in reactions has its basis in simultaneous involvement of direct attack of hydroxyl ion on the −SS− bond or of subtle

(14) T. Mukaiyama and K. Takahashi, *Tetrahedron Lett.*, 5907 (1968).

TABLE IV

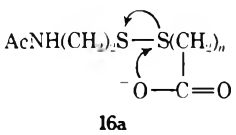
DISPROPORTIONATION OF 11–14 AND OF 11′–14′ IN H_2O

Expt	Compd	Base	Molar ratio, compd:base	pH	Temp, °C	Time to equilibrium point, min[a]
1	**11**			2.5	61	Slow[b]
2	**12, 13, 14**			3.2, 3.5, 3.5	61	Very slow[c]
3	**11**	NaOH	1:1.04	8	25	Very fast[d]
4	**12, 13, 14**	NaOH	1:1.04	8	40	110
5	**12, 13, 14**	NaOH	1:1.04	8	61	10
6	**14**	NaOH	1:2	~13	40	5[e]
7	**2**			6.8	40	90
8	**14′**	NEt_3	1:2	~12	40	240[e]
9	**11′**			6.6	61	~465
10	**12′**			6.6	61	~7200
11	**13′**			6.8	61	~8600
12	**14′**			6.8	61	~8880
13	**2**			6.8	61	30

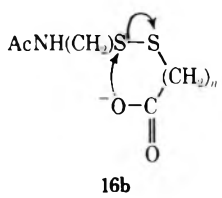
[a] *I.e.*, the time at which the tlc spot area of **3** became constant. [b] Began to disproportionate after 4 days. [c] Began to disproportionate after 16 days. [d] Compound **11** disproportionated immediately at pH 8 at 25°. [e] At these high values of pH, direct attack of OH^- on –SS– or $-CH_2S-$ is probable.

changes in amounts of catalytic thiolate species as a function of pH.

For further studies, the salts **11′–14′** were prepared by precipitation from methanol. Tlc analyses for **3** could be used to follow their reactions and those of **11–14** approximately, much as with **2**. Table IV shows times required for attainment of equilibrium of **11–14** and **11′–14′** under various conditions. There are three notable points. (1) As was the case with 2-(phenyldithio)benzoic acid (**15**),[9] the rapidity of disproportionation is highly sensitive to pH (*cf.* expt 1 *vs.* 3 and 2 *vs.* 5, 6). (2) The salt with $n = 1$ (**11′**) disproportionates far more rapidly than those with $n = 2$–4 (**12′–14′**); *cf.* expt 3 *vs.* 5 and 9 *vs.* 10, 11, and 12); compounds **12′–14′** seem roughly comparable (*cf.* expt 4 or 5 and also 10–12). Analogy with Scheme I suggests involvement of **16a** for participation of $-CO_2^-$ in disproportionation.[15]



16a



16b

There is little basis at present for speculation, however, as to why **11′** disproportionates so much more rapidly than **12′–14′** or why **12′–14′** are comparable. It may be that, in generation of thiolate ion catalyst from **11′**, a four-membered ring (**16a**, $n = 1$) is unexpectedly effective, or that **16b** becomes important, or that the greater acidity of the methylene group in **11′** (flanked both by –S– and $-CO_2^-$) leads to loss of $AcNH(CH_2)_2S^-$ by α elimination. (3) The sulfinate **2** disproportionates faster than the comparable carboxylate **14′** by a factor of ~300 (*cf.* expt 12 *vs.* 13).

Although a neighboring-group effect seems much more clear-cut for $-SO_2^-$ than for $-CO_2^-$, points that support neighboring-group acceleration by $-CO_2^-$ can be summarized as follows. (a) Although the free acids **11–14** strongly resist disproportionation, the salts do not. (b) The rapidity of disproportionation is highly dependent on pH near the neutral point, presumably increasing as the amount of $-CO_2^-$ increases. (c) Variation of the distance separating the carboxylate and disulfide functions has a marked effect, even though its meaning is not clear at present.

Overall, the general conclusions seem justified that neighboring-group effects of both 4-sulfinate and ω-carboxylate moieties accelerate disproportionation of disulfides, although the effect with carboxylate is considerably more speculative, less effective, and more complex in its interaction.

(15) A five-membered ring evidently is involved in anchimerically assisted racemization of sulfoxides that contain $-CO_2H$ moieties. See S. Allenmark and C.-E. Hagberg, *Acta Chem. Scand.*, **24**, 2225 (1970), and earlier papers.

Experimental Section[16]

Materials.—Compounds **2**,[3] **3**,[17] **4**,[3] **8**,[18] **10**,[19] and 2-acetamidoethanethiol[20] were prepared using the procedures cited. The aminosulfone **1**, the acetamidosulfone **5**, and the acetamidosulfonate **6** were available from the work of Barbee.[2] Commercial mercaptoacetic acid (H_2O solution, dried to an oil at 0.1 mm), 3-mercaptopropionic acid, and 4-mercaptobutyric acid (Distillation Products Industries) were used after checking them by ir and nmr. All other materials were commercial products used as received.

Disproportionation of Sodium 4-(Acetamidoethyldithio)butanesulfinate (2). A. Isolation of 2-Acetamidoethyl Disulfide (3) and Disodium 4,4′-Dithiobis(butanesulfinate) (4).—Details were reported earlier for isolation of **3** and **4**.[3] Briefly, after **2** has been heated in MeOH (8 hr, 61°), evaporation and extraction gave **3** in 50% yield, which was characterized by melting point and ir. A similarly heated methanolic solution was treated with Me_2CO to precipitate **2** and **4**; the precipitate then was reheated in MeOH and reprecipitation was carried out until **4** resulted that contained only a trace of **2** by ir or tlc and no **3**; the yield of **4** was 42%, and analyses were satisfactory (C, H, Na, S). This analytically pure **4** was used for the tlc calibration curves described in section C.

B. Reversibility of Eq 1.—Solutions of **3** (4.00 mg, 0.017 mmol) and **4** (6.0 mg, 0.017 mmol) in 1 ml each of H_2O and MeOH

(16) Melting points are corrected, and boiling points are uncorrected. Nmr spectra were obtained with a Varian Model A-60 and ir spectra with a Beckman Model IR-10 using KBr pellets or NaCl plates (bands reported are at least of medium intensity). Moist extracts were dried over the anhydrous agent specified; solvent then was evaporated in a rotary evaporator. Brinkmann precoated tlc sheets of silica gel (F-254, 0.25 mm) and Eastman Chromagram sheets of alumina (Type 6063 with fluorescent indicator) were used for tlc; with the former, spots were observed after exposure to I_2 vapor in a sealed container, and with the latter, spots were observed under a uv lamp. Other details were essentially as given in footnote 13 of ref 1a.

(17) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Amer. Chem. Soc.*, **83**, 4414 (1961).

(18) L. Field and R. B. Barbee, *J. Org. Chem.*, **34**, 36 (1969).

(19) J. D. Buckman and L. Field, *ibid.*, **32**,454(1967).

(20) R. Kuhn and G. Quadbeck, *Chem. Ber.*, **84**, 844 (1951).

were heated at 61° in a constant-temperature oil bath. From time to time, 10 μl of the solution was withdrawn and spotted on a silica-gel layer. The amount of **2** present was obtained by tlc as described in section C. The results are shown in Table I.

C. Rapidity of Disproportionation.—Tlc on silica gel[16] with 1:2 MeOH–Me_2CO was used to separate **2** (R_f 0.66), **3** (R_f 0.84), and **4** (R_f 0.33); the starting point for spots was 2.5 cm from the bottom of the tlc plate and the final solvent front was ~12 cm. Calibration curves for semiquantitative analysis were obtained by measuring the spot areas (by counting squares on a spot of equivalent size on graph paper) of **2**, **3**, and **4**, corresponding to known weights, using usual methods;[21] in constructing the curve, five mixtures of **2**, **3**, and **4** were used in which the respective amounts and proportions were varied; for example, a solution (30% disproportionation supposed) containing **2** (21.0 mg), **3** (3.6 mg), and **4** (5.4 mg) was spotted on three silica-gel plates as described above and then areas of the spots of **2** and **4** were measured and the average value was calculated. In such chromatography the square root of the spot area (A) is proportional to the logarithm of the amount of substances (W), so that $\sqrt{A} = m \log W + c$.[21] Hence a graph prepared by plotting $\sqrt{A}$ as a function of log W (using 1.8–9.0 mg of **4** in solution) could be used to estimate the amount present of **4**, and similarly for **2**; m and c, constants, were 0.40 and 0.67, respectively. This method gave, for example, the amounts of **4** in mixtures of **2**, **3**, and **4** within about ±5% as evidenced by comparisons of percentages of **4** in prepared mixtures with percentages found (in parentheses): 10 (8, 12), 20 (18, 15), 30 (26, 35), 40 (37, 43), 50 (56).

In a typical experiment on the rapidity of disproportionation of **2** to give **3** and **4**, a solution of **2** (30 mg, 0.102 mmol) in MeOH (5 ml) was heated at 60.8 ± 0.2° in a constant-temperature oil bath. From time to time 10 μl of the reaction solution was withdrawn using a microsyringe and was spotted on a silica gel layer. Comparison of the spot areas of **4** with those of the calibration curves gave the amounts of **4**. All of the reactions summarized in Figure 1 and Table II were done under essentially the same conditions, and no solid was present in any of the solutions. Values of k_{approx} (Table II) were calculated by converting the mass of **4** from the tlc plot to moles, considering C_0 based on 0.102 mmol, subtracting twice the moles of **4** at time t from 0.102 to get C, plotting log $(0.102/C)$ *vs.* t (min), taking the slope, and multiplying by 2.303. The disproportionation per cent (Table II and Figure 1) was calculated as (100)(2)·(mmoles of **4**)/(0.102).

D. Isolation of 1,2-Dithiane 1,1-Dioxide (8).—*N*-Ethylmaleimide (0.214 g, 1.71 mmol) was added slowly to a mixture of H_2O (10 ml) and benzene (15 ml) containing **2** (0.500 g, 1.71 mmol) at 0°. After the reaction mixture had been heated at 60° for 50 min with good stirring, the H_2O layer was separated and was washed with benzene. The combined benzene layers were washed with H_2O, dried (Na_2SO_4), and concentrated. The crude **8** obtained (0.100 g, 39%) had mp 45–49°. Recrystallization from Et_2O–hexane gave **8**, mp and mmp 52–53° (lit.[18] mp 54.5–55°), which had an ir spectrum identical with that of authentic **8**.[18]

(2-Acetamidoethyldithio)ethanoic Acid (11).—A solution of NaOH (4.21 g, 0.105 mol) in H_2O (15 ml) was added slowly (~0.5 hr) to mercaptoacetic acid (9.65 g, 0.105 mol) in MeOH (40 ml) at 0°. The resulting solution was kept at 0° and was added (~2 hr) to **10** (26.8 g, 0.100 mol) in MeOH (100 ml) at ~0° with good stirring during ~2 hr. Tlc then showed no spot on alumina corresponding to **10**. The solution was carefully concentrated to about 40 ml at 25° (rotary evaporator, condenser at 0°), saturated with NaCl, and extracted with several 150-ml portions of $CHCl_3$. The extract, dried ($MgSO_4$) and concentrated at ~25°, gave 17.0 g (81%) of white **11**, mp 85–88°. Recrystallization by dissolution in Me_2CO at ~25°, addition of Et_2O to incipient turbidity, and chilling gave **11** as white crystals of constant mp 92–93°: nmr ($CDCl_3$) δ 2.03 (s, CH_3CO), 5.81 (CO_2H); ir 3360, 1690, 1570, 1540, 1300, 1190, 1175, and 890 cm^{-1}; mass spectrum m/e (rel intensity) 43 (100), 60 (65), 86 (90), 118 (50), 151 (5), 186 (4), 209 (1).

Anal. Calcd for $C_6H_{11}NO_3S_2$: C, 34.41; H, 5.27; N, 6.70; S, 30.62; mol wt, 209. Found: C, 34.42; H, 5.34; N, 6.79; S, 30.84; mol wt, 209 (mass spectrum).

3-(2-Acetamidoethyldithio)propanoic Acid (12).—Aqueous NaOH solution (3.76 g, 93.3 mmol in 100 ml of H_2O) was added slowly (40 min) to a mixture of **10** (25.0 g, 93.30 mmol) and 3-mercaptopropionic acid (9.90 g, 93.30 mmol) in 200 ml of H_2O at 0–5° with stirring; solid began to appear at once. The mixture was kept at 25° for 1 hr and then was chilled (0°); filtration gave 13.0 g of white **12**. The mother liquor, extracted with $CHCl_3$, gave 3.0 g of **12**. Accordingly, 16.0 g (77%) of **12** was obtained, mp 80–83°. Recrystallization as with **11** gave **12** as white plates of constant mp 85–86°: nmr ($CDCl_3$) δ 2.03 (s, CH_3CO), 9.60 (s, CO_2H); ir (KBr) 3340, 1705, 1615, 1560, 1540, 1330, 1240, 1185, 900 cm^{-1}; mass spectrum m/e (rel intensity) 43 (100), 60 (30), 86 (95), 118 (22), 164 (9), 210 (3), 223 (1).

Anal. Calcd for $C_7H_{13}NO_3S_2$: C, 37.68; H, 5.83; N, 6.28; S, 28.69; mol wt, 223. Found: C, 37.88; H, 6.01; N, 6.16; S, 28.48; mol wt, 223 (mass spectrum).

4-(2-Acetamidoethyldithio)butanoic Acid (13).—As with **12**, NaOH (2.8 g, 70.0 mmol) in H_2O (50 ml) was added in part to **10** (20.0 g, 74.5 mmol) and 4-mercaptobutanoic acid (8.40 g, 70.0 mmol) at 0–5° with stirring. Immediate precipitation made stirring difficult. Water (200 ml) was added, and addition of NaOH was continued. The mixture was let stand at ~25° for 2 hr. Treatment as for **12** gave 15.0 g (90%) of white **13**, mp 82–85°. Recrystallization as with **11** gave **13** of constant mp 87–88°: nmr ($CDCl_3$) δ 2.03 (s, CH_3CO), 17.1 (s, CO_2H); ir (KBr) 3330, 1715, 1635, 1585, 1300, 1220, 1180 cm^{-1}; mass spectrum m/e (rel intensity) 43 (100), 60 (15), 86 (80), 118 (14), 151 (12), 178 (2), 237 (1).

Anal. Calcd for $C_8H_{15}NO_3S_2$: C, 40.55; H, 6.34; N, 5.91; S, 27.00; mol wt, 237. Found: C, 40.31; H, 6.19; N, 5.80; S, 26.91; mol wt, 237 (mass spectrum).

5-(2-Acetamidoethyldithio)pentanoic Acid (14).—**5-Mercaptopentanoic acid** was synthesized as follows.[22] A mixture of δ-valerolactone (100 g, 1.19 mol) and thiourea (83.6 g, 1.10 mol) in 48% HBr (1.2 mol) was heated under reflux for 10 hr. The mixture then was made strongly basic with 50% aqueous NaOH until a homogeneous solution resulted, which was heated under reflux for 2.5 hr and then was allowed to stand overnight. The solution was acidified with H_2SO_4, and an Et_2O extract was washed with H_2O, dried ($MgSO_4$), and concentrated. Distillation gave 85.0 g (58%) of 5-mercaptopentanoic acid: bp 103–105° (0.7 mm); nmr ($CDCl_3$) δ 1.27 (t, SH), 12.06 (s, CO_2H); ir 2940, 2660, 2580, 2320, 1715, 1420, 1285, 1230 cm^{-1}.

Much as with **12**, NaOH (2.80 g, 70.0 mmol) in 50 ml of H_2O then was added to **10** (20.0 g, 74.5 mmol) and 5-mercaptopentanoic acid (9.40 g, 70.0 mmol) in 100 ml of H_2O at 5–10°, giving 17.0 g (97%) of **14**, mp 60–65°. Recrystallization as with **11** gave **14** of constant mp 69–70°; nmr δ 2.03 (s, CH_3CO), 9.67 (s, $-CO_2H$); ir (KBr) 3370, 2955, 2880, 1715, 1630, 1560, 1425, 1285, 1210, 1185 cm^{-1}; mass spectrum m/e (rel intensity) 43 (100), 60 (17), 86 (90), 118 (14), 192 (1), 251 (2).

Anal. Calcd for $C_9H_{17}NO_3S_2$: C, 43.10; H, 6.78; N, 5.58; S, 25.58; mol wt, 251. Found: C, 42.90; H, 6.60; N, 5.42; S, 25.52; mol wt, 251 (mass spectrum).

Disproportionation of the Acids 11–14 and Their Salts 11′–14′.

A. Of 11–14.—In a typical experiment, a solution of **12** (111.5 mg, 0.05 mmol) in 5 ml each of MeOH in H_2O was heated at 61°. From time to time 10 μl of the solution was withdrawn by a microsyringe and spotted on an alumina layer (solvent, 1:2 benzene–Me_2CO). After 3 days of heating, tlc showed no spot of **3** (R_f of **3**, 0.45; of **11–14**, 0).[23]

When **12** (45 mg, 0.2 mmol) in MeOH (10 ml) was heated at 61° for 3 days, 44 mg (98%) was recovered (identity was assured by melting point and ir). After 3 days, **11**, **13**, and **14** were stable in both H_2O and MeOH at 61°; **11**, **13**, and **14** were each recovered (~100% from MeOH).

B. Isolation of 3 after Heating of 11′–14′.—Illustratively, aqueous NaOH (82.0 mg, 2.04 mmol) was added to **12** (446 mg, 2.00 mmol) in H_2O (25 ml); the pH then was ~8. The solution was heated at 55–60° for 13 hr and then was extracted with $CHCl_3$ three times. The extract was washed with cold H_2O, dried ($MgSO_4$), and concentrated: yield of **3**, 85.0 mg (36%); ir spectrum identical with that of authentic **3**; mp 91–92° (lit.[17]

(21) K. Randerath, "Thin-Layer Chromatography," 2nd ed, Academic Press, New York, N. Y., 1966, p 70 ff.

(22) Based on the procedure of Kodak Society, Belgian Patent No. 593,048 (1960); *Chem. Abstr.*, **55**, 14142 (1961).

(23) Eastman Chromagram sheet Type 6063 alumina with fluorescent indicator; uv was used in searching for **3**.

mp 92–93°). The values for disproportionation per cent of 37–46% mentioned for **13** and **14** (see discussion) were obtained similarly.

C. **Equilibration of 13′ and 14′.**—A solution of the acid **13** (1.04 g, 4.39 mmol) in H_2O (50 ml) containing NaOH (0.176 g, 4.40 mmol) was heated at 61° (pH ~8). From time to time, 10 ml was withdrawn, saturated with NaCl, and extracted with $CHCl_3$. Removal of $CHCl_3$ gave **3**, which was recrystallized from Me_2CO–Et_2O and then identified by ir and melting point. Compound **14** was treated similarly, and disproportionation per cent was calculated as described above (previous section C). The results based on the weight of **3** isolated are shown in Table III.

D. **Disproportionation of Salts 11′–14′.**—For the preparation of the sodium salts **11′–14′** of the acids **11–14**, illustratively, a solution of NaOMe in MeOH (2.2 ml of 1.0 *N*) was added to **14** (0.55 g, 2.2 mmol) in MeOH (3 ml) to a pH of 6.8–7.0. Addition of dry Me_2CO then immediately precipitated white **14′**. Decantation and drying at 0.1 mm gave **14**, which was washed with acetone and then was dried again at 0.1 mm under vacuum, mp 188° dec. Compounds **11′**, **12′**, and **13′** were obtained similarly, except that with **11′** and **12′** dry Et_2O was used instead of Me_2CO because **11′** and **12′** are slightly soluble in Me_2CO. Melting points follow: **11′**, 280° dec; **12′**, 120–122°; and **13′**, 215° dec. The purity of **11′–14′** was confirmed by checking absence of any **3** by tlc on alumina.

The disproportionation results of Table IV were obtained using ~1 mmol in 10 ml of H_2O of **11′–14′** (or **11–14** where specified). Illustratively, a solution of **14′** (273 mg, 1 mmol) in 10 ml of H_2O was heated at 61 ± 0.5° in a constant-temperature bath. From time to time, 5 μl was withdrawn by a microsyringe and spotted for tlc on an alumina layer.[23] The spot for disulfide **3** then was observed, and the time was reported in Table IV at which the area no longer increased.

Registry No.—**2**, 34915-80-5; **3**, 638-44-8; **4**, 34915-82-7; **11**, 34915-83-8; **11′**, 34915-84-9; **12**, 34915-85-0; **12′**, 34915-86-1; **13**, 34915-87-2; **13′**, 34915-88-3; **14**, 34915-89-4; **14′**, 34915-90-7.

Electron-Accepting Through-Conjugation Effects in Organosulfur Compounds

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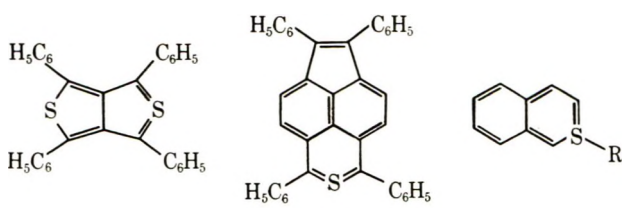
The importance of cyclic conjugation involving (p → d)-π bonding has been investigated in attempted syntheses of thianaphthalene derivatives and in the transmission of substituent effects through sulfur in *S*-phenacyl-*S*-phenyl-*S*-methylsulfonium salts as evaluated from pK_a measurements. No evidence was obtained to support the concept of through-conjugation in the systems chosen for study.

There now exists a large body of experimental evidence regarding the electron-accepting properties of sulfur. These properties are generally described as valence-shell expansion by π bonding in which overlap occurs between a vacant 3d sulfur orbital and a filled 2p orbital of an adjacent first-row atom.[2] The importance, however, of 3d orbitals in supporting electron delocalization *through* sulfur remains a controversial issue. For example, the question of participation of 3d orbitals in the bonding of thiophene has been frequently discussed,[3] and it now appears that 3d and higher energy orbitals contribute very little to the bonding in thiophene in its ground state.[4] Positive evidence for through-conjugation by way of sulfur stems from the synthesis of stable sulfur heterocycles of the type **1**,[5] **2**,[6] **3**,[7] and **4**[8] in which sulfur may be



1 **2** **3**

viewed as quadricovalent in a delocalized π system. However, the stability of thiaaromatic compounds varies widely. For example, thiabenzenes **5**[7,9] and thianaphthalenes **3**[7] vary in stability according to the nature and position of substituents; the thiabenzene 1-oxide **6** is remarkably stable[9] although the chemical behavior of **6** more closely resembles that expected for an ylide structure than for a delocalized benzenoid structure. Likewise, the aromaticity of thiaphenalenes **2** is open to question,[3b] while thiepin dioxide **7** and related compounds, which are formally 6-π-electron systems related to tropone, do not appear to possess aromatic character.[10] The acidity of the cyclic sulfone **8** is unexceptional relative to that of the open-chain analog **9**, and this suggests that the carbanion derived from **8** lacks aromaticity.

While the experimental evidence is both positive and negative on the issue of through conjugation, theoretical arguments are not clear-cut either. Calculations illustrating the importance of cyclic conjugation

(1) The authors wish to gratefully acknowledge the support received for this work from the National Science Foundation (GP 7278 and GP 12828).

(2) For reviews on the topic of sulfur bonding see (a) G. Cilento, *Chem. Rev.*, **60**, 147 (1960); (b) A. B. Burg in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, pp 30–40; (c) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1962; (d) D. T. Clark in "Organic Compounds of Sulfur, Selenium, and Tellurium," Special Publication of the Chemical Society, D. H. Reid, Ed., London, 1970; (e) K. A. R. Mitchell, *Chem. Rev.*, **69**, 157 (1969).

(3) For recent reviews on valence-shell expansion in sulfur heterocycles, see (a) W. G. Salmond, *Quart. Rev., Chem. Soc.*, **22**, 253 (1968); (b) D. H. Reid in "Organic Compounds of Sulfur, Selenium and Tellurium," Vol. I, Special Publication of the Chemical Society, D. H. Reid, Ed., London, 1970.

(4) D. T. Clark, *Tetrahedron*, **24**, 2663 (1968); D. T. Clark and D. R. Armstrong, *Chem. Commun.*, 319 (1970); U. Gelius, B. Roos, and P. Siegbahn, *Chem. Phys. Lett.*, **4**, 471 (1970); M. J. S. Dewar and M. Trinajstić, *J. Amer. Chem. Soc.*, **92**, 1453 (1970).

(5) M. P. Cava and G. E. M. Husbands, *ibid.*, **91**, 3952 (1969).

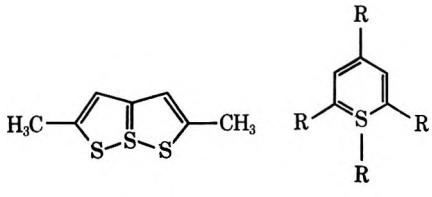
(6) J. M. Hoffman, Jr., and R. H. Schlessinger, *ibid.*, **91**, 3953 (1969).

(7) (a) G. Suld and C. C. Price, *J. Amer. Chem. Soc.*, **83**, 1770 (1961); **84**, 2090 (1962); (b) C. C. Price, M. Hori, T. Parasaran, and M. Polk, *ibid.*, **85**, 2278 (1963); (c) C. C. Price and D. H. Follweiler, *J. Org. Chem.*, **34**, 3202 (1969); (d) C. C. Price, M. Siskin, and C. K. Miao, *ibid.*, **36**, 794 (1971).

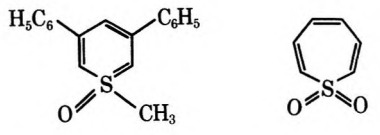
(8) For a concise summary of the historical development of thiathiophenes, see ref 3a.

(9) (a) A. G. Hortmann, *J. Amer. Chem. Soc.*, **87**, 4972 (1965); (b) Y. Kishida and J. Ide, *Chem. Pharm. Bull.*, **15**, 360 (1967); (c) B. Holt, J. Howard, and P. A. Lowe, *Tetrahedron Lett.*, 4937 (1969); (d) A. H. Hortman and R. L. Harris, *J. Amer. Chem. Soc.*, **92**, 1803 (1970).

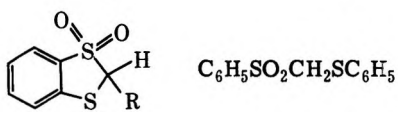
(10) W. L. Mock, *J. Amer. Chem. Soc.*, **89**, 1281 (1967); W. E. Truce and F. J. Lotspeich, *ibid.*, **78**, 848 (1956); V. J. Traynelis and R. F. Love, *Chem. Ind. (London)*, 439 (1958); *J. Org. Chem.*, **26**, 2728 (1961); H. Hofmann and H. Westernacher, *Angew Chem., Int. Ed. Engl.*, **5**, 958 (1966).



4 5



6 7



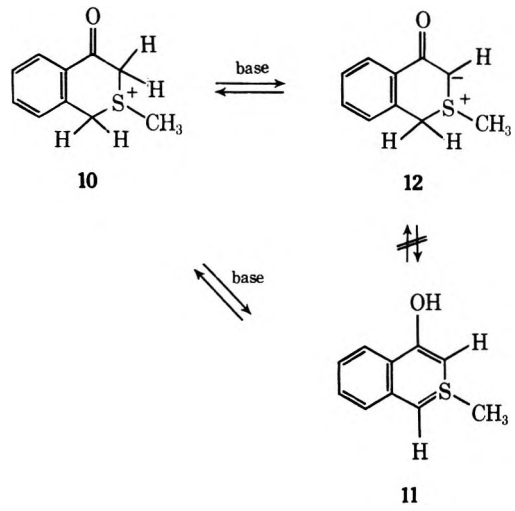
8 9

through 3d orbitals of second-row elements has been advanced by Craig[11] and questioned by Dewar.[12] Their arguments were initially concerned with the question of delocalization in phosphonitrilic compounds, but they may be applied equally well to other systems which may in principle support (p → d)-π bonding.[13]

A somewhat different approach has been advanced by Price[7c] to explain the benzenoid properties of compounds of type **3**. He has suggested that the delocalized π system of **3** may utilize a sulfur 3p and carbon 2p orbitals with the nonbonding electron pair on sulfur promoted to a 3d orbital. The heterocycle would by this theory be planar and would accordingly be destabilized by bulky substituents ortho to the heteroatom that would force nonplanarity on the ring system. Evidence in support of this theory has been given.[7c]

It was with this background to the topic of through-conjugation that we initiated an investigation designed to test the driving force for aromaticity in thianaphthalene derivatives and to measure the transmission of substituent effects in the C–S–C system which we describe in this paper.

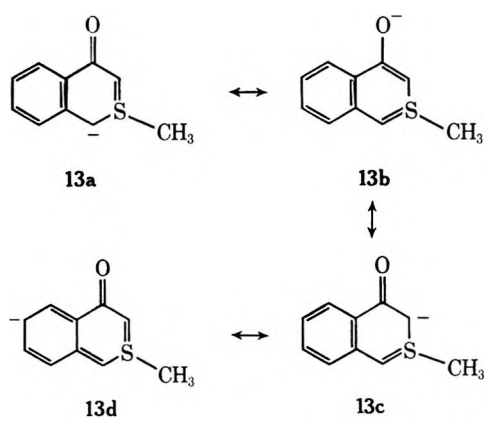
Thianaphthalene–Ylide Tautomerism.—In order to contribute to the question of thiabenzene aromaticity, an investigation of the behavior of 2-methylisothiachroman-4-one fluoroborate (**10**) with base was undertaken. We reasoned that, if resonance stabilization is significant in a cyclic system of ten π electrons delocalized through sulfur and nine carbons, then treatment of **10** with base might afford the thianaphthol derivative **11**, or an equilibrium mixture of **11** and the cyclic ylide **12**. When **10** was treated with an equivalent of aqueous sodium hydroxide, sodium methoxide in ether–methanol, or sodium hydride in tetrahydrofuran, a single compound was isolated in high yield (90%). This compound was clearly not the thianaphthol derivative **11** but had all the characteristics expected of a β-carbonyl-stabilized sulfonium ylide **12**. Thus, its infrared spectrum showed a strong band at 1510 cm^{-1} typical of β-keto ylides;[14] it was formed from **10** *reversibly* by the addition of appropriate amounts of acid or base, and its nmr spectrum in various solvents listed in Table I leaves no doubt that its structure is correctly assigned as **12**. In particular, the broad temperature-dependent resonance near 3.7 ppm is typical of an exchange-broadened resonance of an ylide proton,[15] and the nonequivalence of the benzylic protons establishes that the structure is nonplanar. No resonances that could be ascribed to the thianaphthol **11** were evident and any rapidly established equilibration between **11** and **12** is ruled out by the observation that the benzylic protons of **12** are coupled (J = 15.8 Hz) and are not exchanged by the addition of D_2O to solutions of **12** in DMSO-d_6 or acetonitrile. In contrast, the methine proton of **12** is exchanged instantly, typical of ylide behavior.[16]



10 12

11

Rapid exchange of the benzylic protons of **12** was observed, however, on addition of aqueous base (NaOD–D_2O) to solutions of **12** in DMSO-d_6. Enhanced acidity of the benzylic protons is anticipated if the resulting anion can support electron delocalization suggested by structures **13a**, **13b**, **13c**, and **13d**. To obtain



13a 13b

13d 13c

(11) (a) D. P. Craig, A. Maccoll, R. S. Nyholm, L. E. Orgel, and L. E. Sutton, *J. Chem. Soc.*, 332 (1954); (b) D. P. Craig and E. A. Magnusson, *ibid.*, 4895 (1956); (c) D. P. Craig, *ibid.*, 997 (1959); D. P. Craig and N. L. Paddock, *ibid.*, 4118 (1962).

(12) M. J. S. Dewar, E. A. C. Lucken, and M. A. Whitehead, *J. Chem. Soc.*, 2423 (1960); M. J. S. Dewar and V. P. Kubba, *J. Amer. Chem. Soc.*, **82**, 5685 (1960).

(13) Conjugation effects in the related system N–Si–N are discussed by C. H. Yoder and J. J. Zuckerman, *Inorg. Chem.*, **6**, 103 (1967).

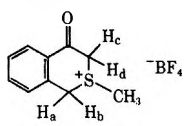
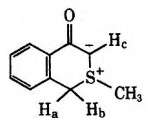
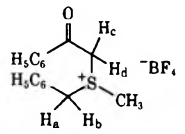
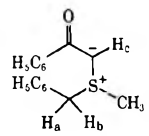
(14) A. J. Speziale and K. W. Ratts, *J. Amer. Chem. Soc.*, **85**, 2790 (1963); H. Nozaki, D. Tunemoto, Z. Morita, K. Nakamura, K. Watanabe, M. Takaku, and K. Kondo, *Tetrahedron*, **23**, 4279 (1967).

(15) S. H. Smallcombe, R. J. Holland, R. H. Fish, and M. C. Caserio, *Tetrahedron Lett.*, 5987 (1968).

(16) H. Nozaki, D. Tunemoto, S. Matubara, and K. Kondo, *Tetrahedron*, **23**, 545 (1967); F. J. Randall and A. W. Johnson, *Tetrahedron Lett.*, 2841 (1968); H. J. Bestman, H. G. Liberda, and J. P. Snyder, *J. Amer. Chem. Soc.*, **90**, 2963 (1968); P. Crews, *ibid.*, **90**, 2961 (1968).

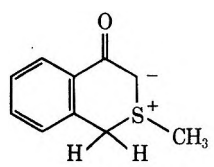
TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA OF β-KETOSULFONIUM SALTS AND YLIDES[a]

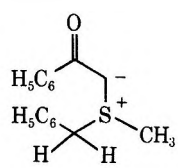
Compd		δaromatic	δH_a[b]	δH_b[b]	$\Delta\nu_{ab}$	J_{ab}	δH_c	δH_d	J_{cd}	J_{ac}	δSCH_3	Solvent
10		7.67 (3 H) 8.05 (1 H)	4.91	4.56	21.2	16.6	4.45[b]	4.09[b]	18.0	2.0	2.83	CH_3CN
		7.58 (3 H) 7.92 (1 H)	4.98	4.64	20.1	16.0	4.59[b,c]	4.27[b]	18.0	c	2.80	CH_3SOCH_3
			5.07	4.69	22.4	16.2					2.93	D_2O[e]
12		7.39 (3 H) 8.16 (1 H)	3.93	4.51	34.9	15.8	3.75[d]				2.42	$CDCl_3$
		7.32 (3 H) 7.75 (1 H)	4.16	4.54	22.5	15.8	3.63[d]				2.35	CD_3SOCD_3
		7.40 (3 H) 8.00 (1 H)	4.49	3.97	31.6	15.8	2.53[d]				2.35	CH_3CN
		7.5 (8 H) 8.0 (2 H)	4.8	4.8			5.7	5.7			2.90	CD_3SOCD_3
14		7.3 (8 H) 7.75 (2 H)	4.85	4.42	25.7	12.0	4.11[d]				2.85	$CDCl_3$
		7.28 (8 H) 7.63 (2 H)	4.86	4.30	33.4	12.0	4.03[d]				2.80	CD_3SOCD_3
			4.98	4.00	58.8	12.0	4.00[d]				2.51	C_6H_6

[a] Chemical shifts are in parts per million downfield from TMS as internal standard; coupling constants are in hertz measured at 60 MHz. [b] Part of AB quartet. [c] Broadened line shape of δH_c obscured long-range coupling J_{ac}. [d] Exchange broadened. [e] External reference, TMS.

evidence on this point, a comparison was made of the acidities of the benzylic protons of **12** and the benzylic protons of the related acyclic ylide **14**, which cannot



12

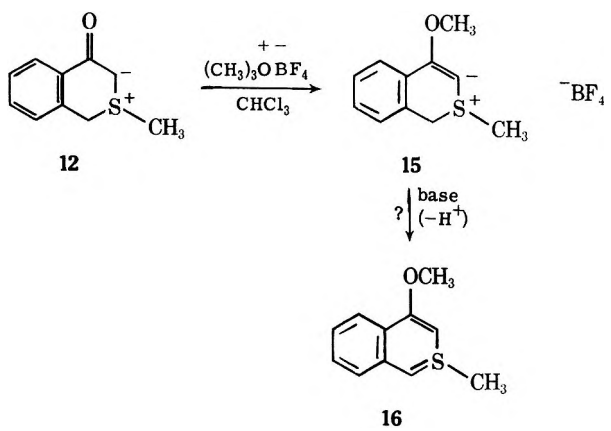


14

form an anion stabilized by cyclic conjugation. Qualitatively, there was no apparent difference in the behavior of **12** and **14** with base. When a mixture of **12** and **14** in DMSO-d_6 was allowed to compete for less than an equivalent amount of NaOD–D_2O, the nmr spectrum of the mixture showed changes in the benzylic AB quartets of *both* ylides. The progressive changes observed in both ylides with increasing added base showed that the exchange rates were not remarkably different and we are forced to conclude that the benzylic protons of **12** are not unusually acidic relative to those of **14**. The significance of delocalization implied in **13** is therefore questionable.

The cyclic ylide **12** was converted to the methyl ether derivative **15** by O-methylation with trimethyloxonium fluoroborate. The behavior of **15** with base is of some importance to the question of cyclic conjugation, since it is conceivable that a stable thianaphthalene derivative **16** might be formed.

No significant reaction occurred on treating **15** with sodium methoxide in methanol or with sodium hydride suspended in dry ether. However, potassium *tert*-butoxide in DMSO and sodium hydride in dry THF both reacted with **15** to give highly colored reaction mixtures from which an amorphous, reddish-brown solid could be isolated. This material defied purification; it could not be recrystallized and its nmr spectrum in chloroform was broad and ill-resolved sug-



12 **15** **16**

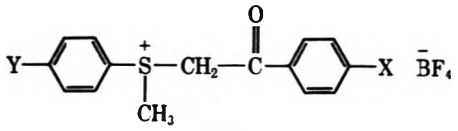
gesting a polymeric composition. On following the exchange of **15** with NaOD–D_2O in acetonitrile–DMSO-d_6 by nmr, it was observed that the *S*-methyl, vinylic, and benzylic protons exchanged at comparable rates. We conclude from these experiments that, if a compound of structure **16** is formed, it is not notably stable and rapidly reprotonates.

Transmission of Substituent Effects in β-Ketosulfonium Ylides.—Several comparative studies of the pK_a values of nitrogen, phosphorus, arsenic, and sulfur onium compounds have been reported.[17-20] The order of ylide stability may be established from the data as N < As < P < S, which parallels the order of increasing importance of (p → d)-π bonding. Linear free energy relationships have also been established from pK_a's of structures **17**,[18] **18**,[19] and **19**.[20] Thus, transmission of the electrical effects of the phenacyl X substituent in **17**, **18**, and **19** follows a Hammett $\rho\sigma$ relationship with ρ = +2.1, +2.3, and +2.3, respectively. It will be noted that there is no direct conjugation of the X sub-

(17) A. W. Johnson and R. T. Amel, *Can. J. Chem.*, **46**, 461 (1968).
(18) K. W. Ratts and A. N. Yao, *J. Org. Chem.*, **31**, 1185 (1966).
(19) S. Fliszar, R. F. Hudson, and G. Salvadori, *Helv. Chim. Acta*, **46**, 1580 (1963).
(20) W. G. Phillips and K. W. Ratts, *J. Org. Chem.*, **35**, 3144 (1970).

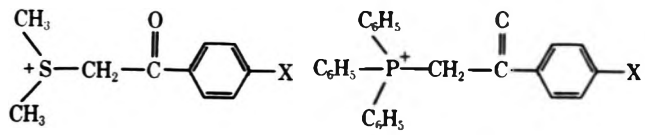
TABLE II

PHENACYLSULFONIUM FLUOROBORATE SALTS[a]

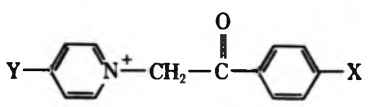


Compd 20	Y	X	Mp, °C	pK_a	δ_{CH_2},[b] ppm	δ_{SCH_3},[b] ppm	δ_{aryl},[c] ppm	δ_X, ppm	λ_Y, ppm	λ_{max},[d] nm	λ_{max},[e] nm
					Series 1						
a	H	H	102–103	7.32	5.86	3.35	7.5–8.3			297	244
b	H	Br	164–166	6.73	5.86	3.36	7.6–8.3			295	268
c	H	Cl	146–147		5.87	3.37	7.6–8.3			305	266
d	H	CH_3	137.5–138.5	7.63	5.86	3.46	7.3–8.3	2.41		299	266
e	H	OCH_3	137–138	8.13	5.82	3.45	7.0–8.3	3.87		305	243
f	H	NO_2	173.5–175.5	5.79	5.92	3.36	7.2–8.4			343	266
					Series 2						
a	H	H	102–103	7.32	5.86	3.35	7.5–8.3			297	244
g	Br	H	133–135	6.89	5.90	3.38	7.6–8.3			297	245
h	Cl	H	123–125		5.92	3.40	7.6–8.3			298	240
i	CH_3	H	135–137	7.59	4.35	3.45	7.4–8.2		2.42	296	253
j	CH_3O	H	105–107	7.79	3.88	3.34	7.2–8.2		3.88	295	251
k	NO_2	H	129–131	6.19	5.96	3.44	7.5–8.2			283	255

[a] Satisfactory elemental analyses were obtained for all compounds with the exception of X = Br which was consistently 3% high in carbon for no apparent reason. [b] In DMSO-d_6 at 60 MHz; singlet; chemical shift relative to TMS internal standard. [c] Multiplet. [d] Uv of ylide in aqueous base. [e] Uv of salt in aqueous solution.



17 18



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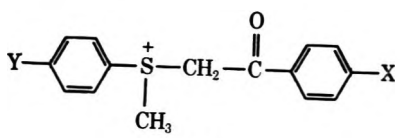
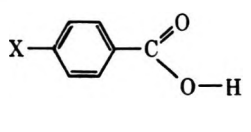


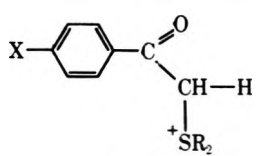
20

stituent with the carbanion center, and in this respect phenacyl ylides parallel substituted benzoic acids (*cf.* **21** and **22**). A linear correlation between the pK_a's of



$\rho = 1$

21



$\rho = 2$

22

phenacylsulfonium ylides and benzoic acids in which there is no enhanced resonance effect is not then surprising.

Of greater interest to the present study is the transmission of substituent effects *through* sulfur in ylides derived from sulfonium salts of type **20**. If the electronic effects of the Y substituent in the ylide derived from **20** can be transmitted through sulfur by d-orbital interactions with the adjacent p-π system, this should be evidenced by an enhanced resonance effect of Y on the acidity of **20**. For example, if resonance stabilization of the nitro-substituted ylide **23** is important due to contributions from the hybrid structure **23b** involving conjugation through sulfur, this should be reflected in a low basicity for **23**, or a low pK_a for its conjugate acid **20** (Y = NO_2).

To test these concepts, we prepared two series of salts of type **20** and determined their pK_a's. In series 1, the Y substituent was held at Y = H as the X substituent was varied from H to CH_3, Br, OCH_3, and NO_2. In series 2, X was held at X = H as Y was varied. The physical and spectral properties of these compounds are summarized in Table II. The pK_a values for the salts in aqueous solution were determined spectrophotometrically and the values obtained are listed in Table II. The acidity data was analyzed by the Ehrenson–Brownlee–Taft dual-parameter equation[21]

$$pK_a = \rho_I\sigma_I + \rho_R\sigma_R$$

where σ_I and σ_R are inductive and resonance substituent constants, respectively, and ρ_I and ρ_R are essentially weighting factors that reflect the relative importance of inductive and resonance effects in the given system. The values of ρ_I and ρ_R were obtained from the best fit of the data to the dual-parameter equation. A reiterative computer procedure was employed to obtain the best fit, which included variation of the substituent constants to include σ_I values, σ_R^+, σ_R, σ_R^0, and σ_R^-.

For series 1 in which X is varied and Y = H, the best fit was obtained using σ_R. The ρ_I and ρ_R values were found to be essentially equal and the data corresponds therefore to a straightforward Hammett $\rho\sigma$ relationship in which $\rho = +2.0$ (Figure 1). This parallels the acidity of the related compounds **17**, **18**, and **19** for which $\rho = 2.1$–2.3. Transmission of substituent effects through the phenacyl ring as measured by the ρ value

(21) S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Prog. Phys. Org. Chem.*, **10**, in press

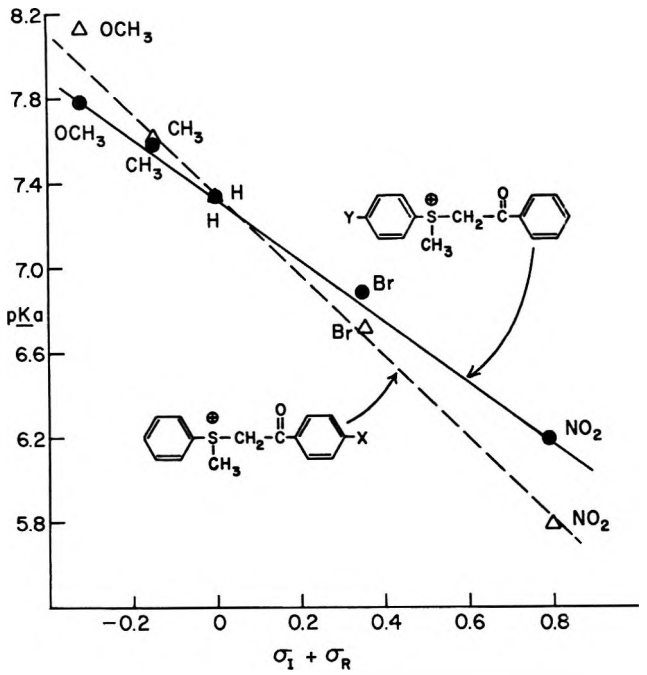
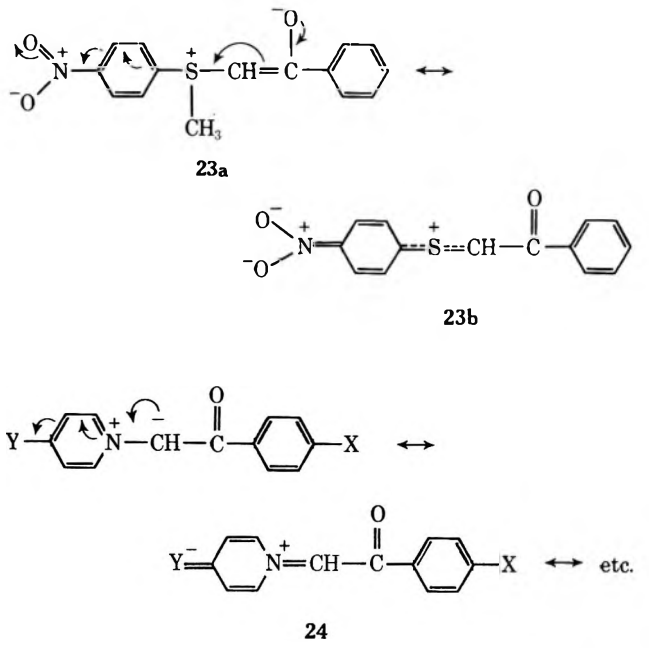


Figure 1.—Plot of pK_a's of substituted β-ketosulfonium salts **20** against inductive and resonance parameters of the substituents X or Y. The data refer to aqueous solutions at 25°, △ to series 1, Y = H, and ● to series 2, X = H.

is therefore independent of the nature of the onium group and is roughly twice as effective as in the benzoic acids (ρ = 1 by definition). However, the pK_a's of the pyridinium salts **19**[20] are higher by about 2.6 pK units than the pK_a's of the structurally related sulfonium salts **20**. This notable difference provides one of the strongest arguments for the involvement of d orbitals in the bonding of sulfonium ylides.

For series 2 in which Y is varied and X = H, the best fit was again obtained using σ_R values. The ρ_I and ρ_R values were also found to be equal and correspond to a Hammett ρ value of +1.4 (Figure 1). The fact that a Hammett type of free-energy relationship for series 2 was observed is inconsistent with the concept of an enhanced resonance contribution due to conjugation through sulfur and indicates that the substituent effects are mainly inductive in nature. Furthermore, the smaller ρ value (+1.4) for series 2 relative to series 1 (+2.0) means that substituent effects are transmitted less effectively through the phenylsulfonium group than through the phenacyl group. In particular the difference of 0.4 pK units in the acidities of **20k** (Y = NO_2, X = H) and **20f** (Y = H, X = NO_2) implies that the ylide **23** derived from **20k** is more basic (less stable relative to **20k**) than the ylide from **20f**, which argues against the importance of structure **23b** in stabilizing the ylide.

The data for series 2 may be compared with the pK_a data for the pyridinium salt **19** for which ρ = +2.9 as Y is varied with X constant. This ρ value is notably higher than the ρ values for series 1 and 2 as well as for **17** and **18**, and it has been suggested that this relatively high value reflects direct conjugation of the carbanion center with the pyridine ring in the derived ylide **24**. This being so, the validity of related conjugation effects in the sulfonium ylides obtained from **20** is placed further in doubt.



In summary, the evidence at hand does not support conjugation effects transmitted *through* sulfur. An orbital description of (p → d)π bonding need not therefore be invoked to explain the chemistry of the sulfonium salts and ylides described in this paper.

Experimental Section

2-Methylisothiachroman-4-one fluoroborate (**10**) was prepared in 95% yield by the methylation of isothiachroman-4-one[22] with 1 equiv of trimethyloxonium fluoroborate as a suspension in methylene chloride.[23] Recrystallization of the crude product from absolute ethanol gave colorless crystals, mp 153–154°.

Anal. Calcd for $C_{10}H_{11}BF_4OS$: C, 45.12; H, 4.16. Found: C, 45.01; H, 4.06.

2-Methylisothiachroman-4-one-3-ylide (**12**) was prepared from **10** on treatment with aqueous sodium hydroxide and extracting with chloroform, or with sodium hydride in dry THF, or with sodium methoxide in methanol–ether solution. The latter method proved to be the most satisfactory. To 1.70 g (7.87 mmol) of sodium methoxide as a 25% solution in methanol was added 2.50 g (9.4 mmol) of **10** and 25 ml of ether. The mixture was stirred for 10 min and the solvents were removed by evaporation at reduced pressure. The residual yellow solid was extracted with 50 ml of chloroform. The chloroform was evaporated and the residue was worked up with pentane and then air dried to give 1.31 g of **12** as a yellow solid, mp 126–128° dec.

Anal. Calcd for $C_{10}H_{10}OS$: C, 65.83; H, 5.66. Found: C, 65.58; H, 5.56.

Methylation of 2-Methylisothiochroman-4-one-3-ylide.—To a solution of 1.31 g of **12** in 50 ml of chloroform was added 1.9 g of trimethyloxonium fluoroborate. The mixture was stirred for 30 min and then decanted from any insoluble material, and the solvent was removed by evaporation at reduced pressure. The residual oil crystallized after washing with pentane and was subsequently recrystallized from absolute ethanol. The product **15** was obtained as almost white crystals, mp 121–122°, and gave an nmr spectrum in $CDCl_3$ showing a complex four-proton aromatic resonance near 7.5 ppm, a one-proton vinylic singlet at 5.75 ppm, a two-proton singlet at 4.55 ppm, a three-proton singlet at 4.00 ppm, and a three-proton singlet at 2.75 ppm. In acetonitrile, the benzylic protons of **15** appeared as an AB quartet (J = 16 Hz) with coupling of the upfield proton to the vinylic proton. On adding a D_2O–OD^- solution to the sample of **15** in CH_3CN in an nmr tube, the exchange of the vinylic, benzylic, and SCH_3 proton was observed.

(22) A. K. Kiang and F. G. Mann, *J. Chem. Soc.*, 1909 (1951).

(23) M. C. Caserio, R. E. Pratt, and R. J. Holland, *J. Amer. Chem. Soc.*, **88**, 5747 (1966).

Anal. Calcd for $C_{11}H_{13}BF_4OS$: C, 47.15; H, 4.67. Found: C, 46.95; H, 4.50.

Reaction of **15** (0.2 g in 1 ml of DMSO-d_6) with 1 equiv of potassium *tert*-butoxide was observed directly by nmr. The AB pattern of the benzylic protons disappeared rapidly but there was no significant change in the chemical shift of the vinylic, SCH_3, or OCH_3 resonances of **15**. Attempts to isolate the product(s) of this reaction led only to the isolation of a sticky red solid which could not be recrystallized. Reaction of **15** with sodium hydride in dry THF in an inert atmosphere led to the immediate evolution of hydrogen, precipitation of $NaBF_4$, and formation of a dark red solution which, after evaporating at reduced pressure, gave a red oil which solidified on washing repeatedly with pentane. Analysis by tlc showed the presence of at least three components. Separation was unsuccessful, and the nmr of the crude product in $CDCl_3$ gave very broad signals which were uninformative as to structure.

***S*-Benzyl-*S*-methyl-*S*-phenacylsulfonium ylide (14)** was prepared from the corresponding sulfonium bromide salt by treatment with sodium hydride in THF.[24] The sulfonium bromide was prepared from benzyl methyl sulfide and phenacyl bromide in benzene.

Preparation of Sulfonium Salts 20.—Each of the salts was prepared from the corresponding sulfide by methylation with trimethyloxonium fluoroborate, as described above for **10**. The salts so obtained were recrystallized to analytical purity from absolute ethanol. The sulfides were in turn prepared by the reaction of the appropriate thiophenol under basic conditions (sodium ethoxide in ethanol) with the appropriate phenacyl bromide. The procedure used was typically as follows for the preparation of *p*-methylphenacyl phenyl sulfide. To a solution of 2.88 g (0.125 g-atom) of sodium metal in 250 ml of ethanol was added all at once 13.8 g (0.125 mol) of thiophenol. To this stirred solution was added 26.7 g (0.125 mol) of *p*-methylphenacyl bromide. The mixture was gently refluxed and stirred for 1 hr, during which time sodium bromide precipitated out. The cooled mixture was filtered and evaporated. The residual oil solidified on cooling and was recrystallized from hexane to give 26.3 g (87%) of product.

Determination of pK_a for Sulfonium Salts 20.—Aqueous solutions of each of the sulfonium salts were prepared using oxygen-free distilled water. These stock solutions were diluted accordingly with standard KOH and standard HBF_4 such that 8–10 solutions of a given salt at different pH were prepared, the net concentration of salt + ylide remaining constant. The pK_a value is expressed by the relationship pH = pK_a − log [salt]/[ylide] and a plot of pH *vs.* log [salt]/[ylide] should be linear and of unit slope. The relative amount of salt and ylide present at a given pH was determined spectrophotometrically, and a plot was made of pH *vs.* log [salt]/[ylide]. In each case, the slope was verified as unity. The pK_a was determined directly from the plot for the condition [salt] = [ylide].

Registry No.—**10**, 24806-67-5; **12**, 24310-06-3; **14**, 15876-09-2; **15**, 34881-62-4; **20a**, 34881-63-5; **20b**, 34881-64-6; **20c**, 33043-77-5; **20d**, 34881-66-8; **20e**, 34881-67-9; **20f**, 34881-68-0; **20g**, 33043-72-0; **20h**, 33192-02-8; **20i**, 33043-70-8; **20j**, 34881-71-5; **20k**, 33043-73-1; $PhCOCH_2S(Me)CH_2Ph \cdot BF_4$, 17069-29-3.

(24) K. W. Ratts and A. N. Yao, *J. Org. Chem.*, **33**, 70 (1968).

Mechanisms of Alkaline Hydrolysis of *p*-Nitrophenyl Glucopyranosides

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Received January 24, 1972

The alkaline hydrolysis of *p*-nitrophenyl-α- and -β-D-glucopyranosides has been studied by gas chromatographic, uv spectrophotometric, and nmr spectroscopic methods. The α anomer is hydrolyzed to a degradative product of D-glucose whereas the β anomer yields the degradative product of D-glucose and 1,6-anhydroglucopyranose. The formation of the degradative product of D-glucose and the detection of a free radical during the hydrolysis suggest the complexity of the over-all pathways for the alkaline hydrolysis of *p*-nitrophenyl glucopyranosides. *p*-Nitrophenyl-β-D-glucopyranoside is hydrolyzed by mixed mechanisms, C-2 oxyanion participation, and nucleophilic aromatic substitution. In alkaline media, *p*-nitrophenyl-α-D-glucopyranoside forms a Meisenheimer-type complex, 1,2-*O*-*p*-nitrophenylidene-α-D-glucopyranose, as the intermediate which undergoes hydrolysis.

In spite of the general agreement concerning mechanisms of acidic hydrolysis of aryl glucopyranosides,[1,2] alkaline hydrolysis of aryl glucopyranosides has not been successfully rationalized on the basis of generalized mechanisms. In particular, exalted rates of hydrolysis of *p*-nitrophenyl-α- and -β-D-glucopyranosides in alkaline media remain enigmatic.

Previous studies on the alkaline hydrolysis of aryl glucopyranosides[2,3] have shown that β anomers react by a process (Scheme I) which yields 1,6-anhydroglucopyranose (**1**) *via* neighboring C-2 oxyanion participation.[4,5] A trend toward the nucleophilic aromatic substitution (Scheme II) was noted as the electron-withdrawing character of substitutents increased.[6,7]

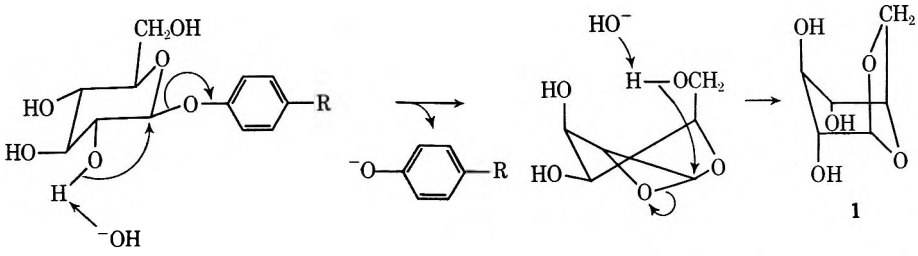
In the case of aryl-α-D-glucopyranosides, a nucleophilic aromatic substitution mechanism analogous to Scheme II was proposed.[8] This mechanism explains the fact that 1,6-anhydroglucopyranose is not formed when the α anomers are treated with alkali. However, it does not explain the formation of *p*-nitrophenol when the experiment is carried out with sodium methoxide in methanol. To resolve some of these uncertainties, the present work was undertaken. The knowledge concerning mechanisms of hydrolysis of *p*-nitrophenyl-α- and -β-D-glucopyranosides is desirable because they have been extensively used as substrates in the studies of α- and β-glucosidases.[9,10]

Results

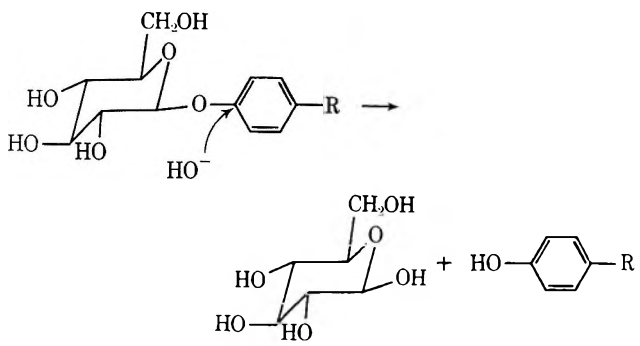
In the range of alkaline concentrations studied, the rate of *p*-nitrophenol liberation was first order in substrate concentrations until the hydrolysis is 50% completed. Figure 1 shows that the specific rate of alkaline hydrolysis of *p*-nitrophenyl-β-D-glucopyranoside (**3**)

(1) J. N. BeMiller, *Adv. Carbohyd. Chem.*, **22**, 25 (1967).
(2) B. Capon, *Chem. Rev.*, **69**, 407 (1969).
(3) C. E. Ballou, *Adv. Carbohyd. Chem.*, **9**, 59 (1954).
(4) E. M. Montgomery, N. K. Richtmeyer, and C. S. Hudson, *J. Amer. Chem. Soc.*, **65**, 3 (1943).
(5) A. Dyfverman and B. Lindberg, *Acta Chem. Scand.*, **4**, 878 (1950).
(6) C. M. McCloskey and G. H. Coleman, *J. Org. Chem.*, **10**, 184 (1945).
(7) R. C. Gasman and D. C. Johnson, *ibid.*, **31**, 1830 (1966).
(8) A. N. Hall, S. Hollingshead, and H. N. Rydon, *J. Chem. Soc.*, 4290 (1961).
(9) R. Heyworth and P. G. Walker, *Biochem. J.*, **83**, 331 (1962).
(10) M. V. Kelemen and W. J. Whelan, *Arch. Biochem. Biophys.*, **117**, 423 (1966).

SCHEME I



SCHEME II



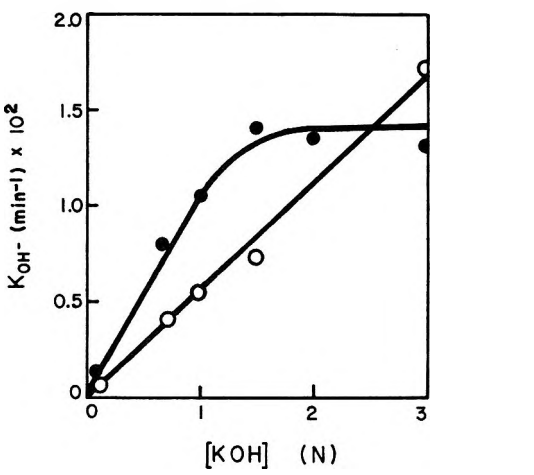


Figure 1.—Effect of hydroxide concentration on specific rates of hydrolysis of *p*-nitrophenyl-D-glucopyranosides for α anomer (●) and β anomer (○).

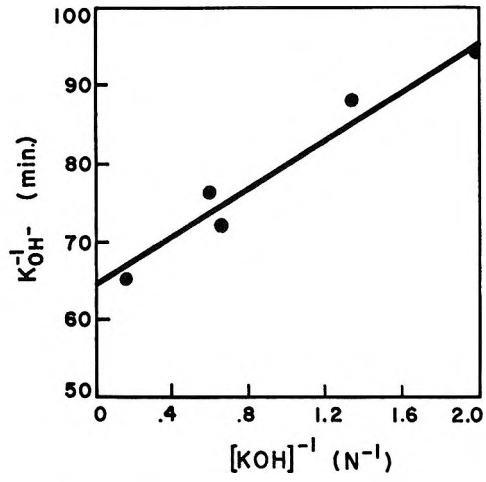


Figure 2.—Double reciprocal plot of specific rates of alkaline hydrolysis of *p*-nitrophenyl-α-D-glucopyranosides *vs.* hydroxide ion concentrations.

is first order with respect to hydroxide concentrations. For *p*-nitrophenyl-α-D-glucopyranoside (2), the linear relationship holds at low hydroxide concentrations but deviates at high concentrations, suggesting the formation of a kinetically significant intermediate. If one assumes that the alkaline hydrolysis of *p*-nitrophenyl-α-D-glucopyranoside proceeds *via* eq 1, the observed

$$2 + OH^- \overset{K}{\rightleftharpoons} X \xrightarrow{k} P \qquad (1)$$

specific rate of alkaline hydrolysis (by equilibrium treatment) can be expressed by eq 2. K is the equilibrium

$$k_{OH^-} = \frac{kK[OH^-]}{1 + K[OH^-]} \qquad (2)$$

constant for the formation of the intermediate X, and k is the specific rate for the formation of product(s) P from X. The relationship describes the observed kinetic behavior; *i.e.*, at low hydroxide concentrations, k_{OH^-} is linearly related to $[OH^-]$ by $k_{OH^-} = kK[^-OH^-]$ whereas, at high hydroxide concentrations, k_{OH^-} is independent of $[OH^-]$ according to $k_{OH^-} = k$. Furthermore, the plot of $k_{OH^-}{}^{-1}$ *vs.* $[OH^-]^{-1}$ as shown in Figure 2 gives a straight line of intercept k^{-1} and slope $(kK)^{-1}$ from which k and K are estimated to be 1.55×10^{-2} min^{-1} and 4.17 mol^{-1}, respectively.

The results for *p*-chlorophenyl-α- and -β-D-glucopyranosides are shown in Figure 3. In these cases, the specific rates of alkaline hydrolysis are first order with respect to hydroxide concentrations and follow a linear relationship at low and high concentrations of base. These results again suggest that *p*-nitrophenyl-α-D-glucopyranoside is hydrolyzed by a mechanism different from other α derivatives or its β anomer.

Because of the presence of different mechanisms and the possibility of molecular rearrangement with subsequent degradation, kinetic studies alone do not provide sufficient information concerning mechanisms of alkaline hydrolysis. Alternative approaches were explored. An attempt was made to analyze hydrolysis products by gas chromatography, which has been used successfully for the analysis of glycoses and their derivatives.[11] Gas chromatographic analyses of hydrolysis products of *p*-nitrophenyl-α- and -β-D-glucopyranosides indicate that the α anomer is degraded by alkali to *p*-nitrophenol (retention time of 20.5 ± 1.0 min) and an unidentified major product (D with a retention time of 14.0 ± 1.0 min) which was shown to be the degradative product of D-glucose in alkaline solution. The work is in progress to isolate D for characterization. The β anomer yields, in addition to *p*-nitrophenol and D, 1,6-anhydroglucopyranose (retention time of 16.5 ± 0.5 min). Although D was not detected in the hydroly-

(11) (a) C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Chem. Soc.*, **85**, 2497 (1963); (b) M. Bolan, and J. W. Steele, *J. Chromatogr.*, **36**, 22 (1968); (c) G. G. S. Button, K. B. Gibney, G. D. Jensen, and P. E. Reid, *ibid.*, **36**, 152 (1968).

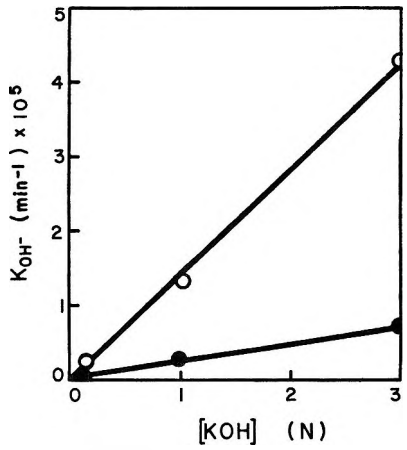
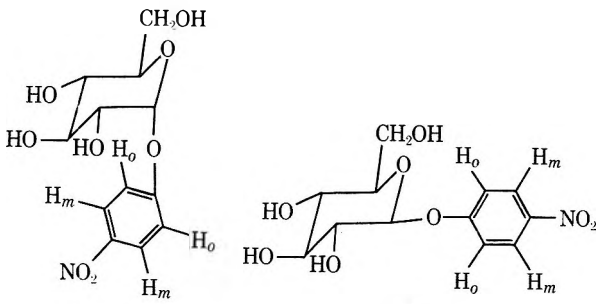


Figure 3.—Effect of hydroxide concentration on specific rates of hydrolysis of *p*-chlorophenyl-D-glucopyranosides for α anomer (●) and β anomer (○).

zate of phenyl-β-D-glucopyranoside, it was barely detectable in the hydrolyzate of *p*-chlorophenyl-β-D-glucopyranoside. None of three aryl-α-D-glucopyranosides yielded 1,6-anhydroglucopyranose. Both anomers produced small quantities of carboxylic acids such as lactic acid, suggesting the complexity of the degradative processes.

Nuclear magnetic resonance studies of alkaline hydrolysis provided unexpected results. *p*-Nitrophenyl-α-D-glucopyranoside (**2**) exhibits two pairs of aromatic protons: ortho protons (H_o) at δ 7.30 ppm (doublet, J = 9 cps) and meta protons (H_m) at δ 8.26 ppm (doublet, J = 9 cps). Immediately after the addition of 0.1 ml of 1.0 *N* NaOH, H_o and H_m split into a complex



2 3

multiplet centered at δ 7.20 ppm and a pair of doublets with a separation of 3.0 Hz. These signals broaden with time until complete disappearance. This is followed by the appearance of two new pairs of doublets corresponding to aromatic protons of *p*-nitrophenolate anion (Figure 4). By contrast, aromatic protons of *p*-nitrophenyl-β-D-glucopyranoside (**3**), H_o at δ 7.74 ppm (doublet, J = 10 cps) and H_m at δ 8.22 ppm (doublet, J = 10 cps), undergo broadening and disappearance without prior splitting (Figure 5). The reduction of aromatic nitro compounds by D-glucose in aqueous NaOH to produce amino aromatics is known;[12] however, *p*-aminophenol was not detected under these experimental conditions.

Decoupling experiments with **2** in aqueous NaOH were carried out. When the multiplet is irradiated, the signal at δ 8.26 ppm (H_m) turns into a singlet (Δf =

(12) H. W. Galbraith, E. F. Degering, and E. F. Hitch, *J. Amer. Chem. Soc.*, **73**, 1323 (1951).

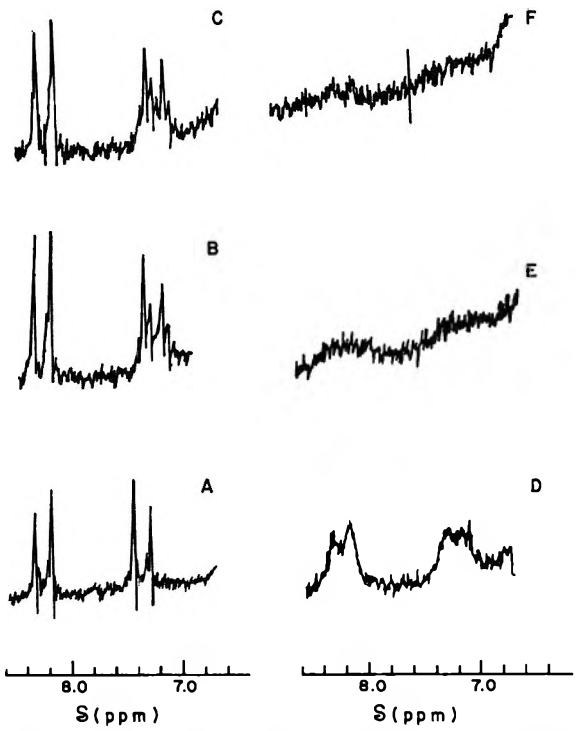


Figure 4.—Nmr studies of alkaline hydrolysis of *p*-nitrophenyl-α-D-glucopyranoside. 60-MHz spectra in H_2O were taken 0 (A), 6 (B), 12 (C), 16 (D), 22 (E), and 26 min (F) after the addition of NaOH.

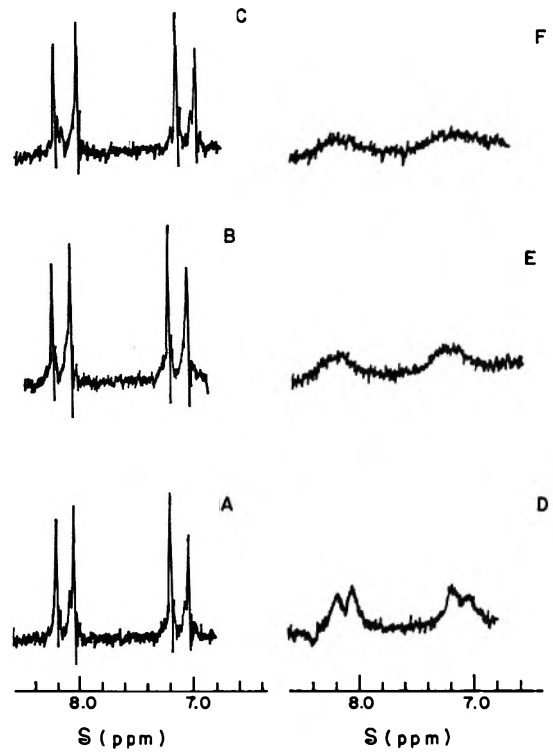


Figure 5.—Nmr studies of alkaline hydrolysis of *p*-nitrophenyl-β-D-glucopyranoside. 60-MHz spectra in H_2O were taken 0 (A), 12 (B), 24 (C), 40 (D), 45 (E), and 50 min (F) after the addition of NaOH.

100 Hz) and, when the low-field signal is irradiated, the multiplet (H_o) turns into a quartet (Figure 6).

The broadening and subsequent disappearance of nmr signals of aromatic protons are due to the formation of a paramagnetic species in the system. Figure 7 shows the esr signals corresponding to *p*-nitrophenoxyl

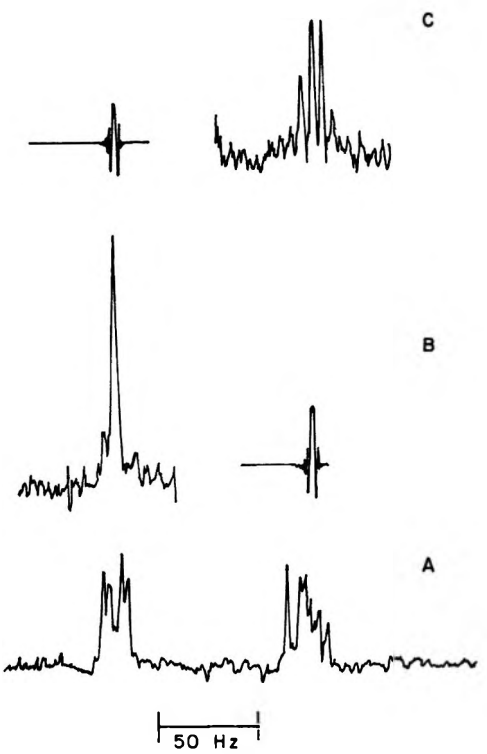


Figure 6.—Decoupling spectra (100 MHz) of aromatic region of *p*-nitrophenyl-α-D-glucopyranoside in NaOH before the irradiation (A) and irradiated at δ 7.30 ppm (B) and 8.26 ppm (C).

radical[13] which is formed by dissolving **2** in 1.0 *N* NaOH. Identical esr signals are also observed by dissolving **3** in 1.0 *N* NaOH or D-glucose and *p*-nitrophenol in 1.0 *N* NaOH.[14]

When the alkaline hydrolysis of **2** and **3** in NaOD (D_2O) and $NaOCH_3$ (CH_3OH) was studied by nmr spectroscopy, the following observations were made. (1) Nuclear magnetic spectra are not altered by replacing NaOH(H_2O) with NaOD(D_2O). (2) In $NaOCH_3$ (CH_3OH), **2** yields *p*-nitrophenol exclusively, whereas **3** produces *p*-nitrophenol and *p*-nitroanisol with an approximate ratio of 9:1.

Discussion

The alkaline hydrolysis of aryl-β-D-glucopyranosides in which the aryl group and the C-2 hydroxyl group of D-glucopyranose are in the trans 1,2 configuration proceeds *via* Scheme I or Scheme II depending on the electron-withdrawing character of aryl substituents. Phenyl-β-D-glucopyranoside is hydrolyzed *via* Scheme I, whereas *p*-nitrophenyl-β-D-glucopyranoside is hydrolyzed *via* mixed mechanisms of Scheme I and Scheme II. This is consistent with the observation that *p*-nitrophenyl-β-D-glucopyranoside in alkali yields 1,6-anhydroglucopyranose and the degradative product (D) of D-glucose. In methanolic $NaOCH_3$, the *p*-nitrophenyl group is liberated as *p*-nitrophenol and *p*-nitroanisole.

No general mechanism is ascribed to alkaline hydrolysis of aryl-α-D-glucopyranosides. A mechanism analogous to Scheme II is implicated from the study

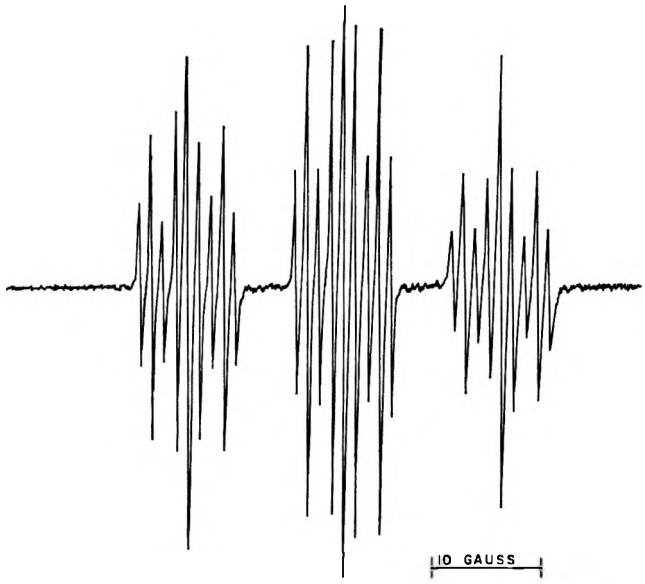


Figure 7.—Esr spectrum of *p*-nitrophenyl-α-D-glucopyranoside in NaOH. The spectrum was taken with a Varian Model E-9 esr spectrometer 10 min after dissolving 90 mg of *p*-nitrophenyl-α-D-glucopyranoside in 1.0 *N* NaOH solution (0.3 *M* solution).

of the effect of para substituents on the alkaline hydrolysis of aryl-α-D-glucopyranosides which exhibit a high positive reaction constant.[8] This mechanism is inconsistent with the formation of *p*-nitrophenol when *p*-nitrophenyl-α-D-glucopyranoside is hydrolyzed with $NaOCH_3$ in methanol. A mechanism involving nucleophilic substitution at the glucosyl carbon is considered unlikely for the *p*-nitro derivative because of the positive deviation of the *p*-nitro substituent from the Hammett plot[8] and the participation of the C-2 hydroxyl group in facilitating the alkaline hydrolysis of *p*-nitrophenyl-α-D-glucopyranoside (see below). The participation of the trans C-6 oxyanion in the alkaline hydrolysis of phenyl-α-D-galactopyranoside has been deduced from the formation of 1,6-anhydrogalactopyranose.[2] This mechanism is precluded because of the failure to detect 1,6-anhydroglucopyranose from *p*-nitrophenyl-α-D-glucopyranoside even after a prolonged alkali treatment.

The mechanism consistent with present experimental observations for *p*-nitrophenyl-α-D-glucopyranoside is presented in Scheme III.

That the formation of the intermediate which is in a rapid equilibrium with **2** and hydroxide ion is supported by the linear relationship between $k_{OH^-}{}^{-1}$ and $[OH^-]^{-1}$. Thus, the rate of alkaline hydrolysis of **2** is first order in base at low hydroxide ion concentrations and zero order in base at high hydroxide ion concentrations. The nature of the intermediate is characterized by nmr studies. The change in the aromatic region of the nmr spectrum of **2** upon the addition of NaOH suggests the formation of a Meisenheimer complex[15-18] of the type **4** in which the two ortho protons (H_o) become nonequivalent due to the restricted rotation when the ring is formed. The involvement of the C-2 hydroxyl group in the formation of **4** is deduced from following observations. (1) A molecular model

(13) K. Umenoto, Y. Deguchi, and T. Fujinaga, *Bull. Chem. Soc., Jap.*, **36**, 1539 (1963).

(14) Under the identical condition (30°), D-glucose in NaOH does not yield a radical, but on boiling an esr signal is detected. See also C. Lagercrantz, *Acta Chem. Scand.*, **18**, 1321 (1964).

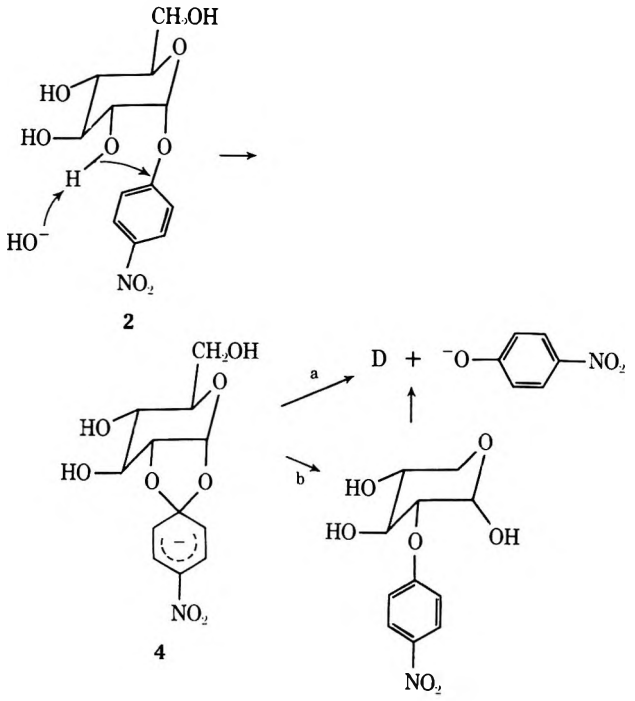
(15) J. Meisenheimer, *Justus Liebigs Ann. Chem.*, **323**, 205 (1902).

(16) K. L. Servis, *J. Amer. Chem. Soc.*, **87**, 5495 (1965).

(17) M. R. Crampton and V. Cold, *J. Chem. Soc. B*, 893 (1966).

(18) C. A. Fyfe, *Can. J. Chem.*, **47**, 2331 (1969).

SCHEME III



indicates that the C-2 hydroxyl oxygen is approximately 2.8 Å away from C-1 of the aryl ring when the aryl ring of *p*-nitrophenyl-α-D-glucopyranoside exists in a syn configuration with respect to the pyranose ring as in **2**. (2) The aromatic protons of *p*-nitrophenyl-β-D-glucopyranoside whose aryl ring exist in an anti configuration with respect to pyranose ring as in **3** do not exhibit nmr splitting upon the addition of NaOH. (3) A comparison of rates of the alkaline hydrolysis of *p*-nitrophenyl-α-D-glucopyranoside and its 2-deoxy derivative indicates that the C-2 hydroxyl group facilitates the liberation of *p*-nitrophenol.[19]

The exact nature of the release of *p*-nitrophenolate anion from **4** *via* a or b is not known. *p*-Nitrophenyl-α-D-glucopyranoside in alkaline solution yields *p*-nitrophenoxy radical[20] when the hydrolysis is approximately 50% completed. The radical is also formed immediately upon mixing D-glucose with *p*-nitrophenol in aqueous NaOH. It is likely that the radical formation is the consequence rather than the cause of the alkaline liberation of the *p*-nitrophenyl group. Recently Horton and Luetzow[21] observed the O-migration of the *p*-nitrophenyl group prior to its release. This is in agreement with the formation of **4**, which is hydrolyzed *via* pathway b of Scheme III.[22]

Experimental Section

Melting points were determined on a Fisher-Johns hot stage apparatus. Optical rotations in aqueous solutions were measured with a Perkin-Elmer Model 141 polarimeter. Ultraviolet spectra were taken with a Cary 14 spectrophotometer. Nuclear magnetic resonance spectra were obtained with Varian Associates T-60 and XL-100 instruments. Chemical shifts are reported on the δ scale, parts per million (ppm) downfield from sodium 3-(trimethylsilyl)-1-propanesulfonate. Adjustments of pH were made with a Radiometer TTTlc. Phenols were obtained from Eastman Organic Chemicals. 1,6-Anhydroglucopyranose, mp 175–176.5°, was synthesized by Rayle Chemical Ltd., Edmonton, Alberta. Chromosorb W (AW-DMCS treated, 80–100 mesh) and XE-60 were purchased from Chromatographic Specialties Ltd. Tri-sil, *p*-nitrophenyl-α-D-glucopyranoside, mp 214–215°, [α] +210 (*c* 0.38), and *p*-nitrophenyl-β-D-glucopyranoside, mp 170–171°, [α] −96.4 (*c* 1.07), were products of Pierce Chemical Co.

Synthesis of Aryl-α- and -β-D-glucopyranosides.—Phenyl-α-D-glucopyranoside, mp 160–161°, $[\alpha]_D$ +179 (*c* 1.25), and *p*-chlorophenyl-α-D-glucopyranoside, mp 195–197°, $[\alpha]_D$ +59.3 (*c* 2.23), were synthesized by the condensation of penta-*O*-acetyl-β-D-glucopyranose[23] with phenol or *p*-chlorophenol in the presence of $ZnCl_2$[24] followed by O-deacetylation.[25] Phenyl-β-D-glucopyranoside, mp 176–177°, $[\alpha]_D$ −67.5 (*c* 1.03), and *p*-chlorophenyl-β-D-glucopyranoside, mp 179–179.5°, $[\alpha]_D$ −96.4 (*c* 1.08), were synthesized by the condensation of penta-*O*-acetyl-β-D-glucopyranose with phenol or *p*-chlorophenol in the presence of *p*-toluenesulfonic acid[25] followed by O-deacetylation.

Gas Chromatographic Analysis of Hydrolysis Products.—An F & M Model 402 gas chromatograph (Hewlett-Packard) equipped with a recorder Model 7101B (Moseley) and a Disc integrator Model 229 (Moseley) was used for the product analysis. Aryl-α- or -β-D-glucopyranoside (0.5 g) was dissolved in 30 ml of 0.1 *N* NaOH and incubated at 40°. At time intervals, an aliquot (0.5 ml) of the reaction mixture was withdrawn and neutralized with HCl. The hydrolyzate was evaporated to the dryness and trimethylsilated with 0.5 ml of Tri-sil.[27] The trimethylsilyl derivative (5 μl) was injected into the glass U-shaped column (6 ft × 0.125 in.) packed with 3.8% (w/w) XE-60 on Chromosorb W (AW-DMCS treated, 80–100 mesh). The injection temperature was 290° and the analysis (column temperature) was carried out isothermally at 150°. Products were detected by a hydrogen flame detector (270°). Occasionally, mannitol was added as the internal standard.

Spectrophotometric Determination of Rates of Hydrolysis.—*p*-Nitrophenyl-α- or -β-D-glucopyranoside (8×10^{-5} *M*) was dissolved in a KOH solution (ionic strength of the solution was maintained at $\mu = 0.3$ *M* with KCl) and placed into a Beckman DB spectrophotometer equipped with a recorder, a scale expander, and a thermostat circulator maintained at 40 ± 0.5°. Rates of hydrolysis were followed at 400 nm. For *p*-chlorophenyl-α- or -β-D-glucopyranoside (1.6×10^{-3} *M*) and phenyl-α- or -β-D-glucopyranoside (1.6×10^{-3} *M*), rates of hydrolysis were followed at 300 and 285 nm, respectively. The observed pseudo-first-order rate constants (k_{obsd}) were calculated from plots of log $[A_\infty - A_0)/(A_\infty - A_t)]$ *vs.* time (*t*) as usual. After substraction of the first-order rate constant for spontaneous hydrolysis (k_0), the observed rate constant gives the second-order rate constant for alkaline hydrolysis (k_{OH^-}).[28]

Nuclear Magnetic Resonance (Nmr) Spectroscopic Studies of Hydrolysis.—The hydrolysis of *p*-nitrophenyl-α- or -β-D-glucopyranoside (4.4×10^{-2} *M*) in 0.1 *N* NaOH (H_2O), 0.1 *N* NaOD (D_2O), or 0.1 *N* $NaOCH_3$ (CH_3OH) was followed in a Varian nmr spectrometer T-60 or XL-100. Sodium 3-(trimethylsilyl)-1-propanesulfonate or tetramethylsilane was used as the internal standard for aqueous or methanol solution, respectively.

Registry No.—**2**, 3767-28-0; **3**, 2492-87-7.

Acknowledgment.—The financial support of the National Research Council of Canada is gratefully acknowledged. The authors thank Dr. P. M. Laughton for reading the manuscript and Dr. I. C. P. Smith of the National Research Council for taking esr spectra. Comments made by one of the reviewers were greatly appreciated.

(19) R. J. Ferrier, W. G. Overend, and A. E. Ryan, *J. Chem. Soc.*, 3484 (1965).

(20) An identical observation was made when the hydrolysis was carried out in methanolic $NaOCH_3$ or under the N_2 atmosphere.

(21) D. Horton and A. E. Luetzow, *Chem. Commun.*, 79 (1971).

(22) Horton and Luetzow[21] reported that the *p*-nitrophenyl group migrated from C-1 to C-2 and then C-3 hydroxyl groups before its release as the *p*-nitrophenolate anion.

(23) M. L. Wolfrom and A. Thompson in "Methods in Carbohydrate Chemistry," Vol. 2, R. L. Whistler and M. L. Wolfrom, Ed., Academic Press, New York, N. Y., 1963, p 211.

(24) J. Conchie and G. A. Levvy, in ref 23, p 345.

(25) A. Thompson and M. L. Wolfrom, in ref 23, p 215.

(26) B. Weissmann, *J. Org. Chem.*, **31**, 2505 (1966).

(27) C. S. Tsai, *Anal. Biochem.*, **36**, 114 (1970).

(28) T. C. Bruice and S. Benkovic, "Bioorganic Mechanisms" Vol. 1, W. A. Benjamin, New York, N. Y., 1966, p 4.

Total Dealkylation of Esters of Trivalent Phosphorus and Promotion of Anhydride Formation by *N,N,N',N'*-Tetramethylchloroformamidinium Chloride

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Received February 8, 1972

N,N,N',N'-Tetramethylchloroformamidinium chloride (1) exhibits two unusual reactions with esters of trivalent phosphorus acids. (1) It fully dealkylates the esters, in most cases, giving tetramethylformamidinium phosphorus(V) compounds. (2) It extracts oxygen from the resulting acid anions, causing condensation to anhydrides, an effect that 1 may have on acid anions in general. The reaction of 1 with trialkyl phosphites at ordinary temperatures results in the formation of the double inner salt (*N,N,N',N'*-tetramethylformamidinium)phosphonic anhydride, $[(Me_2N)_2C^+PO_2^-]_2O$, along with tetramethylurea and alkyl chloride; presumably, the esters $(Me_2N)_2C^+P(O)(OR)_2Cl^-$ and $(Me_2N)_2C^+P(OR)O_2^-$ are intermediates. Basic hydrolysis of the anhydride gives disodium dimethylcarbamylphosphonate. Acid hydrolysis converts it to (*N,N,N',N'*-tetramethylformamidinium)phosphonic acid. Diethyl phenylphosphonite, $PhP(OEt)_2$, and 1 give *N,N,N',N'*-tetramethyl(ethoxyphenylphosphinyl)formamidinium chloride, which readily loses ethyl chloride, forming the inner salt (*N,N,N',N'*-tetramethylformamidinium)phenylphosphinate, $(Me_2N)_2C^+P(Ph)O_2^-$. Ethyl diphenylphosphinite, Ph_2POEt, undergoes a normal Michaelis–Arbuzov reaction with 1, giving *N,N,N',N'*-tetramethyl(diphenylphosphinyl)formamidinium chloride, $Ph_2P(O)C^+(NMe_2)_2Cl^-$. Structural identifications were made principally by nmr (^{31}P and ^1H) spectroscopy and X-ray crystallography.

In the normal course of the reaction of a trialkyl phosphite ester with an alkyl halide, a carbon–phosphorus bond is formed, a carbon–oxygen bond is cleaved, and phosphorus is converted from trivalency to pentavalency. This is the classical Michaelis–Arbuzov reaction.[1-3]

$$(RO)_3P + R'X \longrightarrow (RO)_2\overset{O}{\overset{\|}{P}}R' + RX$$

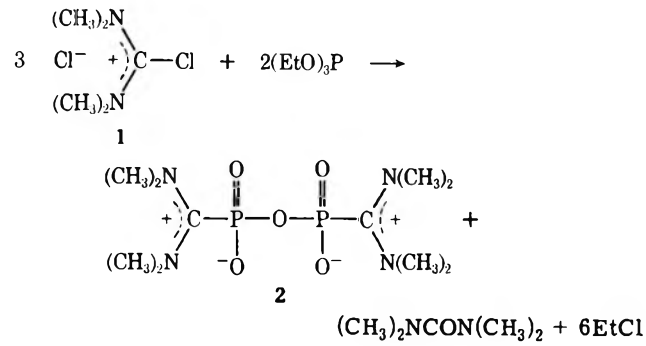
The resulting phosphonate ester is relatively unreactive compared to the phosphite precursor, and further structural changes do not ordinarily occur readily. Alkyl exchange reactions with phosphonates and phosphinates have been shown to take place as side effects in certain Michaelis–Arbuzov reactions at high temperatures. For example, Harwood and Grisley found that, when dimethyl phenylphosphonite and β-bromoethyl acetate were warmed at 160–175° for 5 hr, β-acetoxyethyl phenyl(methyl)phosphinate was the major product rather than the expected methyl phenyl(β-acetoxyethyl)phosphinate;[4] and Laughlin found that 40% of the product obtained when trimethyl phosphite and dodecyl bromide were warmed at 180–200° for 20 hr was the alkyl exchange product, methyl dodecyl methylphosphonate.[5] Chlorides required even higher temperatures (200–250°) for exchange.[6]

This paper describes a new multistep reaction in which all three alkyl groups of trialkyl phosphites are rapidly cleaved at ordinary temperatures by *N,N,N',N'*-tetramethylchloroformamidinium chloride (1).[7] Besides causing the displacement of the alkyl groups, 1 extracts oxygen from phosphorus, resulting in the formation of a dizwitterionic phosphonic anhydride. Related transformations of phosphonite and phosphinite esters are also described.

(1) A. Michaelis and R. Kaehne, *Ber.*, **31**, 1048 (1898).
(2) A. E. Arbuzov, *J. Russ. Phys. Chem. Soc.*, **38**, 687 (1906).
(3) R. G. Harvey and E. R. DeSombre "Topics in Phosphorus Chemistry," Vol. 1, Interscience, New York, N. Y., 1964.
(4) H. J. Harwood and D. W. Grisley, *J. Amer. Chem. Soc.*, **82**, 423 (1960).
(5) R. G. Laughlin, *J. Org. Chem.*, **27**, 1005 (1962).
(6) V. V. Korshak, I. A. Gribova, and V. K. Shitikov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 210 (1958); *Chem. Abstr.*, **52**, 12804 (1958).
(7) H. Eilingsfeld, G. Neubauer, M. Seefelder, and H. Weidinger, *Chem. Ber.*, **97**, 1232 (1964).

Results and Discussion

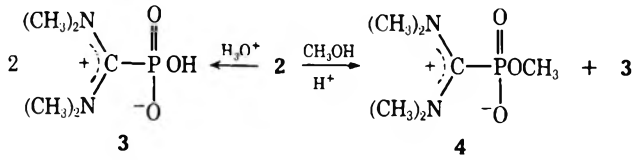
When triethyl phosphite was mixed with 1 in acetonitrile, a moderate temperature rise was observed, followed a short time later by separation of a white, crystalline product, mp 272–274° dec. This product exhibited only a single line in both its ^1H and ^{31}P nmr spectra. The proton resonance occurred at δ 3.45, a position typical of amidinium *N*-methyl groups (*e.g.*, 1 has a singlet at δ 3.43). These results, along with mass spectra, elemental analyses, molecular weight measurement, and identification of by-products (*cf.* Experimental Section), suggested the phosphonic anhydride–inner salt, structure 2, formed according to the following equation.



Based on this equation, the yield of 2 was 61%. Trimethyl and tris(2-chloroethyl) phosphites gave 82 and 29% yields of 2, respectively. Tetramethylurea and the appropriate chlorides (ethyl and methyl chloride and ethylene dichloride) were formed in approximately the amounts called for by the above equation. In one case tetramethylurea was isolated and identified by its nmr and mass spectra and glc retention time.

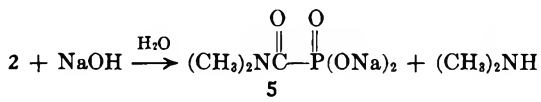
The presence of the anhydride linkage in 2 was supported by changes that occurred during hydrolysis and methanolysis. After hydrolysis with aqueous acid, the ^{31}P nmr spectrum consisted of a single line 8.9 ppm downfield from the line assigned to 2 (14.2 ppm in H_2O); however, after methanolysis (dry HCl in methanol), two signals of equal area were present, a singlet 8.3 ppm downfield from that of 2 and a quartet (J_{POCH_3} = 12 Hz) 10 ppm downfield. The proton

nmr spectrum of the methanol solution contained a doublet at δ 3.73 (J_{CH_3OP} = 12 Hz). The patterns and positions of these resonances are consistent with the formation of acid **3** and methyl ester **4** from **2**, changes that only an anhydride could undergo.



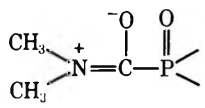
3 **4**

The presence of P–C bonds in **2** was demonstrated by hydrolysis with aqueous NaOH to disodium *N*,*N*-dimethylcarbamylphosphonate (**5**).



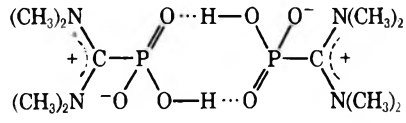
5

The ^{1}H nmr spectrum of **5** contained doublets of equal areas at δ 3.23 (J = 1.2 Hz) and 2.84 (J = 1.2 Hz), reflecting dissimilar environments for the methyl groups and the coupling of each with phosphorus. Diethyl *N*,*N*-dimethylcarbamylphosphonate has a similar pair of ^{1}H nmr doublets for the nitrogen-bonded methyl groups. This nonequivalence of the methyl groups, characteristic also of *N*,*N*-dimethylcarboxamides, results, presumably, from existence of the carbamyl phosphonates to some degree in the charge-separated state



Final confirmation of structure **2** was provided by an X-ray crystal structure study carried out by J. J. Daly.[8] This study showed that the P–O–P angle is bent at 126°, the P–O bond lengths in this group being 1.617 Å. The remaining P–O bond lengths average 1.469 Å. The P–C bond length is 1.878 Å, slightly longer than found in other phosphonates. The C–N bond lengths (average 1.330 Å) at the central carbon atom are close to the conjugated heterocyclic value (1.339 Å) and are characteristic of formamidinium compounds.[8]

For an anhydride, **2** is surprisingly resistant to hydrolysis. In one experiment a sample was recovered unchanged after having been in neutral aqueous solution for 24 hr at room temperature. As mentioned, **2** hydrolyzes in dilute aqueous acids to the acid **3**. Crystals of **3** (^{31}P nmr 5.8 ppm in CH_3OH) were inadvertently obtained when **2** was recrystallized from moist chloroform. A crystal structure study showed that **3** forms hydrogen-bonded dimers (**3a**) across

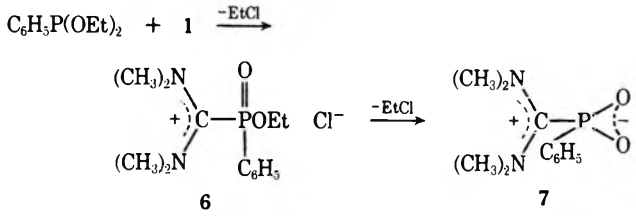


3a

centers of symmetry (O···O = 2.57 Å across the hydrogen bond). Its P–C and C–N bond lengths are close to those of the anhydride **2**.[8]

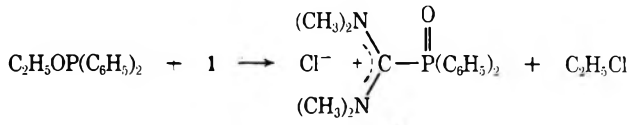
(8) J. J. Daly, submitted for publication in *J. Chem. Soc.*

While an attempt to isolate an intermediate in the formation of **2** was unsuccessful even when an excess of trimethyl phosphite was used, the addition of **1** to an excess of diethyl phenylphosphonite gave *N*,*N*,*N*′,*N*′-tetramethyl(ethoxyphenylphosphinyl)formamidinium chloride (**6**), an isolable product which could be converted to the stable inner salt, (*N*,*N*,*N*′,*N*′-tetramethylformamidinium) phenylphosphinate (**7**), by gentle warming. The phenyl group evidently has a stabilizing effect on **6**.



6 **7**

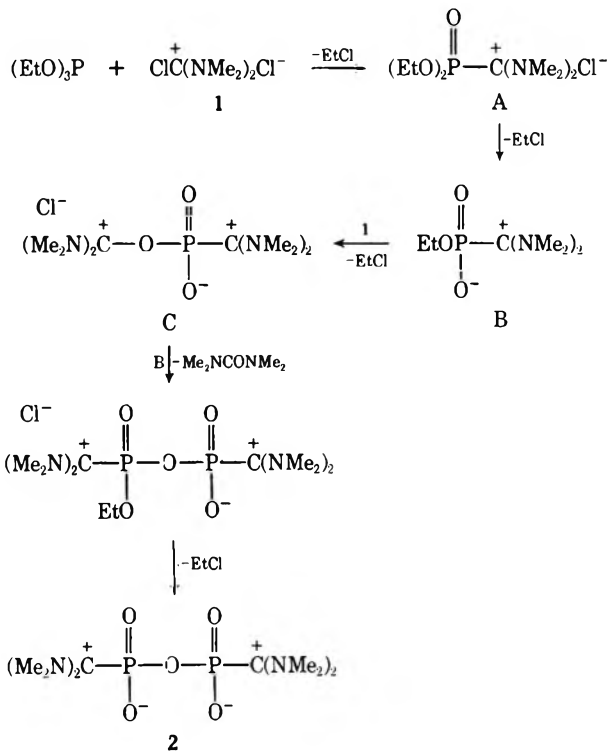
Ethyl diphenylphosphinite, having only one displaceable alkyl group, was limited to a normal Michaelis–Arbuzov reaction with **1**, giving the outer salt, *N*,*N*,*N*′,*N*′-tetramethyl(diphenylphosphinyl)formamidinium chloride (**8**).



8

The reaction of **1** with trialkyl phosphites presumably proceeds according to Scheme I. The covalently

SCHEME I



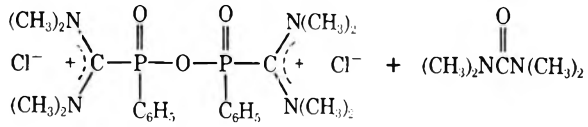
2

bonded chlorine on **1** is displaced by phosphorus *via* a typical Michaelis–Arbuzov reaction, giving ethyl chloride and intermediate A. The presence of the cationic center adjacent to phosphorus apparently weakens the remaining alkyl–oxygen bonds to the extent that

another molecule of ethyl chloride is lost, giving a second intermediate, B, which can react with more 1 to form uronium salt C. Displacement of tetramethylurea from C by a molecule of B and then cleavage of the remaining *O*-ethyl group leads to the final product, 2.

The effectiveness of 1 in converting an intermediate of 2 to the anhydride suggested that it might be possible to similarly convert 7 to its anhydride by treatment with 1. The product from this reaction was a viscous liquid that could not be induced to crystallize, possibly because of the presence of two asymmetric centers. Formation of the required amount of tetramethylurea and a ^{31}P nmr change from -9.0 ppm for 7 to -19.0 ppm for the product (related structure 6 has -20.6 ppm) indicated that the anhydride 9 may have been formed.

7 + 1 ⟶



9

Preliminary results suggest that 1 may also convert other acid anions, *e.g.*, acetate, to their corresponding anhydrides.

Experimental Section

Melting points were obtained in a Thomas-Hoover Unimelt instrument. Infrared spectra were determined in potassium bromide disks on a Beckman IR-4 spectrophotometer. Proton nuclear magnetic resonance (nmr) spectra were obtained at 60.0 or 100.0 MHz on Varian T-60 or HR-100 spectrometers with tetramethylsilane as an internal standard. Phosphorus nmr spectra were determined at 24.3 or 40.5 MHz on Varian HR-60 or HR-100 instruments and are reported with respect to 85% H_3PO_4 contained in a capillary. The nmr measurements were generally made on saturated solutions. Mass spectra were obtained on a Consolidated Engineering Corp. Type 21-104 spectrometer fitted with a probe for direct introduction of solids. Elemental analyses and molecular weights were determined by Galbraith Laboratories, Knoxville, Tenn.

(*N,N,N′,N′*-Tetramethylformamidinium)phosphonic Anhydride (2).—A 20.5-g (0.12 mol) portion of *N,N,N′,N′*-tetramethylchloroformamidinium chloride (1)[7] (^1H nmr δ 3.43 ppm) was stirred with 40 g of dry acetonitrile under N_2 in a drybox as 13.3 g (0.08 mol) of freshly distilled triethyl phosphite was added dropwise in 5 min. The temperature of the uncooled reaction mixture increased to 40°, and all of the solid 1 dissolved to give a clear, colorless solution from which a white solid began separating after about 35 min. Stirring at room temperature was continued overnight. The reaction mixture was then filtered under N_2, and the solid was washed with CH_3CN and dried to give 7.9 g (58% yield), mp 272–274° dec; 7.4 g with the melting point unchanged was recovered after the product was stirred in 40 ml of boiling CH_3CN and filtered hot. The white solid had a ^{31}P nmr singlet at 13.0 ppm ($CDCl_3$); ^1H nmr δ 3.45 ppm (s); mass spectrum (70 eV) *m/e* 342 (molecular ion), 298, 270, 227, 163; ir (KBr) 3.43 (m), 6.60 (s), 7.16 (s), 7.8 (vs), 8.28 (m), 8.53 (m), 9.22 (s), 11.1 (vs), 11.46 (s), 13.66 μ (s); mol wt ($CHCl_3$) 340 (calcd 342).

Anal. Calcd for $C_{10}H_{24}N_4O_5P_2$: C, 35.08; H, 7.07; Cl, 0.00; N, 16.37; P, 18.10. Found: C, 34.94; H, 7.21; Cl, 0.12; N, 16.28; P, 18.35.

The filtrate contained a ^1H nmr singlet at δ 2.75 for tetramethylurea as well as a quartet at δ 3.63 and a triplet at δ 1.45 for ethyl chloride. In another preparation of 2 carried out under similar conditions (yield 61%), a sample of the liquid phase was removed before the filtration step and found by gas chromatography to contain 27.6% ethyl chloride (theory 30.8%) and 10.7% tetramethylurea (theory 9.2%).

The use of trimethyl phosphite with 1 at a 2:3 molar ratio gave a 74% yield of 2. In another run, excess trimethyl phosphite was used in an attempt to limit the reaction to an intermediate stage. In this run 8.6 g (0.05 mol) of 1 was added in portions over a period of 1 hr to a stirred solution of 24.8 g (0.2 mol) of freshly distilled trimethyl phosphite and 25 g of dry CH_3CN under N_2 at room temperature. After this mixture was stirred overnight, an 82% yield of 2 was isolated.

Tris(2-chloroethyl) phosphite and 1 at a 2:3 molar ratio gave a 29% yield of 2.

Hydrolysis of 2 with Sodium Hydroxide.—A solution of 1.7 g (0.005 mol) of 2 in 5 g of distilled H_2O was stirred as 0.025 mol of NaOH (10% aqueous solution) was added dropwise. Most of the water was allowed to evaporate, and the salt was washed twice with warm ethanol and dried to give 1.6 g of disodium *N,N*-dimethylcarbamylphosphonate, ^{31}P nmr 1.1 ppm (D_2O). Recrystallization of a portion from ethanol–water gave a white solid: ^{31}P nmr 1.1 ppm (D_2O); ^1H nmr δ 3.23 (d, 3, J = 1.2 Hz), 2.84 (d, 3, J = 1.2 Hz).

Anal. Calcd for $C_3H_6NNa_2O_4P$: C, 18.28; H, 3.07; N, 7.11; P, 15.72. Found: C, 18.48; H, 3.15; N, 7.26; P, 15.69.

Hydrolysis and Methanolysis of 2 in Acidic Solutions.—A solution of 2 in distilled H_2O had a ^{31}P nmr singlet at 14.2 ppm and a ^1H nmr singlet at δ 3.35. After standing for 24 hr at room temperature, the H_2O was removed at 0.2 mm over $CaSO_4$ to give a white solid having a melting point and ir and nmr spectra identical with those of 2.

When a catalytic amount of hydrochloric acid was added to a solution of 2 in distilled H_2O, a new ^1H nmr peak began forming at δ 3.32. This new peak represented ~60% of the total peak area after 2 hr and 100% after 24 hr. A new ^{31}P nmr peak formed at 5.3 ppm.

A solution of 2 in anhydrous trifluoroacetic acid showed a ^{31}P nmr peak at 15.4 ppm and a ^1H nmr peak at δ 3.47. When H_2O was slowly added to this solution, the ^{31}P peak gradually decreased and was finally completely converted to a new peak at 4.8 ppm; at the same time the ^1H peak at δ 3.47 disappeared and a new peak formed at δ 3.43.

A solution of 2 in methanol showed a ^{31}P nmr peak at 14.6 ppm. As trifluoroacetic acid was slowly added, this peak disappeared and peaks of about equal areas formed at 4.6 (q, J = 12 Hz, $POCH_3$) and 6.3 (s); the ^1H nmr spectrum had a doublet at δ 3.73 (J = 12 Hz, $POCH_3$) as well as a singlet at δ 3.46 for NCH_3.

N,N,N′,N′-Tetramethyl(ethoxyphenylphosphinyl)formamidinium Chloride (6).—An 8.6-g (0.05 mol) portion of 1 was added in about 1-g portions to 29.7-g (0.15 mol) of diethyl phenylphosphonite which was stirred under N_2. Stirring was continued overnight at room temperature, giving a thick, white slurry. Benzene was added to aid stirring, the reaction mixture was filtered, and the solid was washed with benzene and ether and dried at room temperature to give 11.5 g (96% yield) of white solid (6): mp 94–95° (with foaming); ^{31}P nmr ($CDCl_3$) -20.6 ppm (on fresh solution); ^1H nmr δ 1.51 (t, 3, J = 7 Hz, CH_2CH_3), 3.60 (s, 12, NCH_3), 4.55 (m, 2, $J \cong 7$ Hz, CH_2CH_3), 7.5–8.2 (m, 5, C_6H_5). When nmr measurements were not made immediately on a freshly prepared solution, new ^1H peaks and a new ^{31}P peak developed; after 2 days the ^{31}P peak at -20.6 ppm was replaced by a peak at -9.6 and the ^1H peak at δ 3.60 was replaced by a peak at 3.36.

(*N,N,N′,N′*-Tetramethylformamidinium)phenylphosphinate (Inner Salt) (7).—Diethyl phenylphosphonite, 6.0 g (0.03 mol), was added rapidly to a stirred mixture of 5.1 g (0.03 mol) of 1 in 10 g of dry CH_3CN under N_2. The heat of reaction raised the temperature to 52°, and all of the solid dissolved. Stirring was continued at room temperature for 20 hr, and then the clear solution was diluted with ether, which caused 4.7 g of white solid to separate. Recrystallization twice from diglyme–CH_3CN gave 3.6 g (50% yield) of 7: mp 186–188°; ^{31}P nmr ($CDCl_3$) -9.0 ppm; ^1H nmr δ 3.30 (s, 12, CH_3), 7.2–7.9 (m, 5, C_6H_5); ir (KBr) 2.9 (m), 6.32 (s), 7.17 (m), 7.97 (s), 8.80 (s), 9.40 μ (s).

Anal. Calcd for $C_{11}H_{17}N_2O_2P$: C, 54.99, H, 7.13, N, 11.66; P, 12.89. Found: C, 55.08, H, 7.08, N, 11.76; P, 12.77.

In another preparation of 7 a 5.0-g portion of 6 in 25 ml of diglyme was stirred and warmed at 115–120° as enough CH_3CN was added to give a clear solution. After 5 min at this temperature, the reaction mixture was cooled and filtered. The solid

obtained was recrystallized from diglyme–CH_3CN to give 2.3 g of **7**, mp 186–188°, and having nmr and ir spectra essentially identical with those of the product obtained by the first method.

Treatment of (*N,N,N',N'*-Tetramethylformamidinium)-phenylphosphinate (7) with *N,N,N'N'*-Tetramethylchloroformamidinium Chloride (1).—A mixture of 4.1 g (0.017 mol) of **7** and 1.45 g (0.0085 mol) of **1** in 10 g of dry CH_3CN was stirred under N_2 at room temperature for 22 hr. Nmr measurements on the resulting clear, slightly yellow solution showed a ^{31}P signal at −19.0 ppm and ^1H signals at δ 2.73 (s, 12), 3.43 (s, 24), and 7.6–8.4 (m, 10). The ^1H signal at δ 2.73 was enhanced by addition of tetramethylurea. Stripping of the reaction mixture at reduced pressure and extraction of the residue with ether left a gum having a ^{31}P nmr signal at −19.0 ppm and ^1H nmr signals at δ 3.45 (s, 24) and 7.6–8.4 (m, 10). It could not be induced to crystallize. Tetramethylurea was isolated from the ether extract and identified by mass spectra.

***N,N,N',N'*-Tetramethyl(diphenylphosphinyl)formamidinium Chloride (8).**—Ethyl diphenylphosphinite, 6.9 g (0.03 mol), was added dropwise to a stirred mixture of 5.1 g (0.03 mol) of **1** in 20 g of CH_3CN under N_2. All of **1** dissolved during the addition, and then another solid separated. The reaction mixture was stirred at room temperature overnight and then filtered to give 9.6 g (94% yield) of **8**, mp 137–138.5°. Recrystallization from acetonitrile gave a white solid: mp 137.5–138.5°; ^{31}P nmr −28.8 ppm; ^1H nmr δ 3.46 (s, 12, CH_3), 7.5–8.3 (m, 10, C_6H_5); ir (KBr) 2.9 (m), 6.3 (s), 6.95 (m), 7.15 (m), 8.3–8.4 (s), 8.95 (s).

Anal. Calcd for $C_{17}H_{22}ClN_2OP$: C, 60.62; H, 6.58; Cl, 10.53; N, 8.32; P, 9.20. Found: C, 60.33; H, 6.65; Cl, 10.54; N, 8.20; P, 9.07.

Registry No.—**1**, 13829-06-6; **2**, 34959-65-4; **5**, 34959-66-5; **6**, 34982-10-0; **7**, 34959-67-6; **8**, 34982-11-1.

Degradation of Penicillin G Methyl Ester with Trifluoroacetic Acid[1]

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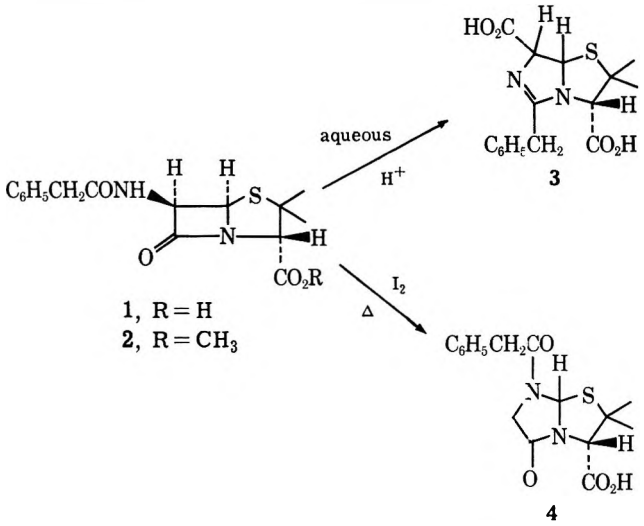
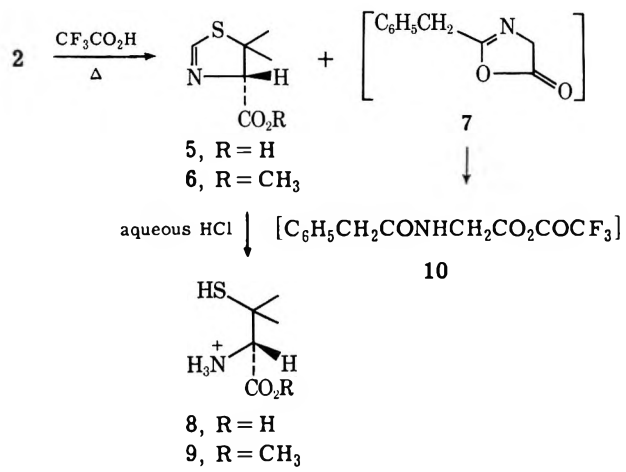
Penicillin G methyl ester (**2**) is degraded to methyl D-5,5-dimethyl-Δ^2-thiazoline-4-carboxylate (**6**) in trifluoroacetic acid. The *N*-phenylacetylglycyl fragment was isolated by conversion to its *N*-benzylamide. Methicillin and penillonic acid methyl esters were also degraded to **6**. A mechanism for the degradation is presented with special emphasis on the relationship to the penillic acid and penillonic acid rearrangements.

The penillic acid and the penillonic acid rearrangements are two well-known rearrangements of benzylpenicillin (**1**).[2] These rearrangements may be carried out by exposure of **1** to dilute aqueous mineral acid or by heating **1** in toluene with iodine, processes which respectively yield penillic acid (**3**) and penillonic acid (**4**).



We have discovered a new and potentially useful degradation of benzylpenicillin which we believe is closely related in mechanism to the penillic acid and penillonic acid rearrangements.

The nmr spectrum of a solution of either benzylpenicillin (**1**) or its methyl ester (**2**) in trifluoroacetic acid (TFAA) which had been briefly warmed exhibited the characteristic nmr signals of the thiazolines **5** or **6**. To facilitate isolation of the thiazoline, degradation was performed on the ester **2**. Optically active D-thiazoline ester could be obtained easily in 50–60% yield. That the configuration at C-4 has been retained was shown by comparison of its melting point with that reported in the literature[3] and by hydrolysis to D-penicillamine (**8**).[4]



The fate of the phenylacetylglycyl portion of **2** is not known with certainty. The fragment has clearly retained the capacity to acylate, since addition of the reaction mixture to an excess of benzylamine in pyridine led to the isolation of the benzylamide of *N*-phenylacetylglycine. As a result there appear to be at least three choices among monomeric species for the structure of the phenylacetylglycyl fragment: the oxazolone **7**, the mixed anhydride **10**, and the acylaminoketene **11**. An analogous ketene has been pro-

$C_6H_5CH_2CONHCH{=}C{=}O$

11

(1) A preliminary communication has been published: M. R. Bell, J. A. Carlson, and R. Oesterlin, *J. Amer. Chem. Soc.*, **92**, 2177 (1970).

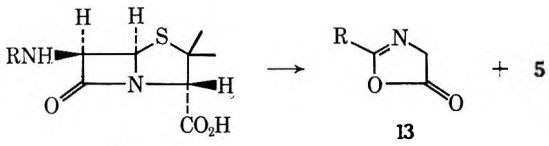
(2) (a) A. H. Cook in "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949, p 126; (b) R. L. Peck and K. Folkers, ref 2a, p 188.

(3) Merck Report No. 63, p 18, April 1945, cited by H. M. Crooks, Jr., in ref 2a, p 1057.

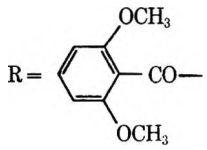
(4) "The Merck Index," P. G. Stecher, Ed., Merck and Co., Rahway, N. J., 1968, p 789.

posed as an intermediate to account for the products observed upon irradiation of an aqueous solution of 6-aminopenicillanic acid,[5] but it seems unlikely that **11** would have an appreciable lifetime in trifluoroacetic acid.

The nmr spectrum of the reaction mixture from **2** does not show the characteristic signals of the oxazolone **7**, although this compound is reasonably stable alone or in the presence of the thiazoline in hot trifluoroacetic acid. Addition of authentic benzyloxazolone **7** to the reaction mixture from **2** resulted in a rapid loss of its characteristic nmr signals. We do not have a satisfactory explanation for the instability of **7** under these circumstances. Possibly ring opening of **7** is promoted by side products generated in the degradation of **2**. We favor, therefore, the mixed anhydride structure **10** for the *N*-phenylacetylglycyl fragment, since this is the simplest alternative to the oxazolone which would retain the capacity to acylate a nucleophile. In contrast, oxazolone **13** was clearly present in



12 **13**



the reaction mixture from methicillin (**12**);[6] this reaction appears to be quantitative.

The trifluoroacetic acid degradation is apparently limited to those penicillins which possess an acyl side chain, since 6-aminopenicillanic acid failed to yield detectable amounts of thiazoline. A few cephalosporin structures were examined but the results were not considered promising. Penillic acid (**3**) was stable in boiling trifluoroacetic acid, but penillonic acid (**4**) as the methyl ester was quantitatively transformed to the oxazolone **7** and the thiazoline **6**. The nmr spectrum of the reaction mixture showed that equal parts of **6** and **7** had been formed. Thiazoline **6** was isolated and the *N*-phenylacetylglycyl fragment was characterized as the benzylamide.

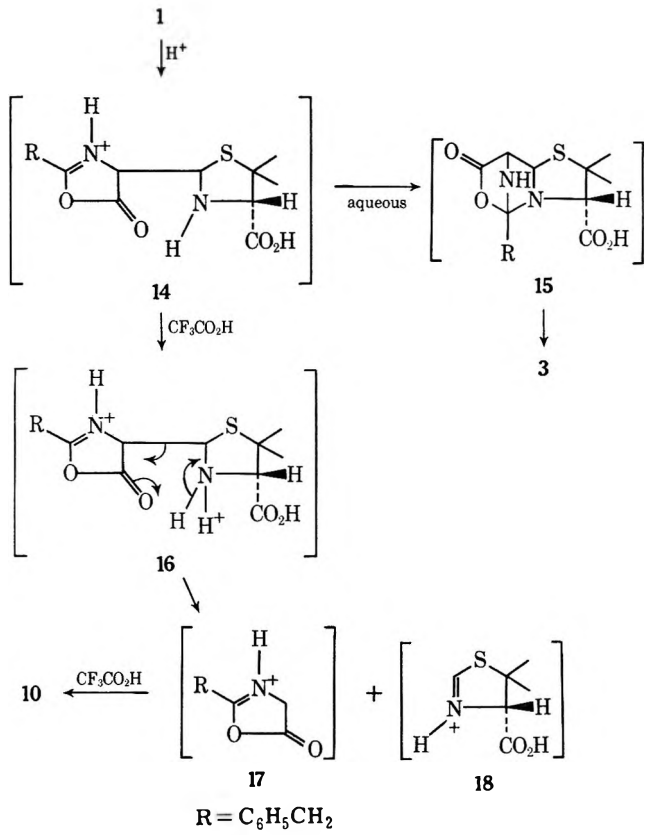
Our proposal for the mechanism of the trifluoroacetic acid degradation and its relationship to the penillic acid rearrangement is outlined in Scheme I. The intermediate **14** is identical with that which has been proposed for the penillic acid rearrangement.[7] This rearrangement is carried out in dilute aqueous mineral acid, and under these conditions it was suggested that nucleophilic addition of the thiazolidine ring amino function to the imino ether function of the oxazolone in intermediate **14** gave **15**, which then yields penillic acid (**3**). We suggest that in trifluoroacetic acid the intermediate **14** is diverted from this course by protonation of the thiazolidine ring nitrogen followed by fragmentation of the new intermediate **16** to give **17** and **18**.

(5) W. O. Godtfredsen, W. von Daehne, and S. Vangedal, *Experientia*, **23**, 280 (1967).

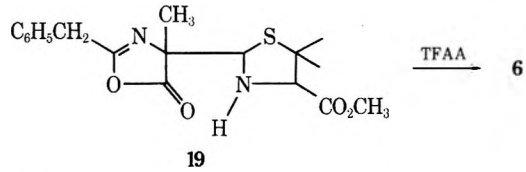
(6) F. P. Doyle, K. Hardy, J. H. C. Nayler, M. J. Soulal, E. R. Stove, and H. R. J. Waddington, *J. Chem. Soc.*, 1453 (1962).

(7) R. B. Woodward, ref 2a, pp 445–446.

SCHEME I



Where R is benzyl, the oxazolone is solvolyzed to the mixed anhydride **10**. Support for the step **16** → **17** + **18** is provided by the observation that synthetic oxazolone–thiazolidine[8] **19** is cleaved in trifluoroacetic acid to thiazoline **6**.



19

Jansen and Robinson have reported that penillonic acid methyl ester is formed by the condensation of oxazolone **7** with thiazoline **6** in benzene and on this basis proposed that the penillonic acid rearrangement proceeds by dissociation of penicillin to oxazolone and thiazoline followed by recombination to penillonic acid.[9] Although the degradation of penicillin to the thiazoline under acid conditions provides support for the first step of the Robinson pathway, it does not exclude the mechanisms proposed by Bird[10] and Woodward.[11]

The simplicity of the process for the preparation of the D-thiazoline[12] may be of some practical importance

(8) M. R. Bell, S. D. Clemans, R. Oesterlin, and J. A. Carlson, Abstracts, 23rd International Congress of Pure and Applied Chemistry, Boston, Mass., July 1971, p 74.

(9) A. B. A. Jansen and R. Robinson, *Monatsh. Chem.*, **98**, 1017 (1967).

(10) C. W. Bird, *Tetrahedron*, **22**, 2489 (1966).

(11) R. B. Woodward, ref 2a, p 447.

(12) A. K. F. Bose, G. Spiegelman, and M. S. Manhas, *J. Amer. Chem. Soc.*, **90**, 4506 (1968). These workers reported that DL-**6** could be prepared by heating DL-*N*-formylpenicillamine with boron trifluoride etherate in methanol. Prior to their publication we had synthesized DL-**6** by hydrogen chloride catalyzed esterification of DL-**5** in the presence of trimethyl orthoformate. The Merck group[3] prepared D-**6** by the reaction of ethyl formimidate hydrochloride and D-penicillamine methyl ester (**9**).

in view of the need to develop methods for the synthesis of pencillins with a modified nucleus. Our initial efforts to synthesize a 6-substituted penicillin utilizing the D-thiazoline **6** as a relay have recently been reported.[8] Sheehan has reported that a DL and L penicillin have respectively one-half and negligible antibacterial activity when compared with the corresponding D isomer. This underlines the importance of the absolute configuration of a penicillin for maximum biological activity.[13] The advantages of the D-thiazoline as a starting material for penicillin total syntheses are that it is readily available and inexpensive, and that it has the correct absolute configuration.

Experimental Section

All melting points were taken in capillary tubes in an oil bath and are uncorrected. Nmr spectra were determined under the supervision of Dr. R. K. Kullnig with a Varian Model A-60 spectrometer; TMS was used as the internal standard.

Penicillin G Methyl Ester (2).—A suspension of 344 g (0.9 mol) of penicillin G potassium salt (Chas. Pfizer) in 2 l. of anhydrous DMF (distilled, then stored over molecular sieves) was stirred at room temperature for 6 hr with 59 ml (0.9 mol) of methyl iodide. The clear solution was left under nitrogen at room temperature overnight. It was poured slowly into 6 l. of ice–water with vigorous stirring. The white solid was filtered and washed with cold water. The solid was dissolved in 2.5 l. of methylene dichloride and washed (cold H_2O, brine). The dried (Na_2SO_4) filtrate was evaporated at 40° and the residual oil was triturated with *ca.* 1 l. of absolute ether. The solid was filtered to afford 250 g (80%) of ester, mp 95–96.5° (lit.[14] mp 97–98°). Concentration of the mother liquor gave a second crop, 21 g (7.5%): mp 94–95°; ir ($CHCl_3$) 5.61 (β-lactam C=O), 5.73 (ester C=O), and 5.99 μ (amide C=O); nmr ($CDCl_3$) δ 1.45(s, 3), 1.5 (s, 3), 3.6 (s, 2, $ArCH_2$), 3.7 (s, 3, OCH_3), 4.4 (s, 1, $CHCO_2CH_3$), 5.5 (d, 1, J = 4 Hz, CHS) 5.6 (dd, 1, J = 4, 10 Hz, NCHCO), 6.3 (d, 1, J = 10 Hz, NH), and 7.3 ppm (5, ArH).

Methyl D-5,5-Dimethyl-Δ²-thiazoline-4-carboxylate (6).—Penicillin G methyl ester (150 g, 0.43 mol) was added to 1.5 l. of TFAA and the solution was heated on a steam bath in a nitrogen atmosphere for 20 min. The excess TFAA was recovered by distillation *in vacuo* (water aspirator, pot temperature not to exceed 40°) and was used in subsequent reactions. The residual yellow oil was dissolved in 1.5 l. of dry methylene dichloride and added slowly during 1 hr to a vigorously stirred, ice-cooled solution of 600 ml of concentrated ammonium hydroxide in 3 l. of ice–water. The organic phase was separated. The aqueous layer was extracted once with chloroform. The combined organic fractions were washed (H_2O, brine). The dried (Na_2SO_4) filtrate was evaporated at 40° and the residual brown gum was distilled twice to afford 43 g (58%) of thiazoline **6**: bp 74° (0.3 mm); mp 50.5–51.5° (lit.[3] mp 50°); $[\alpha]^{25}D$ +51.9° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 1.35 (s, 3), 1.73 (s, 3), 3.8 (s, 3, OCH_3), 4.6 (d, 1, J = 3 Hz, $CHCO_2CH_3$), and 8.15 ppm (d, 1, J = 3 Hz, N=CHS); nmr (TFAA) δ 1.7 (s, 3), 1.9 (s, 3), 3.95 (s, 3), 5.15 (d, 1, J = 2 Hz), and 8.15 ppm (d, 1, J = 2 Hz).

D-Penicillamine Hydrochloride (8).—Two grams of the thiazoline **6** dissolved in 21 ml of 2.5 *N* HCl and 11 ml of H_2O was heated at reflux for 16 hr under nitrogen and evaporated *in vacuo*. The amorphous residue was crystallized from acetonitrile to give 1.3 g (61%) of **8**: mp 177–179.5° dec; $[\alpha]^{25}D$ −48.6° (*c* 1, 1 *N* NaOH) [lit.[4] mp 177.5° dec, $[\alpha]^{25}D$ −55° (*c* 1, 1 *N* NaOH)]. An additional recrystallization left the melting point unchanged but raised the rotation to $[\alpha]^{25}D$ −49.8°. Its isopropylidene derivative was obtained in 57% yield: mp 199–201° dec; $[\alpha]^{25}D$ +92.0° (c 1, H_2O) [lit.[15] 198°, $[\alpha]^{17}D$ +94° (*c* 1, H_2O)].

Commercial D-penicillamine (Aldrich Chemical Company) was converted to its hydrochloride, mp 177–180° dec, $[\alpha]^{25}D$ −50.6° (*c* 1, 1 *N* NaOH). Its isopropylidene derivative was obtained in 72% yield, mp 199–200° dec, $[\alpha]^{25}D$ +92.8° (*c*, 1, H_2O).

***N*-Benzyl-2-(2-phenylacetamido)acetamide.**—Penicillin G methyl ester (5 g) in 50 ml of TFAA was heated at reflux for 15 min in a nitrogen atmosphere. After cooling, the solution was added slowly with stirring to ice-cooled benzylamine (80 ml) in 100 ml of pyridine. Stirring was continued for 1.5 hr at room temperature. The mixture was poured into 2 l. of water and extracted with ethyl acetate. The organic fractions were washed (H_2O, 10% H_3PO_4 until acidic, H_2O, saturated brine), dried (Na_2SO_4), and evaporated to yield a yellow solid. Recrystallization from THF afforded 1.1 g (27%) of the amide, mp 173–175°, identical with a sample (mixture melting point, ir) prepared from phenylacetylglycine, benzylamine, and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate.

TFAA Degradation of Methyl Benzylpenillonate (4-Methyl Ester).—A solution of methyl benzylpenillonate (8 g) in 38 ml of TFAA was allowed to stand at room temperature in a nitrogen atmosphere. After 30 hr the nmr spectrum of this solution indicated that an equimolar mixture of thiazoline **6** and oxazolone **7** had formed. The acid was evaporated *in vacuo* at room temperature.

Most of the oxazolone **7** initially present in the reaction mixture was destroyed during this evaporation, as evidenced by nmr. An aliquot (1.03 g) was added to 2 g of benzylamine in 15 ml of pyridine. After standing at room temperature for 2 hr, the phenylacetylglycyl benzylamide was isolated by the above procedure, yield 63 mg, mp 173–174.5°, mixture melting point with an authentic sample was undepressed. The thiazoline **6** was isolated from the remaining reaction mixture by the above procedure, yield 1.6 g, mp 49–51°.

TFAA Degradation of Penicillin G (1).—Penicillin G (1 g) prepared from Potassium Penicillin G (Chas. Pfizer) was dissolved in 5 ml of TFAA. The nmr spectrum indicated essentially complete conversion to thiazoline **5** within 5 min after mixing. Heating the solution at reflux for 15 min completed the degradation. The nmr spectrum of this solution exhibited sharp signals at δ 1.7 (s, 3), 2.0 (s, 3), 5.35 (d, 1, J = 2 Hz, $CHCO_2H$), and 9.75 ppm (d, 1, J = 2 Hz, NCHS), characteristic of thiazoline **5** in addition to broad undefined absorptions at δ 1.7, 4.3, and 7.5 ppm (ArH).

2-Benzyl-2-oxazolin-5-one (7)[9].—This compound was prepared from phenylacetylglycine by dehydration with dicyclohexylcarbodiimide: bp 92–98° (0.003 mm) [lit.[9] bp 90–100° (0.005 mm)]; nmr (TFAA) δ 4.35 (t, 2, J = 1.5 Hz, $ArCH_2$), 4.8 (t, 2, J = 1.5 Hz, NCH_2CO), and 7.3–7.6 ppm (5, ArH). The nmr spectrum of **5** was essentially unchanged after heating the TFAA solution at reflux for 30 min.

Stability of Oxazolone 7 to TFAA Degradation.—Penicillin G methyl ester (2) (350 mg) and benzyloxazolone **7** (175 mg) were dissolved in 3 ml of TFAA. After heating at reflux for 30 min the nmr spectrum of this solution exhibited signals at δ 1.65 (s, 3), 2.0 (s, 3), 3.95 (s, 3), 5.15 (d, 1, J = 2 Hz), and 9.75 ppm (d, 1, J = 2 Hz) characteristic of thiazoline **6**. Additional undefined signals at δ 1.3–2.1, 3.6–3.8, 4.1–4.5, and 7.2–7.6 ppm (ArH) were also present.

TFAA Degradation of Methicillin (12).—Sodium methicillin (200 mg, Bristol-Myers) was heated at reflux in 1 ml of TFAA for 30 min. The nmr spectrum of this solution exhibited signals at δ 1.75 (s, 3), 2.05 (s, 3), 5.2 (d, 1, J = 2 Hz), and 9.75 ppm (d, 1, J = 2 Hz) characteristic of thiazoline **6** in addition to signals at δ 4.2 (s, 6, OCH_3), 4.6 and 4.7 (s, AB, NCH_2CO), 7.0 (d, 1, J = 10 Hz, ArH), 7.05 (d, 1, J = 9.5 Hz, ArH), and 9.75 ppm (dd, 1, J = 9.5 10 Hz, Ar*H*) characteristic of oxazolone **13**.

TFAA Degradation of Adduct 19.—Adduct 19[8] (100 mg) was dissolved in 0.3 ml of TFAA and heated at 60° for 15 min. The nmr spectrum of this solution exhibited signals characteristic of **6** at δ 1.7 (s, 3), 1.9 (s, 3), 3.95 (s, 3), 5.15 (d, 1, J = 2 Hz), and 9.75 ppm (d, 1, J = 2 Hz) in addition to broad undefined resonances at δ 1.4–1.8, 3.8–4.2, and 7.3–7.8 (ArH).

Registry No.—**2**, 653-89-4; **6**, 27494-11-7; trifluoroacetic acid, 76-05-1; *N*-benzyl-2-(2-phenylacetamido)-acetamide, 15440-34-3.

(13) J. C. Sheehan and J. R. Henry-Logan, *J. Amer. Chem. Soc.*, **81**, 3089 (1959).

(14) O. Wintersteiner, W. R. Boon, H. C. Carrington, D. W. MacCorquodale, F. H. Stodola, J. L. Wachtel, R. D. Coghill, W. C. Risser, J. E. Philip, and O. Touster, ref 2a, p 93.

(15) E. P. Abraham, W. Baker, W. R. Boon, C. T. Calam, H. C. Carrington, E. Chain, H. W. Florey, G. G. Freeman, R. Robinson, and A. G. Sanders, ref 2a, p 26.

Attempted Duplication of the Methyl Shift in Eremophilane Biosynthesis

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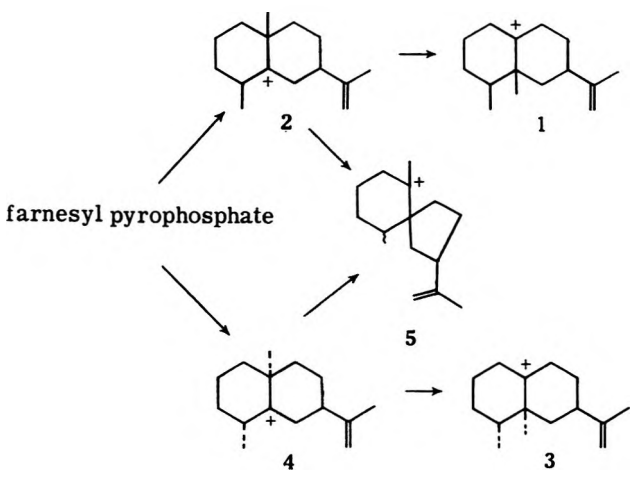
In an attempt to duplicate the proposed biosynthetic conversion of a 10-epieudesmane to a nootkatane derivative, 10-epieudesm-3-en-2-on-5β-ol (**10**) was prepared from 10-epieudesm-4-en-3-one by a four-step sequence patterned on the synthesis of α-agarofuran. Dehydration of **10** with phosphoryl chloride–pyridine gave as the only product the linear dienone, 10-epieudesma-3,5-dien-2-one (**15**). Hydrogenation of **10** gave 10-epieudesman-3-on-5β-ol (**16**), which on dehydration with boron trifluoride etherate–acetic acid gave 10-epieudesm-5-en-2-one (**20**), 10-epieudesm-3-en-2-one (**19**), and 5-epi-10-epieudesm-3-en-2-one (**18**). Dehydration of **16** with aqueous sulfuric acid gave only **18** and **19**. The factors governing the course of these reactions and the CD curves of compounds **10**, **16**, **18**, **19**, and **20** are discussed.

It was suggested a number of years ago by Robinson that the eremophilane (**1**) group of sesquiterpenes could be derived biosynthetically from a eudesmane (**2**) precursor.[1] In recent years this proposal has been modified slightly to give the currently accepted scheme for the biosynthesis of these sesquiterpenes and the closely related nootkatanes (**3** from a 10-epieudesmane **4**) and vetispirans (**5**).[2]

Although the conversions outlined in Scheme I can

SCHEME I



be represented as simple carbonium ion rearrangements, with one exception they have yet to be duplicated in the laboratory. The rearrangements of several epoxides of gross structure **6** have been investigated,[3] while the apparent methyl migration encountered in the rearrangement of **7**[4] has been shown to proceed *via* spiro intermediates.[5] The only chemical analogy to the biochemical interconversions described in Scheme I is the rearrangement on dehydration of β-rotunol (**8**) to a spirovetivane derivative **9**.[6]

In an attempt to duplicate the biosynthetic methyl shift it was felt that the conversion of a 10-epieudesmane to a nootkatane derivative (**4** → **3**) would be more favorable than the conversion of **2** → **1**, since it would result in a net conversion of an axial to equatorial isopropyl group. Also, by analogy with the β-rotunol rearrangement, it seemed desirable to design a model which would afford a conjugated system on rearrangement. The simplest compound which fulfills these requirements is the hydroxy enone **10**, which could afford a dehydronootkatone derivative **11** on dehydration and rearrangement.

The synthesis of **10** as outlined in Scheme II followed the general procedure utilized by Büchi for the synthesis of α-agarofuran.[7] The only significant modification of Büchi's method was the use of the Dauben–Shapiro method[8] for the preparation of homoannular diene **12**. As expected, photosensitized oxidation of **12** gave a dienone **14** as well as the desired peroxide **13**. The stereochemistry of **13**, and the derived hydroxy ketone (**10**), was assigned by analogy with the agarofuran series[7] and confirmed by the CD curve of **10**, which showed a positive Cotton effect for the $n \rightarrow \pi^*$ transition ($[\theta]_{363}$ + 799) which is of the same magnitude, but of opposite sign, to that of α-rotunol (**8**, with the hydroxyl α) and a 5α-androst-3-en-2-one derivative.[6]

Treatmentof **10** with phosphoryl chloride–pyridine under a variety of conditions gave a single product, although in mediocre yield. The spectral data for this compound (see Experimental Section) were not those predicted for the rearranged dienone **11**, but indicated that dehydration to a linear dienone (**15**), a reaction which has some precedent in the steroid series,[9] had occurred. After standing at room temperature for a number of hours, the original aqueous phase from the isolation of the products of this reaction gave significant quantities of recovered **10**. Apparently, **10** under the conditions of the reaction is converted to a phosphoric acid ester, which is soluble in the mildly basic aqueous pyridine solution, and slowly hydrolyzes to give recovered **10**.

In order to attempt to avert the formation of a simple conjugated system, **10** was reduced catalytically to give a single, saturated hydroxy ketone **16**. The stereochemistry assigned to **16** is based on the nmr spectrum,

(1) R. Robinson in A. R. Penfold and J. L. Simonsen, *J. Chem. Soc.*, 87 (1939).

(2) (a) W. Parker, J. S. Roberts, and R. Ramage, *Quart. Rev., Chem. Soc.*, 331 (1971); (b) N. H. Andersen, M. S. Falcone, and D. D. Syrdal, *Tetrahedron Lett.*, 1759 (1970).

(3) (a) G. Mehtu, G. L. Chetty, U. R. Nayak, and S. Dev, *Tetrahedron*, **24**, 3775 (1967); (b) H. Hikino, T. Kohana, and T. Takemoto, *ibid.*, **25**, 1037 (1968).

(4) C. H. Heathcock and T. R. Kelly, *ibid.*, **24**, 3753 (1968).

(5) D. T. Dunham and R. G. Lawton, *J. Amer. Chem. Soc.*, **93**, 2075 (1971). These authors have proposed a mechanistically plausible alternative to Scheme I, which, however, suffers from a severe phytochemical flaw in that it predicts the existence of two new groups of sesquiterpenes, and is in addition based on the incorrect assumption that 10-epieudesmanes are not encountered in nature.

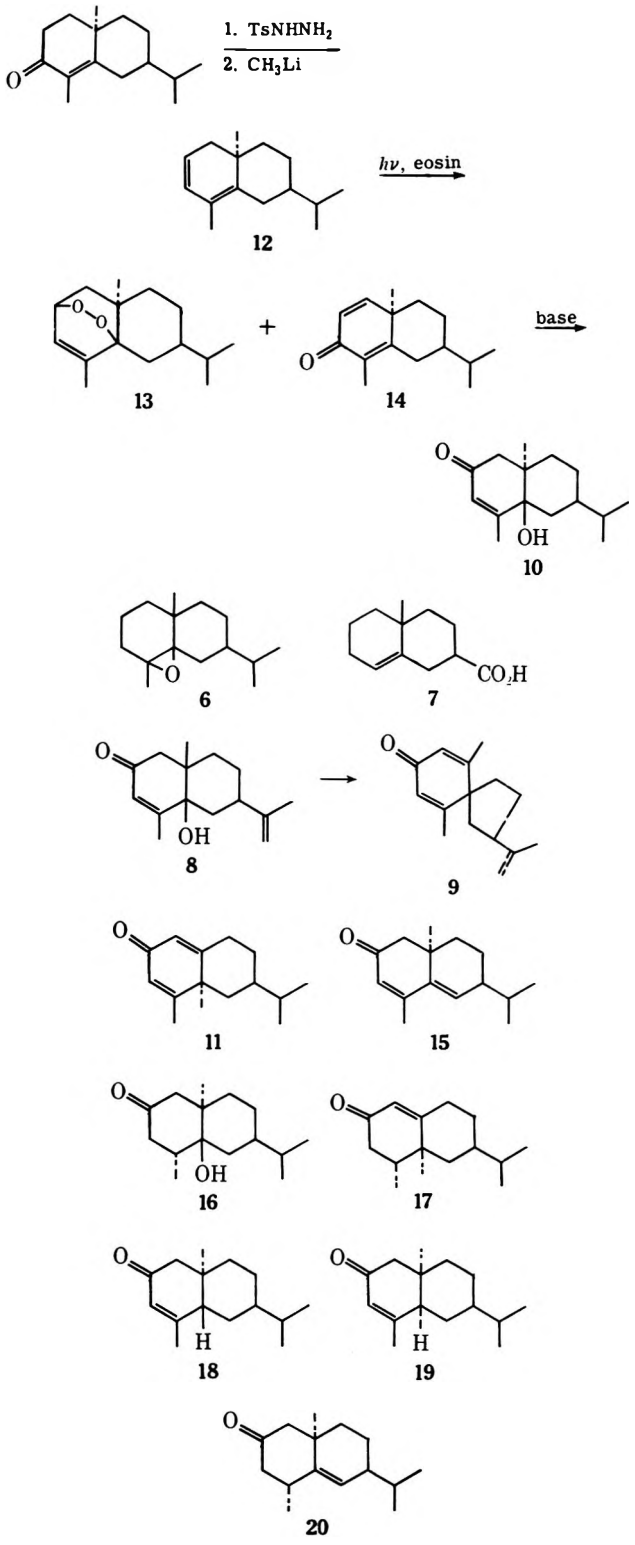
(6) H. Hikino, K. Aota, D. Kuwano, and T. Takemoto, *Tetrahedron Lett.*, 2741 (1969); *Tetrahedron*, **27**, 4831 (1971).

(7) H. C. Barrett and G. Büchi, *J. Amer. Chem. Soc.*, **89**, 5665 (1967). More recently this route has been used by J. A. Marshall, R. A. Ruden, L. K. Hirsch, and M. Phillipe, *Tetrahedron Lett.*, 3795 (1971), for the synthesis of a number of compounds similar to **10**.

(8) W. G. Dauben, M. E. Lorber, N. D. Vietmeyer, R. H. Shapiro, J. H. Duncan, and K. Tomer, *J. Amer. Chem. Soc.*, **90**, 4762 (1968).

(9) R. J. Conca and W. Bergman, *J. Org. Chem.*, **18**, 1104 (1953).

SCHEME II



which shows a doublet (J = 7 Hz) with the coupling constant indicative of an axial methyl group.[10] Also, the chemical shift of the secondary methyl is nearly the same as that of the angular methyl in both benzene-d_6 and deuteriochloroform, indicating that both methyl groups have a similar spatial relationship to the ketone carbonyl. The ORD and CD curves of **16** show the expected negative Cotton effect curve; however, rather than the usual smooth curve obtained for ketones of this type,[11] a curve with two inflections and an amplitude (ORD) of −63 is obtained. This is almost the same amplitude as that of several model compounds, which however lack the secondary methyl group at C-4.[11] This methyl group should make a contribution of +20 to +25[12] to the amplitude of the Cotton effect of **16**, giving a predicted amplitude of about −40 to −50 for **16** assuming a normal, undistorted, all-chair conformation. On the basis of the ORD data, it seems probable that the ring containing the carbonyl group is either considerably flattened, or in a twist conformation, caused by the interaction of the axial secondary methyl group, with the angular methyl.

Reaction of **16** with phosphoryl chloride–pyridine gave no dehydration product, but only material soluble in aqueous pyridine which afforded starting hydroxy ketone on standing in solution. Treatment with aqueous sulfuric acid gave a mixture of two ketones, neither of which was dihydronootkatone (**17**).[13] By varying the reaction time it was found that one ketone could be obtained as the principal reaction product (Table I) and that this compound was probably not that initially formed. Separation and characterization indicated that the products were α,β-unsaturated ketones, and were both isomeric with dihydronootkatone. In the nmr each ketone showed a vinyl proton as a broadened singlet, a vinyl methyl group, an angular methyl, and an isopropyl group. The mass spectra of these compounds were very similar to that of dihydronootkatone (see Experimental Section), and on the basis of these data it was apparent that these compounds were the stereoisomeric eudesmenones, **18** and **19**. The ketone of shorter retention time, which is the more stable isomer, must be the cis isomer (**19**), which can exist in a nonsteroid conformation with an equatorial isopropyl group. The trans isomer, **18**, must be formed initially, *via* a hydride shift from C-4, and is then isomerized to **19** on prolonged treatment with acid. Further evidence for these structural assignments was obtained when it was found that treatment of **18** with acid or base gave predominantly **19**, and the CD curves of **18** and **19** provided additional evidence for the assigned stereochemistry. The CD curve of trans ketone **18** showed a positive Cotton effect for the $n \rightarrow \pi^*$ transition ($[\theta]_{356}$ +146) which is opposite in sign to that of α-rotunol and a 5α-androst-3-en-2-one derivative.[6] The cis isomer also exhibits a positive Cotton effect curve ($[\theta]_{353}$ +440), which is that predicted by the inverse octant rule[14] for a ketone of structure **19**, having a nonsteroid conformation.

In an effort to probe the course of this reaction, and also to effect the desired methyl migration, hydroxy ketone **16** was treated with boron trifluoride etherate in acetic acid under a variety of conditions. Prolonged treatment at room temperature gave essentially the

(10) (a) F. Johnson, N. A. Starkowsky, and W. D. Gurowitz, *J. Amer. Chem. Soc.*, **87**, 3492 (1965). (b) The nmr spectrum of **16** is quite complex in the methyl region, and, in order to assign the position of the signals, the spectrum was run at both 60 and 90 MHz. We would like to thank Dr. G. B. Savitsky of this department for the 90-MHz spectra.

(11) (a) C. Djerassi and D. Marshall, *Tetrahedron*, **1**, 238 (1957); (b) W. Klyne, *ibid.*, **13**, 29 (1961).

(12) W. Klyne in G. Snatzke, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Heyden and Son, London, 1967, pp 139–152.

(13) Dihydronootkatone was prepared from (±)-nootkatone by hydrogenation using a homogeneous catalyst (see Experimental Section).

(14) G. Snatzke in G. Snatzke, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Heyden and Sons, London, 1967, pp 208–223.

same mixture of **18** and **19** obtained with sulfuric acid; however, 3% of a new compound could be detected by glc. By carrying out the dehydration for a short time, a mixture containing 16% of the new product plus 37 and 47% of **19** and **18**, respectively, was obtained. Separation of this minor reaction product and characterization by spectral methods (see Experimental Section) showed that it contained a saturated cyclohexanone carbonyl, an angular methyl group, a secondary methyl, an isopropyl group, and an isolated trisubstituted double bond. The only structure consistent with these data is that of the direct dehydration product **20**. The CD curve of **20** exhibits a weak negative Cotton effect (θ_{306} −680), and, although a negative Cotton effect is predicted by the octant rule, the small amplitude was unexpected. A study of models suggests that the most favorable conformation of **20** has a twist conformation for ring A which balances groups in positive and negative octants in such a manner that the amplitude of the Cotton effect will be minimal.

Although it was not anticipated that dihydronootkatone would be the exclusive product of the dehydration of **16**, it is *a priori* surprising that no trace of this compound was formed. The most probable explanation for the failure to observe any methyl migration is that the direct dehydration of **16** to **20** with the loss of the isopropyl–hydroxyl axial–axial interaction and relief of the methyl–methyl interaction is a much more rapid process. Protonation of **20** from the less hindered α face with migration of the β hydrogen at C-4 would lead to **18**, which is subsequently isomerized to the more stable cis isomer **19**.[15]

Experimental Section[16]

10-Epieudesm-4-en-3-one.—This compound was prepared from 10-epieudesm-11-en-3-on-5α-ol[17] by a modification of the method of Hikino.[3b]

10-Epieudesma-2,4-diene (12).—To a solution of 2.98 g of *p*-toluenesulfonylhydrazine in 35 ml of tetrahydrofuran was added 3.51 g of 10-epieudesm-4-en-3-one and 3 drops of concentrated hydrochloric acid. The reaction mixture was stirred and heated at reflux for 6 hr, benzene was added, and the solvents were distilled off until the boiling point reached 80°. The reaction flask was cooled with an ice bath and 30 ml of 1.91 *M* methyllithium was added dropwise over 30 min. Water was added cautiously, the mixture was extracted with two portions of hexane which were combined and dried, and the solvent was removed at reduced pressure to give 2.72 g of pale yellow oil. The crude product was taken up in hexane and filtered through a column of 75 g of Merck alumina to give 2.22 g (68%) of diene **12** as a rather unstable colorless oil, which was homogeneous to tlc (hexane, silica gel G) and glc: mass spectrum *m/e* (rel intensity) 204 (52), 189 (74), 145 (17), 132 (98), 131 (72), 118 (40), 117 (100); nmr δ 0.88, 0.90 (d, *J* = 6 Hz, isopropyl), 0.92 (s, 3 H, CH_3), 1.72 (d, *J* = 1 Hz, CH_3C=CH–), 5.68 (m, 2 H, HC=CH); uv 269 nm (log ε 3.73).

Photooxygenation of 12.—A solution of 0.81 g of homoannular diene was dissolved in 160 ml of a 1:1 mixture of benzene–ethanol and 0.020 g of eosin was added. The reaction mixture was irradiated with a Westinghouse 275W sun lamp while oxygen was bubbled through the reaction mixture. Analysis of aliquots by glc showed that no diene remained after 12 hr and the reaction mixture was filtered through Celite and charcoal and concentrated to a small volume *in vacuo*. The residue was taken up in benzene, washed with water until the washings were colorless, and dried, and the benzene was removed to give 0.73 g of yellow oil which partially crystallized. The crude product was taken up in hexane and chromatographed on 25 g of Merck acid-washed alumina. Elution with hexane–benzene (2:1) gave 0.216 g (23%) of endo peroxide **13** as white crystals, mp 72–73°. Recrystallization from aqueous methanol gave the analytical sample: mp 73–74°; nmr δ 0.88, 0.90 (d, *J* = 7 Hz, isopropyl), 0.92 (s, 3 H, CH_3), 1.85 (d, 3 H, *J* = 2 Hz, CH_3C=CH), 4.48 (m, 1 H, HCO), 6.20 (q, 1 H, HCCH=CCH_3); mass spectrum *m/e* (rel intensity) 236 (12), 204 (52), the balance of the spectrum was identical with that of the starting diene.

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23 H, 10.24. Found: C, 76.00 H, 9.94.

Elution with benzene gave 0.035 g (4%) of **10-epieudesma-2,4-dien-3-one (14)** as a colorless oil, which was homogeneous to tlc [benzene–acetone (10:1), silica gel G]: ir 6.03 and 6.14 μ; nmr δ 0.88, 0.90 (d, *J* = 7 Hz, isopropyl), 1.09 (s, 3 H, CH_3), 1.95 (s, 3 H, CH_3C=C), 6.21, 6,83 (2 H, AB, *J* = 10 Hz, –CH=CH–); mass spectrum *m/e* (rel intensity) 219 (62), 218 (23), 204 (18), 175 (100), 161 (41), 147 (75).

Elution with methylene chloride gave 0.115 g (12%) of 10-epieudesm-3-en-2-on-5β-ol (**10**) as white crystals, mp 140–142°. The analytical sample, mp 143–144°, was prepared by recrystallization from hexane: ir 2.94 and 6.04 μ; nmr δ 0.91, 0.98 (d, *J* = 6 Hz, isopropyl), 1.05 (s, 3 H), CH_3), 1.96 (d, *J* = 1 Hz, 3 H, CH_3C=CH), 5.76 (br s, 1 H, HC=CCH_3); mass spectrum *m/e* (rel intensity) 236 (2), 208 (5), 193 (15), 175 (12), 126 (13), 123 (18), 111 (100), 110 (76); uv 237 nm (log ε 4.12); CD (*c* 0.00205, 25°) $[\theta]_{396}$ 0, $[\theta]_{379}$ +418, $[\theta]_{373}$ +351, $[\theta]_{363}$ +799, $[\theta]_{354}$ +351, $[\theta]_{348}$ +684, $[\theta]_{340}$ 0, $[\theta]_{339}$ −57, $[\theta]_{336}$ 0, $[\theta]_{333}$ +38, $[\theta]_{332}$ 0, $[\theta]_{326}$ −380, $[\theta]_{320}$ −285, $[\theta]_{314}$ −380.

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23 H, 10.24. Found: C, 76.38 H, 10.40.

10-Epieudesm-3-en-2-on-5β-ol (10). A.—A solution of 0.117 g of peroxide **13** in 6 ml of 1 *M* ethanolic sodium hydroxide was heated at reflux for 15 min, cooled, acidified with glacial acetic acid, and diluted with water. The aqueous suspension was extracted with three portions of methylene chloride, which were combined, washed with water and 5% aqueous sodium hydroxide, and dried, and the solvent was removed at reduced pressure to give 0.077 g (66%) of white crystals, mp 138–140°, identical (ir, mixture melting point) with the material obtained as described above.

B.—The crude product from the photooxygenation of 1.36 g of diene **12** was dissolved in 60 ml of 1 *N* sodium hydroxide and treated as described in part A. Recrystallization of the crude product from hexane gave 0.415 (26%) of **10**, mp 136–139°. Concentration of the mother liquors gave 0.52 g of yellow oil which on tlc showed the presence of dienone **14**, hydroxy ketone **10**, and traces of two other compounds. By chromatography of the mother liquors and sublimation (0.5 mm, 100°) of the fractions eluted with methylene chloride, an additional 0.078 g (5%) of **10** could be obtained.

10-Epieudesma-3,5-dien-2-one (15).—To a solution of 0.078 g of hydroxy ketone **10** in 5 ml of pyridine was added 0.15 ml of phosphoryl chloride; the reaction mixture was heated at reflux for 1 hr, cooled, and poured into water; and the aqueous solution was extracted with three portions of ether. The ethereal extracts were combined, washed with two portions of water, 5% hydrochloric acid, and again with water and dried, and the solvent was removed at reduced pressure to give 0.021 g (29%) of yellow oil which gave essentially one spot on tlc (silica gel G,

(15) A study of models of **20** show that with ring A in the twist conformation mentioned above the steric relationship between the double bond and the β hydrogen at C-4 should favor this reaction path.

(16) All melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infrared spectra were taken as potassium bromide disks or liquid films on sodium chloride plates using a Perkin-Elmer Model 137 spectrophotometer and are reported in microns. Ultraviolet spectra were taken in methanol using a Perkin-Elmer Model 202 spectrophotometer and are reported as λ_{max} in nanometers (log ε). Nuclear magnetic resonance spectra were obtained using a Varian Associates A-60 nuclear magnetic resonance spectrophotometer with deuteriochloroform as a solvent unless stated otherwise. All spectra are reported in parts per million relative to tetramethylsilane (δ). Gas–liquid chromatography was carried out on an F & M Model 810 analytical gas chromatograph using helium as the carrier gas at a flow rate of 35 ml/min through a 10 ft × 0.125 in. copper column of 20% Carbowax on 'HP' Chromosorb W (80–100 mesh). Preparative glc was carried out on an Aerograph Autoprep, Model A-700, using helium as a carrier gas at a flow rate of 300 ml/min using a 25 ft × 0.375 in. copper column of 25% Carbowax on Chromosorb W. Optical rotatory dispersion and circular dichroism measurements were made in dioxane solution using a Jasco ORD/UV-5 spectropolarimeter. Mass spectra were determined using a Du Pont 21-490 mass spectrometer at 70-eV ionization potential. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(17) The author would like to thank Professor A. R. Pinder for the gift of a generous sample of this material.

benzene–acetone, 10:1). Preparative tlc using the same system gave 0.010 g of **12** as a colorless oil: ir 6.02, 6.18, 6.30 μ; mass spectrum *m/e* (rel intensity) 218 (46), 203 (11), 175 (100), 161 (46), 147 (43), 133 (29), 131 (43); nmr δ 0.92, 0.99 (d, J = 7 Hz, isopropyl), 1.10 (s, 3 H, CH_3), 2.05 (d, J = 1 Hz, 3 H, CH_3C=CH), 5.85 (br s, 1 H, HC=CCH_3), 6.15 (d, 1 H, J = 3 Hz, CHCH=C–); uv 284 nm (log ϵ 4.27).

After standing overnight at room temperature, the original aqueous pyridine solution deposited 0.034 g (43%) of starting hydroxy ketone, mp and mmp 140–142°.

Similar results were obtained at steam bath temperature for 1–2 hr and at reflux for 2 hr.

10-Epieudesman-3-on-5β-ol (16).—A solution of 0.040 g of hydroxy ketone **10** in 10 ml of 95% ethanol was hydrogenated at 30 psig using 0.010 g of 5% rhodium on alumina catalyst. The reaction mixture was filtered through Celite, and the solvent was removed at reduced pressure to give 0.027 g (68%) of white crystals, mp 157–159°, which were homogeneous to tlc.[18] Recrystallization from hexane gave the analytical sample: mp 161–162°; ir 2.89 and 5.91 μ; mass spectrum *m/e* (rel intensity) 238 (35), 223 (4), 220 (4), 203 (13), 193 (33), 154 (100); nmr ($CDCl_3$) δ 0.98, 1.00 (d, J = 6 Hz, isopropyl), 1.09 (d, J = 7 Hz, 3 H, CH_3CH), 1.10 (s, 3 H, CH_3); nmr (C_6H_6); nmr (C_6D_6) δ 0.77 (d, J = 7 Hz, isopropyl), 0.83 (s, 3 H, CH_3), 0.89 (d, J = 7 Hz, CH_3CH); CD (*c* 0.000212) θ_{332} 0, θ_{314} −2020, θ_{304} −3520, θ_{295} −3710; ORD ϕ_{380} −795°, ϕ_{322} −3640; ϕ_{314} −3060°, ϕ_{302} −900°, ϕ_{295} 0°, ϕ_{286} +2700°.

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.57; H, 11.04.

Dehydration of 10-Epieudesman-2-on-5β-ol. A.—To a solution of 0.164 g of hydroxy ketone **16** in 4 ml of acetic acid was added with stirring 0.20 ml of redistilled boron trifluoride etherate. The reaction mixture was stirred at room temperature for 15 min, poured into ice water, and extracted with three portions of ether. The ethereal extracts were washed with water, 10% sodium hydroxide, and saturated brine and dried, and the solvent was removed *in vacuo* to give 0.074 g of pale brown oil. Analytical glc showed three compounds listed in order of increasing retention time in a ratio of 14:54:32, and the mixture was separated by preparative glc to give respectively, **20**, **19**, and **18**.

10-Epieudesm-5-en-2-one (20) (0.004 g) had ir 5.85 μ; mass spectrum *m/e* (rel intensity) 220 (34), 205 (23), 193 (18), 178 (49), 163 (21), 151 (25), 139 (70), 138 (100); nmr δ 0.91, 0.93 (d, J = 7 Hz, isopropyl), 1.12 (s, 3 H, CH_3), 1.20 (d, J = 7 Hz, 3 H, CH_3CH); CD (*c* 0.0014) θ_{370} 0, θ_{316} −528, θ_{306} −680. Glc indicated that this material contained 15% of cis ketone **19** and 5% of the trans isomer **16**.

10-Epieudesm-3-en-2-one (19) (0.008 g) had ir 6.01 and 6.10 μ; mass spectrum *m/e* (rel intensity) 220 (100), 205 (25), 178 (87), 177 (64), 136 (42), 135 (43); nmr δ 0.88, 0.90 (d, J = 6 Hz, isopropyl), 0.98 (s, 3 H, CH_3), 1.98 (d, J = 1 Hz, CH_3-CH_3C=CH), 5.82 (br s, 1 H, HC=CCH_3); CD (*c* 0.0029) θ_{380} 0, θ_{369} +302, θ_{361} +176, θ_{353} +440, θ_{344} 0, θ_{338} +137, θ_{335} 0, θ_{330} −274, θ_{325} −176, θ_{318} −376, θ_{310} −274, θ_{306} −302; uv 243 nm (log ϵ 4.00). Glc indicated that this material contained less than 5% of the other two isomers.

5-Epi-10-epieudesm-3-en-2-one (18) (0.007 g) had ir 6.00 and 6.10 μ; mass spectrum *m/e* (rel intensity) 220 (96), 205 (25), 178 (100), 177 (73), 135 (91); nmr δ 0.92, 0.96 (d, J = 6 Hz), 1.02 (s, 3 H, CH_3), 1.89 (d, 3 H, J = 1 Hz, CH_3C=CH), 5.88 (br s, 1 H, HC=CCH_3); CD (*c* 0.0021) θ_{384} 0, θ_{372} +90, θ_{363} +42, θ_{356} +146, θ_{350} 0, θ_{347} −35, θ_{344} 0, θ_{341} +49, θ_{338} 0, θ_{333} −167, θ_{325} −28, θ_{320} −167, θ_{310} 0; uv 244 nm (log ϵ 3.79) Glc indicated that this compound contained less than 5% of the other two isomers. The retention time of **18** was the same (two columns) as that of 11,12-dihydronootkatone.

When the boron trifluoride catalyzed dehydration was carried out for varying periods and the mixture of ketones was isolated as described above and subjected to analytical glc, the results recorded in Table I were obtained.

TABLE I

DEHYDRATION OF 10-EPIEUDESMAN-2-ON-5β-OL (16)

		Compd, %		
Time, hr	Catalyst	**20**	**19**	**18**
0.25[a]	Boron trifluoride	16	37	47
1	Boron trifluoride	8	51	41
18	Boron trifluoride	3	64	33
1.5	Sulfuric acid	0	47	53
3[a]	Sulfuric acid	0	67	33
18	Sulfuric acid	0	76	24

[a] Product were isolated, separated, and characterized.

B.—To 0.042 g of hydroxy ketone **16** at 0° was added with efficient stirring 4.0 ml of cold (0°) 50% aqueous sulfuric acid. The reaction mixture was allowed to warm to room temperature, stirred for 3 hr, and poured into ice water, and the aqueous suspension was extracted with three portions of methylene chloride. The organic extracts were combined, washed with water, and dried and the solvent was removed to give 0.039 g of yellow oil. Although this material was homogeneous to tlc (silica gel G, benzene–acetone 10:1), glc indicated the presence of two compounds in a ratio of 2:1. Preparative glc as described in part A gave 0.010 g of **19** and 0.004 g of **18**, the infrared, nmr, and mass spectra of which were identical with those of the compounds obtained in part A.

C.—A solution of 0.031 g of **16** in 2 ml of dry pyridine was treated with 0.10 ml of phosphoryl chloride and the product was isolated as described above to give 0.003 g (10%) of impure hydroxy ketone. The initial aqueous extracts after standing overnight gave an additional 0.015 g (48%) of **16**.

Isomerizations of 5-Epi-10-epieudesm-3-en-2-one. A.—To a solution of 0.001 g of **18** in 0.5 ml of dioxane was added 1 drop of concentrated hydrochloric acid, and the mixture was heated on the steam bath for 12 hr. Analysis by glc indicated a ratio of **19** to **18** of 7:1.

B.—To a solution of 0.001 g of **18** in 1 ml of methanol was added 0.050 g of sodium methoxide, and the mixture was heated at reflux for 18 hr. Glc indicated only the presence of cis ketone **19**.

(±)-11,12-Dihydronootkatone (17).—To a solution of 0.281 g of (±)-nootkatone[19] in 30 ml of dry benzene was added 0.147 g of tris(triphenylphosphine)rhodium chloride. The reaction flask was swept with hydrogen, sealed, and stirred overnight at room temperature. The reaction mixture was filtered through a short column of Merck alumina and the solvent was removed to give 0.234 g (83%) of **17** as a colorless oil, the infrared spectrum of which was identical with that of a sample prepared from (+)-nootkatone by Pinder:[20] mass spectrum *m/e* (rel intensity) 220 (81), 205 (12), 178 (100), 177 (21), 135 (95); nmr δ 0.90 (d, J = 6 Hz, isopropyl), 0.97 (d, J = 6 Hz, 3 H, CH_3CH), 1.09 (s, 3 H, CH_3), 5.75 (br s, HC=C). Glc indicated the presence of trace amounts of unreduced nootkatone and tetrahydronootkatone.

Registry No.—**10**, 34996-35-5; **12**, 34996-36-6; **13**, 34969-20-5; **14**, 34996-37-7; **16**, 34996-38-8; **18**, 34996-39-9; **19**, 34996-40-2; **20**, 34996-41-3.

Acknowledgments.—The spectropolarimeter and mass spectrometer were obtained through National Science Foundation Research Instruments Grants.

(18) Both this material and hydroxy enone **10** sublime readily at 100° and atmospheric pressure, which undoubtedly contributes to the mediocre yields encountered in their preparation.

(19) The author would like to thank Professor A. R. Pinder for making available a sample of (±)-nootkatone which had been supplied to him by Dr. P. Schudel.

(20) A. R. Pinder, unpublished work.

Further Studies on the Sesquiterpene Lactones Tulipinolide and Epitulipinolide from *Liriodendron tulipifera* L.[1]

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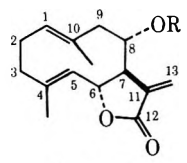
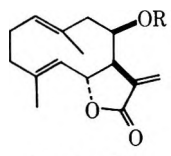
Received February 14, 1972

The dihydro derivatives **3** and **4** of tulipinolide (**1**) and epitulipinolide (**2**) were prepared by $NaBH_4$ reduction since catalytic hydrogenation gave other reduction products. The stereochemistry at the reduced center of these derivatives was determined by cyclization to the already known β-cyclo compounds **6** and **7**. Minor alkaline-hydrolysis products of epitulipinolide (**2**) were established as the methoxy Michael adducts **13** and **15** if methanol was a cosolvent. Without methanol the eudasmanolide diol **16** was formed along with the unusual cadinene lactone **22**, but in no case was the C-8 cis γ-lactone germacranolide (isoeupatolide) detected. A product of alkaline hydrolysis of tulipinolide (**1**) was desacetylisotulipinolide (**23**), a C-8 trans γ-lactone which was also obtained by treatment of eupatolide methanesulfonate (**25**) with hydroxide ion. The acetate of **23** (isotulipinolide) was shown to be identical with the recently isolated germacranolide, laurenobiolide.

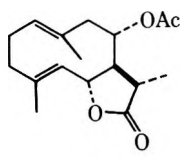
The cytotoxic sesquiterpene lactones, tulipinolide and epitulipinolide, from the root bark of *Liriodendron tulipifera* L., were recently assigned structures **1** and **2**, respectively.[2] We report herein new transformation products of these compounds and show a direct conversion of epitulipinolide to the tulipinolide skeleton by epimerization at the 8 carbon.



1, R = Ac
26, R = H



2, R = Ac
11, R = H
25, R = SO_2Me



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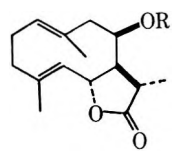
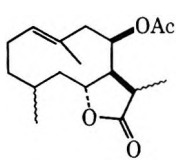


4, R = Ac
12, R = H



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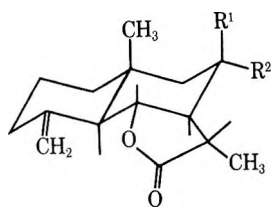


6, R^1 = H, R^2 = OAc
7, R^1 = OAc, R^2 = H

The 11,13-dihydro derivatives **3** and **4** of tulipinolide (**1**) and epitulipinolide (**2**), respectively, were prepared by sodium borohydride reduction, since catalytic hydrogenation gave undesired products. For example, the product of tulipinolide (**1**) and 1 mol of hydrogen still contained the exocyclic methylene protons as seen in the nmr spectrum, while epitulipinolide (**2**), which very rapidly took up 2 mol of hydrogen, gave a substance without the exocyclic methylene but, in addition to the expected secondary C-11 methyl group (δ 1.12, J = 7.1 Hz), the nmr spectrum also showed a three-proton broadened singlet (δ 1.05, $W_{1/2}$ = 7 Hz) reminiscent of a "virtually coupled" methyl group.[3] The physical data support formulation of this substance as **5**.

Dihydrotulipinolide (**3**) has physical properties close to those of acetylbalchanolide,[4] and comparison of their ir spectra[5] indicate that they are most probably identical. The methyl group at C-11 was placed α on the basis that cyclization of dihydrotulipinolide (**3**) produced the known compound dihydrocyclotulipinolide (**6**), for which all of the asymmetric centers were established.[2] Dihydroepitulipinolide (**4**) on cyclization gave the 11 *R* epimer **7** of the two known dihydro-β-cyclo-epitulipinolides.[2] The cyclization reaction on dihydrotulipinolide and dihydroepitulipinolide also made available the corresponding α-cyclo compounds **8** and **9** as coproducts. To complete the series of dihydrocyclo-epitulipinolides, the remaining γ isomer **10** was made by sodium borohydride reduction of γ-cycloepitulipinolide.[2] Eupatolide (**11**)[2] was reduced with sodium borohydride to dihydroeupatolide (**12**) with the 11*R* configuration, since on acetylation it gave dihydro-epitulipinolide (**4**).

Alkaline hydrolysis of epitulipinolide (**2**) in dilute aqueous methanolic KOH gave mainly eupatolide (**11**) and two additional substances, as observed by thin layer chromatography of the mother liquor. Column chromatography yielded these as crystalline compounds that were characterized as the epimeric Michael addition products of eupatolide and methanol. The major epimer **13** exhibited a methoxy peak at δ 3.34, two olefinic methyls at δ 1.62 and 1.70, and the split AB pattern found typical of H_5 and H_6 protons in the C-6 trans γ-lactone germacranolides.[2] In addi-

(1) Antitumor Agents. VI. Previous paper: R. W. Doskotch, M. Y. Malik, C. D. Hufford, S. N. Malik, J. E. Trent, and W. Kubelka, *J. Pharm. Sci.*, **61**, 570 (1972). This investigation was supported by Public Health Service research grant CA-08133 from the National Cancer Institute and equipment grant FR-00328 from Special Research Resources for purchase of a Varian A-60A nmr spectrometer plus accessories.

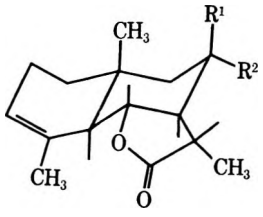
A detailed listing (Table I) of the nmr peaks for the compounds in this publication will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-72-2740. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(2) R. W. Doskotch and F. S. El-Feraly, *J. Org. Chem.*, **35**, 1928 (1970).

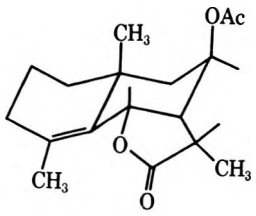
(3) F. A. L. Anet, *Can. J. Chem.*, **39**, 2262 (1961).

(4) J. Hochmannova, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, **26**, 1826 (1961); V. Herout, M. Suchy, and F. Sorm, *ibid.*, 2612 (1961).

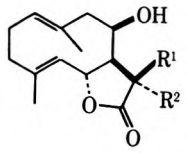
(5) We thank Professor F. Sorm for a copy of the ir spectrum of acetylbalchanolide. Since an authentic sample of the compound was unavailable, our comparison of spectra, one determined on a prism instrument and the other on a grating instrument, precludes a statement about their complete identity. No major differences were noted.



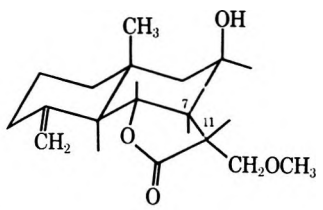
8, $R^1 = H; R^2 = OAc$
9, $R^1 = OAc; R^2 = H$



10



13, $R^1 = H; R^2 = CH_2OCH_3$
15, $R^1 = CH_2OCH_3; R^2 = H$



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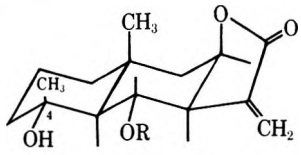
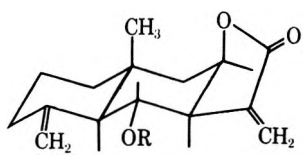


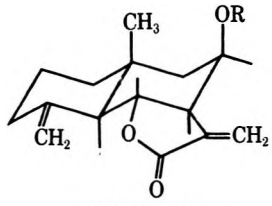
16, R = H
17, R = Ac



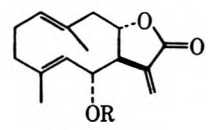
18, R = Ac
19, R = H

tion, a two-proton, eight-peak pattern, the AB part of an ABX system,[6] was observed for the H_{13} protons, and the X part of this system (H_{11}) was seen as four equal peaks further split by H_7 (J = 12.0 Hz). The large H_7–H_{11} coupling value would require the H_{11} proton to be pseudoaxial, and confirmation of this assignment was obtained from analysis of the cyclized product, 13-methoxydihydro-β-cycloeupatolide (**14**), in which the H_7–H_{11} coupling constant is 12.8 Hz. Values of this order were shown to be indicative of an axial–pseudoaxial interaction for eudesmanolide C-6 trans α-methyl-γ-lactones.[7] Replacement of the α-methyl group with an α-methoxymethylene would not be expected to greatly alter this relationship. The minor dihydro-13-methoxyeupatolide epimer **15** exhibited an nmr spectrum similar to that of the major isomer except that the H_{13} proton pattern appeared as two sharp singlets at δ 3.91 and 3.95,[8] and the H_{11} absorption was hidden in an envelope of peaks, consequently its detailed analysis was not possible.

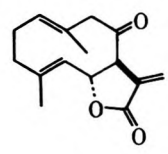
Elimination of methanol as a cosolvent in the alkaline hydrolysis (followed by acidification) of epitulipinolide eliminated the formation of the methanol adducts **13** and **15**, but instead two other compounds were obtained. One of these analyzed for $C_{15}H_{22}O_4$ and had spectral properties in agreement with structure **16**. Acetylation of the diol **16** to the monoacetate **17** followed by dehydration afforded β-cycloisoepitulipinolide (**18**), identical with the acetate of a product **19** obtained on isomerization by hydrolysis of β-cycloeupatolide (**20**)[2] or of β-cycloepitulipinolide (**21**). This established the



20, R = H
21, R = Ac



23, R = H
24, R = Ac



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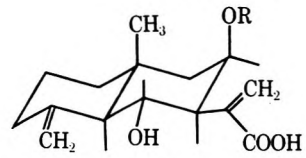
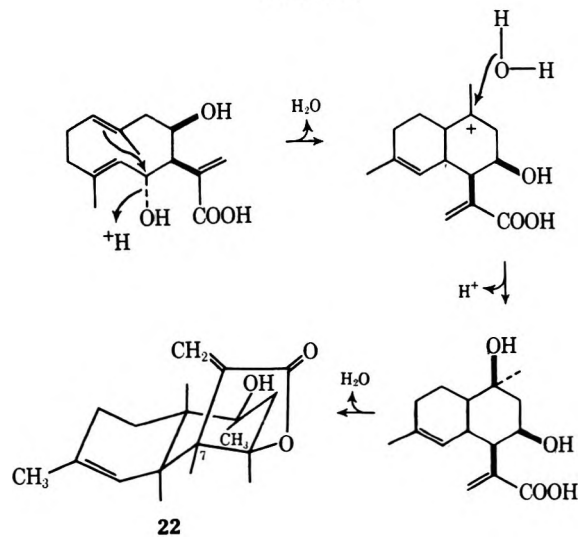


28

structure and stereochemistry for compound **16** except for the configuration at C-4, which was resolved by utilization of the solvent-induced nmr shift correlations of Demarco, *et al.*,[9] although the dehydrated product itself could be taken as supporting an equatorial hydroxyl. The nmr spectrum of the hydroxy acetate **17** in pyridine-d_5 shows the C-10 methyl at δ 1.01, whereas in $CDCl_3$ it appears at δ 1.09. Since a deshielding effect did not occur, a 1,3-diaxial relationship for the C-4 hydroxyl group and the C-10 methyl does not exist, and the hydroxyl group must be equatorial.

The second minor product from the hydrolysis of epitulipinolide (**2**) analyzed for $C_{15}H_{20}O_3$ and showed from the ir spectrum the presence of a hydroxyl, a γ-lactone, and ethylenic groups. The structure **22** bearing a cadinene-ring system was proposed for the compound from nmr studies, and its formation from the hydroxy acid of eupatolide was rationalized as occurring during the lactone closing phase of the reaction (Scheme I). A pair of doublets typical of the exocyclic methyl-

SCHEME I



22

ene protons was present at δ 6.23 and 5.75 and found, by double-irradiation experiments, to be coupled (J = 3.2 and 3.0 Hz, respectively) to a proton at δ 3.22 which was assigned position 7. Splitting of the H_7 pattern was caused by two additional couplings of J = 4.8 (H_6)

(6) Analysis of this system was carried out as given by R. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, pp 86–92.

(7) C. R. Narayanan and N. K. Venkatasubramanian, *J. Org. Chem.*, **33**, 3156 (1968).

(8) These are undoubtedly the larger inner peaks of an AB quartet for which the smaller outside peaks were too weak to be observed.

(9) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, **90**, 5480 (1968). Methyl groups 1,3 diaxial to a hydroxyl show a deshielding of 0.2–0.4 ppm in pyridine relative to chloroform.

and 7.2 Hz (H_8), values in accord with two equatorial–axial interactions, if the twist of the relevant dihedral angle by the lactone ring is taken into account. The olefinic methyl at δ 1.75 and the one-proton (H_5) peak ($W_{1/2}$ = 5 Hz) at δ 5.35 are related as shown, since irradiation of one causes marked sharpening of the other. The C-10 tertiary hydroxyl group (D_2O exchangeable sharp singlet at δ 1.93) was placed equatorial because a large deshielding of the H_8 proton was not observed in the nmr spectrum taken in pyridine-d_5.[9] The uncommon cyclization of a germacranolide to a cadinene, as we have observed, has been previously reported for the simple sesquiterpene hydrocarbon, bicyclogermacrene,[10] but not to our knowledge for a germacranolide lactone.

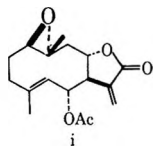
It is of note that none of the products from hydrolysis of epitulipinotide (**2**) is the C-8 cis lactone, isoeupatolide. On the other hand, the hydrolysis of tulipinolide (**1**) does yield deacetylisotulipinolide (**23**), a C-8 trans lactone. An unusual feature of the nmr spectrum of this compound is the presence of a broad singlet ($W_{1/2}$ = 6 Hz) at δ 6.19 for the H_{13} proton situated trans to the lactone and is probably due to long-range coupling to H_6 or H_8, or both. The other H_{13} proton appears at δ 6.38 as a pair of doublets, J = 2.8 and 1 Hz. The latter value is the characteristic geminal coupling commonly noted for the C-6 trans α,β'-unsaturated γ-lactones,[11] which appears to hold in this case for an α-C-8 trans α,β'-unsaturated γ-lactone with C-6 α-OH. Acetylation of **23** to isotulipinolide (**24**) restored the exocyclic methylene proton pattern to a pair of double doublets.[12] After this study was completed, a communication appeared on the isolation of a substance named laurenobiolide from *Laurus nobilis* L.[13] which has the same constitution as isotulipinolide (**24**). A comparison of the nmr and ir spectra and tlc mobility of the two substances showed them to be identical.

Deacetylisotulipinolide (**23**) was obtained in low yields in another way: from eupatolide methanesulfonate (**25**) by inversion of the C-8 center on treatment with potassium hydroxide. The other product of the reaction was eupatolide. Attempts to obtain deacetyltulipinolide (**26**) by sodium borohydride reduction of dehydroeupatolide[2] (**27**) were unsuccessful; the products were eupatolide, 11,13-dihydroeupatolide, and what was tentatively identified from the nmr spectrum as 11,13-dihydrodehydroeupatolide.

(10) K. Nishimura, N. Shinoda, and Y. Hirose, *Tetrahedron Lett.*, 3097 (1969).

(11) H. Yoshioka, T. J. Mabry, M. A. Irwin, T. A. Geissman, and Z. Samek, *Tetrahedron*, **27**, 3317 (1971).

(12) Although geminal coupling does not appear to be common for C-6 α-oxygenated, C-8 α-germacranolides (ref 11), it does occur in some cases, *e.g.*, pyrethrosin (i), where the exocyclic methylenes are found at δ_{CDCl_3} 6.37 (J = 3.0, 0.8 Hz) and 5.93 (J = 2.6, 0.8 Hz).



i

X-Ray studies on pyrethrosin were reported by E. J. Gabe, S. Neidle, D. Rogers, and C. E. Nordman, *Chem. Commun.*, 559 (1971), and chemical studies by S. Iriuchijima and S. Tamura, *Agr. Biol. Chem. (Tokyo)*, **34**, 204 (1970); R. W. Doskotch, F. S. El-Feraly and C. D. Hufford, *Can. J. Chem.*, **49**, 2103 (1971), and references cited therein.

(13) H. Tada and K. Takeda, *Chem. Commun.*, 1391 (1971). We thank Dr. Tada for the copies of the ir and nmr spectra and the sample of laurenobiolide.

Experimental Section[14]

Dihydrotulipinolide (3).—An 80-mg sample of tulipinolide (**1**) suspended in 4 ml of absolute EtOH was treated with 20 mg of $NaBH_4$. When the suspension cleared (10 min) the acidified (10% HOAc) solution was evaporated at reduced pressure and the residue was dissolved in chloroform. The chloroform solution was washed with H_2O and dried (Na_2SO_4), and the crystalline residue remaining after solvent removal crystallized from *n*-hexane to give **3** as needles (57 mg): mp 120–122°; $[\alpha]^{22}D$ +45° (*c* 0.056, MeOH); CD (c 0.056, MeOH), 22°, $[\theta]_{220}$ + 141,000; uv end absorption 210 nm (log ϵ 3.93); ir 1770 (γ-lactone), 1740 (acetate), 1660 (olefin) and 1240 cm^{-1} (CO stretching); mass spectrum *m/e* (rel intensity) M^+ 292 (0.4), 250 (1.2), 232 (33), 121 (68), 93 (68), and 43 (100).[15]

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.61; H, 8.16.

The physical properties of **3** were very close to those of acetylbalchanolide [lit.[4] mp 125°, $[\alpha]^{20}D$ +128.1° (*c* 3.38, $CHCl_3$)], and the ir spectra were the same.[5]

Dihydroepitulipinolide (4).—A 100-mg sample of epitulipinolide (**2**) in 5 ml of absolute EtOH was treated with 30 mg of $NaBH_4$. After 15 min the acidified (10% HOAc) solution was evaporated at reduced pressure to remove the EtOH; the residue was taken up in $CHCl_3$, washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. The colorless residue was chromatographed on 7 g of silica gel G to give an oil (85 mg) that crystallized from diethyl ether–pentane as needles (59 mg): mp 102–103°, $[\alpha]^{22}D$ +135° (*c* 0.048, MeOH); CD (*c* 0.048, MeOH), 22°, $[\theta]_{220}$ + 162,000; uv end absorption 220 nm (log ϵ 3.80); ir 1770, 1740, 1670, 1240 and 965 cm^{-1}; R_f 0.5 on tlc (silica gel G) with $CHCl_3$–Et_2O (1:1); mass spectrum *m/e* (rel intensity) M^+ 292 (0.5), 250 (0.9), 232 (36), 121 (42), 93 (46) and 43 (100).

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.62; H, 8.30.

Catalytic Hydrogenation of Epitulipinolide (2).—A sample (100 mg) of **2** dissolved in 20 ml of absolute EtOH was reduced over 20 mg of 5% Pd/C presaturated with hydrogen at ambient temperature and atmospheric pressure. Two moles of hydrogen was rapidly absorbed and uptake ceased. The residue, after removal of catalyst and solvent, crystallized (33 mg) from ether: mp 147–148°; $[\alpha]^{22}D$ −218° (*c* 0.070, MeOH); CD (*c* 0.070, MeOH) 22°, $[\theta]_{225}$ +1030; ir 1770 (γ-lactone), 1735 (acetate), and 1235 cm^{-1} (C–O stretching); mass spectrum *m/e* (rel intensity) M^+ 294 (2), 252 (11), 234 (16), 161 (38), and 43 (100).

Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36 H, 8.90. Found: C, 69.29 H, 8.70.

Structure **5** is proposed on the basis of the physical data, in particular the nmr spectrum.

Cyclization of Dihydroepitulipinolide (4).—A sample (70 mg) of **4** in 4 ml of $CHCl_3$ was treated with 0.2 ml of $SOCl_2$ for 30 min at room temperature. The residue remaining, after evaporation of the reaction mixture, was chromatographed on 5 g of silica gel G containing 10% $AgNO_3$ with $CHCl_3$–Et_2O (5:1) as eluting solvent. Fractions (4 ml) were collected. The α-cyclo isomer **9** emerged first and was crystallized from *n*-hexane to give colorless plates (15 mg): mp 102–104°; $[\alpha]^{22}D$ −36° (*c* 0.19, MeOH); ir 1775, 1740, and 1245 cm^{-1}; mass spectrum *m/e* (rel intensity) M^+ 292 (35), 232 (58), 217 (81), 108 (77), and 43 (100).

(14) Melting points were taken in capillaries on a Thomas-Hoover apparatus or on a Fisher-Johns hot stage, and are uncorrected. Elemental analyses were by Dr. Alfred Bernhardt, Germany, or the Scandinavian Microanalytical Laboratory, Denmark. Infrared spectra were taken in $CHCl_3$ or in KBr pellets on a Perkin-Elmer Model 237 or 257 spectrophotometer and ultraviolet spectra were obtained in CH_3OH on a Cary Model 15 spectrophotometer. The nmr spectra were measured in $CDCl_3$ or as stated otherwise on a Varian A-60A or T-60 instrument with $(CH_3)_4Si$ as internal standard, and chemical shifts are reported in δ (parts per million) units. The ORD, CD, and optical rotation values were determined on a Jasco ORD/UV-5 spectropolarimeter with CD attachment. Mass spectra were obtained on an AEI MS-9 double focusing instrument and samples were introduced *via* the direct inlet probe. Thin layer chromatography (tlc) was performed on silica gel G (Merck) with detection by iodine vapor or spraying with 0.3% $KMnO_4$ solution. Plates incorporating $AgNO_3$ were poured as a slurry with the per cent (w/w) of complexing agent indicated. Columns poured with such adsorbents were made from the powdered (through 100 mesh), dried (110°) slurries prepared for the plates and continuously protected from light.

(15) For the mass spectral data we are grateful to Dr. R. L. Foltz of Battelle Memorial Institute, which was made possible by the National Institutes of Health Contract No. NIH-71-2483, and to Mr. R. Weisenberger of our Chemistry Department for results from their instrument.

Dihydro-β-cycloepitulipinolide (**7**) was eluted next and crystallized from *n*-pentane as needles (12 mg), mp 84–85°, and showed identical ir and nmr spectra with a sample of the same substance produced by another route.[2]

Cyclization of Dihydrotulipinolide (3).—A 77-mg sample of **3** was cyclized and the products were separated in a manner given for dihydroepitulipinolide (**4**). Dihydro-α-cyclotulipinolide (**8**, 11 mg) was crystallized from *n*-hexane: mp 95–97°; $[\alpha]^{22}D$ +552° (*c* 0.038, MeOH); ir 1775, 1740, and 1240 cm^{-1}; mass spectrum *m/e* (rel intensity) M^+ 292 (8), 232 (100), 217 (39), 136 (50), and 43 (49).

Dihydro-β-cyclotulipinolide (**6**, 17 mg), mp 139–141°, crystallized from isopropyl ether–*n*-hexane and was identical (melting point, ir, and nmr) with the same compound produced by a different route.[2]

Dihydro-γ-cycloepitulipinolide (10).—γ-Cyclotulipinolide[2] (46 mg) dissolved in 2 ml of absolute EtOH was treated with 12 mg of $NaBH_4$ for 10 min at room temperature. After acidification with 10% HOAc and evaporation of solvent, the $CHCl_3$ solution of the residue was washed with water and evaporated to dryness. The solid crystallized from EtOH–H_2O as fine white needles (33 mg): mp 114–115°; $[\alpha]^{22}D$ −14° (*c* 0.036, MeOH); ir 1775, 1740, and 1245 cm^{-1}; mass spectrum *m/e* (rel intensity) M^+ 292 (28), 232 (68), 217 (94), 188 (86), and 173 (96).

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 70.18; H, 8.35.

Dihydroeupatolide (Deacetyldihydroepitulipinolide) (12).—Eupatolide (deacetylepitulipinolide) (**11**, 60 mg) was suspended in 2 ml of absolute EtOH and treated, while stirring, with 20 mg of $NaBH_4$. After 10 min, the clear solution was worked up as reported for dihydrotulipinolide. Crystallization from benzene gave 42 mg of dihydroeupatolide (**12**) as colorless needles: mp 184–187°; $[\alpha]^{22}D$ +215° (*c* 0.070, MeOH); ir 3605, 3460, 1760, and 1665 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97 H, 8.86. Found: C, 72.24 H, 9.01.

Catalytic hydrogenation (Pd on C) of eupatolide gave the same dihydroeupatolide but in much lower yield.

The acetate of dihydroeupatolide made by Ac_2O and pyridine treatment was identical (melting point, ir, and nmr) with dihydroepitulipinolide (**4**).

Hydrolysis of Epitulipinolide (11) in Aqueous MeOH.—A 3-g sample of epitulipinolide dissolved in 120 ml of MeOH was stirred and treated with 480 ml (3 g) of aqueous KOH. After 2 days at room temperature, the acidified solution was evaporated to remove MeOH, saturated with NaCl and extracted with 3 × 300 ml of $CHCl_3$. The $CHCl_3$ solution was extracted with 1% $NaHCO_3$ and H_2O, dried (Na_2SO_4), and evaporated to dryness. The residue (2.6 g) gave from isopropyl ether 1.47 g of eupatolide,[2] mp 186–188°.

Chromatography of 470 mg of the mother liquor residue, which showed two spots (R_f 0.8 and 0.5) on tlc [silica gel G, EtOH—Et_2O (1:100)], on 21 g of silica gel G with 1% EtOH in Et_2O as solvent gave 123 mg of (11*R*)-13-methoxydihydroeupatolide (**13**), identical with the product obtained when epitulipinolide (**2**) was treated with $NaOCH_3$.[2] Later column fractions gave an oil (90 mg), which yielded from isopropyl ether–EtOH 46 mg of (11*S*)-13 methoxydihydroeupatolide (**15**): mp 98–99°; mass spectrum *m/e* (rel intensity) M^+ 280 (6), 262 (14), 235 (16), 217 (100), and 45 (36).

Cyclization of (11*R*)-13-Methoxydihydroeupatolide (13).—A 400-mg sample of **13** in 50 ml of $CHCl_3$ containing 0.2 ml of $SOCl_2$ was stirred for 30 min at room temperature. Evaporation of the solvent left a residue from which 240 mg of a crystalline mixture was deposited from isopropyl ether. Chromatography of the mixture on 14 g of silica gel G containing 5% $AgNO_3$ with Et_2O as eluent gave from the first eluted fraction (66 mg) (11*R*)-13-methoxydihydro-α-cycloeupatolide (44 mg, isopropyl ether–$CHCl_3$): mp 146–148°; mass spectrum *m/e* (rel intensity) M^+ 280 (25), 217 (50), and 45 (100); nmr δ 5.35 (br m, H_3) and 1.84 (br, C-4 Me). The second column fraction (135 mg) yielded from the same solvent system the β isomer **14** (111 mg): mp 173–174°; $[\alpha]^{22}D$ +94° (*c* 0.072, MeOH); ir 3610, 1770, and 1655 cm^{-1}.

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.53; H, 8.65.

Hydrolysis of Epitulipinolide (2) in H_2O.—A 5-g sample of **2** was stirred in 1 l. of 0.28 *N* KOH for 48 hr at room temperature. After acidification to pH 3 with 1 *N* H_2SO_4, saturation with NaCl, and stirring for 2 hr, the solution was extracted with four 900-ml portions of $CHCl_3$. The combined $CHCl_3$ extract was washed with 5% $NaHCO_3$ and H_2O, dried (Na_2SO_4), and evaporated to dryness. The 4.2 g residue was crystallized from isopropyl ether to give 2.34 g of eupatolide (**11**).[2]

Chromatography of the mother liquor residue on 64 g of silica gel G with ether as eluent gave a fraction (211 mg) that was still a mixture (nmr). Elution with EtOAc gave a fraction (174 mg) that crystallized from $CHCl_3$–Et_2O to give the lactone diol **16** (100 mg): mp 196–197°; $[\alpha]^{22}D$ +15° (*c* 0.092, MeOH); ir 3580, 3400, 1760, and 1665 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.45; H, 8.29.

Rechromatography of the first-eluted fraction (211 mg) on 15 g of silica gel G impregnated with 10% $AgNO_3$ and elution with EtOAc gave a crystalline fraction that on recrystallization from Et_2O–benzene yielded the cadinene **22** (80 mg): mp 137–138°; $[\alpha]^{22}D$ +36° (*c* 0.078, MeOH); ir 3680, 3450, 1760 and 1660 cm^{-1}; mass spectrum *m/e* (rel intensity) M^+ 248 (2), 230 (8), 139 (70), 94 (100), and 95 (91).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.57 H, 7.95.

Acetylation of Lactone Diol 16.—Compound **16** (50 mg) was treated with 1 ml of pyridine and 0.4 ml of Ac_2O at 40° for 40 hr. Work-up of the reaction in the usual manner gave a residue that yielded 29 mg of the monoacetate **17** from EtOH–hexane: mp 133–134°; $[\alpha]^{22}D$ +46° (*c* 0.076, MeOH); ir 3590 (sharp), 1770, 1735 (sh, d), and 1670.

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 65.84; H, 7.84.

Dehydration of Acetate 17.—The monoacetate **17** (12 mg) was dissolved in 1 ml of dry pyridine, cooled at 5°, and treated with 0.1 ml of $SOCl_2$ for 10 min. The solution was diluted with water, $CHCl_3$ was added, and the organic layer was washed with dilute acid, base, and H_2O. The crystalline residue (13 mg) from the $CHCl_3$ solution gave 4 mg of β-cycloisoepitulipinolide (**18**) from benzene–pentane as colorless needles, mp 193–194°, identical (mixture melting point, ir, and nmr) with a sample of the same compound prepared from β-cycloepitulipinolide (**21**) or β-cycloeupatolide (**20**).

Hydrolysis of β-Cycloepitulipinolide (20).—A 60-mg sample of β-cycloepitulipinolide (**21**)[2] was stirred in 10 ml of 0.33 *N* KOH for 25 hr at room temperature. The clear solution was acidified (1 *N* HCl) and extracted with 3 × 10 ml of $CHCl_3$. The extract was washed with 1% $NaHCO_3$ and H_2O, dried (Na_2SO_4), and evaporated to leave a residue (14 mg) of deacetyl-β-cycloisoepitulipinolide (**19**). Acetylation with Ac_2O–pyridine at room temperature for 50 hr gave β-cycloisoepitulipinolide (**18**), which was crystallized from benzene–pentane to give 6 mg of product: mp 193–194°; $[\alpha]^{22}D$ +168° (*c* 0.086, MeOH); ir 1765, 1740, and 1650 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.49; H, 7.72.

From the bicarbonate extract after acidification was isolated a crystalline residue (45 mg) that on recrystallization from EtOH–pentane yielded 21 mg of hydroxy acid **28**: mp 174°; $[\alpha]^{22}D$ −49° (*c* 0.036, MeOH); ir (KBr) 3290, 2600 (bonded OH of COOH), 1740 (acetate), 1675 (unsaturated acid), 1650, and 1630 cm^{-1}; mass spectrum *m/e* (rel intensity) M^+ 308 (absent), 290 (4), 248 (8), 230 (23), 161 (24), and 43 (100).

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 65.72; H, 7.80.

Isomerization of β-Cycloeupatolide (20).—A 317-mg sample of lactone **20** was stirred in 48 ml of aqueous KOH (640 mg) solution for 2 hr at room temperature. The clear solution was acidified (1 *N* HCl) and extracted with 3 × 10 ml of $CHCl_3$. The crystalline residue from $CHCl_3$ was dissolved in 3 ml of absolute EtOH, 1 drop of 1 *N* HCl was added, and the contents were left overnight at room temperature for relactonization. The residue on removal of EtOH was recrystallized twice from Et_2O–hexane to give 202 mg of β-cycloisoeupatolide (**19**): mp 147–148°; $[\alpha]^{22}D$ +143° (*c* 0.15, MeOH); ir 3590, 3500, 1765, 1670, and 1648 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.22; H, 8.17.

Acetylation of β-Cycloisoeupatolide (19).—A 50-mg sample of **19** in 2 ml of dry pyridine was treated with 0.2 ml of Ac_2O at 40° for 43 hr. Evaporation of the mixture at reduced pressure left a crystalline residue that gave 38 mg of β-cycloisoepitulipinolide (**18**) from benzene–hexane, that had identical properties [ir,

nmr, melting point, mixture melting point, and tlc mobility (R_f 0.36, silica gel G, ether)] as the previously prepared sample.

Isotulipinolide (24).—Tulipinolide (1, 175 mg) was suspended in 1 *N* KOH and warmed for 2 hr on a steam bath. The solution was quickly evaporated, treated with 3 ml HOAc, and evaporated, and the process repeated again. The residue was dissolved in $CHCl_3$, extracted with 5% $NaHCO_3$ and H_2O, dried (Na_2SO_4), and evaporated to leave a 50-mg residue. Chromatography of the residue over 4 g of silica gel G with $CHCl_3$–Et_2O (1:1) as eluting solvent gave 27 mg of an oil that was one spot on tlc and was formulated as desacetylisotulipinolide (**23**): $[\alpha]^{22}D$ +130° (c 0.054, MeOH); ir 3610, 3460, 1760, and 1660 cm^{-1}; mass spectrum *m/e* (rel intensity) M^+ 248.1417 (3.5) ($C_{15}H_{20}O_3$ calcd 248.1412), 230 (3), 108 (13), 84 (36), and 18 (100).

Acetylation of desacetylisotulipinolide (**23**, 27 mg) with Ac_2O–pyridine at room temperature for 20 hr gave a residue that after chromatography on silica gel G using $CHCl_3$–Et_2O (20:1) as eluting solvent gave 15 mg of an oil that was one spot on tlc and was formulated as isotulipinolide (**24**): $[\alpha]^{22}D$ +36 (*c* 0.056, MeOH), ir 1760, 1735, 1660, and 1250 cm^{-1}; mass spectrum *m/e* (rel intensity) M^+ 290.1507 (0.6) ($C_{17}H_{22}O_4$ calcd 290.1518), 230 (5), 107 (14), 84 (50), and 43 (100). A comparison (ir, nmr, and tlc) of this material with laurenobiolide[13] showed them to be the same.

Eupatolide Methanesulfonate (25).—A 500-mg sample of eupatolide (11) dissolved in 4 ml of pyridine and cooled in an ice bath was treated with 0.3 ml of CH_3SO_2Cl. After 17 hr the solution was diluted with H_2O and extracted with $CHCl_3$ and the $CHCl_3$ extract was washed with 1% HCl and H_2O. The $CHCl_3$-soluble residue was crystallized from EtOH–isopropyl ether to give 412 mg of eupatolide methanesulfonate (**25**): mp 112–113°; ir 1770, 1670, 1350, and 1175 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}O_5S$: C, 58.88 H, 6.80 S, 9.81. Found: C, 58.57 H, 6.93 S, 9.68.

Treatment of Eupatolide Methanesulfonate (25) with KOH.—A 400-mg sample of **25** was stirred with 8 ml of EtOH, and 72 ml of 0.4 *N* KOH was added. After 24 hr at room temperature, the reaction solution was acidified with dilute HOAc, saturated with NaCl, and extracted with ether. The ether extract was washed with water, dried (Na_2SO_4), and evaporated to leave 243 mg of an oily residue. Chromatography of the oil was on 15 g of silica gel G with $CHCl_3$–Et_2O (1:1) as eluting agent. Early fractions gave 37 mg of deacetylisotulipinolide (**23**) identical (tlc, ir, and nmr) with the product of alkaline hydrolysis of tulipinolide (**1**). Later fractions contained eupatolide (**11**).

Reduction of Dehydroeupatolide (27).—To a solution of dehydroeupatolide[2] (100 mg) in 7 ml of *i*-PrOH at 40° was added 6 mg of $NaBH_4$. After 10 min the solution was acidified with dilute HOAc, diluted with H_2O, and extracted with ether. The ether-soluble residue (95 mg) showed three spots on tlc. Separation of these substances was accomplished on 5 g of silica gel G using $CHCl_3$–Et_2O (1:1) as solvent system. Two products were identified as eupatolide (**11**) and dihydroeupatolide (**12**), while the third from spectral evidence appeared to be 11,13-dihydrodehydroeupatolide, but deacetyltulipinolide (**26**) was not detected.

Registry No.—**1**, 24164-12-3; **2**, 24164-13-4; **3**, 35001-07-1; **4**, 35001-08-2; **5**, 35001-09-3; **6**, 24164-20-3; **7**, 24165-31-9; **8**, 35001-12-8; **9**, 35001-13-9; **10**, 35001-14-0; **12**, 35001-16-2; **13**, 35001-15-1; **14**, 35001-17-3; **15**, 35001-18-4; **16**, 35001-19-5; **17**, 35001-20-8; **18**, 35001-21-9; **19**, 35001-22-0; **22**, 35001-23-1; **23**, 35001-24-2; **24**, 35001-25-3; **25**, 35001-26-4; **28**, 35001-27-5.

1,4 Addition of Organometallic Reagents to α,β-Unsaturated Ketones in the Presence of (−)-Sparteine

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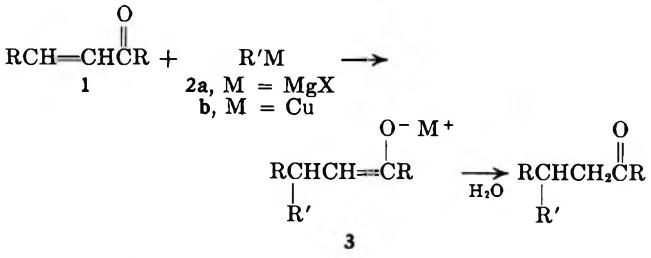
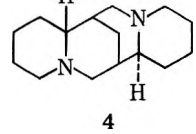
The reaction of 2-cyclohexenone, 3-penten-2-one, and 1,3-diphenyl-2-propen-1-one with a series of Grignard reagents has been studied in the presence of (−)-sparteine (**4**) and other additives. The resulting conjugate addition products possess an optical purity of 3–6% and represent the first examples of asymmetric 1,4 addition of achiral organometallic reagents to prochiral α,β-unsaturated ketones. Subsequent reactions of enolate anions initially produced by conjugate addition of the organometallic reagents are discussed. (−)-Sparteine is shown to reduce the reactivity of methylmagnesium iodide toward α,β-unsaturated ketones.

The ability of α,β-unsaturated ketones (**1**) to add Grignard reagents (**2a**)[1] and organocopper(I) compounds (**2b**)[2] in a 1,4 manner is well documented in



the literature. Recently, it has been shown that the course of this reaction can be influenced to some extent by solvent or the ligands attached to the organometallic reagent.[2b,c] In view of this, we have examined the reaction of some α,β-unsaturated ketones with Grignard reagents in the presence of (−)-sparteine (**4**). The



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results, indicated in Tables I and II, represent the first examples of asymmetric 1,4 addition of achiral organometallic reagents to prochiral α,β-unsaturated ketones.

The most apparent effect of an equimolar amount of (−)-sparteine (**4**) on an ether solution of methylmagnesium iodide is a drastic reduction of reactivity toward the enone substrates (Table I). Both 2-cyclohexenone and 1,3-diphenyl-2-propen-1-one were recovered unchanged after exposure to this reagent system for over 1 hr at room temperature. Enolization

(1) (a) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, New York, N. Y., 1954, pp 196–234; (b) J. Munch-Petersen, *Bull. Soc. Chim. Fr.*, 471 (1966).

(2) (a) H. Gilman, R. G. Jones, and L. A. Woods, *J. Org. Chem.*, **17**, 1630 (1952); (b) H. O. House, W. L. Respess, and G. M. Whitesides, *ibid.*, **31**, 3128 (1966); (c) H. O. House and W. F. Fischer, *ibid.*, **33**, 949 (1968).

Table I

1,4 Addition of Grignard Reagents to α,β-Unsaturated Ketones in the Presence of Various Additives

Run	Organometallic (mol %)[a]	Additive (mol %)	Substrate	Product	Time, hr[b]	Solvent	Yield, %[c]	Substrate recovery, %[c]
1	CH_3MgI (124)	Sparteine (124)	2-Cyclohexenone	3-Methylcyclohexanone	1	Et_2O	<1[d]	38
2	CH_3MgI (125)	Sparteine (125)	2-Cyclohexenone	3-Methylcyclohexanone	18[e]	Benzene	<1	<1[f]
3	CH_3MgI (100)	Sparteine (200) + CuCl (99)	2-Cyclohexenone	3-Methylcyclohexanone	0.5[g]	Et_2O	17	2[f]
4	C_6H_5MgBr (124)	Sparteine (221) + CuCl (110)	2-Cyclohexenone	3-Phenylcyclohexanone	1	Et_2O	17	*f*
5	CH_3MgI (156)	None	1,3-Diphenyl-2-propen-1-one	1,3-Diphenyl-3-methyl-1-propanone	0.5	Et_2O	39	*f*
6	CH_3MgI (155)	Sparteine (170)	1,3-Diphenyl-2-propen-1-one	1,3-Diphenyl-3-methyl-1-propanone	1.5	Et_2O		100
7	CH_3MgI (120)	Sparteine (120)	1,3-Diphenyl-2-propen-1-one	1,3-Diphenyl-3-methyl-1-propanone	16[e]	Benzene	45	<1[f]
8	CH_3MgI (124)	Sparteine (260) + CuI (131)	1,3-Diphenyl-2-propen-1-one	1,3-Diphenyl-3-methyl-1-propanone	1	Et_2O	7[d]	25[d,f]
9	CH_3MgI (125)	Sparteine (249) + CuCl (130)	1,3-Diphenyl-2-propen-1-one	1,3-Diphenyl-3-methyl-1-propanone	1	Et_2O	50 (64)[d]	
10	CH_3MgI (140)	Sparteine (281) + LiCl (136)	1,3-Diphenyl-2-propen-1-one	1,3-Diphenyl-3-methyl-1-propanone	1.5	Et_2O	<1	80
11	C_2H_5MgBr (124)	Sparteine (250) + CuCl (131)	3-Penten-2-one	4-Methyl-2-hexanone	0.5[g]	Et_2O	10	5[f,h]

[a] Mole per cent of Grignard reagent calculated on the basis of the amount of magnesium employed. [b] At room temperature unless otherwise indicated. [c] Isolated yield unless otherwise indicated. [d] Determined by nmr. [e] At reflux temperature. [f] Uncharacterized higher molecular weight material was formed in this reaction. [g] At ice-bath temperature. [h] 4-Methyl-3-*sec*-butyl-2,6-heptanedione was obtained in 27% yield.

Table II

Optical Activity of Products Resulting from 1,4 Addition of Organometallic Reagents to α,β-Unsaturated Ketones in the Presence of (−)-Sparteine

Registry no.	Run[a]	Product	$[\alpha]^{25}D$	Configuration	Optical purity, %
13368-65-5	3	3-Methylcyclohexanone[b]	+0.91[c]	R[d]	6.3[e]
34993-51-6	4	3-Phenylcyclohexanone[b]	+0.12[f]	R[g]	
20698-96-8	7	1,3-Diphenyl-3-methyl-1-propanone[h]	−0.38	R[i]	3.1[i]
	9	1,3-Diphenyl-3-methyl-1-propanone[h]	−0.61[j]	R[i]	5.0[i]
1731-00-6	11	4-Methyl-2-hexanone[b]	+0.36	S[k]	4.6[k]
34994-54-9	11	4-Methyl-3-*sec*-butyl-2,6-heptanedione	+1.04		

[a] Numbering identical with that used in Table I. [b] Purified by preparative gas chromatography on a 15 ft × 0.25 in. column packed with 10% silicon QF-1 on Chromosorb P. [c] $CHCl_3$ solution, *c* 2.14. [d] E. J. Eisenbraun and S. M. McElvain, *J. Amer. Chem. Soc.*, **77**, 3383 (1955); R. Adams, C. M. Smith, and S. Loewe, *ibid.*, 64, 2087 (1942). [e] Optically pure (*R*)-3-methylcyclohexanone has $[\alpha]^{25}D$ +14.35° (*c* 9.674, $CHCl_3$). [f] $CHCl_3$ solution, c 16.30. [g] Assigned on the basis of a positive Cotton effect in ethanol. [h] Purified by preparative gas chromatography on a 5 ft × 0.25 in. column packed with 15% silicone SF-96 on Chromosorb P. [i] J. H. Brewster and M. W. Kline, *J. Amer. Chem. Soc.*, **74**, 5179 (1952). [j] CCl_4 solution. [k] C. Djerassi and L. E. Geller, *J. Amer. Chem. Soc.*, **81**, 2789 (1959).

does not appear to be responsible for this recovery of starting material, since 1,3-diphenyl-2-propen-1-one is incapable of undergoing this type of reaction. These results are not entirely surprising, however, in view of the ability of pyridine and quinoline to surpress the rate of reaction of phenylmagnesium bromide with benzophenone.[3] When ether was replaced by benzene as the solvent, reaction did take place between methylmagnesium iodide and 1,3-diphenyl-2-propen-1-one, after prolonged reflux, to give the conjugate addition product in 45% yield. An attempt to react 2-cyclohexenone with methylmagnesium iodide under these conditions afforded large quantities of nonvolatile, carbonyl-containing material, but no isolable conjugate addition product.

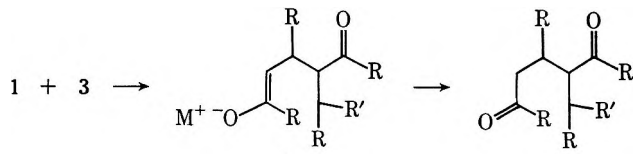
Alkyl- and arylcopper(I) compounds can be prepared by reaction of the corresponding organomagnesium halide with a copper(I) salt.[2a,4] Treatment of α,β-unsaturated ketones with these organocopper(I) reagents frequently results in predominant or exclusive 1,4 addition to the enone.[2] In view of this, 1,3-diphenyl-2-propen-1-one was allowed to react with an ether solution of methylmagnesium iodide in the presence of an equimolar amount of cuprous chloride and enough (−)-sparteine (**4**) to chelate all of the metal atoms present. Under these conditions, a 64% yield of conjugate addition product was obtained. A control experiment utilizing lithium chloride in place of cuprous chloride resulted in recovery of starting material and suggests that methylmagnesium chloride, which could be obtained by simple halogen exchange, is not responsible for the observed conjugate addition. Lack of reactivity by the Grignard–sparteine system in the absence of cuprous chloride makes it appear likely that the reactive intermediate contains copper. It

(3) (a) F. Drahowzal and H. Kōnig, *Monatsh. Chem.*, **85**, 654 (1954). (b) Bidentate ligands such as *N,N,N',N'*-tetramethylethylenediamine have also been shown to retard the rate of reaction of dimethylmagnesium with benzophenone: H. O. House and J. E. Oliver, *J. Org. Chem.*, **33**, 929 (1968).

(4) H. Gilman and J. M. Straley, *Recl. Trav. Chim. Pays-Bas*, **55**, 821 (1936); (b) G. Costa, A. Camus, L. Gatti, and N. Marsich, *J. Organometal. Chem.*, **5**, 568 (1966).

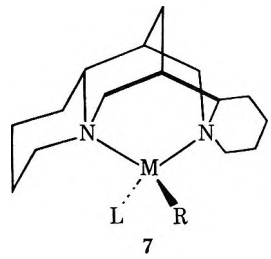
is also noteworthy that cuprous iodide was an unsatisfactory substitute for cuprous chloride and resulted primarily in conversion of 1,3-diphenyl-2-propen-1-one to uncharacterized, high molecular weight, carbonyl-containing material. This seems to further imply that halide ion exerts some control over the intermediates reactivity and must also be included in its description.

Reaction of other α,β-unsaturated ketones with the reagent systems obtained by addition of (−)-sparteine (**4**) and cuprous chloride to ether solutions of various Grignard reagents resulted in the successful production of additional conjugate addition products, although in low yield (Table I). The formation of high molecular weight, carbonyl-containing material represented the major reaction in most cases. This is unfortunate but not without precedent, and appears to be a function of the ligands present.[2c] These high molecular weight by-products appear to result from Michael addition of enolate anion **3** to a molecule of starting material **1** to give a new enolate anion **5**, which could undergo further reaction with excess enone **1** or organometallic reagent 2. Alternatively, hydrolysis of **5** would afford 1,5-diketone **6**.[5] Thispr ocess was substantiated for the reaction of 3-penten-2-one with ethylmagnesium bromide in the presence of (−)-sparteine (**4**) and CuCl (Table I). A major product (27%) of this reaction was



4-methyl-3-*sec*-butyl-2,6-heptanedione (**6**, R = CH_3; R′ = C_2H_5). The unenolized ketone carbonyl of **5** would not be expected to survive an ordinary Grignard reaction. In this example, however, the organometallic reagent present is presumably either largely or exclusively a copper(I) derivative. The lack of reactivity by organocopper(I) reagents toward carbonyl groups is well documented.[2b] In the event of incomplete conversion of Grignard reagent to the corresponding organocopper(I) derivative, the lack of reactivity by methylmagnesium iodide in the presence of an equimolar amount of (−)-sparteine (**4**) (Table I) makes the survival of the unenolized carbonyl group of **5** unsurprising. In this context, it should be noted that no hydroxyl-containing products were observed in the series of experiments utilizing CuCl and (−)-sparteine (**4**). It appears, therefore, that in the presence of diamine **4**, Michael reaction of the initially formed enolate anion **3** can compete effectively with conjugate addition by the organometallic reagent.

Without exception, the conjugate addition products obtained by reaction in the presence of (−)-sparteine (**4**) possessed a low degree of optical activity (Table II). These results require that the optically active diamine **4** be considered in a description of the organometallic intermediate. The asymmetric synthesis can be rationalized most simply as proceeding through the intermediacy of an organometallic–sparteine complex such as **7**, where M may be either magnesium or copper[6] and L represents a ligand such as chloride ion. This model is also consistent with the



7

ability of (−)-sparteine (**4**) to reduce the reactivity of methylmagnesium iodide in the absence of added CuCl (Table I). The diamine ring system, folded about the magnesium atom, would be expected to interfere sterically with approach by the enone substrate. Although the mechanism involved in the conjugate addition of organometallic reagents is not well understood, the results reported here are consistent with a transfer of the alkyl or aryl group from the metal to the β carbon of the enone **1** through a transition state which contains (−)-sparteine (**4**) coordinated to the metal atom. Correlation of the absolute configuration[8] of (−)-sparteine (**4**) with that of the resulting conjugate addition products has not been attempted in view of the low optical yields and lack of definitive mechanistic information.

Experimental Section[9]

Reaction of 3-Penten-2-one with Ethylmagnesium Bromide in the Presence of (−)-Sparteine (4) and Cuprous Chloride.—The following preparation is representative of the general procedure utilized for the reactions carried out in ether solution and summarized in Tables I and II. A solution of ethylmagnesium bromide was prepared under nitrogen by dropwise addition of a solution of 4.850 g (0.045 mol) of ethyl bromide in 75 ml of anhydrous ether into a flask containing 0.8986 g (0.037 g-atom) of magnesium turnings over a period of 30 min with mechanical stirring at ice-bath temperature. Stirring was continued at room temperature for an additional 30 min after addition was complete, resulting in complete reaction of the magnesium. The Grignard solution was then cooled at ice-bath temperature, and a solution of 17.426 g (0.074 mol) of (−)-sparteine (**4**) [distilled from CaH_2 prior to use, bp 112.0–116.5° (0.45 mm)] in 60 ml of anhydrous ether was added, resulting in formation of a white precipitate. Next, 3.860 g (0.039 mol) of cuprous chloride was added and the mixture was stirred for 15 min to give a yellow precipitate. To this was added a solution of 2.505 g (0.030 mol) of 3-penten-2-one in 75 ml of anhydrous ether dropwise over a period of 20 min with stirring. Stirring was continued at ice-bath temperature for 30 min after addition was complete. The resulting mixture was decomposed with 150 ml of 3 *M* HCl. The ether layer was separated, washed three times with 50-ml portions of 3 *M* HCl and once with 50 ml of saturated brine, and dried over anhydrous $MgSO_4$. Solvent was removed from the ether extract

(5) E. P. Kohler and W. D. Peterson, *J. Amer. Chem. Soc.*, **55**, 1073 (1933).

(6) Organocopper(I) reagents produced by treatment of cuprous salts with Grignard reagents are of uncertain structure and may be complex compounds containing both copper and magnesium.[4b,7] If this is the case, (−)-sparteine (**4**) could be coordinated with either or both metal atoms of the reagent.

(7) N.-T. Luong-Thi and H. Riviere, *Tetrahedron Lett.*, 587 (1971).

(8) S. Okuda and K. Tsuda, *Chem. Ind. (London)*, 1115 (1961).

(9) Melting points are uncorrected. The infrared spectra were determined with a Beckman IR-8 infrared spectrophotometer. Nmr spectra were recorded with a Varian A-60 spectrometer using tetramethylsilane as an internal standard. The mass spectra were obtained with a Varian MAT CH7 mass spectrometer. Optical rotations were measured with an O. C. Rudolph and Sons, Inc., Model 200 photoelectric polarimeter equipped with a Model 340 oscillating polarizer. The optical rotatory dispersion curve for (+)-3-phenylcyclohexanone was determined with a Cary Model 60 spectropolarimeter. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich.

by distillation through a 10-cm Vigreux column, and the pale yellow, liquid residue was fractionated *in vacuo*. The first fraction consisted of 0.486 g of colorless liquid, bp 56–58° (31–43 mm). A second 0.786-g fraction of pale yellow oil, bp 123–141° (5.0–7.0 mm), and a third 0.947-g fraction of yellow oil, bp 142–168° (0.4–5.0 mm), were also collected. The low-boiling fraction was shown to contain two components by gas chromatography.[10] The minor component, identified on the basis of its glpc retention time, consisted of recovered 3-penten-2-one. The major component (66%) was 4-methylhexan-2-one, which was obtained as a colorless liquid by preparative gas chromatography[13] (>99% pure by glpc), $[\alpha]^{25}D$ +0.36° (*c* 6.84, $CHCl_3$), and identified by spectroscopic comparison with an authentic sample.

A 0.589-g portion of the second distillation fraction was chromatographed on 30.0 g of 60–200 mesh silica gel. Fractions eluted with 2:98 and 5:95 eher–benzene contained 0.424 g of 4-methyl-3-*sec*-butylheptane-2,6-dione. Short-path distillation (2.4 mm and 117° bath) afforded the analytical sample as a colorless liquid: $[\alpha]^{25}D$ +1.04° (*c* 6.46, hexane); ir (neat) 1709 cm^{-1} (C=O); nmr (CCl_4) δ 2.04 (3 H, s, $COCH_3$) and 2.07 (3 H, s, $COCH_3$); mass spectrum (70 eV) *m/e* 198 (M^+).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.96; H, 11.08.

The high-boiling distillation fraction showed strong carbonyl absorption at 1709 cm^{-1} but no hydroxyl absorption in the infrared spectrum. No further attempt was made to characterize this material.

Reaction of 1,3-Diphenyl-2-propen-1-one with Methylmagnesium Iodide in the Presence of (−)-Sparteine (4) in Benzene Solution.—The following preparation is representative of the reactions carried out in benzene solution and in the presence of (−)-sparteine (4) which are summarized in Tables I and II. A solution of methylmagnesium iodide was prepared under nitrogen by dropwise addition of a solution of 4.429 g (0.031 mol) of methyl iodide in 50 ml of anhydrous ether into a flask containing 0.630 g (0.026 g-atom) of magnesium turnings over a period of 20 min at ice-bath temperature with magnetic stirring. After addition was completed, stirring was continued at room temperature for an additional 40 min, resulting in complete reaction of the magnesium. A solution of 6.105 g (0.026 mol) of (−)-sparteine (4) [distilled from CaH_2 prior to use, bp 119.0–124.0° (0.75–0.90 mm)] in 100 ml of benzene was then added. Ether was removed by distillation through a 10-cm Vigreux column in a nitrogen atmosphere. A total of 86 ml of solvent was distilled with a final distillation temperature of 80.0°. The resulting mixture was cooled to room temperature and a solution of 4.512 g (0.022 mol) of 1,3-diphenyl-2-propen-1-one, mp 58.0–58.5°, in 50 ml of benzene was added over a period of 3 min with stirring. The mixture was then heated at reflux, under nitrogen, and with stirring for 16 hr. After cooling, the mixture was decomposed with 100 ml of 3 *M* HCl. The organic layer was separated, washed once with 50 ml of 3 *M* HCl and once with 50 ml of water, and dried over anhydrous $MgSO_4$. Concentration *in vacuo* afforded 4.633 g of amber-colored oil. The principal product, 1,3-diphenyl-3-methylpropan-1-one, was isolated by preparative gas chromatography[11] as a white solid, mp 68.5–71.0°, $[\alpha]^{25}D$ −0.38° (c 10.78, CCl_4), and identified by spectroscopic comparison with an authentic sample. Distillation of 3.446 g of the crude product afforded 1.632 g (45%) of amber-colored oil, bp 129–136° (0.20 mm), which crystallized on seeding with the 1,3-diphenyl-3-methylpropan-1-one obtained by preparative gas chromatography, mp 70.0–72.0°. The distillation residue showed strong carbonyl absorption at 1677 cm^{-1} but no hydroxyl absorption in the infrared spectrum (measured in $CHCl_3$ solution).

Registry No.—**4**, 90-39-1; methylmagnesium iodide, 917-64-6; phenylmagnesium bromide, 100-58-3; ethylmagnesium bromide, 925-90-6; 2-cyclohexenone, 930-68-7; 1,3-diphenyl-2-propen-1-one, 91-41-7; 3-penten-2-one, 625-33-2.

Acknowledgment.—Financial support by the Petroleum Research Fund of the American Chemical Society is gratefully acknowledged.

(10) A 15 ft × 0.25 in. column packed with 10% silicone QF-1 on Chromosorb P was employed.

(11) A 5 ft × 0.25 in. column packed with 15% silicone SF-96 on Chromosorb P was employed.

Notes

The Reaction of Benzalacetophenone with Methylmagnesium Iodide. A Novel Grignard Reaction

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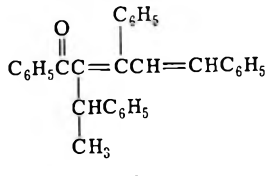
Received March 10, 1972

The reaction of Grignard reagents with many α,β-unsaturated ketones to give exclusive or predominant 1,4-addition products is well known.[1] It is less generally recognized, however, that, unless the Grignard reagent is used in large excess, products of high molecular weight are often formed in high yield.[2] These by-products have been regarded as arising from either ketol condensations or from diene polymerizations,[1a] but almost without exception they have not been carefully studied. The reaction of methylmagnesium bromide with benzalacetophenone (**1**) represents an isolated example where such a by-product was examined. This reaction has been reported to afford dienone **2**, in addition to β-phenylbutyrophenone (**3**), the anticipated 1,4-addition product.[2b]



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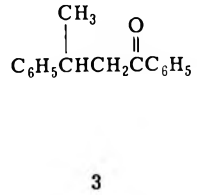

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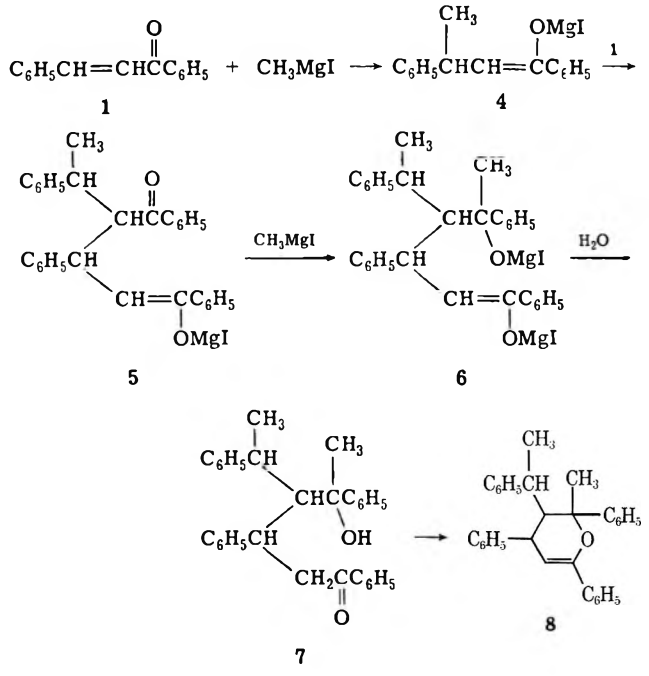
We recently had occasion to examine the reaction between **1** and methylmagnesium iodide. A major product (20%) of this reaction had properties consistent with those reported for **2**, but the spectroscopic data

(1) (a) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, New York, N. Y., 1954, pp 196–234; (b) J. Munch-Petersen, *Bull. Soc. Chim. Fr.*, 471 (1966).

(2) (a) E. P. Kohler and W. D. Peterson, *J. Amer. Chem. Soc.*, **55**, 1073 (1933); (b) M. S. Kharasch and D. C. Sayles, *ibid.*, **64**, 2972 (1942).

were clearly incompatible with structure 2.[3] The mass spectrum indicated a molecular weight of 430, while the nmr contained a methyl doublet at δ 1.20 and a methyl singlet at δ 1.67. In addition, the infrared spectrum failed to confirm the presence of a carbonyl group. The available data appear most consistent with the formulation of this compound as dihydropyran **8**. This compound is, presumably, formed through initial 1,4 addition of methylmagnesium iodide to benzalacetophenone (**1**) to give magnesium enolate **4** (Scheme I). Michael addition of **4** to another mole-

SCHEME I



cule of starting material would then afford 1,5-diketone **5**, containing one of the carbonyl groups in enolic form.[4] The unenolized carbonyl group of **5** would not be expected to survive in the presence of excess methylmagnesium iodide, and subsequent reaction should afford **6**. Hydrolysis of **6** would give hydroxy ketone **7**, which under acidic conditions would be expected to cyclize and dehydrate to give **8**.[5]

The formation of **8**, under these conditions, indicates that magnesium enolate **4** is able to compete favorably with Grignard reagent for unreacted enone **1**. Utilization of a large excess of Grignard reagent in this reaction would obviously act to surpress the Michael reaction responsible for formation of **5**. It is interesting to speculate that a process similar to that of Scheme I may be responsible for the high molecular weight byproducts obtained in the Grignard reactions of other α,β-unsaturated ketones.

Experimental Section[6]

Reaction of Methylmagnesium Iodide with Benzalacetophenone.—A solution of methylmagnesium iodide was prepared under nitrogen by dropwise addition of a solution of 4.136 g (0.0291 mol) of methyl iodide in 50 ml of anhydrous ether into a flask containing 0.590 g (0.0243 g-atom) of magnesium turnings over a period of 18 min, at ice-bath temperature, and with magnetic stirring. After addition was completed, stirring was continued at room temperature for 30 min, resulting in complete reaction of the magnesium. The Grignard solution was cooled at ice-bath temperature, and a solution of 3.251 g (0.0156 mol) of benzalacetophenone (**1**), mp 58–58.5°, in 90 ml of anhydrous ether was added dropwise, with stirring, over a period of 24 min. The resulting mixture was stirred at room temperature for 30 min and then decomposed with 100 ml of 3 *M* HCl. The ether layer was washed twice with 50-ml portions of 3 *M* HCl and once with 50 ml of saturated NaCl, and dried over anhydrous $MgSO_4$. Concentration *in vacuo* afforded an amber-colored oil which was chromatographed on a 40-g column of 60–200 mesh silica gel. Fractions eluted with hexane and with 1:19 benzene–hexane were crystallized from ether to give 0.677 g (20%) of **8** as small white needles, mp 176.0–177.5°. Recrystallization from ether afforded the analytical sample: mp 178.0–179.0° (lit.[2b] mp 176°); ir (KBr) 1658 (m, C=C), 760 (s, aromatic CH), 745 (s, aromatic CH), and 697 cm^{-1} (s, aromatic CH); nmr (CCl_4) δ 1.20 (3, H, d, J = 7 Hz, $CHCH_3$), 1.67 (3, H, s, CH_3), 2.33–3.00 (2 H, complex m, aliphatic CH), 4.41 (1 H, q, J_{ab} = 6.8, J_{bc} = 2.2 Hz, $CH_aCH_bArCH_c{=}C$), 5.74 (1 H, br, $W_{1/2}$ = 4 Hz, $ArCHCH{=}C$), and 6.0–8.0 (20 H, aromatic CH); mass spectrum (70 eV) *m/e* (rel intensity) 430 (M^+, 12), 325 (65), 222 (27), 221 (35), 208 (14), 207 (76), 206 (78), 205 (81), 105 (100), 91 (29), and 77 (5).

Anal. Calcd for $C_{32}H_{30}O$: C, 89.26; H, 7.02. Found: C, 89.58; H, 7.17.

Fractions eluted with 1:9 and 1:1 benzene–hexane contained 1.634 g of solid, which afforded 0.981 g (28%) of pure β-phenylbutyrophenone after crystallization from aqueous ethanol and from hexane, mp 73.5–75.0° (lit.[7] mp 74°).

Registry No.—**1**, 94-41-7; **2**, 34959-76-7; methylmagnesium iodide, 917-64-6.

(3) Kharasch and Sayles reported the independent synthesis of **2** in quantitative yield by reaction of benzalacetophenone with β-phenylbutyrophenone in the presence of pyridine.[2b] We have been unable to duplicate this preparation.

(4) The Michael reaction of a magnesium enolate with benzalacetophenone has previously been reported.[2a]

(5) *Cf.* M. Julia and A. Rouault, *Bull. Soc. Chim. Fr.*, 1833 (1959).

(6) Melting points are uncorrected. The infrared spectra were determined with a Beckman IR-8 spectrophotometer. Nmr spectra were recorded with a Varian A-60 spectrometer using tetramethylsilane as an internal standard. The mass spectra were obtained with a Varian MAT CH7 mass spectrometer. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich.

(7) M. A. Spielman and C. W. Mortenson, *J. Amer. Chem. Soc.*, **61**, 666 (1939).

Silver(II) Oxide as a Reagent. Reactions with Aromatic Amines and Miscellaneous Related Compounds

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Lee and Clarke have effected the oxidation of aliphatic amines, alcohols, aldehydes, and aromatic hydrocarbons[1,2] by means of the complexes of silver(II) oxide.[3] Syper[4] utilized the same reagent in acidic media to oxidize alcohols and aromatic hydrocarbons, while Corey, Gillman, and Ganem[5] employed it in neutral or slightly basic media for the stereospecific con-

(1) J. B. Lee and T. G. Clarke, *Tetrahedron Lett.*, 415 (1967).

(2) T. G. Clarke, N. A. Hampson, J. B. Lee, J. R. Morley, and B. Scanlon, *ibid.*, 5685 (1968).

(3) R. N. Hammer and J. Kleinberg, *Inorg. Syn.*, **4**, 12, (1953).

(4) L. Syper, *ibid.*, 4193 (1967).

(5) E. J. Corey, N. W. Gillman, and B. E. Ganem, *J. Amer. Chem. Soc.*, **90**, 5616 (1968).

TABLE I

OXIDATION OF VARIOUS AMINES WITH SILVER(II) OXIDE

Registry no.	Amine	Solvent	Temp, °C	Time, hr	Equiv AgO	Product	Yield, %
62-53-3	Aniline	Benzene		0.5			
		Chloroform	25	2	2	Azobenzene	20
		Acetone		2			
		Methanol		72			
87-62-7	2,2-Dimethylaniline	Benzene	72	5	2	2,2′,6,6′-Tetramethylazobenzene	33
106-49-0	*p*-Toluidine	Benzene	25	8	2	4,4′-Dimethylazobenzene[a]	17
99-98-9	*N,N*-Dimethyl-*p*-phenylenediamine	Benzene	25	1	2	4,4′-Dimethylamino-*N,N*′-azobenzene[b]	59
106-47-8	*p*-Chloroaniline	Benzene	72	9	2	4,4′-Dichloroazobenzene[a]	47
134-32-7	α-Naphthylamine	Benzene	25	1	2	1,1′-Azonaphthalene[c]	15
95-54-5	*o*-Phenylenediamine	Ether	25	72	3	*o,o*-Azodianiline	40
	o-Phenylenediamine	Benzene	72	4	4	1,4-Dicyanobutadiene	30
95-55-6	*o*-Aminophenol	Benzene	25	2	3	*o*-Benzoquinone azine	45

[a] K. Tabei and M. Yamaguchi, *Bull. Chem. Soc. Jap.*, **40**, 1539 (1967). [b] E. Noelting, *Ber.*, **18**, 1143 (1885). [c] *Beilstein*, 2nd ed, **16**, 25.

TABLE II

OXIDATION OF VARIOUS FUNCTIONALLY SUBSTITUTED COMPOUNDS WITH SILVER(II) OXIDE

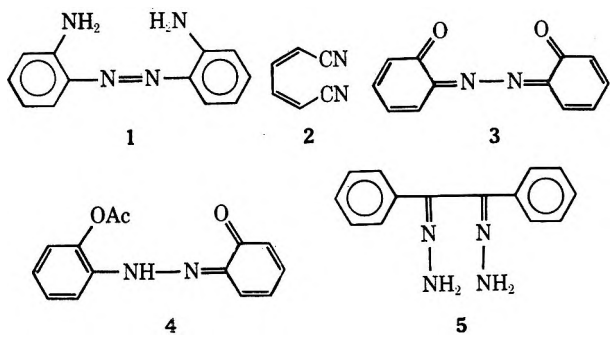
Registry no.	Substrate	Solvent	Temp, °C	Time, hr	Equiv AgO	Product	Yield, %
5350-57-2	Benzophenone hydrazone	Benzene	72	4	2	Benzophenone[a] azine	18
5344-88-7	Benzil monohydrazone	Benzene	25	14	2	Benzil	82
4702-78-7	Benzil dihydrazone	Benzene	25	10	4	Diphenylacetylene	95
613-94-5	Benzoic acid hydrazide	Benzene	72	10	2	1,2-Dibenzoylhydrazine[b]	40
787-84-8	Dibenzoylhydrazine	Benzene	72	22	4	Biphenyl	37
3619-22-5	*p*-Toluic acid hydrazide	Ethanol	72	1	2	1,2-bis-*p*-toluylhydrazine[c]	55
100-63-0	Phenylhydrazine	Benzene	25	2	3	Biphenyl	95
119-26-6	2,4-Dinitrophenylhydrazine	Methanol	58	2	3	*m*-Dinitrobenzene	87
		Chloroform	53	6	2	Citral	80
106-24-1	Geraniol	Benzene	72	10	2	Citral	70
		Acetone	50	10			70
34562-09-9	α-Methylgeraniol	Chloroform	53	20	3	*cis*- and *trans*-4,8-dimethyl-	91
		Benzene	72	20	3	nona-3,7-dien-2-one[d]	70
		Acetone	50	20	3		60
110-00-9	Tetrahydrofuran	THF	75	78	Excess	Butyrolactone	18

[a] W. Lirmre, L. Horner, and H. Farnekess, *Chem. Ber.*, **94**, 712 (1961). [b] C. Neogeli and G. Stefanovitsch, *Helv. Chim. Acta*, **2**, 636 (1928). [c] W. Autervieth and G. Thomae, *Chem. Ber.*, **57**, 436 (1924). [d] C. Aguilar, M. Salmón, and F. Walls, *Bol. Inst. Quim. Univ. Nac. Auton. Mex.*, **21**, 226 (1969).

version of allylic alcohols to conjugated acids. We have examined the behavior of silver(II) oxide with a wide variety of functionally substituted compounds.

With each of the amines, aniline, *p*-toluidine, *N,N*-dimethyl-*p*-phenylenediamine, 2,6-dimethylaniline, *p*-chloroaniline, and α-naphthylamine, the principal product after the disappearance of the starting material was the corresponding azo derivative in yields as high as 59%. This reaction can be carried out at room temperature or at the boiling temperature of several solvents, such as ethyl ether, acetone, chloroform, methanol, or benzene (Table I). Among these, benzene proved, in general, to be the best solvent.

No reaction took place with *p*-nitroaniline, 2,4-dinitroaniline, *m*-phenylenediamine, or *p,p*′-methylenedianiline, either at room temperature or at the boiling temperature of the solvents mentioned above. However, the oxidation of *o*-phenylenediamine with 3 equiv of silver(II) oxide in ether at room temperature produced *o,o*′-azodianiline (1) in 40% yield. On the other hand, using 4 equiv of AgO produced a 30% yield of 1,4-dicyanobutadiene (2). Willstatter and Pfannenstiehl[6] obtained diaminophenazine in 12% and *o,o*′-azodianiline in 10% yield when *o*-phenylenediamine was treated with Ag_2O or PbO_2. Nakagawa[7] obtained (only) 2 from the same substrate in 14 and 50% yields, respectively, using nickel peroxide and lead tetraacetate.



Hydroquinone and methylhydroquinone in benzene or acetone were oxidized in less than 10 min to give the corresponding *p*-quinones in 100 and 90% yields, respectively; pyrocatechol produced *o*-benzoquinone in 2 hr in 40% yield.

(6) R. Willstatter and A. Pfannenstiehl, *Chem. Ber.*, **38**, 2350 (1905).

(7) K. Nakagawa and H. Onoue, *Tetrahedron Lett.*, 1433 (1965); *Chem. Communn.*, 396 (1965).

o-Aminophenol, in benzene at room temperature, gave rise to the azine **3**, which on subsequent reduction produced *o*-benzoquinone mono(*o*-acetoxy phenylhydrazone) (**4**).

It is interesting to point out that the oxidation of benzil dihydrazone (**5**) treated with silver(II) oxide produced diphenylacetylene in 95% yield, a better yield than that obtained by oxidation with HgO (81%).[8]

The results of oxidation involving a wide range of functional groups are summarized in Table II.

Experimental Section

The general method employed for the reactions was to dissolve the substance to be oxidized (1–5 mmol) in a suitable solvent. Then the silver(II) oxide, prepared according to Hammer and Kleinberg,[1] was added and the mixture was allowed to stand at room temperature with stirring and sampling at frequent intervals for tlc analysis of the extent of the reaction. If the chromatoplate spot corresponding to the starting material remained after several hours, the mixture was heated to the boiling point of the solvent. When the starting material had been used up, the reaction was stopped by filtering the silver or Ag_2O formed in the reaction. The purification of the products was carried out by chromatography either on alumina or on silica gel. The yields given are those of the pure products that were identified by melting point, uv, ir, nmr, and mass spectra and compared with authentic samples or spectra described in some detail.

2,6,2′,6′-Tetramethylazolenzene.—A solution of 1 g of silver(II) oxide was allowed to reflux for 5 hr. The solution was filtered and chromatographed on alumina, Alcoa F-20 (150 g). From the fractions eluted with benzene, 320 mg (33%) of orange-red crystals, mp 50°, was obtained: λ_{max} 213 nm (ϵ 26,400), 243 (10,100), 248 (11,600), 254 (12,300), 260 (10,250), 300 (8850), and 455 (840); ir 1585 cm^{-1}; nmr δ 2.4 (singlet) (TMS = 0) (12 protons of methyl on aromatic ring) and 7.1 ppm (singlet) (six protons, aromatic). *Anal.* Calcd for $C_{16}H_{16}N_2$: C, 80.63; H, 7.61; N, 11.76; mol wt, 238.32. Found: C, 80.49; H, 7.41; N, 11.52; mol wt, 238 (mass spectrum).

o-Benzoquinone Azine 3.—A mixture of 6 g of *o*-aminophenol and 21 g of silver(II) oxide in 200 ml of benzene was stirred at room temperature for 2 hr. After filtering, 2.8 g (45%) of crystals were obtained: mp 245°; λ_{max} 235 nm (ϵ 30,400) and 430 (28,700); ir 3370 and 1575 cm^{-1}. *Anal.* Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; O, 15.08; N, 13.20; mol wt, 212.2. Found: C, 67.46; H, 3.80; O, 15.17; N, 12.74; mol wt, 212 (mass spectrum).

***o*-Benzoquinone Mono(*o*-acetoxy)phenylhydrazone (4).**—A mixture of 200 mg of *o*-benzoquinone azine (**3**), 10 ml of acetic acid, 10 ml of acetic anhydride, and 2 g of zinc dust was heated for 2 hr at the steam bath, filtered, and poured into ice. The solid formed was crystallized from methanol: yield 152 mg (63%); mp 279–280°; λ_{max} 240 nm (ϵ 17,200) and 396 (24,000); ir 3270, 1700, and 1605 cm^{-1}. *Anal.* Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93; O, 18.73; mol wt, 256.25. Found: C, 65.78; H, 4.34; N, 10.81; O, 18.93; mol wt, 256 (mass spectrum).

Diphenylacetylene.—To 240 mg of benzildihydrazone, obtained by the method of Cope, Smith, and Cotter,[8] in 50 ml of benzene, 500 mg of silver(II) oxide was added and the mixture was stirred for 2 hr. After filtering, the solvent was evaporated and the residue was sublimed at 60° (0.5 mm); the yield was 170 mg (95%), mp 58°. *Anal.* Calcd for $C_{14}H_{10}$: C, 94.34; H, 5.66; mol wt, 178.22. Found: C, 94.09; H, 5.74; mol wt, 178 (mass spectrum).

Registry No.—**1**, 554-55-2; **3**, 34562-05-5; **4**, 34562-06-6; diphenylacetylene, 501-65-5; AgO, 1301-96-8.

Acknowledgments.—We thank the Consejo Nacional de Ciencia y Tecnología de México for financial help in the publication of this work, and Dr. Harold Kwart for aid in the preparation of the manuscript.

(8) A. C. Cope, D. S. Smith, and R. J. Cotter, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 377.

The Hydrochlorination of Thujopsene

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Received February 15, 1972

In recent years much work has been done on the chemistry of the cyclopropylcarbinyl cation system.[1] The naturally occurring sesquiterpene (−)-thujopsene (**1**) contains a conjugated cyclopropyl olefin functionality which is readily protonated to form the rearrangement-prone cyclopropylcarbinyl cation system. Most of the isomerization studies on this interesting molecule have been performed in aqueous media with oxygen-containing acids.[2–8] We recently reported[9] the results of our study on the isomerization products obtained under nonaqueous conditions employing oxygen-containing acids. Friedrich[10] has also shown that the major product obtained upon treatment of (−)-thujopsene in refluxing 12 *M* HCl in dioxane is the bicyclic neopentyl chloride **5**. We have subsequently investigated the action of anhydrous hydrogen chloride on (−)-thujopsene and report our results below.

Treatment of **1** with anhydrous hydrogen chloride at 5° led to a rapid absorption of the gas. The initial crystalline product, although stable for days at −20° either as a solid or in a nonprotic solvent, rearranged upon warming to room temperature to other isomeric products. The formation of these products was easily followed by nmr spectroscopy and the pertinent spectral data are summarized in Table I. From this data the structures of the various intermediates were assigned.

The initial crystalline hydrochlorination product exhibited four methyl singlets and no vinyl hydrogen absorption in the nmr spectrum at −10°, and clearly was expected simple 1,2-addition product, tertiary chloride **2**. The stereochemistry of the chlorine atom is assigned by approach from the less hindered α face, as has been found in the stereochemistry of hydroboration and epoxidation of (−)-thujopsene.[11]

Subsequent warming of the deuteriochloroform solution to 20° showed the gradual disappearance of resonance peaks due to **2** and the concomitant appearance of new peaks, notably the transformation of one of the original methyl singlets into a vinyl methyl and the appearance of a vinyl hydrogen singlet at δ 5.05 and a two-proton singlet at δ 3.59 of an isolated chloromethyl grouping. This data is consistent with structure **3**, the 1,4-addition product of hydrogen chloride to thujopsene.

Further warming or standing at 20° for a longer time afforded a new set of resonance peaks containing a well-

(1) See R. Breslow in "Molecular Rearrangements," Vol. 1, P. DeMayo, Ed., Interscience, New York N. Y., 1963, pp 233–294.
(2) S. Nagahama, *Bull. Chem. Soc. Jap.*, **33**, 1467 (1960).
(3) W. G. Dauben and L. E. Friedrich, *Tetrahedron Lett.*, 1735 (1967).
(4) W. G. Dauben and L. E. Friedrich, *ibid.*, 2675 (1964).
(5) W. G. Dauben and E. I. Aoyagi, *Tetrahedron*, **26**, 1249 (1970).
(6) S. Itô, M. Yatagai, and K. Endo, *Tetrahedron Lett.*, 1149 (1971).
(7) S. Itô, M. Yatagai, K. Endo, and M. Kodama, *ibid.*, 1153 (1971).
(8) W. G. Dauben and L. E. Friedrich, *J. Org. Chem.*, **37**, 241 (1972).
(9) H. U. Daeniker, A. R. Hochstetler, K. Kaiser, and G. C. Kitchens, *ibid.*, **37**, 1 (1972).
(10) L. E. Friedrich, Dissertation 67-8559, University Microfilms, Inc., Ann Arbor, Mich.
(11) S. P. Acharya and H. C. Brown, *J. Org. Chem.*, **35**, 3874 (1970).

TABLE I

NMR CHEMICAL SHIFTS FOR THE THUJOPSENE HYDROCHLORIDES[a]

2	3	4	Widdrol (6)[b]	5
0.55 (s, 3)	1.00 (s, 3)	1.08 (s, 6)	1.08 (s, 6)	1.05 (s, 6)
1.00 (s, 3)	1.04 (s, 3)	1.22 (s, 3)	1.22 (s, 6)	1.08 (s, 3)
1.12 (s, 3)	1.08 (s, 3)	1.59 (s, 3)		1.17 (s, 3)
1.81 (s, 3)	1.70 (s, 3)	2.27 (d, d, 1, J = 14, 9 Hz)	1.94	3.31 (s, 2)
	3.59 (s, 2)	2.95 (d, d, 1, J = 14, 6 Hz)	2.48	5.11 (s, 1)
	5.05 (s, 1)	5.48 (d, d, 1, J = 9, 6 Hz)	5.48	

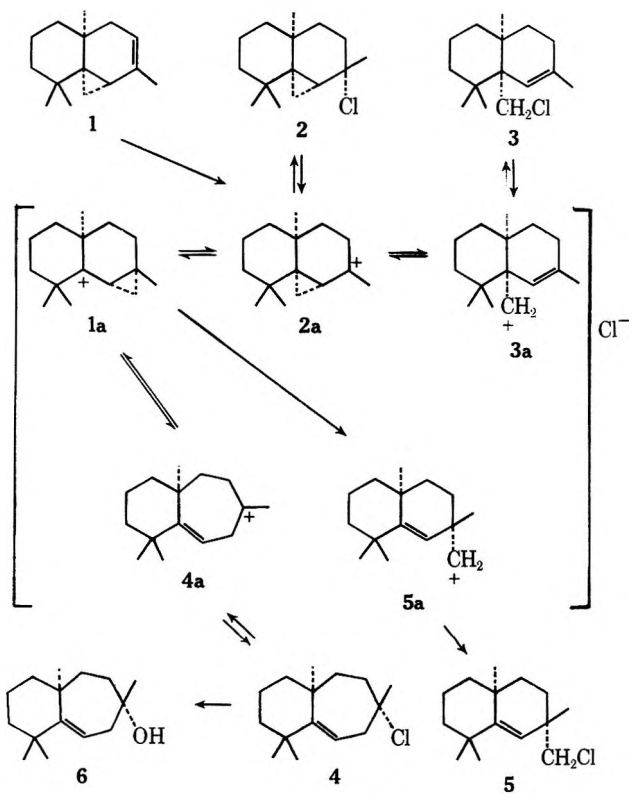
[a] Expressed as δ values from TMS in $CDCl_3$. [b] Coupling constants for the last three entries are identical with those shown for compound 4.

defined doublet of doublets at δ 5.48 coupled with upfield nonequivalent allylic protons at δ 2.95 and 2.27 as the resonances for compound **3** vanished. Bicyclic structure **4** is assigned to this new compound by the close similarity of its nmr spectrum with that of the known[12] tertiary alcohol widdrol (see Table I), and by the fact that widdrol can be isolated when this intermediate is treated with refluxing aqueous sodium carbonate.

The final thermodynamic product obtained upon warming to 40° afforded an nmr spectrum identical in all respects with that of the neopentyl chloride **5** previously reported by Friedrich[10] as the major product obtained by treatment of thujopsene with 12 *M* HCl in refluxing dioxane.

The formation of these products is readily rationalized *via* the cyclopropylcarbinyl cation intermediates outlined in Scheme I. Protonation of (−)-thujopsene

SCHEME I



to cation **2a** and chloride ion capture leads directly to the crystalline 1,2-addition product **2**. Subsequent thermal ion pair decomposition then affords cation **3a**, which generates the 1,4-addition product **3**. Further rearrangement to cation **4a** has been previously well documented by Dauben and Friedrich[4] and the capture of chloride ion by this cation to give tertiary chloride **4** should afford the same stereochemistry as that of widdrol (**6**) itself, formed under acid hydration conditions.[4] Final thermal ion pair decomposition *via* homoallylic cation **5a** then leads to the most stable neopentyl chloride **5**, as has been reported previously by Friedrich[10] *via* the same mechanistic rationale.

Earlier studies[13-15] have shown that such rearrangements are quite general for cyclopropylcarbinyl systems. Our present observations on the formation of intermediate chlorides in the hydrochlorination reaction lends additional support to the finite existence of homoallylic cations such as **3a**, **4a**, and **5a**. No chloride product consistent with the capture of cation **1a** was detected by nmr, a result not too surprising since this tertiary ring fusion cation should be quite sterically hindered to capture by an external nucleophile.

Neopentyl chloride **5** is completely stable to the action of refluxing 10% aqueous sodium carbonate, whereas similar treatment of crystalline chloride **2** afforded a mixture of thujopsene (**1**) and widdrol (**6**) in a 2:1 ratio. The same ratio was also obtained upon the identical treatment of a 50:50 mixture (by nmr) of chlorides **3** and **4** which contained less than 5% of **2**. These results imply the rapid interconversion of ion pairs **2a**, **3a**, and **4a** to afford the same product ratio irrespective of starting material under these mildly basic conditions.

A recent report[16] that treatment of (−)-thujopsene (**1**) with anhydrous hydrogen bromide at 0° leads to the neopentyl bromide analog of **5** has been confirmed by us. No crystalline 1,2-addition tertiary bromide product could be obtained under these conditions, undoubtedly due to the higher reactivity of such a molecule as compared with the corresponding chloro compound **2**.

Experimental Section

Materials and Equipment.—(−)-Thujopsene was readily obtained in 99% purity by careful fractional distillation of Hiba wood oil through a 2-ft Goodloe column, bp 67–68° (0.5 mm), $n^{20}D$ 1.5050, $[\alpha]^{25}D$ −92.5° (neat).

Spectra were recorded using a Perkin-Elmer 457 grating ir spectrophotometer and a Varian A-60A nmr spectrometer. Com-

(12) C. Enzell, *Acta Chem. Scand.*, **16**, 1553 (1962).

(13) R. H. Mazur, W. N. White, D. A. Semenow, C. C. Lee, M. S. Silver, and J. D. Roberts, *J. Amer. Chem. Soc.*, **81**, 4390 (1959).

(14) E. F. Cox, M. C. Caserio, M. S. Silver, and J. D. Roberts, *ibid.*, **83**, 2719 (1961).

(15) S. Winstein and E. M. Kosower, *ibid.*, **81**, 4399 (1959).

(16) M. Itô, K. Abe, H. Takeshita, and M. Yatagai, *Bull. Chem. Soc. Jap.*, **44**, 2168 (1971).

bustion analyses were determined by Schwartzkoff Microanalytical Laboratory, Woodside, N. Y.

2α-Chloro-1α,9α-methano-2β,8,8,10α-tetramethyldecalin (2).—(−)-Thujopsene (102 g, 0.5 mol) was cooled to 5° and vigorously agitated while anhydrous hydrogen chloride was passed in over 1.7 hr. Gas absorption ceased when 1 molar equiv had been added and the reaction mixture crystallized with an attendant temperature rise to 25°. Ice-cold hexane (100 ml) was added and the mixture was rapidly filtered through a cold sintered glass funnel to afford 63 g of solid material, mp 40–43° dec. A sample recrystallized from hexane at −50° exhibited mp 42–45° dec: ir (CCl_4, 0°) 1255, 1160, 1150, 1030, 1000, 827 cm^{-1}; nmr ($CDCl_3$, −10°) δ 0.55, 1.00, 1.12, 1.81 (s, 3 each); $[\alpha]^0D$ −95° (*c* 20%, $CHCl_3$).

A crystalline sample stored under nitrogen at −20° for 10 days showed little signs of decomposition.

Anal. Calcd for $C_{15}H_{25}Cl$: C, 74.81; H, 10.46; Cl, 14.72. Found: C, 74.91; H, 10.48; Cl, 14.53.

9α-Chloromethyl-2,8,8,10α-tetramethyl-1-octalin (3).—The nmr sample (at −10°) of tertiary chloride **2** was warmed to 20° for 0.4 hr and the spectra were recorded. The major component showed the following nmr resonances: δ 1.00, 1.04, 1.08 (s, 3 each), 1.70 (s, 3, vinyl CH_3), 3.59 (s, 2), 5.05 (s, 1, $W_{h/2}$ = 4 Hz); ir (CCl_4) 1080, 845, 648 cm^{-1}.

4α-Chloro-4β,7α,11,11-tetramethylbicyclo[5.4.0]undec-1-ene (4).—The above nmr sample was warmed to 40° for an additional 1.0 hr and the spectra were recorded. The major component showed the following nmr resonances: 1.08 (s, 6), 1.22, 1.59 (s, 3 each), 2.27 (d, d, 1, *J* = 14, 9 Hz), 2.95 (d, d, 1, *J* = 14, 6 Hz), 5.48 (d, d, 1, *J* = 9, 6 Hz); ir (CCl_4) 1230, 672 cm^{-1}.

2α-Chloromethyl-2β,8,8,10α-tetramethyl-1(9)-octalin (5).—Continued warming of the above nmr sample at 40° for an additional 20 hr gave the stable neopentyl chloride **5** with the following nmr resonances: δ 1.05 (s, 6), 1.08, 1.17 (s, 3 each), 3.31 (s, 2), 5.11 (s, 1, $W_{h/2}$ = 2.5 Hz); ir (CCl_4) 1020, 925, 860, 718, 662 cm^{-1}; $[\alpha]^{25}D$ +75° (*c* 20%, $CDCl_3$). These data are identical with those reported by Friedrich[10] for chloride **5**.

Treatment of neopentyl chloride **5** at reflux for 6 hr with 10% aqueous sodium carbonate gave recovered unchanged starting material.

4β,7α,11,11-Tetramethylbicyclo[5.4.0]undec-1-en-4α-ol (Widdrol) (6).—An 18-g sample of crystalline chloride **2** was heated to 60° for 2.0 hr. The nmr spectrum showed that the products at this point were approximately an equimolar mixture of chlorides **3** and **4** with only trace amounts of chlorides **2** and **5**. Water (150 ml) and sodium carbonate (10 g) were added and the mixture was allowed to reflux for 6 hr. The mixture was cooled and the organic layer was separated. Analysis by gas chromatography showed three peaks identified as thujopsene (**1**, 57%), an unidentified hydrocarbon (18%), and widdrol (**6**, 25%). Distillation on a micro-still head afforded 12.2 g of liquid fractions, bp 100–110° (1.5 mm), with an infrared spectrum virtually identical with that of thujopsene (**1**). The fractions boiling at 125–135° (1.5 mm) (4.0 g) crystallized and were recrystallized from methanol to afford widdrol (**6**): mp 89–90°; nmr ($CDCl_3$) δ 1.08, 1.22 (s, 6 each), 1.94 (d, d, 1, *J* = 14, 9 Hz), 2.48 (d, d, 1, *J* = 14, 6 Hz), 5.48 (d, d, 1, *J* = 9, 6 Hz). The infrared spectrum was identical with that reported by Enzell[12] for widdrol.

The same products were also obtained in a similar ratio when the crystalline hydrochloride **2** was treated directly with 10% aqueous sodium carbonate at reflux for 3 hr.

Treatment of Thujopsene with Anhydrous Hydrogen Bromide.—(−)-Thujopsene (51 g, 0.25 mol) was cooled to 0° and vigorously agitated while anhydrous hydrogen bromide was passed in. Absorption was slow and the theoretical amount was consumed in 4.5 hr. The dark colored mixture did not crystallize as had been the case for the chloride analog. Hexane (50 ml) was added and the mixture was washed neutral with cold 10% aqueous sodium carbonate solution. The solvent was removed at reduced pressure and distilled, affording 51.5 g of yellow oil: bp 125–128° (1.0 mm); $n^{20}D$ 1.5170; $\alpha^{25}D$ +68° (neat); ir (neat) 1630, 1250, 1230, 1021, 985, 925, 868, 668, 650 cm^{-1}; nmr ($CDCl_3$) δ 1.06 (s, 6), 1.08, 1.17 (s, 3 each), 3.25 (s, 2), 5.10 (s, 1). The spectral data are identical with those reported by Itô[16] and coworkers for the bromide analog of chloride **5**.

Registry No.—**1**, 470-40-6; **2**, 34905-90-3; **3**, 34905-91-4; **4**, 34905-92-5; **5**, 32540-35-5; **5** bromide analog, 34905-94-7; **6**, 6892-80-4.

Aniline Derivatives of Tetrakis(hydroxymethyl)phosphonium Chloride

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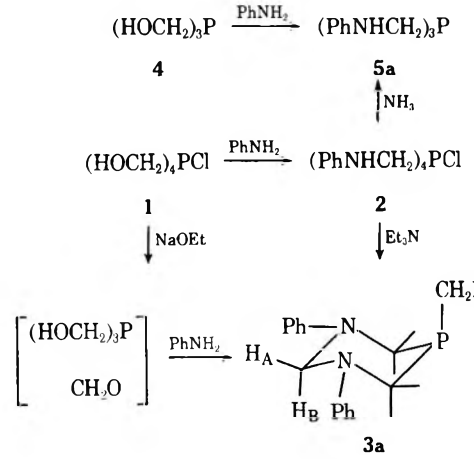
The development of flame-retardant finishes for cotton based on the reaction of tetrakis(hydroxymethyl)phosphonium chloride (**1**) with polyfunctional amines such as melamine[2] has led to the investigation of many other nitrogen compounds as resin-forming substrates.[3,4] Secondary amines give well-defined monomeric products,[5,6] but primary amines, such as cetylamine,[7–9] have thus far given only polymeric products.[7–12] In this paper we report our investigation of the reaction of **1** and some of its derivatives with aniline, which led to a series of well-defined crystalline compounds.

Aniline reacts readily with **1** in ethanol or acetone at room temperature, displacing all four hydroxyl groups (Scheme I).[13] The product, tetrakis(anilino-

SCHEME I



3a

(1) One of the laboratories of the Southern Marketing and Nutrition Research Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) W. A. Reeves and J. D. Guthrie, *Text. World*, **104** (2), 101 (1954).

(3) G. L. Drake, Jr., "Encyclopedia of Chemical Technology," Vol. 9, 2nd ed, Wiley, New York, N. Y., 1966, p 300.

(4) K. A. Petrov and V. A. Parshina, *Usp. Khim.*, **37**, 1218 (1968) (Engl. transl., 532).

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(6) D. J. Daigle, W. A. Reeves, and D. J. Donaldson, *Text. Res. J.*, **40**, 580 (1970).

(7) W. A. Reeves and J. D. Guthrie, *Ind. Eng. Chem.*, **48**, 64 (1956).

(8) W. A. Reeves and J. D. Guthrie (to United States of America as represented by the Secretary of Agriculture), U. S. Patent 2,809,941 (1957); *Chem. Abstr.*, **52**, 2421 (1958).

(9) J. G. Evans, G. Landelle, J. R. W. Perfect, B. Topley, and H. Coates [to Bradford Dyers' Assoc. Ltd. and Albright & Wilson (Mfg.) Ltd.], British Patent 761,985 (1956); *Chem. Abstr.*, **51**, 9178 (1957).

(10) W. A. Reeves and J. D. Guthrie (to United States of America as represented by the Secretary of Agriculture), U. S. Patent 2,668,096 (1954); *Chem. Abstr.*, **48**, 6710 (1954).

(11) Anon. [to Albright & Wilson (Mfg.) Ltd.], Belgian Patent 626,626 (1963); *Chem. Abstr.*, **61**, 7144 (1964).

(12) E. V. Kuznetsov, R. K. Valetdinov, Ts. Ya. Roitburd, and L. B. Zakharova, *Tr. Kazan. Khim.-Tekhnol. Inst.*, **29**, 20 (1960); *Chem. Abstr.*, **58**, 547 (1963).

(13) A 1:1 molar ratio of aniline to **1** is reported to give a yellow polymer (ref 9, example 18).

methyl)phosphonium chloride (2), is unaffected by water or ethanol, which would remove aniline hydrochloride if it were present. Aniline is apparently too weak a base ($pK_a = 4.58$)[14] to cause the displacement of formaldehyde and HCl which is characteristic of secondary (eq 1)[5] and tertiary[15,16] amines.

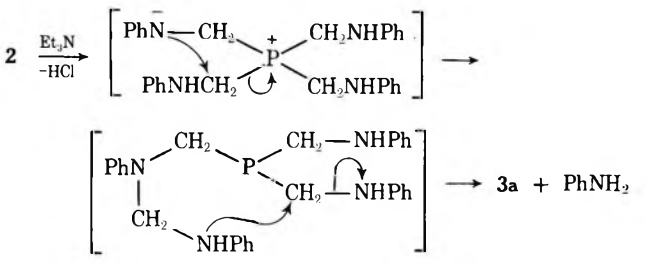
$$4R_2NH + 1 \longrightarrow (R_2NCH_2)_3P + CH_2O + R_2NH\cdot HCl \quad (1)$$

When stirred with a slight excess of triethylamine in acetone for 1 hr at room temperature, 2 gives triethylamine hydrochloride (correct ir,[17] melting point, 84.0%), aniline (correct ir, n_D, 62.5%), and a white, crystalline solid (76.0%) identified as 5-anilinomethyl-1,3-diphenyl-1,3,5-diazaphosphorinane (**3a**, Scheme I). The ir spectrum of **3a** shows a weak but sharp N–H band at 3340 cm^{-1}. The ^1H nmr spectrum shows overlapping multiplets in the 3.2–4.0-ppm region (PCH_2, NH), an ABX sextet (NCH_2N) in the 4.0–5.2-ppm region, and a multiplet (C_6H_5) in the 6.3–7.4-ppm region, in the ratio 7.0:2.0:15. The ABX pattern, which appears as a sextet owing to coupling of the upfield proton to phosphorus (X = ^{31}P), is assigned to the NCH_2N protons because its position (mean chemical shift, δ = 4.65 ppm) is close to the 4.77 ppm reported for hexahydro-1,3,5-triphenyl-*s*-triazine,[18] and the separation ($\Delta\mu$ = 49.9 Hz) between the chemical shifts of the two protons is close to the 52.8 and 53.8 Hz reported[19,20] for hexahydro-1,3,5-trimethyl-*s*-triazine at low temperatures.[21–26]

The mass spectrum of **3a** exhibits the fragmentation pattern characteristic of methyleneaniline derivatives,[27,28] with *m/e* 93 ($PhNH_2\cdot^+$), 104 ($PhN{\equiv}CH^+$) and 105 ($PhN{=}CH_2^+$) as the most abundant ions.

This product is evidently formed by the displacement of aniline and HCl from 2, perhaps *via* the intramolecular mechanism shown in Scheme II.[29–31]

SCHEME II



The same product (**3a**) is obtained in 77.0% yield when **1** is neutralized with sodium ethoxide in ethanol *prior* to reaction with aniline (Scheme I).

Oxidation of **3a** with hydrogen peroxide in acetone gives the phosphine oxide **3b** in 93.1% yield. The corresponding phosphine sulfide **3c** is obtained from **3a** and sulfur in benzene in 60.4% yield, together with 7.9% unidentified by-product.

An entirely different series of products is obtained from formaldehyde-free tris(hydroxymethyl)phosphine (**4**). Reaction of **4** with aniline in benzene, carried out at reflux with azeotropic removal of the water,[32] gives tris(anilinomethyl)phosphine (**5a**) as a white, crystalline solid in 81.3% yield (Scheme I). **5a** shows a much stronger N–H band in the ir than **3a**, and its nmr spectrum shows none of the fine structure associated with **3a**. There is a sharp doublet at δ 3.52 (PCH_2), a singlet at 3.64 (NH), and a multiplet (C_6H_5) in the 6.6–7.2-ppm region, in the ratio 6.1:2.9:15.

Oxidation of **5a** with hydrogen peroxide in acetone gives the phosphine oxide **5b** in 82.9% yield. The corresponding phosphine sulfide **5c** is obtained from **5a** and sulfur in benzene in 94.2% yield. The physical properties and spectra of these derivatives are clearly different from those of **3b** and **3c**.

5a can also be prepared from 2 in 61.9% yield by reaction with ammonia instead of triethylamine (Scheme I). The ammonia presumably functions by tying up the excess formaldehyde as hexamethylenetetramine,[33] though none was found in this experiment.

Still another method is the displacement of dimethylamine from tris(dimethylaminomethyl)phosphine (**6**) by aniline, which takes place smoothly at 160–170° giving **5a** in 45.4% yield (eq 2).

$$\underset{\mathbf{6}}{(Me_2NCH_2)_3P} + 3PhNH_2 \longrightarrow \mathbf{5a} + 3Me_2NH \quad (2)$$

This type of displacement has not been reported previously, though compounds like **6** are known to react with active hydrogen compounds such as acetoacetic ester or phenol or dialkyl phosphites with the displacement of 1 equiv of secondary amine.[5]

Efforts to prepare *N*-methylol or *N*-methylene (*e.g.*, **3a**) derivatives of **5a** by reaction with aqueous formalin or with paraformaldehyde in ethanol were unsuccessful, owing to the tendency of **5a** to disproportionate to substances richer and poorer in N–H. This tendency

(14) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962, p 144.

(15) K. A. Petrov, V. A. Parshina, and M. B. Luzanova, *Zh. Obshch. Khim.*, **32**, 553 (1962); *Chem. Abstr.*, **58**, 5714 (1963).

(16) S. E. Ellzey, Jr., W. J. Connick, Jr., and G. J. Boudreaux, *Can. J. Chem.*, **49**, 3581 (1971).

(17) Sadtler Infrared Prism Spectra, No. 6605, Sadtler Research Laboratories, Philadelphia, Pa., 1959.

(18) L. Stefaniak, T. Urbanski, M. Witanowski, and H. Januszewski, *Rocz. Chem.*, **43**, 1687 (1969); *Chem. Abstr.*, **72**, 21072 (1970).

(19) R. F. Farmer and J. Harmer, *Chem. Commun.*, 866 (1966).

(20) H. S. Gutowsky and P. A. Temussi, *J. Amer. Chem. Soc.*, **89**, 4358 (1967).

(21) The nmr spectrum is consistent with a model in which there is rapid inversion of the diazaphosphorinane ring and of the nitrogen atoms, but not of the phosphorus atom. This allows two stable chair conformations for the diazaphosphorinane ring, depending on whether the phosphorus lone pair (or, in the case of **3b** or **3c**, the oxygen or sulfur atom) is equatorial or axial. If the preferred conformation is equatorial, as in other phosphorinane ring systems,[22–26] the trans NCH_2N proton (H_A) is in a favorable zig-zag geometry for long-range splitting by phosphorus. Neither conformation for the cis proton (H_B) has this feature. On this basis, H_A is tentatively assigned the upfield chemical shift, δ 4.23 ($^4J_{PH_A}$ = 3.0 Hz), and H_B the downfield chemical shift, δ 5.06 ($^4J_{PH_B}$ = 0 Hz). The preferred conformation is illustrated in Scheme I.

(22) L. D. Hall and R. B. Malcolm, *Chem. Ind. (London)*, 92 (1968).

(23) H. J. Geise, *Recl. Trav. Chim. Pays-Bas*, **86**, 362 (1967).

(24) K. D. Bartle, R. S. Edmundson, and D. W. Jones, *Tetrahedron*, **23**, 1701 (1967).

(25) D. Gagnaire, J. B. Robert, and J. Verrier, *Bull. Soc. Chim. Fr.*, 2392 (1968).

(26) J. B. Lambert and W. L. Oliver, Jr., *Tetrahedron*, **27**, 4245 (1971).

(27) E. Schumacher and R. Taubenest, *Helv. Chim. Acta*, **49**, 1439 (1966).

(28) R. Colton and Q. N. Porter, *Aust. J. Chem.*, **21**, 2215 (1968).

(29) The direct displacement of an anilinomethyl group as $PhN{=}CH_2$ would probably result instead in the formation of the cyclic trimer, hexahydro-1,3,5-triphenyl-*s*-triazine.[30,31]

(30) C. Eberhardt and A. Welter, *Ber.*, **27**, 1804 (1894).

(31) H. Krässig and H. Ringsdorf, *Makromol. Chem.*, **22**, 163 (1957).

(32) Under these conditions, the reaction of **1** with aniline gives a yellow powder, dec pt 250°, which appears to be the product of displacement of three of the four hydroxyl groups. *Anal.* Calcd for $C_{22}H_{27}ClN_3OP$: C, 63.53; H, 6.54; Cl, 8.53; N, 10.11; P, 7.45. Found: C, 62.97; H, 6.41; Cl, 8.75; N, 9.91; P, 7.40. The product is insoluble in water and in all organic solvents except DMSO and appears to be unaffected by triethylamine or sodium hydroxide.

(33) J. F. Walker, "Formaldehyde," 3rd ed, Reinhold Publ. Corp., New York, N. Y., 1964, p 234.

was manifested to some extent in all of the aniline derivatives described in this paper. The phosphonium chloride 2, for example, appears to be easily recrystallized from methanol or ethanol, but the product which separates on cooling is a high-melting white, crystalline solid, mp 170–171°, having the composition $C_{16}H_{18}N_2P_2$ (41.0%). None of the 2 is recovered. This same substance is obtained from **5a** simply on stirring in ethanol at room temperature overnight (2.1%). The nature of this disproportionation, which seems to be related to the known disproportionation of *N,N'*-diphenylmethanediamine to aniline and hexahydro-1,3,5-triphenyl-*s*-triazine,[30] is currently under investigation.

Experimental Section[34]

Starting Materials.—Tetrakis(hydroxymethyl)phosphonium chloride[35] (1) was recrystallized from 2-propanol: mp 149–149.5°. Tris(hydroxymethyl)phosphine[36] (4), dried by azeotropic distillation with benzene,[37] analyzed[38,39] 73.92% 4 and 0.08% CH_2O, the remainder being tris(hydroxymethyl)phosphine oxide. Tris(dimethylaminomethyl)phosphine (6), bp 65–67° (0.4 mm), was prepared by the reaction of 1 with dimethylamine.[40] Aniline was distilled from a pinch of zinc dust before use.

Tetrakis(anilinomethyl)phosphonium Chloride (2).—Aniline (7.70 g, 83.0 mmol) was added to a solution of 1 (3.83 g, 20.0 mmol) in 75 ml of ethanol. There was a mild exotherm, followed immediately by the separation of solids. The mixture was stirred for 2 hr and filtered, giving 9.15 g (93.0%) of 2 as a white crystalline solid: mp 129–130°; ir (Nujol) 689 (s, C_6H_5), 695 (m, sh), 745 (vs, C_6H_5), 755 (vs, C_6H_5), 786 (w), 795 (w), 875 (w), 885 (w), 908 (m), 922 (m), 1020 (w), 1060 (w), 1090 (w), 1150 (w), 1180 (m), 1205 (m), 1245 (s, CN_{arom}), 1280 (m), 1310 (m, CN_{arom}), 1410 (w), 1500 (vs, $C{=}C_{arom}$), 1510 (s, sh), 1608 (vs, $C{=}C_{arom}$), 3290 (vs, NH) cm^{-1}; ^1H nmr (DMSO-d_6) δ 3.3–5.0 (m, 8 H, CH_2, strong peak at 4.47), 6.3–7.3 (m, 24 H, C_6H_5 and NH).

Anal. Calcd for $C_{28}H_{32}ClN_4P$: C, 68.49; H, 6.57; N, 11.41; P, 6.31. Found: C, 68.18; H, 6.88; N, 11.33; P, 6.33.

No further solids separated from the filtrate in the next 5 hr. The filtrate and washings, stripped under vacuum, left 1.15 g of yellow oil, $n^{20}D$ 1.5923, which contained 2 and the excess aniline (ir).

2 yellows rapidly on exposure to light. It is insoluble in water and in organic solvents, with the exception of dimethyl sulfoxide (DMSO) and dimethylformamide. It dissolves readily in hot chloroform or acetone, giving yellow solutions which deposit gums on work-up, and in hot methanol or ethanol, giving disproportionation products. Even in DMSO there is evidence of partial decomposition (^1H nmr).

A similar reaction with acetone as the solvent gave a 66.0% yield of 2, mp 120–121°, together with deep yellow liquid by-products.

5-Anilinomethyl-1,3-diphenyl-1,3,5-diazaphosphorinane (3a).

A. From 2.—Triethylamine (6.05 g, 60.0 mmol) was added to a well-stirred slurry of 2 (18.85 g, 38.4 mmol) in 250 ml of acetone. There was no exotherm, but the appearance of the solid gradually changed to that of a much less voluminous, granular solid. After 1 hr, the solid was collected on a filter, washed with acetone, and dried, giving 4.45 g (84.0%) of triethylamine hydrochloride, mp 251–253° (correct ir[17]). No more separated on standing, nor upon the addition of more triethylamine. The filtrate was stripped of solvent under vacuum, and the residue, a yellow oil, was shaken vigorously with ethanol (250 ml), whereupon it crystallized. After 2 hr, the solid was collected on a filter, washed with ethanol, and dried, giving 10.50 g (76.0%) of **3a** as a white, granular solid, mp 96–97°. This product was identical (melting point, ir, nmr) to the **3a** from neutralized 1, described below. The filtrate and washings from the **3a** yielded 7.40 g of yellow oil, from which 2.25 g (62.5%) of aniline (ir, n_D) was recovered by extracting with ether, drying over potassium hydroxide, and distilling.

B. From Neutralized 1.—1 (4.75 g, 25.0 mmol) was added to a solution of sodium (0.60 g, 25.0 mmol) in ethanol (25 ml), stirred for 1 hr under nitrogen, and filtered to remove sodium chloride (1.55 g, 26.5 mmol). The filtrate was treated with aniline (9.30 g, 100.0 mmol) and stirred at room temperature overnight. A mild exotherm (from 24 to 32°) occurred, followed by the separation of an oil which solidified after 2.5 hr. After 20 hr, the solid was collected on a filter, washed with ethanol, and dried, giving 6.95 g (77.0%) of **3a** as a white, crystalline solid, mp 96–97°. Two crystallizations from cyclohexane gave an analytical sample: mp 96–97°; ir (Nujol) 687 (s, C_6H_5), 706 (m), 743 (vs, C_6H_5), 748 (s, sh), 774 (m), 850 (m), 860 (m), 897 (m), 910 (m), 925 (m), 995 (m), 1025 (w), 1060 (m), 1095 (m), 1145 (w), 1170 (m), 1180 (s), 1195 (s), 1210 (s), 1230 (s), 1255 (w), 1310 (s, CN_{arom}), 1415 (m), 1490 (vs, $C{=}C_{arom}$), 1600 (vs, $C{=}C_{arom}$), 3340 (s, NH) cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.2–4.0 (m, 7 H, PCH_2 and NH), H_A at 4.23 and H_B at 5.06 (ABX sextet, 2 H, NCH_2N, $^1J_{HH}$ = 13.0, $^4J_{PH_A}$ = 3.0, $^4J_{PH_B}$ = 0 Hz), 6.3–7.4 (m, 15 H, C_6H_5) (the ^1H spectrum was not visibly altered by D_2O, but the integration showed one less proton in the 3.2–4.0-ppm region[41]); mass spectrum *m/e* (% relative abundance, ion fragment), 121 (4), 106 (7, $PhNH{=}CH_2^+$), 105 (71, $PhN{=}CH_2\cdot^+$), 104 (53, $PhN{\equiv}CH^+$), 94 (27), 93 (100, $PhNH_2\cdot^+$), 92 (33, $PhNH^+$), 91 (2, PhN^+), 84 (51), 78 (7), 77 (27, Ph^+), 69 (9), 66 (18, $C_5H_6^+$), 65 (11, $C_5H_5^+$), 56 (27), 55 (9), 52.5 (2, $PhN{=}CH_2^{2+}$), 51 (4, $C_4H_3^+$), 41 (11).

Anal. Calcd for $C_{22}H_{24}N_3P$: C, 73.11; H, 6.69; N, 11.63; P, 8.57; mol wt, 361. Found: C, 73.36; H, 6.73; N, 11.48; P, 8.34; mol wt (osmometric, in $CHCl_3$), 359.

3a is soluble in chloroform, acetone, and benzene and insoluble in water and ether. It can be recrystallized from cyclohexane (10 ml/g) or ethanol, but tends to oil out from either solvent unless seeded or scratched during cooling. Prolonged heating in ethanol, however, results in a hard, transparent gum from which no **3a** can be recovered. **3a** gives a positive test with iodine,[42] but dissolves in carbon disulfide without giving the red color characteristic of tertiary phosphines.[43]

5-Anilinomethyl-1,3-diphenyl-5-oxo-1,3,5-diazaphosphorinane (3b).—**3a** (1.805 g, 5.0 mmol) in acetone (15 ml) was oxidized with 30% hydrogen peroxide, giving 1.755 g (93.1%) of **3b** as a white, crystalline solid, mp 165–168°. One recrystallization from benzene gave an analytical sample: mp 170–171°; ir (Nujol) 690 (m, C_6H_5), 752 (s, C_6H_5), 762 (s, C_6H_5), 782 (w), 822 (w), 897 (s), 932 (w), 990 (w), 1030 (w), 1055 (w), 1090 (w), 1120 (m), 1160 (vs, P=O), 1180 (w), 1200 (w), 1235 (s), 1260 (m), 1320 (s, CN_{arom}), 1410 (w), 1495 (vs, $C{=}C_{arom}$), 1530 (w), 1600 (s, $C{=}C_{arom}$), 3310 (m, NH) cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.3–4.5 (m, 7 H, PCH_2 and NH), H_A at 4.21 and H_B at 5.04

(34) Melting points are corrected. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Ir spectra were taken on a Perkin-Elmer Model 137B instrument with NaCl optics. ^1H nmr spectra were taken on a Varian A-60 spectrometer, using TMS as an internal standard, and ^{31}P nmr spectra were taken on a Varian HA-60-IL instrument at 24.3 Mc, using 85% H_3PO_4 as an external standard.

(35) Hooker Chemical Corp., Niagara Falls, N. Y. Name of firms or their products in this paper does not imply their endorsement by the Department of Agriculture.

(36) M. Reuter and L. Orthner (to Farbwerke Hoechst A.-G.), U. S. Patent 3,030,421 (1962).

(37) R. K. Valetdinov, E. V. Kuznetsov, R. R. Belova, R. K. Mukhaeva, T. I. Malykhina, and M. Kh. Khasanov, *Zh. Obshch. Khim.*, **37**, 2269 (1967); *Chem. Abstr.*, **68**, 87350 (1968).

(38) E. I. Grinshtein, A. B. Bruker, and L. Z. Soborovskii, *Zh. Obshch. Khim.*, **36**, 302 (1966); *Chem. Abstr.*, **64**, 17629 (1966).

(39) A. W. Frank and G. L. Drake, Jr., *J. Org. Chem.*, **36**, 549 (1971).

(40) H. Coates and P. A. T. Hoye [To Albright & Wilson (Mfg.) Ltd.], German Patent 1,077,214 (1960).

(41) The NCH_2N assignment was further supported by the 100-Mc spectrum of **3a**, which also showed an ABX pattern: δ ($CDCl_3$), H_A at 4.15, H_B at 4.98 ppm ($^1J_{HH}$ = 13.0, $^4J_{PH_A}$ = 3.0, $^4J_{PH_B}$ = 0 Hz). The chemical shifts were slightly lower, but the separation (0.83 ppm) was identical.

(42) Iodine test: dissolve sample in a little benzene, ethanol, or chloroform, add 2% iodine in benzene by means of a medicine dropper, and note if the yellow iodine color is discharged. This is a useful test for trivalent phosphorus in organic phosphorus compounds. The test was positive with **4** and **6**, negative with **3b**, **3c**, **5b**, and **5c**, and a slow discharge of the iodine color was observed with **1** and **2**.

(43) G. M. Kosolapoff, "Organophosphorus Compounds," Wiley, New York, N. Y., 1950, pp 25, 26.

(ABX sextet, 2 H, NCH_2N, $^2J_{HH}$ = 13.0, $^4J_{PH_A}$ = 4.0, $^4J_{PH_B}$ = 0 Hz), 6.2–7.4 (m, 15 H, C_6H_5).

Anal. Calcd for $C_{22}H_{24}N_3OP$: C, 70.01; H, 6.41; N, 11.14; P, 8.21. Found: C, 69.92; H, 6.51; N, 10.87; P, 8.10.

3b is soluble in chloroform and insoluble in acetone, water, and other solvents. It can be recrystallized from benzene (40 ml/g) or ethanol (80 ml/g).

5-Anilinomethyl-1,3-diphenyl-5-thiono-1,3,5-diazaphosphorinane (3c).—**3a** (1.805 g, 5.00 mmol) was stirred overnight at room temperature with 0.160 g (5.00 mmol) of sulfur in benzene (30 ml), giving an acetone-soluble product, 1.186 g (60.4%), mp 127–128°, and an acetone-insoluble product, 0.156 g (7.9%), mp 159–160°. The acetone-soluble product, **3c**, a white crystalline solid, was recrystallized from ethanol and dried *in vacuo* at 80°: mp 127–128°; ir (Nujol) 690 (s, C_6H_5), 702 (m), 716 (w), 754 (s, C_6H_5), 772 (m, sh), 806 (w), 818 (w), 834 (w), 855 (w), 904 (m), 931 (w), 978 (w), 998 (w), 1030 (w), 1055 (w), 1075 (w), 1095 (w), 1110 (w, sh), 1190 (m, sh), 1200 (s), 1235 (m), 1315 (m), 1410 (m), 1490 (vs, C=C_{arom}), 1600 (vs, C=C_{arom}), 3370 (w, NH) cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.3–4.5 (m, 8 H, PCH_2, NH, and H_A of NCH_2N), H_B at 5.09 (d, 1 H, H_B of NCH_2N, $^2J_{HH}$ = 13.0, $^4J_{PH_B}$ = 0 Hz), 6.2–7.4 (m, 15 H, C_6H_5). The upfield portion (H_A) of the ABX pattern was not discernible.

Anal. Calcd for $C_{22}H_{24}N_3PS$: C, 67.15; H, 6.15; N, 10.68; P, 7.87, S, 8.15. Found: C, 67.35; H, 6.15; N, 10.60; P, 7.63; S, 7.93.

3c is soluble in acetone, chloroform, and benzene and insoluble in water and cyclohexane. It can be recrystallized from ethanol (60 ml/g) or carbon tetrachloride (20 ml/g).

The acetone-insoluble product was an unidentified white crystalline solid: ir (Nujol) 686 (s, C_6H_5), 740 (s, sh), 750 (vs, C_6H_5), 813 (m), 862 (m), 891 (m), 930 (w), 978 (w), 992 (w), 1030 (w), 1115 (w), 1200 (s), 1210 (s), 1230 (vs, CN_{arom}), 1320 (w), 1410 (m), 1490 (vs, C=C_{arom}), 1600 (vs, C=C_{arom}), 3400 (w, NH) cm^{-1}.

The same two products were obtained when the reaction was carried out at reflux (30 min) instead of room temperature.

Tris(anilinomethyl)phosphine (5a). A. From 4.—A mixture of **4** (3.10 g of 73.92% titer, 18.5 mmol), aniline (9.30 g, 100 mmol), and benzene (25 ml) was heated in a nitrogen atmosphere under reflux in an apparatus equipped with a Dean-Stark trap for azeotropic removal of the water. In 2 hr, a total of 1.00 ml (theory 1.00 g) of water was collected in the trap. The solution was allowed to cool, decanted from the unreacted oil [0.55 g, $n^{20}D$ 1.5550, identified by ir as tris(hydroxymethyl)phosphine oxide], and stripped of solvent under vacuum. The residue, a white, crystalline mass containing **5a** and the excess aniline, was triturated under ether with a mortar and pestle, filtered, and washed with ether, giving 5.30 g (73.7%) of **5a** as white flakes, mp 82–83°. Another 0.55 g (7.6%) of **5a**, and 4.25 g (theory 4.14 g) of aniline (ir, *n*D) was recovered from the ether filtrate. Two recrystallizations from benzene (6 ml/g), followed by thorough drying *in vacuo* at room temperature, gave an analytical sample: mp 85–86°; ir (Nujol) 676 (m, C_6H_6 solvate), 692 (m, C_6H_5), 747 (vs, C_6H_5), 863 (w), 890 (w), 981 (w), 1055 (w), 1080 (w), 1140 (w), 1165 (w), 1195 (w), 1230 (s, CN_{arom}), 1310 (s, CN_{arom}), 1450 (vs), 1500 (vs, C=C_{arom}), 1590 (vs, C=C_{arom}), 3440 (s, NH) cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.52 (d, CH_2, J = 5.0 Hz), 3.64 (s, NH), 6.6–7.2 (m, 15 H, C_6H_5), and 7.37 (s, 3 H, C_6H_6 solvate); ^{31}P nmr δ +32.5 ppm. The NH peak vanished when D_2O was added, changing the C_6H_5:(CH_2 + NH) ratio from 15:9.0 to 15:6.1.

Anal. Calcd for $C_{21}H_{24}N_3P \cdot 0.5C_6H_6$: C, 74.20; H, 7.01; N, 10.82; P, 7.97. Found: C, 73.81; H, 7.17; N, 10.73; P, 7.79.

The presence of solvate benzene was evident in both the ir (676 cm^{-1}) and ^1H nmr (7.37 ppm). The compound retains solvent tenaciously. A sample of **5a** dried in a drying pistol over boiling benzene (80°), however, lost 37.2% of its weight and was no longer crystalline.

5a is insoluble in water or ether, but dissolves instantly in acetone or chloroform. It gives a positive test with iodine,[42] but dissolves in carbon disulfide without giving the red color characteristic of tertiary phosphines.[43]

5a was also obtained when **4** was stirred with aniline in ethanol at room temperature overnight. The product was an off-white, crystalline solid (70.5%), mp 61–63°, ir identical with ir of the product described above except for the C_6H_6 band at 676 cm^{-1}. Prolonged stirring should be avoided, however, as the product disproportionates in ethanol, even at room temperature.

B. From 6.—**6** (10.25 g, 0.05 mol) was added by means of a syringe to 18.60 g (0.20 mol) of aniline under nitrogen in a small distillation assembly and heated rapidly to 160–170°. Gas evolution was strong, but steady, and subsided within 30 min. The solution was kept at this temperature for 1 hr, allowed to cool to 130–140°, and stripped under water-pump vacuum to remove the excess aniline (4.15 g, $n^{24}D$ 1.5803, correct ir, 89.5%). The still contents (17.60 g) solidified on cooling to a waxy, malodorous solid, ir similar to **5a**, but without the C_6H_6 band (676 cm^{-1}). One recrystallization from benzene gave 8.80 g (45.4%) of **5a**, mp 85–86°, identical with the product prepared from **4**.

A preliminary experiment in ethanol solution (3 hr at reflux) produced no dimethylamine until most of the ethanol was distilled off.

C. From 2.—Ammonia was bubbled into a slurry of **2** (4.90 g, 10.0 mmol) in acetone (50 ml) for 5 min at room temperature, during which time the **2** dissolved and was replaced by a finely divided white precipitate. After 30 min, the mixture was filtered, giving 0.50 g (93.5%) of ammonium chloride (ir, NaOH test, Beilstein test) and a pale yellow oil (5.60 g, $n^{25}D$ 1.6117) which contained no chlorine (Beilstein test). The oil, on work-up, yielded 2.40 g (61.9%) of **5a**, isolated as the C_6H_6 hemisolvate, mp 87–88°, and 0.90 g (96.8%) of aniline (ir, *n*D). A careful check of each of the fractions failed to reveal the presence of any hexamethylenetetramine.

Tris(anilinomethyl)phosphine Oxide (5b).—**5a** (1.747 g, 4.50 mmol) in acetone (20 ml) was oxidized with 30% hydrogen peroxide as described for **3a**, giving 1.416 g (82.9%) of **5b**, mp 119–122° after recrystallization from ethanol–water. Two recrystallizations from carbon tetrachloride gave an analytical sample, mp 122–123°, after drying *in vacuo* over refluxing benzene: ir (Nujol) 786 (s, C_6H_5), 793 (m), 745 (vs, C_6H_5), 753 (s), 780 (m), 870 (w), 885 (w), 900 (m), 990 (w), 1030 (w), 1070 (w), 1090 (m), 1110 (w), 1135 (vs, P=O), 1150 (m, sh), 1180 (m), 1220 (w), 1235 (w), 1260 (m, CN_{arom}), 1290 (m), 1315 (m), 1410 (w), 1500 (s, C=C_{arom}), 1530 (s), 1610 (vs, C=C_{arom}), 3340 (vs, NH) cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.66 (d, 6 H, CH_2, J = 7.0 Hz), 4.23 (s, 3 H, NH), 6.6–7.3 (m, 15 H, C_6H_5). The NH peak vanished when D_2O was added.

Anal. Calcd for $C_{21}H_{24}N_3OP \cdot H_2O$: C, 65.78; H, 6.84; N, 10.96; P, 8.08. Found: C, 65.50; H, 6.36; N, 10.70; P, 8.18.

5b is soluble in acetone, chloroform, and ethanol and insoluble in water and ether. It can be recrystallized from carbon tetrachloride (30 ml/g), but must then be dried *in vacuo* over refluxing benzene (80°) or butanol (118°) to remove the solvent (CCl band at 787 cm^{-1} in the ir). Drying over acetone (56°) is insufficient.

Tris(anilinomethyl)phosphine Sulfide (5c).—**5a** (1.747 g, 4.50 mmol) and sulfur (0.160 g, 5.00 mmol) in benzene (20 ml) yielded 1.615 g (94.2%) of **5c**, mp 105–106°. A portion of this compound was recrystallized from acetone–water and dried *in vacuo* over refluxing acetone: mp 105–106°; ir (Nujol) 792 (s, C_6H_5), 725 (w), 747 (vs, C_6H_5), 758 (s, sh), 768 (w), 787 (m), 806 (w), 827 (w), 877 (m), 896 (w), 917 (w), 956 (w), 995 (w), 1020 (w), 1065 (w), 1110 (w), 1155 (w), 1180 (m), 1210 (w), 1240 (m), 1250 (s), 1290 (m), 1315 (s), 1420 (w), 1440 (s), 1505 (vs, C=C_{arom}), 1610 (vs, C=C_{arom}), 3400 (s, NH) cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.66 (d, 6 H, CH_2, J = 5.0 Hz), 4.14 (s, 3 H, NH), 6.5–7.3 (m, 15 H, C_6H_5). The NH peak vanished when D_2O was added.

Anal. Calcd for $C_{21}H_{24}N_3PS$: C, 66.12; H, 6.34; N, 11.02; P, 8.12. Found: C, 65.46; H, 6.27; N, 10.86; P, 7.93.

5c is soluble in acetone, chloroform, and acetonitrile and insoluble in water and ether.

Registry No.—**1**, 124-64-1; **2**, 34885-67-1; **3a**, 34885-68-2; **3b**, 34885-69-3; **3c**, 34885-70-6; **5a**, 34885-71-7; **5b**, 34885-72-8; **5c**, 34885-73-9; **6**, 24577-28-4.

Acknowledgments.—We are indebted to Dr. R. H. Dinius, Auburn University, for the ^{31}P nmr spectrum of **5a** and to Mr. G. J. Boudreaux of this laboratory for the ^1H nmr spectra.

A Novel Ring Expansion of a Diazacyclopentadienone Dioxide[1]

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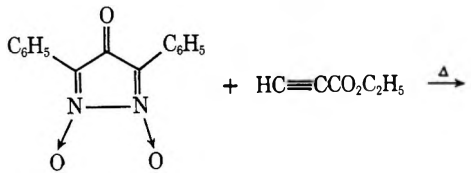
During a study of the cycloaddition reactions of diazacyclopentadienone oxides with acetylenic dipolarophiles,[3] an unusual ring expansion was observed when 2,5-diphenyl-3,4-diazacyclopentadienone 3,4-dioxide (**1**) was heated with ethyl propiolate in benzene. Although the expected[3] oxabicyclooctadienone derivative **2** was present in small amounts,[4] the major product (20%) was a nitrogen-containing compound, **3**.



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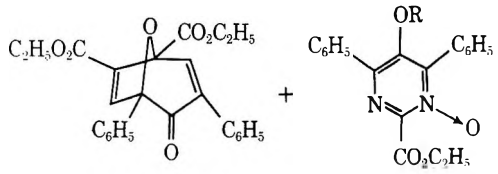
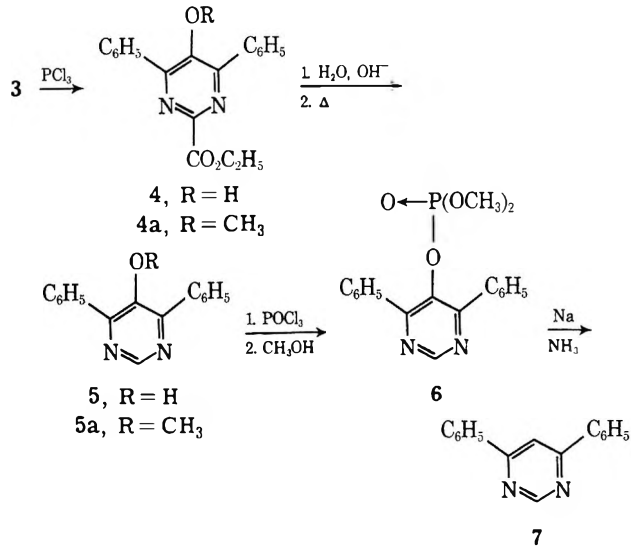


2 **3**, R = H; **3a**, R = CH_3

The structure of **3** is based upon its elementary analysis, spectral properties, its acidic character, and its degradation to 4,6-diphenylpyrimidine (Chart I). Treatment of **3** with phosphorus trichloride produced the corresponding pyrimidine **4**. A comparison of the aromatic proton regions of the nmr spectra of the methyl ethers of **3a** and **4a** was the original clue that a pyrimidine rather than a pyridazine ring was present, since the two phenyl groups, magnetically nonequivalent in **3a**, became equivalent in **4a**.[5] Alkaline hydrolysis of **4** followed by heating produced the hydroxypyrimidine **5**. The structure of **5** is supported

CHART I



by the appearance in its nmr spectrum of a sharp one-proton singlet at δ 9.09, typical of the shift of the 2 proton in pyrimidines.[6] In addition, the isomer of **4** with the hydroxyl and ethoxycarbonyl groups interchanged was synthesized independently by bromine oxidation of the condensation product of benzaldehyde, urea, and ethyl benzoylacetate. This compound proved to be different from **4**. The hydroxyl group of **4** was removed by the method of Pelletier and Locke,[7] which involves the dissolving metal reduction of the dimethyl phosphate ester **6**. The resulting 4,6-diphenylpyrimidine **7**, mp 99.5–101° (lit.[8] mp 102–103°), was identical with an authentic sample prepared by the condensation of dibenzoylmethane with formamide.[8]

This ring enlargement appears to be related to that observed in the reaction of isatogens with acetylenic esters.[9] In those reactions also, one of the acetylenic carbon atoms is lost through an obscure deacylation process. However, the present case differs in that insertion is into an N–N bond rather than into the C–N bond of the original nitrone function. Another ring expansion of the diazacyclopentadienone oxides was observed during oxidation, but in that case C–C bond insertion occurred.[10]

Experimental Section

2,5-Diphenyl-3,4-diazacyclopentadienone 3,4-Dioxide and Ethyl Propiolate.—A mixture of 20.0 g (0.075 mol) of dioxide 1[11] and 15.0 g (0.15 mol) of ethyl propiolate in 150 ml of benzene was heated under reflux for 24 hr. Upon cooling, a yellow solid separated. Recrystallization of this solid from CH_2Cl_2–hexane gave 5.25 g (20%) of **2-ethoxycarbonyl-5-hydroxy-4,6-diphenylpyrimidine 1-oxide (3)**: mp 218–219°; ir (KBr) 1745, 1550 cm^{-1}.

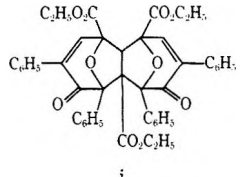
Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.84; H, 4.80; N, 8.30. Found: C, 67.46; H, 5.09; N, 8.43.

(1) This research was carried out under grant number CA-10742 from the National Cancer Institute, National Institutes of Health.

(2) (a) NSF Undergraduate Research Participant, Summer 1970; (b) National Defense Education Act Fellow, 1966–1969.

(3) J. P. Freeman and M. J. Hoare, *J. Org. Chem.*, **36**, 19 (1971).

(4) There is still some uncertainty in structure **2** as to whether the olefinic ester function is α or β with respect to the bridgehead ester group. In addition to **2**, traces of a $C_{38}H_{38}O_{10}$ compound were isolated. Although the structure of this compound has not been completely elucidated, it is believed to be of the type i, resulting from capture of the intermediate zwitterion[3] by product **2** instead of by ethyl propiolate.



i

(5) The spectra of the methyl ethers were used because the low solubility of the parent hydroxy compounds resulted in poor spectra.

(6) G. S. Reddy, R. T. Hobgood, Jr., and J. H. Goldstein, *J. Amer. Chem. Soc.*, **84**, 336 (1962); S. Gronowitz, B. Norrman, H. Gestbloom, B. Mathiasson, and R. A. Hoffman, *Ark. Kemi*, **22**, 65 (1964).

(7) S. W. Pelletier and D. M. Locke, *J. Org. Chem.*, **23**, 131 (1958).

(8) H. Bredereck, R. Gompper, and G. Morlock, *Chem. Ber.*, **90**, 942 (1957).

(9) W. E. Noland and R. F. Modler, *J. Amer. Chem. Soc.*, **86**, 2086 (1964).

(10) J. P. Freeman, D. L. Surbey, and J. E. Kassner, *Tetrahedron Lett.*, 3797 (1970).

(11) J. P. Freeman, D. L. Surbey, and J. J. Gannon, *J. Org. Chem.*, **34**, 184 (1969).

Methyl ether 3a was prepared in the standard way by reaction of **3** with diazomethane in tetrahydrofuran: mp 170–171° (CH_2Cl_2–hexane); nmr ($CDCl_3$) δ 8.09 (m, $W_{1/2}$ = 1[illegible] Hz,[12] 2 H), 7.74 (m, 2 H), 7.50 (m, 6 H), 4.52 (q, J = 7 Hz, 2 H), 3.31 (s, 3 H), and 1.43 (t, J = 7 Hz, 3 H).

Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.41; H, 5.10; N, 8.01.

The benzene mother liquor (above) was concentrated and the residue was taken up in 200 ml of boiling ethanol. After standing overnight the solution deposited 4.5 g (23%) of unreacted **1**. The solution was concentrated to 75 ml and chilled overnight to yield 4.9 g of a tan powder that was recrystallized from C_2H_5OH, then from benzene–Skellysolve B to yield pale yellow needles of **2**: mp 124–126°; nmr ($CDCl_3$) δ 7.90 (s, 1), 7.2–7.6 (m, 11), 4.1–4.5 (overlapping m, 4), 1.2–1.4 (overlapping m, 6); mass spectrum m/e (rel intensity) 418 (12), 373 (22), 344 (10), 317 (10), 215 (10), 106 (11), 105 (100), 77 (22).

Anal. Calcd for $C_{25}H_{22}O_6$: C, 71.76; H, 5.30. Found: C, 71.33; H, 5.48.

The ethanol mother liquor was evaporated to dryness. The residue was dissolved in 1:1 benzene–Skellysolve B and placed on a silica gel column. Elution with the same solvent mixture yielded an additional 0.18 g of **2**, total yield 5.08 g (13%).

Elution with benzene yielded a yellow oil which deposited 0.66 g of yellow crystals from ethanol: mp 189–191°; nmr ($CDCl_3$) δ 6.9–8.1 (m, 20), 5.13 (s, 1), 4.99 (s, 1), 3.75–4.40 (overlapping m, 7), 1.18 (t, J = 7 Hz, 3), 1.00 (t, J = 7 Hz, 3), 0.89 (t, J = 7 Hz, 3); mass spectrum m/e (rel intensity) 738 (8), 321 (41), 320 (16), 319 (9), 291 (24), 105 (100), 77 (11).

Anal. Calcd for $C_{45}H_{38}O_{10}$: C, 73.15; H, 5.20. Found: C, 73.03; H, 5.40.

2-Ethoxycarbonyl-5-hydroxy-4,6-diphenylpyrimidine (4).—A mixture of 1.5 g (4.46 mmol) of **3** and 2 ml (10 mmol) of phosphorus trichloride in 20 ml of $CHCl_3$ was allowed to stand at room temperature overnight. Evaporation of the solvent and recrystallization of the residue from ethanol produced 1 g (76%) of white crystals of **4**, mp 227–228°. Traces of this compound were also found in the eluent from the silica gel column separation of the product from the ethyl propiolate reaction.

Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.23; H, 5.03; N, 8.80. Found: C, 70.05; H, 5.21; N, 8.60.

The acetate ester of 4 had mp 113–115° (C_2H_5OH).

Anal. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.20; H, 5.01; N, 7.73. Found: C, 69.33; H, 5.12; N, 7.50.

Methyl ether 4a had mp 117–119° (C_2H_5OH); nmr ($CDCl_3$) δ 8.17 (m, $W_{1/2}$ = 11 Hz,[12] 4 H), 7.50 (m, 6 H), 4.51 (q, J = 7 Hz, 2 H), 3.38 (s, 3 H), and 1.45 (t, J = 7 Hz, 3 H); mass spectrum m/e (rel intensity) 334 (32), 213 (14), 262 (100), 261 (29), 129 (10), 89 (16), 77 (12).

Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.73; H, 5.55; N, 8.29.

5-Hydroxy-4,6-diphenylpyrimidine (5).—A suspension of 1.0 g (3.2 mmol) of **4** in 25 ml of 20% aqueous KOH was heated on a steam bath for 1 hr. The solution was cooled and acidified to congo red and the solid that separated was collected. It was dried and heated without solvent at 200° for 30 min. Recrystallization of the residue from CH_2Cl_2–hexane gave a pale yellow solid: mp 181–182°; ir (KBr) 3 μ (broad), 1570, 1550, 1520 cm^{-1}; mass spectrum m/e (rel intensity) 248 (82), 247 (100).

Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.39; H, 4.87; N, 11.28. Found: C, 77.09; H, 5.08; H, 11.50.

Methyl ether 5a had mp 69–70° from petroleum ether (bp 30–60°); nmr ($CDCl_3$) δ 9.09 (s, 1 H), 8.12 (m, $W_{1/2}$ = 11 Hz, 4 H), 7.50 (m, 6 H), and 3.35 (s, 3 H); mass spectrum m/e (rel intensity) 263 (13), 262 (73), 261 (100), 89 (28).

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 78.35; H, 5.45; N, 10.79.

Dimethyl 4,6-Diphenyl-5-pyrimidyl Phosphate (6).—A mixture of 0.3 g (1.2 mmol) of 4,6-diphenyl-5-hydroxypyrimidine (**5**) and 5 ml of $POCl_3$ were heated under reflux for 1 hr. After evaporation of excess $POCl_3$ the residue was dissolved in 5 ml of CH_3OH and this solution was diluted with water. The white solid that separated was recrystallized from CH_3OH–H_2O, mp 123–125°.

Anal. Calcd for $C_{18}H_{17}N_2O_4P$: C, 60.67; H, 4.82; N, 7.86. Found: C, 60.87; H, 4.86; N, 7.87.

4,6-Diphenylpyrimidine (7).—Small pieces of sodium (45 mg) were added to a refluxing solution of 356 mg of phosphate **6** in liquid NH_3–tetrahydrofuran. After the usual work-up, 132 mg (57%) of **7**, mp 99.5–101° (n-C_6H_{14}), was obtained. It was identical with an authentic sample[8] (mixture melting point, ir spectra).

Ethyl 2-Hydroxy-4,6-diphenyl-1,6-dihydropyrimidine-5-carboxylate.—A mixture of 10.6 g (0.1 mol) of benzaldehyde and 12.0 g (0.2 mol) of urea in 100 ml of C_2H_5OH was treated with 8 ml of concentrated HCl and warmed on a steam bath for 15 min. Ethyl benzoylacetate, 19.2 g (0.1 mol), was added and the solution was heated under reflux overnight. The solvent was evaporated and the residual oil was crystallized from ethanol–hexane to yield 17.0 g (53%) of pale yellow crystals. Upon recrystallization from ethanol, two forms were observed, mp 158–159° and mp 172–173°. The low-melting modification partially resolidified on heating above its melting point and finally melted at 172–173°: nmr ($CDCl_3$) δ 7.90 (br s, 1), 7.17–7.50 (m, 10), 6.68 (br s, 1), 5.40 (br d, J = 3 Hz, 1 H), 3.81 (q, J = 7 Hz, 2 H), 0.80 (t, J = 7 Hz, 3 H).

Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.56; H, 5.45; N, 8.57.

Ethyl 2-Hydroxy-4,6-diphenylpyrimidine-5-carboxylate.—A solution of 3.22 g (0.01 mol) of the dihydro compound and 1.8 g (0.011 mol) of Br_2 in 30 ml of acetic acid was heated under reflux overnight. The solvent was evaporated *in vacuo* to yield a mixture of the pyrimidine and its dibromo intermediate. The dehydrobromination was completed by dissolving the mixture in ethanol and stirring overnight in the presence of excess solid K_2CO_3 at room temperature. The mixture was filtered, and the filtrate was evaporated to yield 2.68 g (84%) of white solid. A sample was recrystallized from ethanol–water and sublimed at 180° (0.5 mm): mp 215–216°; nmr ($CDCl_3$) δ 7.25–7.80 (m, 10 H), 3.90 (q, J = 7 Hz, 2 H), 0.83 (t, J = 7 Hz, 3 H)

Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.75. Found: C, 71.04; H, 5.12; N, 8.83.

Registry No.—**1**, 34982-07-5; **2**, 34906-18-8; **3**, 34906-19-9; **3a**, 34906-20-2; **4**, 34906-21-3; **4** acetate ester, 34906-22-4; **4a**, 34906-23-5; **5**, 34906-24-6; **5a**, 34906-25-7; **6**, 34906-26-8; **7**, 3977-48-8; ethyl 2-hydroxy-4,6-diphenyl-1,6-dihydropyrimidine-5-carboxylate, 34906-28-0; ethyl 2-hydroxy-4,6-diphenylpyrimidine-5-carboxylate, 34906-29-1.

(12) Band width at half height.

New Synthetic Methods from Dithianes. A Convenient Oxidation of Aldehydes to Acids and Esters

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The considerable literature on the chemistry of 2-lithio-1,3-dithianes which has been accumulating recently[1] attests to their great utility in organic synthesis. This contrasts with the present utility of metalated orthothioformates which suffer from being simultaneously less reactive and somewhat unstable.[2] Furthermore, neither their hydrolysis[2] nor alcoholysis[3] has produced outstanding yields. We wish to report a combination of reactions which leads from 2-substituted 1,3-dithianes to carboxylic acids and esters in good overall yields *via* 2-substituted 2-methylthio-1,3-dithianes.

Treatment of 2-lithio 2-substituted 1,3-dithianes

(1) For a review, see D. Seebach, *Synthesis*, **1**, 17 (1969).
(2) D. Seebach, *Angew. Chem., Int. Ed., Engl.*, **6**, 442 (1967).
(3) R. M. Carlson and P. M. Helquist, *Tetrahedron Lett.*, 173 (1969).

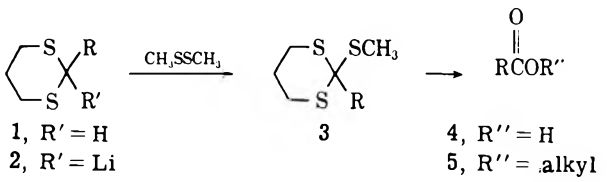
TABLE I

CONVERSION OF DITHIANES 1 INTO ESTERS 5 *via* ORTHOTHIOFORMATES 3[a]

R	Reaction time, hr	Orthothioformates 3 reaction temp, °C	Yield,[c] %	Ethyl esters 5[b] reflux time, hr	Yield,[d] %	Acids 4 reflux time, hr	Yield,[d] %
Phenyl	2	−78	94.5	4.5	92.4	24	65
n-Butyl	3	−20	89.8	4.0	99.0	25	40
trans-Cinnamyl[e]	2	−78	90.0	7.5	92.1[e]	21	46

[a] All new compounds were characterized by nmr and infrared spectra as well as satisfactory elemental analyses. [b] Methyl benzoate was prepared in 95% yield by refluxing for 4.5 hr in 30% aqueous methanol. [c] Crude yield from 1. [d] Crude yield from 3. [e] All trans by nmr analysis.

(2) in tetrahydrofuran with 1 equiv of methyl disulfide gave high yields of the corresponding orthothioformates (**3**).[4] These were converted in similar yields

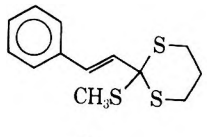


1, R′ = H
2, R′ = Li

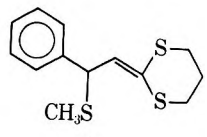
3

4, R″ = H
5, R″ = alkyl

to the corresponding esters by refluxing in aqueous alcohols in the presence of mercury(II) salts for periods of 4.0–7.5 hr. Representative examples are shown in Table I. In keeping with the lower acidity of the butyl derivative (**1**, R = *n*-butyl), reaction times to form the anion were substantially longer than with the benzylic analogs. The orthothioformates were readily recognizable due to a three-proton singlet in their nmr spectra at about δ 2.00 corresponding to the *S*-methyl protons. Interestingly, although the styryl derivative **2** (R = $C_6H_5CH{=}CH{-}$) could in principle be expected to give two methylthio adducts (**6** or **7**), nmr analysis of the product obtained under our conditions showed it to be entirely **6**. Furthermore, treatment of this anion with deuterium oxide resulted in recovery of only monodeuterated starting material (**1**, R = $C_6H_5CH{=}CH{-}$, R′ = D). As may have been expected, there was no evidence for cis product. However, it was subsequently found that **7** may be



6



7

obtained by pyrolysis of **6**. Distillation of **6** at 190° and 50-μ pressure yielded a 2.6:7.4 mixture of **6** and **7** by nmr integration. In accord with expectation, alcoholysis of this mixture yielded typical yields of ethyl cinnamate. It should also be noted that at least in the cinnamyl case alkoxymercuration of the double bond either does not occur or is reversible under the reaction conditions. As the beginning of an exploration of the scope of the alcoholysis, the phenyl orthothioformate was treated with *tert*-butyl alcohol under typical conditions. The reaction time to completion was much longer (*ca.* 70 hr) and gave the unexpected result of producing benzoic acid in 60% yield. Since we have demonstrated that *tert*-butyl benzoate is stable to the reaction conditions, it may be that in this case steric factors permit water to successfully compete with *tert*-butyl alcohol for reaction at the benzylic carbon.

The corresponding carboxylic acids were obtained in lower yield (Table I) by reaction of **3** in refluxing 35% aqueous acetone for 24 hr with mercury(II) salt catalysis. Considerable experimental variation in conditions did not improve these yields. The neutral material recovered from these reactions showed no starting material upon tlc analysis. We are exploring this reaction more thoroughly and will report more details in due course.

We expect the oxidative procedure we have described to be of value in systems which are sensitive to conventional oxidizing reagents and are continuing to explore further ramifications of this work.

Experimental Section

Nmr spectra were recorded on a Varian A-60A spectrometer and chemical shifts are reported in parts per million (δ) from internal tetramethylsilane. Infrared spectra were recorded on a Beckman IR-5A spectrometer. Melting points were taken with a Thomas-Hoover apparatus and are uncorrected. Deuterium oxide (99.7%) was purchased from Merck Sharp and Dohme, Canada. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. The 1,3-dithianes were prepared by the method of Seebach, *et al.*[5]

Ethyl Benzoate.—A solution of 2.0 g (10.68 mmol) of 2-phenyl-1,3-dithiane[4] in 20 ml of tetrahydrofuran in a 50-ml, two-neck, round-bottomed flask equipped with magnetic stirring, nitrogen inlet, and septum cap was cooled to −78°, and 5.70 ml of 2.24 *M* *n*-butyllithium in hexane was injected over 25 min. The clear yellow solution was stirred for 2 hr at −78°, and then 1.73 ml (19.35 mmol) of methyl disulfide was injected over 10 min. The reaction mixture was allowed to warm to 25° and then poured into 100 ml of 0.05 *N* hydrochloric acid. Tetrahydrofuran was removed by rotary evaporation and the remaining aqueous solution was extracted with two 100-ml portions of 1:1 pentane–methylene chloride. The extracts were combined, washed with 10% aqueous sodium bicarbonate, water, and saturated brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to afford 2.44 g (94.5%) of 2-thiomethoxy-2-phenyl-1,3-dithiane as white plates: mp 67–71° (from methanol, 76–78°); nmr (CCl_4) δ 1.90 (s, 3 H, SCH_3). *Anal.* Calcd: C, 54.50; H, 5.82. Found: C, 54.70, H, 5.86. Crude product (238 mg, 0.98 mmol) was placed in a 50-ml round-bottom flask with 27 ml of 95% ethanol, 1.14 g (4.20 mmol) of mercuric chloride, and 353 mg (1.62 mmol) of mercuric oxide and refluxed for 4.5 hr under nitrogen. The mixture was filtered and the solid residue was washed with two 20-ml portions of methylene chloride. The filtrate was diluted with 75 ml of water and extracted with two 75-ml portions of methylene chloride. These extracts were combined, washed with 4 *M* aqueous ammonium chloride and saturated brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to yield 133 mg of ethyl benzoate (92.4%) as a clear oil. Characterization by nmr and infrared spectroscopy indicated no significant impurities: ir

(4) Although it is not an oxidative procedure, we have found that orthothioformates may also be obtained in high yields by treating 2-lithio-2-thiomethoxy-1,3-dithiane with alkyl halides under carefully controlled conditions. See Experimental Section for details.

(5) D. Seebach, B. W. Erickson, and G. Singh, *J. Org. Chem.*, **31**, 4303 (1966).

($CHCl_3$) 5.82 μ; nmr (CCl_4) δ 1.40 (t, 3 H, J = 7.0 Hz), 4.37 (q, 2 H, J = 7.0 Hz).

Methyl Benzoate.—Treatment of 144 mg of phenyl orthothioformate with 665 mg of mercuric chloride and 213 mg of mercuric oxide in 14 ml of 7.7% aqueous methanol under conditions identical with those above yielded 66 mg (95.5%) of methyl benzoate: ir (CCl_4) 5.78 μ, nmr ($CDCl_3$) δ 3.89 (s, 3 H).

Ethyl Pentanoate.—Treatment of 1.88 g (8.46 mmol) of 2-butyl-1,3-dithiane in 20 ml of tetrahydrofuran with 5.70 ml (12.8 mmol) of *n*-butyllithium followed by 1.72 ml (19.35 mmol) of methyl disulfide in a manner identical with the above procedure yielded 2.13 g (89.8%) of crude orthothioformate derivative as an orange oil: nmr (CCl_4) δ 2.00 (s, 3 H). *Anal.* Calcd: C, 48.60; H, 8.16. Found: C, 49.12; H, 8.15. Crude product (222 mg, 1 mmol) was refluxed for 4 hr in 27 ml of 95% ethanol with 1.14 g of mercuric chloride and 353 mg of mercuric oxide. Work-up as above yielded 132 mg (quantitative) of the ester as a clear, light brown oil: ir ($CHCl_3$) 5.80 μ.

Ethyl Cinnamate.—A solution of 2.38 g (10.68 mmol) of 2-(β-styryl)-1,3-dithiane in 20 ml of tetrahydrofuran was treated with 5.70 ml (12.8 mmol) of *n*-butyllithium and subsequently with 1.73 ml (19.35 mmol) of methyl disulfide as above to give 2.56 g (90%) of the orthothioformate derivative as a clear yellow oil: nmr ($CDCl_3$) δ 2.04 (s, 3 H), 6.30 (d, 1 H, J = 10.0 Hz), 6.90 (d, 1 H, J = 10.0 Hz). *Anal.* Calcd: C, 58.16; H, 6.01. Found: 57.80; H, 5.83. Crude product (268 mg, 1 mmol) was refluxed for 7.5 hr in 95% ethanol with 1.14 g of mercuric chloride and 353 mg of mercuric oxide. The standard work-up yielded 162 mg (92.1%) of oily ethyl cinnamate: nmr (CCl_4) 1.24 (t, 3 H, J = 7.0 Hz), 4.15 (q, 2 H, J = 7.0 Hz), 6.37 (d, 1 H, J = 16.5 Hz), 7.63 (d, 1 H, J = 16.5 Hz); ir (CCl_4) 5.82, 6.10 μ.

Isomerization of 6 to 7.—The cinnamyl orthothioformate was bulb to bulb distilled in a Kugelrohr apparatus at 192° and 50 μ to give an oil. The nmr spectrum ($CDCl_3$) of this material showed peaks corresponding to a small amount of **9** and new resonances at δ 1.98 (s, 3 H), 5.08 (d, 1, H, J = 10.0 Hz), and 6.05 (d, 1 H, J = 10.0 Hz) which were attributed to isomer **10**. Integration of the spectrum showed **9** and **10** to be present in a ratio of 2.6:7.4.

Benzoic Acid.—Phenyl orthothioformate **3** (238 mg, 1 mmol) was refluxed in 27 ml of 35% aqueous acetone with 1.14 g of mercuric chloride and 353 mg of mercuric oxide for 24 hr. The reaction was cooled and worked up in a manner identical with the esterification reaction. The methylene chloride extract was washed with 10% aqueous sodium carbonate. Acidification of the aqueous layer followed by extraction with methylene chloride yielded 80 mg (69%) of benzoic acid which was homogeneous in the nmr spectrum, mp 122°.

Cinnamic Acid.—The cinnamyl orthothioformate (508 mg, 2 mmol) was similarly refluxed in 50 ml of 35% aqueous acetone with 1.63 g of mercuric chloride and 1.30 g of mercuric oxide for 21 hr. Typical work-up yielded 131 mg (46%) of cinnamic acid: mp 133–144°; nmr ($CDCl_3$) δ 6.55 (d, 1 H, J = 16.5 Hz), 7.88 (d, 1 H, J = 16.5 Hz), 10.7 (s, 1 H); ir ($CDCl_3$) 5.93, 6.13 μ.

Pentanoic Acid.—Butyl orthothioformate (224 mg, 1 mmol) was similarly refluxed in 25 ml of 35% aqueous acetone with 823 mg of mercuric chloride and 658 mg of mercuric oxide for 25 hr. Typical work-up yielded 42 mg (40%) of oily pentanoic acid: nmr ($CDCl_3$) δ 9.58 (s, 1 H); ir ($CDCl_3$) 3.05–4.35, 5.85 μ.

Reaction of Phenyl Orthothioformate (3, R = Phenyl) with *tert*-Butyl Alcohol.—A mixture of 142 mg (0.6 mmol) of phenyl orthothioformate, 665 mg of mercuric chloride, and 213 mg of mercuric oxide was refluxed with 12 ml of *tert*-butyl alcohol and 1 ml of water for 67.5 hr. The reaction was cooled and filtered and the residue was washed with methylene chloride. The filtrate was washed with 20% aqueous ammonium chloride and saturated aqueous sodium chloride, dried, and evaporated to yield 62 mg of amorphous solid. This material was dissolved in methylene chloride and extracted with 10% aqueous sodium bicarbonate. Acidification of the aqueous layer followed by methylene chloride extraction yielded 43 mg (60.3%) of benzoic acid, mp 119–120°.

Stability of *tert*-Butyl Benzoate.—*tert*-Butyl benzoate was prepared according to procedure 1 of Raha.[6] *tert*-Butyl benzoate (173 mg, 1 mmol) was dissolved in 24 ml of *tert*-butyl alcohol and 2 ml of distilled water with 1.4 g of mercuric chloride and 430 mg of mercuric oxide. The mixture was refluxed for 72 hr and then worked up as above to give 172 mg of recovered *tert*-butyl benzoate. No additional products were evident in the nmr spectrum.

Orthothioformates *via* 2-Thiomethoxy-1,3-dithiane. Ethyl Pentanoate.—2-Thiomethoxy-1,3-dithiane was prepared from 1,3-dithiane (1.0 g, 8.32 mmol) by treatment with *n*-butyllithium (4.0 ml, 8.8 mmol) followed by methyl disulfide (0.752 ml, 8.5 mmol) in a manner identical with that above. The crude product was isolated as an oil (1.72 g, 92%). To 168 mg (1.01 mmol) of crude thiomethoxy derivative in 5 ml of tetrahydrofuran at −20° was injected 0.5 ml (1.02 mmol) of *n*-butyllithium over a period of 1 min. After 3 min of stirring, 0.114 ml (1.0 mmol) of methyl iodide was added and stirring was continued for 2.5 hr. The reaction was brought to 0° and stored for 17 hr followed by 3 hr at 25°. The reaction was subjected to the usual work-up to yield 175 mg of yellow oil with properties identical with those of the butyl orthothioformate previously described. Treatment of 166 mg of this oil with 95% ethanol under typical alcoholysis conditions yielded crude ethyl pentanoate (94 mg, 97%).

Registry No.—Ethyl benzoate, 93-89-0; 2-thiomethoxy-2-phenyl-1,3-dithiane, 34858-82-7; methyl benzoate, 93-58-3; ethyl pentanoate, 539-82-2; ethyl cinnamate, 4192-77-2; benzoic acid, 65-85-0; cinnamic acid, 621-82-9; pentanoic acid, 109-52-4.

Acknowledgment.—We are grateful to the Graduate School of the University of Wisconsin for financial support of this work and to the National Science Foundation for support to C. C. W. under the auspices of the undergraduate research participation program (GY-8817, 1971).

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A Nuclear Magnetic Resonance Technique for Distinguishing Isomers of 3,5-Disubstituted Nortricyclenes[1a]

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Known techniques for assigning relative stereochemistry to the 3,5 positions of nortricyclene derivatives are generally limited to compounds with a "trans" arrangement of substituent groups as in **1a**.[2-6] Nmr techniques for distinguishing between the "cis" isomers **1b** and **1c** (X = Y) have not been reported.

The symmetry of the parent nortricyclene system includes a threefold axis of rotation through the bridgehead carbon (C_4) and the center of the cyclopropyl ring (C_{3v} symmetry). The same sets of rules employed in the interpretation of spectra of norbornene and norbornadiene systems do not apply to the nortricyclyl system. The terms endo and exo do not have the same significance in considering the nortricyclene system, for which of the three carbons chosen as the

(1) (a) Presented in part at the Southeast Regional Meeting of the American Chemical Society, Nashville, Tenn., Nov 4–6, 1971; (b) Abstracted in part from the M.S. Thesis of Stephen Wu, East Tennessee State University, Aug 1970; (c) Corporate Research Laboratories, Esso Research and Engineering Company, Linden, N. J.

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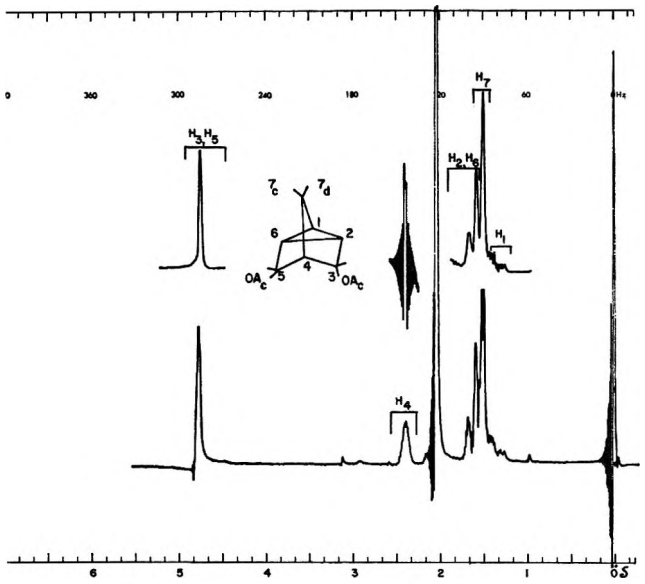
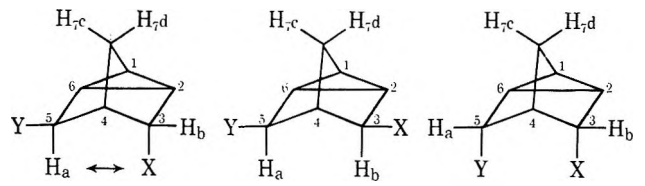


Figure 1.—Nmr spectrum of the 3,5-*endo,endo*-diacetate (**4**). Inset, spectrum of 4 after irradiation of the bridgehead proton H_4.

bridge (C_3, C_5, C_7) is arbitrary. Hence, assignments of stereochemistry based on experience with coupling constants in the norbornyl or norbornadienyl derivatives cannot be made in the nortricyclene case. The use of a monosubstituted reference compound to determine chemical shifts of endo or exo protons is meaningless; there are only *R* and *S* isomers of 3-substituted nortricyclenes.

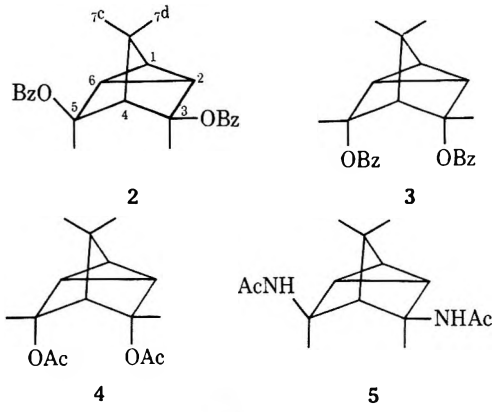


1a **1b** **1c**

A technique based upon nmr analysis of the high-field spectra has been developed in these laboratories for assigning stereochemistry to cis,exo and cis,endo isomers of 3,5-disubstituted nortricyclenes. This technique depends upon the fact that an *exo-Y substituent at position 5* (*as in* **1a** *or* **1b**) *should cause a paramagnetic shift of* H_{7c}, for, owing to the symmetry of the nortricyclene system, the H_{7c}–Y interaction in **1a** and **1b** is similar to the H_a–X interaction in **1a**. In the same vein, an *endo-X substituent at position 3* (*as in* **1a** *or* **1c**) *would not affect the chemical shift of either* H_{7c} *or* H_{7d}.

Nmr analyses of reported 3,5-disubstituted nortricyclenes of known stereochemistry have been carried out with particular emphases on the high-field portions of the spectra (H_1, H_2, H_6, and H_7). The compounds used in these studies were the 3,5-*exo,exo*- and *endo,endo*-dibenzoate derivatives, **2** and **3** respectively,[7] the 3,5-*endo,endo*-diacetate **4**,[7] and the *exo,exo*-diacetamide **5**.[8]

If indeed the paramagnetic shift is a general phenomenon, then the H_{7c}, H_{7d} protons of the "pseudo" exo,exo isomer (**1b**, X = Y) would appear at lower field



2 **3** **4** **5**

Bz ≡ COC_6H_5
Ac ≡ $COCH_3$

(unspecified positions are hydrogens)

(paramagnetic shift) than the H_{7c}, H_{7d} protons of the corresponding "pseudo" endo,endo isomer (**1c**, X = Y). The critical task in these nmr analyses was assignment of H_7 for both the "pseudo" exo,exo and endo,endo isomers. Since H_7 is magnetically coupled to H_4 (and H_1), irradiation of H_4 should sharpen the H_7 signal. Identification of H_4 in each of the spectra presented little problem, since the H_4 signal appeared downfield with respect to the H_1, H_2, H_6, and H_7 absorptions, owing to its bridgehead nature and to its proximity to the electronegative X groups (at C_3 and C_5). In all cases, irradiation of H_4 resulted in sharpening of the downfield protons (H_3, H_5) and sharpening of the bridge protons (H_7). For example, irradiating H_4 of the 3,5-*endo,endo*-diacetate (**4**, X = Y = Ac) resulted in collapse of the signals at δ 1.53 ppm; therefore the absorption at 1.53 ppm can be assigned to H_7 (see Figure 1). The same technique was applied to compounds **2**, **3**, and **5** to ascertain the chemical shift of H_7 in each case. Further proton decoupling and spectral simulation led to chemical shift assignments of the protons in compounds **2**–**5**. These results are shown in Table I.

TABLE I
CHEMICAL SHIFT ASSIGNMENTS

	Chemical shift, δ			
Hydrogen	2	3	4	5
H_1	1.60	1.39	1.44	1.30
$H_{7c} = H_{7d}$	1.99	1.53	1.53	1.56
$H_2 = H_6$	1.70	1.71	1.64	1.36
H_4	2.49	2.59	2.44	2.13
$H_3 = H_5$	4.88	4.96	4.84	3.77

Protons H_7 would be expected to absorb at higher field than H_2, H_6 even though the latter are "cyclopropyl" type hydrogens, since H_7 is one carbon further removed from the electronegative X groups. However, H_7 should absorb at lower field than H_1, for both protons are about equally removed from C_3 and C_5, but H_1 is a "cyclopropyl" type proton. These predictions hold true for the 3,5-di-endo isomers **3** and **4**, wherein H_1 absorbs at higher field than H_7, which in turn absorbs higher than H_2, H_6.

This order of absorption is *not* observed for the 3,5-di-exo compounds **2** and **5**. For compounds **2** and **5**, proton H_1 still absorbs at the highest field, but the

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TABLE II
COUPLING CONSTANTS OF THE NORTRICYCLIC SYSTEM

J	Coupling constant J,[a] Hz 2	3	4	5
$J_{1,2} \equiv J_{1,6}$	5.3–5.5[b]	5.3–5.5	5.3–5.5 (5.46)[e]	5.3–5.5[f]
$J_{1,7}$	1.2–1.5	1.2–1.5	1.2–1.5	1.2–1.5
$J_{4,7}$	1.8–2.0	1.8–2.0	1.8–2.0	1.8–2.0
$J_{2,3} \equiv J_{5,6}$	0.5[c]	0.75[d]	0.75	
$J_{3,4} \equiv J_{4,5}$	1.3–1.5	1.3–1.5	1.3–1.5	1.3–1.5
$J_{3,7} \equiv J_{5,7}$	0.0[d]	0.9[d]		
$J_{2,4} \equiv J_{4,6}$		≤0.3[c]	≤0.3	

[a] It was not possible to obtain signs of coupling constants in this work. [b] This coupling constant was assumed from analogy with compound **3** and was found to fit the spectral simulation. The order of magnitude was also checked by the hand calculation of an AB_2 type spectrum. [c] Estimated from sharpening of peak after irradiation. Such coupling constants are known to be small. See M. Barfield and B. Chakrabati, *Chem. Rev.*, 69, 757 (1969). [d] Estimated from sharpening of peak from triple resonance. [e] Based on coupling constants from endo,endo compounds and the spectral simulation. [f] This was based on a hand calculation of an AB_2 system. See, for example, J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution NMR Spectroscopy," Vol. I, Pergamon Press, New York N. Y., 1965, pp 321–329.

H_2, H_6 signals are at *higher* field than H_7. It is quite clear from Table I that H_7 (in compound **2**) absorbs about 0.3 ppm lower than H_2, H_6; in compound **5**, H_7 absorbs at 0.2 ppm lower than H_2, H_6. These results are completely consistent with previous observations showing that protons spatially adjacent to electron-attracting groups suffer a paramagnetic (downfield) shift.

Additional evidence corroborating the H_{7c}–H_{7d} assignment (δ 1.57 ppm) for the endo,endo isomer **3** and the H_{7c}–H_{7d} assignment (δ 1.99 ppm) for the exo,exo isomer **2** came from observation of the chemical shifts of each of these compounds (**2** and **3**) in the presence of tris(dipivalomethanato)europium, $Eu(DPM)_3$.[9–13] Since the effect of $Eu(DPM)_3$ decreases with distance it was anticipated that all the protons in the 3,5-*exo,exo*-dibenzoate **2** would suffer some paramagnetic shift, for the $Eu(DPM)_3$ should be spatially proximate to all the hydrogens in **2**. In contrast to the exo,exo isomer **2**, the $Eu(DPM)_3$ would be expected to interact with all the protons of the 3,5-*endo,endo*-dibenzoate **3** *except the bridge hydrogens* (*7c*, *7d*). Addition of $Eu(DPM)_3$ to **2** resulted in a chemical shift of all signals; addition of $Eu(DPM)_3$ to **3** resulted in a sizable chemical shift of all signals *except those for* H_{7c} and H_{7d}.

The generality of paramagnetic shifts for various electronegative X groups has been shown for chloride,[3,5] bromide,[2,5] acetate,[4] carbomethoxy,[6] and phenylsulfone groups.[2] This study has extended the above grouping to include benzoates, acetates,[14] and acetamides wherein the groups are identical (X = Y).[15]

In summary, paramagnetic shifts of bridge protons (H_7) in contrast to "cyclopropyl" hydrogens (H_2 and H_6) are observed for 3,5-di-exo compounds, whereas bridge proton absorptions are observed at higher fields than those for "cyclopropyl" hydrogens in 3,5-di-endo derivatives. One can distinguish between 3,5-di-exo and 3,5-di-endo derivatives by irradiation of the bridgehead hydrogen (H_4), thereby revealing the decoupled signals for the bridge protons (H_7). If the bridge hydrogens absorb at lower field than the "cyclopropyl" protons (H_2 and H_6), then the compound is di-exo; if not, it is di-endo.

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(14) A sample of the "trans" 3,5-diacetate (**1a**, X = Y = OAc) showed two different downfield signals for H_3 and H_5 with a difference in chemical shift of about 0.3 ppm.
(15) We sympathize with a referee's query as to how many cases are necessary to demonstrate the generality of a phenomenon; we hope that the seven different electronegative groupings that have shown this effect are sufficient to establish the generality of the paramagnetic shift effect.

Experimental Section

Nmr spectra (60 and 100 MHz) were run on a JEOLCO C-60H at East Tennessee State University and on a JNM-4H-100 at Medford, Mass. A JEOLCO-SD-30 was used for homonuclear spin decoupling. Samples for nmr analysis were dissolved in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. Chloroform-*d*, however, was not used as solvent for compound **5**; CD_3CO_2D (99.5% isotopically pure from Diaprep, Inc.) was used as solvent with TMS as internal standard. All compounds were prepared as previously described,[7,8] and had the correct elemental analyses.

Although the chemical shifts and coupling constants assigned in this study do not necessarily form a unique set,[16,17] these parameters have been so chosen that they are consistent with those values found in analogous systems. Values of bridge–bridgehead coupling constants of 1.5–2.5 Hz are consistent with previous studies;[18–21] the 5.5-Hz coupling constants ($J_{1,2} \equiv J_{1,6}$) of "nortricyclic" three-membered ring cis protons are not inconsistent with other literature values.[22–26] These results are summarized in Table II.

Spectral Simulation.—Spectral simulation was done using an (8K) IBM-1130 with plotter and a computer program designed for five spins. Comparison spectra were obtained from both double and triple resonance (homonuclear) experiments. These were compared to the simulated spectra. The 3,5-disubstituted nortricyclyl system has eight protons, but the chemical shift of the 3,5 hydrogens are the same, reducing the number of spins to seven. Decoupling was necessary in order to reduce the number of spins to five for comparison of simulated spectra with actual spectra.

Experiments with Chemical Shift Reagent.—To an nmr tube, containing about 100 mg of 3,5-*exo,exo*-dibenzoate (**2**) and 0.5 ml of $CDCl_3$, about 12 mg of $Eu(DPM)_3$ was introduced. A solution containing about 90 mg of the 3,5-*endo,endo*-dibenzoate (**3**), 0.5 ml of $CDCl_3$, and about 16 mg of $Eu(DPM)_3$ was prepared

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in an nmr tube. The paramagnetic shifts undergone by various protons (TMS as internal standard) are shown in Table III.

TABLE III

3,5-*exo*,*exo*-Dibenzoate (**2**)	3,5-*endo*,*endo*-Dibenzoate (**3**)
Hydrogens	Ppm	Ppm
H_1		0
H_2, H_6	0.05	0.12
H_{7c}, H_{7d}	0.07	0
H_4	0.10	0.17
H_3, H_5	0.10	0.27

The chemical shifts and coupling constants obtained in this study were reliable enough to be used for computer simulation of the actual high-field spectra of compounds **3** and **4**. Long-range coupling could not be demonstrated on the simulated spectrum owing to the five-spin computer limitation. However, irradiation of H_4 eliminated the long-range coupling of H_1, resulting in a better correlation of simulated with experimental spectra.

Registry No.—**2**, 4054-86-8; **3**, 4118-49-4; **4**, 17290-03-8; **5**, 24694-55-1.

Acknowledgment.—We are indebted to Mr. C. A. Boye of Tennessee Eastman for furnishing us the basic five-spin computer program and to Dr. E. I. Snyder, Visiting Professor of Chemistry, 1969–1970, for rewriting certain segments of this program to fit the (8K) IBM-1130 at East Tennessee State University. We would also like to acknowledge the aid of Mr. Ogawa at JEOLCO for running the 100-MHz spectra. We acknowledge considerable assistance from the East Tennessee State University Research Advisory Council.

Structure of 1,3-Dicyanobicyclo[1.1.0]butane Using X-Ray Analysis

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Bicyclo[1.1.0]butane and its derivatives are of current interest because of the favorable properties of some of the polymers formed. The structure of bicyclobutane has been assessed using a wide variety of physical methods, including infrared and Raman spectroscopy,[1] microwave spectroscopy,[2,3] electron diffraction,[4] and nuclear magnetic resonance spectroscopy.[5,6] The instability of bicyclobutane makes X-ray diffraction analysis on this compound difficult. However, a substituted bicyclobutane, 1,3-dicyanobicyclobutane (I), is a solid at room temperature and is stable for a sufficient time to collect X-ray data. We wish to report the results of a single-crystal X-ray determination of this substituted bicyclobutane which was kindly supplied to us by Dr. S. C. Cherkofsky of the Du Pont Company.

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Experimental Section

Compound I crystallizes as colorless needles elongated about the *b* crystallographic axis. The lattice constants, as determined by a least-squares analysis on the settings for the angles on a four-angle diffractometer for six reflections (Cu K_α, λ = 1.54178 Å) are a = 10.397 (7), b = 5.813 (4), c = 9.358 (8), V = 566 (2) Å^3. The systematic absences, $0kl$ when $k = 2n + 1$, $h0l$ when $l = 2n + 1$, $hk0$ when $h + k = 2n + 1$, $h00$ when $h = 2n + 1$, $0k0$ when $k = 2n + 1$, and $00l$ when $l = 2n + 1$, determine the space group to be $Pbcn$. The molecular weight, $C_6N_2H_4$, is 104; $F(000)$ is 216. The observed and calculated densities are 1.20 and 1.22 g cm^{-3}, respectively.

All data in the 2θ range 0–120° were collected with a Picker FACS-I diffractometer. A θ–2θ scan was used; the scan rate was 2 deg/min and 10-sec backgrounds were collected before and after each scan. There were 425 unique reflections of which 321 were considered to be above backround using the criteria $I > 3\sigma(I)$. Lorentz and polarization factors were applied but no absorption corrections were made. The maximum and minimum transmission factors to be applied to the intensities are estimated to be 0.97 and 0.94. A standard reflection was measured every 50th reflection. The intensity of the standard at the end of data collection was 81% of the original. This was corrected for by assuming that the decline in intensity for all reflections followed the decline of the standard. A linear interpolation between each pair of standards was used to arrive at the individual reflections scale factor.

The structure was solved using Long's program for the reiterative application of Sayre's equation.[7] The first E map yielded the positions of all nonhydrogen atoms. After full matrix least-squares refinement, the hydrogen atoms were located from a difference map. Further refinement with carbon and nitrogen vibrating anisotropically while hydrogen vibrated isotropically yielded a final R value of 0.057. The final atomic coordinates are given in Table I and the thermal parameters are in Table II.

TABLE I

FINAL ATOMIC COORDINATES OF DINITRILE BICYCLOBUTANE IN FRACTIONS OF THE UNIT CELL EDGE, WITH STANDARD DEVIATIONS IN PARENTHESES

	x	y	z
N-1	0.3506 (3)	0.5118 (6)	0.0813 (4)
C-2	0.3940 (3)	0.3523 (6)	0.1321 (4)
C-3	0.4492 (3)	0.1507 (5)	0.1929 (3)
C-4	0.4218 (4)	0.0515 (6)	0.3355 (4)
H-5	0.417 (3)	−0.124 (7)	0.340 (4)
H-6	0.367 (3)	0.130 (6)	0.406 (3)

TABLE II

FINAL ANISOTROPIC THERMAL PARAMETERS FOR THE NONHYDROGEN ATOMS EXPRESSED AS exp $-(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + 2b_{12}hk + 2b_{13}hl + 2b_{23}kl)$. FINAL ISOTROPIC TEMPERATURE FACTORS FOR THE HYDROGEN ATOMS (B_θ Å^2)

	b_{11}(× 10^4)	b_{22}(× 10^4)	b_{33}(× 10^4)	b_{12}(× 10^4)	b_{13}(× 10^4)	b_{23}(× 10^4)
N-1	160 (4)	485 (13)	291 (7)	48 (7)	8 (4)	132 (7)
C-2	121 (4)	396 (13)	171 (5)	−10 (6)	3 (3)	31 (7)
C-3	123 (4)	293 (10)	133 (4)	−6 (5)	−14 (3)	0 (5)
C-4	154 (5)	360 (13)	146 (5)	−47 (6)	5 (4)	18 (7)

	B_θ	
H-5	7.3	(9)
H-6	5.0	(7)

Results and Discussion

The bond lengths are given in Figure 1 and the bond angles are given in Table III. Most of the parameters found in this study are in agreement with the results of previous structural studies using other methods.[1–6] A notable difference comes in the dihedral angle formed

(7) R. E. Long, Ph.D. Thesis, University of California at Los Angeles, 1965, part II, pp 86–126.

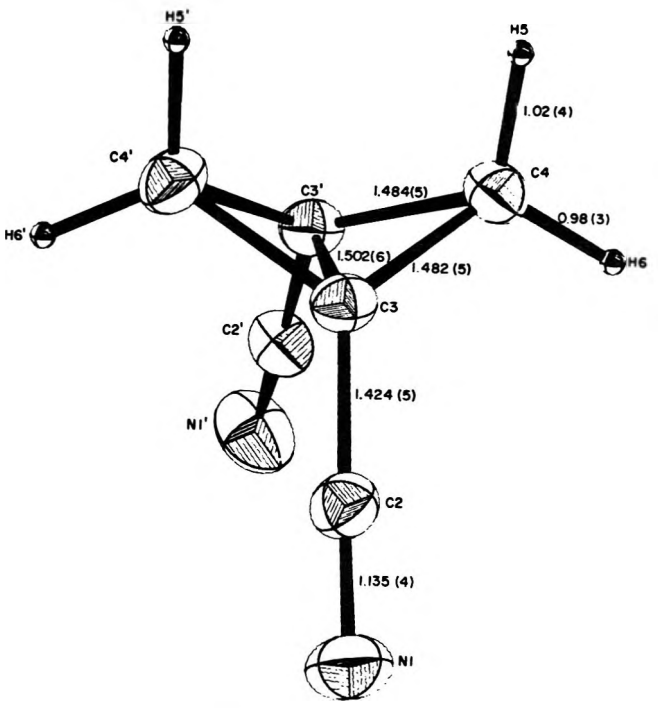

Figure 1.—Bond lengths for 1,3-dicyanobicyclo[1.1.0]butane in angstroms.

TABLE III
INTRAMOLECULAR ANGLES BETWEEN ATOMS OF 1,3-DICYANOBICYCLO[1.1.0]BUTANE

N-1-C-2-C-3	178.8 (3)
C-2-C-3-C-4	127.1 (3)
C-2-C-3-C-3′	124.6 (3)
C-2-C-3-C-4′	127.8 (3)
C-3-C-4-H-5	115.9 (14)
C-3-C-4-H-6	112.3 (12)
C-3-C-4-C-3′	60.9 (2)
C-4-C-3-C-3′	59.6 (2)
C-3-C-3′-C-4	59.5 (2)
C-4-C-3-C-4′	100.6 (3)
C-3-C-4′-H-5′	116.4 (14)
C-3-C-4′-H-6′	117.7 (12)
H-5-C-4-H-6	113.7 (15)

by the two three-membered carbon rings. The X-ray diffraction results of 126.4 ± 0.4° is larger than the values previously found, which ranged from 120.2° to 126°.[1-6] Perhaps the substitution of a nitrile group for hydrogen affects this dihedral angle.

In a survey of previous information on the structure of bicyclobutane, the largest discrepancy occurs in the C–C–H angle corresponding to C_3'–C_3–C_2 of dinitrile bicyclobutane where C_2 is substituted for H. The C–C–C angle found in this paper is 124.6 ± 0.2°, which is in moderate agreement with the microwave spectra[2,3] result of 130° 22′, the nmr spectra[5,6] result of 128.0°, and the electron diffraction result[4] of 125.5°. In contrast, the infrared work[1] placed this angle (CCH) as 163 ± 3°. They do state that the moments of inertia are rather insensitive to this angle.

There are no anomalous intermolecular contacts in this structure. Two interesting intramolecular contacts are the H_5–H_5' distance of 2.42 (5) Å and the C_2–C_2' distance of 3.118 (5) Å. The hydrogen atom repulsions appear to be of little importance because twice the van der Waals radius of hydrogen is about 2.4 Å. However, the C_2–C_2' repulsions may affect the geometry of the bicyclobutane moiety of this compound.

Two review articles on bicyclobutane describe the chemistry of these compounds in detail.[8,9] A model for the electronic structure has been proposed,[10] but, at the time of these calculations, only an inexact knowledge of the structure of bicyclobutane was known. More recently, calculations of the valence electron density distribution[11] and the first excited state charge density[12] have been made for bicyclobutane.

Registry No.—1,3-Dicyanobicyclo[1.1.0]butane, 27184-67-4.

(8) K. B. Wiberg, *Rec. Chem. Progr.*, **26**, 143 (1965).
(9) K. B. Wiberg, G. M. Lampman, R. P. Ciula, D. L. Conner, P. Schertler, and J. Lavanish, *Tetrahedron*, **21**, 2749 (1965).
(10) M. Pomerantz and E. W. Abrahamson, *J. Amer. Chem. Soc.*, **88**, 3970 (1966).
(11) O. Martensson, *Acta Chem. Scand.*, **24**, 3123 (1970).
(12) O. Martensson, *ibid.*, **25**, 3196 (1971).

Buffered Permanganate Reactions. Effect of Calcium on the Rate of Disproportionation of Manganate(VI)

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The pronounced influence pH exerts on the kinetic course of many permanganate oxidations is well recognized.[1] This effect is rarely related to variations in oxidation potential, but can be usually explained by mechanistic factors, such as ionization of the substrate or protonation of permanganate, for example. Furthermore, permanganate oxidations tend to give rise to simultaneous operation of several mechanisms and, consequently, to the formation of multiple reaction products under unfavorable reaction conditions.

Control of pH by employment of suitable buffer systems is a common method for manipulation of yields and product ratios in the application of oxidations to organic synthesis. A typical example is the neutral oxidation of certain organic substrates in Mg^{2+}-ion buffered systems, in which the equilibrium concentration of OH^- ions in solution is limited by the solubility of magnesium hydroxide.[2]

$$Mg^{2+} + 2OH^- \longrightarrow Mg(OH)_2\,(s) \qquad (1)$$

Permanganate oxidations of organic compounds often proceed at faster rates in alkaline than in neutral solutions. In many such instances the observed rate enhancement is associated with an increasing degree of substrate ionization. The reaction pattern of alkaline permanganate oxidations is, however, usually highly complex in view of the different pathways by

(1) R. Stewart, "Oxidation in Organic Chemistry," Part A, Academic Press, New York, N. Y., 1965, Chapter 1, pp 2–25.
(2) S. G. Powell, *J. Amer. Chem. Soc.*, **45**, 2707 (1923).

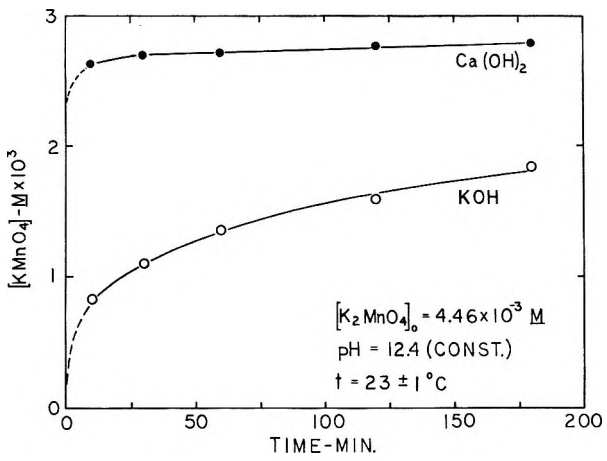

Figure 1.—Rate of potassium manganate(VI) disproportionation in the presence of calcium and potassium hydroxide at pH 12.4 and at 23 ± 1°.

which permanganate ion may be reduced to its final end products.

Organic substrates, which reduce alkaline permanganate directly beyond manganate(VI) (eq 2) have

$$MnO_4^- + e \longrightarrow MnO_4^{2-} \quad (2)$$

not been reported,[3] and permanganate is known[1] to oxidize a vast number of compounds at a rate much faster than does manganate(VI). Thus, the full utilization of permanganate, as usually represented by a 3-equiv net reduction (eq 3) depends to a large extent

$$MnO_4^- + 3e + 4H^+ \longrightarrow MnO_2 + 2H_2O \quad (3)$$

on the rate of disproportionation of manganate(VI) yielding permanganate and manganese dioxide (eq 4).

$$3MnO_4^{2-} + 2H_2O \rightleftharpoons 2MnO_4^- + MnO_2 + 4OH^- \quad (4)$$

There is sufficient evidence for this reaction to be reversible, but much uncertainty remains with regard to kinetic parameters and the magnitude of the equilibrium constant.[1] This inconsistency is believed to stem from differences in the reactivity of manganese dioxide, since the numerical position of the disproportionation equilibrium is strongly affected by the direction of its approach.

The rate of manganate(VI) disproportionation is most strongly influenced by the hydroxide ion concentration and by temperature, among other factors. The reaction is immeasurably fast in acid and extremely slow in 3 *N* base. Decomposition of manganate(VI) yielding hypomanganate or manganate(V) (eq 5) has

$$MnO_4^{2-} + OH^- \longrightarrow MnO_4^{3-} + OH\cdot \quad (5)$$

been observed to occur in 8 *N* KOH solution.[1] Thus, an experimental examination of manganate(VI) disproportionation (eq 4) is limited to a narrow range of hydroxide ion concentrations only. Decomposition of permanganate (eq 6) is an additional factor complicating the study of alkaline systems containing manganate species. The reaction is strongly catalyzed by hydroxyl ions and by manganese dioxide, which is almost always present in these solutions. Low permanganate yields, as have been observed in certain alkaline oxidations, are in great part attributed to this decomposition reaction.[4]

$$4MnO_4^- + 4OH^- \longrightarrow 4MnO_4^{2-} + O_2 \quad (6)$$

We have observed a significant acceleration of the rate of manganate(VI) disproportionation in the presence of calcium. As shown in Figure 1 near stoichiometric disproportionation of manganate(VI) occurs in less than 10 min in calcium hydroxide, as compared to an exceedingly slow approach to equilibrium in a KOH system under otherwise identical conditions. The rate acceleration was found to increase with increasing concentration of calcium and to reach a limiting value under conditions (pH 12.4) corresponding to saturation with respect to solid calcium hydroxide ($K_{sp} = 5.5 \times 10^{-6}$).

Although an exhaustive interpretation of the role of calcium in the disproportionation of manganate(VI) requires further experimental exploration, the author tends to favor a mechanism involving the precipitation of highly reactive tetravalent species of manganese by Ca^{2+} ions. Some of the following observations related to the chemistry of this system are in support of this interpretation. (1) Attainment of the disproportion equilibrium is extremely slow when approached by reaction of inactive or precipitated forms of manganese dioxide with permanganate in basic solution. This indicates that only highly reactive species of manganese(IV) are capable of participating in the backward reaction. (2) Colloidal forms of hydrous manganese dioxide exhibit a strong sorption tendency for calcium ions with subsequent sol destabilization being observed.[5,6] Whether Ca^{2+}-ion interaction with tetravalent manganese operates *via* the mechanism of sorption and counterion destabilization or by the formation of an inactive calcium manganate(IV) is not presently understood. Apart from certain mechanistic implications, the calcium ion induced acceleration of the disproportionation of manganate(VI) is felt to be of immediate importance to synthetic applications of permanganate reactions, because of an associated net gain in permanganate yields. This effect has been experimentally verified in the oxidation of cyanide with permanganate.

In the range pH 12–14, cyanide is quantitatively oxidized to cyanate[7,8] (eq 7) with a concurrent 1-equiv net reduction of permanganate yielding manganate(VI). The reaction is quantitative in this pH range only and exhibits a nonstoichiometric pattern with a variety of reaction products being formed at lower pH regimes.

$$2MnO_4^- + CN^- + 2OH^- \longrightarrow 2MnO_4^{2-} + CNO^- + H_2O \quad (7)$$

A rapid and 3-equiv net reduction of permanganate was realized when conducting the reaction under conditions of saturation with respect to calcium hydroxide (eq 8). This result was found to be independent of an

$$2MnO_4^- + 3CN^- + H_2O \xrightarrow[\text{pH 12.4}]{Ca(OH)_2} 3CNO^- + 2MnO_2 + 2OH^- \quad (8)$$

(3) J. W. Ladbury, and C. F. Cullis, *Chem. Rev.*, **58**, 403 (1958).

(4) L. F. Fieser, and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, pp 942–952.

(5) H. S. Posselt, A. H. Reidies, and W. J. Weber, Jr., *J. Amer. Water Works Ass.*, **60**, 48, 1366 (1968).

(6) H. S. Posselt, F. J. Anderson, and W. J. Weber, Jr., *Environ. Sci. Technol.*, **2**, 1087 (1968).

(7) R. Stewart and R. van der Linden, *Can. J. Chem.*, **38**, 2237 (1960).

(8) T. Freund, *J. Inorg. Nucl. Chem.*, **15**, 371 (1960).

excess of calcium hydroxide, which tends to rule out the possibility of heterogeneous catalysis. While this favorable yield shift was demonstrated for cyanide oxidation only, a dependence of this effect on the nature of the substrate seems highly unlikely considering that manganate(VII) is usually the primary oxidant[1,3] in alkaline aqueous systems. In light of these evidences it becomes apparent that the reaction is of considerable interest to the field of organic synthesis.

It should further be noted that the observed effect is probably limited to calcium among the alkaline earth metals, because the higher members of this group (Sr^{2+}, Ba^{2+}) tend to form insoluble salts with the transient manganate(VI) ion.

Since the observed phenomena discussed in this paper promise to lead to more and deeper insights into the chemistry of oxyanions of manganese, the author hopes to encourage further investigations of these reactions.

Experimental Section

Potassium Manganate(VI).—Pure crystalline potassium manganate(VI) was prepared according to the method described by Scholder and Waterstradt[9] as follows. Powdered reagent grade potassium permanganate (20 g) was slowly added to a 1000-ml round flask containing a cold solution of 250 g of KOH in 250 ml of distilled water. The solution was heated to boiling for 20 min under a reflux condenser, which was attached to an absorption tube containing "Ascarite" to prevent back-diffusion of carbon dioxide. After cooling to ambient temperature and crystallization, the reaction product was separated by filtration through a Gooch filtering crucible of medium pore size. The following solutions were employed for further purification of the raw product: I, 50 ml of 40% KOH (filtered); II, 50 ml of CH_3OH and 5 g of KOH (filtered); III, 100 ml of CH_3OH and 3 g of KOH (filtered); IV, 50 ml of CH_3OH and 0.5 g of KOH (filtered); V, 100 ml of ethyl ether (water free). Solutions II–V were precooled to −15°. The crystals were first washed with 50 ml of I at room temperature, then with 50 ml of II, and finally with 40 ml of III, both at −15°. Further removal of adhering KOH was accomplished by resuspension and shaking of the crystals in 50 ml of III, followed by filtration and successive washing with 50 ml of IV, and four times each with 25 ml of ether (V). The temperature was kept below −10° during each of the latter operations. The crystals were then vacuum dried over P_2O_5 for a minimum period of 3 hr.

Differential spectrophotometric analysis at 526 and 603 mμ of a solution of a weighed amount of the product in 2 *N* KOH revealed a purity of 100 ± 0.2% as K_2MnO_4 with no detectable trace of permanganate present. The assay of K_2MnO_4 prepared by this method is usually in the order of 99.8%.

Disproportionation of K_2MnO_4 in Aqueous KOH.—A quantity of 0.44 g of K_2MnO_4 was dissolved under magnetic stirring in 500 ml of 0.025 *N* KOH, which was preadjusted to pH 12.4 employing a pH meter. Control of pH throughout the duration of the experiment was accomplished by addition of small increments of 0.5 *N* nitric acid delivered from a microburette and by simultaneous pH monitoring. The solution was kept agitated with a magnetic stirrer. The temperature was maintained at 23 ± 1°.

The reaction was arrested by addition of 5 ml of a saturated solution of $Ba(OH)_2$ to 20-ml aliquots followed by rapid mixing for 10 min in order to facilitate the agglomeration of manganese(IV) and barium manganate. After filtration of this mixture through a fine Gooch crucible, the concentration of permanganate in the filtrate was determined by spectrophotometric analysis[7] at 526 mμ, with appropriate volume corrections taken into account.

Disproportionation of K_2MnO_4 in Aqueous $Ca(OH)_2$.—The disproportionation reaction in systems saturated with calcium hydroxide was conducted under conditions identical with those described for aqueous KOH with the following exceptions.

K_2MnO_4 was dissolved in 500 ml of distilled water containing 1 g of $Ca(OH)_2$. The pH of this solution remained at a constant value of 12.4 without necessitating adjustments throughout the duration of the experiment.

Oxidation of Cyanide.—The alkaline oxidation of cyanide with permanganate was investigated under a variety of experimental conditions and over a wide range of reactant concentrations.[10] A description of the experimental details of those studies relevant to this paper is given below.

Standardized solutions of KCN and $KMnO_4$ were employed. The reaction was initiated by addition of permanganate solution to solutions saturated with $Ca(OH)_2$ and containing KCN under conditions of rapid mixing and at room temperature. Initial concentrations varied for cyanide and permanganate between 10^{-3} and 10^{-2} *M* and between 3×10^{-4} and 3×10^{-3} *M*, respectively. An excess of each individual reactant was applied in some of the cases. The stoichiometric relationship postulated for the reaction in the presence of calcium hydroxide was established during advanced stages and after completion of the reaction, usually no later than 30 min after initiation. Quenching of the reaction, *i.e.* reduction of excess permanganate to manganese dioxide, was accomplished by dropwise addition of hydrogen peroxide or manganese nitrate. Manganese dioxide was separated by filtration through membrane filters (220 mμ); its removal by this method was readily accomplished by virtue of its precipitation in the presence of calcium ions. The concentration of cyanide was determined argentometrically by the Liebig method,[8] whereas permanganate was measured spectrophotometrically[7] in those cases in which an excess of the oxidant had been applied.

Registry No.—K_2MnO_4, 10294-64-1; KOH, 1310-58-3; $Ca(OH)_2$, 1305-62-0; KCN, 151-50-8.

(9) R. Scholder, and H. Waterstradt, *Z. Anorg. Allg. Chem.* 172 (1954).

(10) Unpublished research, Carus Chemical Co., LaSalle, Ill.

Conversion of Hetacillin into Cephalexin

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In 1963 Morin and collaborators[1] showed that thermal treatment of esters of penicillin V sulfoxide in acidic media gave rise to the corresponding esters of 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylic acid.[2] Later, when cephalexin[3] was shown to be of commercial importance, Chauvette and coworkers[4] reported the synthesis of cephalexin in a multistep sequence from penicillin V sulfoxide ester. We wish to report the synthesis of cephalexin from commercial hetacillin[5] by a four-step series of reactions. Hetacillin (**1**) was nitrosated[6,7] to block its secondary amino function and subsequently oxidized to the sulfoxide **3** with sodium metaperiodate.[8] The sulfoxide **3** was thermally rearranged as the free acid in the presence of *p*-toluenesulfonic acid to the cephalosporin derivative **4**, de-

(1) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, **85**, 1896 (1963); **91**, 1401 (1969).

(2) R. B. Morin, B. G. Jackson, E. H. Flynn, and R. W. Roeske, *ibid.*, **84**, 3400 (1962).

(3) C. W. Ryan, R. L. Simon, and E. M. Van Heyningen, *J. Med. Chem.*, **12**, 310 (1969).

(4) R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. Jose, I. G. Wright, E. M. Van Heyningen, and G. W. Huffman, *J. Org. Chem.*, **36**, 1259 (1971).

(5) G. A. Hardcastle, Jr., D. A. Johnson, C. A. Panetta, A. I. Scott, and S. A. Sutherland, *ibid.*, **31**, 897 (1966).

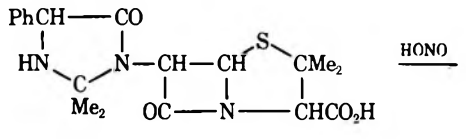
(6) P. Quitt, R. O. Studer, and K. Vogler, *Helv. Chim. Acta*, **47**, 166 (1964).

(7) F. H. C. Stewart, *Aust. J. Chem.*, **22**, 2451 (1969).

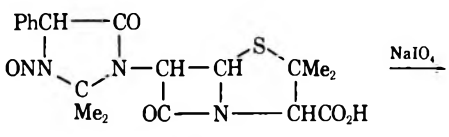
(8) J. M. Essery, K. Dadabo, W. J. Gottstein, A. Hallstrand, and L. C. Cheney, *J. Org. Chem.*, **30**, 4388 (1965).

nitrosated with dry hydrogen chloride, and hydrolyzed to cephalexin (6).

The nitrosation of hetacillin (1) proceeded readily in 70% yield to "nitrosohetacillin" (2). Oxidation of 2 to the sulfoxide 3 in 90% yield was attained with sodium metaperiodate. However, it was found that one main contaminant of 3 was its C_6 epimer. The production



1



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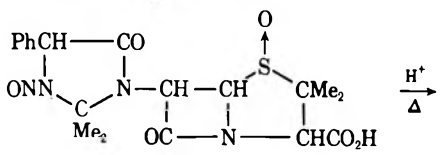

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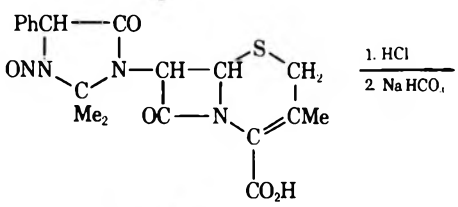

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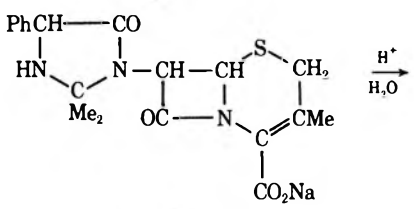

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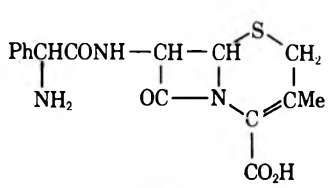

6

of this unwanted isomer was obviated by carefully controlling the acidity of the oxidation reaction. When the reaction mixture was kept at pH 5 or below, the α isomer was reduced to less than 5%. The sulfoxide 3 was thermally rearranged to 4, which was isolated as its *N,N'*-dibenzylethylenediammonium (DBED) salt. Conversion of this salt to "nitrosohetacephalexin" (4) afforded an average yield of 32%. The final denitrosation of 4 to "hetacephalexin" (5) was accomplished in yields averaging 60%. Hydrolysis of 5 afforded cephalexin (6) in 70% yield.

However, when cephalexin was the desired product, "nitrosohetacephalexin" (4) could be advantageously denitrosated and hydrolyzed without isolation of 5 to obtain cephalexin in a yield of 30%.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus, and are uncorrected. The ir spectra were recorded on a Beckman IR-9 spectrometer. The nmr spectra were run on a Varian A-60 spectrometer at a sweep width of 500 cps using dimethyl sulfoxide as a solvent. The authors wish to thank Mr. R. M. Downing and Miss Elizabeth A. Ragan for the microanalyses, and Mr. D. F. Whitehead and Mr. A. L. Vulcano for the spectral data.

6β-(D-2,2-Dimethyl-3-nitroso-5-oxo-4-phenyl-1-imidazolidinyl)penicillanic Acid (2).—To a suspension of 142 g (0.37 mol) of commercial hetacillin (1) in 2 l. of water at room temperature was added 69 g (0.41 mol) of sodium nitrite. The mixture was layered with 1.5 l. of ethyl acetate, and with vigorous stirring 6 *N* hydrochloric acid was added dropwise until both layers were clear (pH of aqueous layer 1.9). The addition took 15 min. Stirring was continued for an additional 15 min, and the ethyl acetate was separated, washed with water, and evaporated at 40° (15 mm). The crystalline solid was collected, washed with ether, and recrystallized from methanol–water to yield 110 g (71%): mp 195° dec; ir (KBr) 2800–3600 (carboxyl OH), 1803–1790 (β-lactam C=O), 1750 and 1730 (carboxyl C=O and imidazolidinyl C=O), 700 cm^{-1} (C_6H_5–); nmr (DMSO-d_6) δ 7.30 (s, 5, C_6H_5–), 5.64 (s, 1, C_6H_5CHN), 5.60 (d, 1, J = 4 cps, NCHCO), 5.45 (d, 1, J = 4 cps, NCHS), 4.35 (s, 1, $NCHCO_2$), 2.00 (s, 6, CH_3CH_3CN), 1.48 (s, 6, CH_3CH_3CS).

Anal. Calcd for $C_{19}H_{22}N_4O_5S$: C, 54.54; H, 5.30; N, 13.39. Found: C, 54.55; H, 5.58; N, 13.33.

6β-(D-2,2-Dimethyl-3-nitroso-5-oxo-4-phenyl-1-imidazolidinyl)penicillanic Acid Sulfoxide (3).—To a mixture of 110 g (0.263 mol) of 6β-(D-2,2-dimethyl-3-nitroso-5-oxo-4-phenyl-1-imidazolidinyl)penicillanic acid (2) in 2.5 l. of water was added with vigorous stirring 66 g (0.31 mol) of sodium metaperiodate. The solution was adjusted to pH 5 with 10% sodium hydroxide, and the mixture was stirred at room temperature for 3 hr with periodic adjustment of the pH. When the mixture became clear, the solution was stirred for an additional 1 hr. The final pH of this solution was 4.1. The sulfoxide was precipitated by addition of 40% H_3PO_4 to pH 2, collected, washed well with water, air dried to constant weight, and finally dried *in vacuo* over P_2O_5 to yield 103 g (91%) of white crystals. An analytical sample was obtained by recrystallization from dimethylformamide and water: mp 160° slow dec; ir (KBr) 3540 (hydrate OH), 2400–3400 (carboxyl OH), 1804 (β-lactam C=O), 1720–1750 (imidazolidinyl C=O and carboxyl C=O), 1050 (SO), 705 cm^{-1} (C_6H_5–); nmr (DMSO-d_6) δ 7.32 (s, 5, C_6H_5–), 5.77 (s, 1, C_6H_5CHN), 5.72 (d, 1, J = 4.5 cps, NCHCO), 4.83 (d, 1, J = 4.5 cps, NCHS), 4.30 (s, 1, $NCHCO_2$), 2.12 and 2.05 (2 s, 6, CH_3CH_3CN), 1.47 and 1.20 (2 s, 3, 3, CH_3CH_3CS).

Anal. Calcd for $C_{19}H_{22}N_4O_6S$: C, 52.52; H, 5.11; N, 12.92. Found: C, 52.66; H, 5.37; N, 13.45.

7β-(D-2,2-Dimethyl-3-nitroso-5-oxo-4-phenyl-1-imidazolidinyl)-3-methyl-3-cephem-4-carboxylic Acid (4).—A stirred solution of 10 g (0.022 mol) of 6β-(D-2,2-dimethyl-3-nitroso-5-oxo-4-phenyl-1-imidazolidinyl)penicillanic acid sulfoxide monohydrate (3) and 2.5 g of anhydrous *p*-toluenesulfonic acid (prepared by azeotropic drying of the monohydrate with ethyl acetate) in 250 ml of tetramethylurea was heated in a preheated bath at 135° for 2 hr. The solvent was removed at 40° (0.1 mm) to obtain an oil which was dissolved in 100 ml of ethyl acetate. The ethyl acetate solution was washed twice with 100-ml portions of water and extracted twice with 100 ml of saturated aqueous sodium bicarbonate solution (final pH 6.7). The aqueous layers were separated, combined, and stirred with 100 ml of ethyl acetate. The aqueous solution was adjusted to pH 2 with 40% H_3PO_4 and the organic extract was separated. The solution was extracted twice more with 100-ml portions of ethyl acetate and the extracts were combined and azeotroped to obtain an oil at 35° (15 mm). The residue was slurried with Skellysolve B and collected as a tan, amorphous powder which weighed 6.2 g. The solids were suspended in 80 ml of water, and saturated sodium bicarbonate solution was added until all the material dissolved (final pH 7.5). A solution of 4 g (0.011 mol) of *N,N'*-dibenzylethylenediammonium diacetate (DBED) in 75 ml of water was added, and the mixture was stirred for 0.5 hr with 150 ml of MIBK in a two-phase system. The mixture was stored at 25° for 5 days. The crystalline DBED salt of 4 was collected and washed with water and finally with acetone. After air drying the salt weighed 4 g: mp 150–152° dec; ir

(KBr) 3200–3600 (water OH), 2200–3200 (NH_2^+), 1770 (β-lactam C=O), 1730 (imidazolidinyl C=O), 1600 (COO^-), 760, 705 cm^{-1} (C_6H_5–); nmr (DMSO-d_6) δ 7.0–7.6 (m, 20, C_6H_5–), 5.3–6.0 (m, 15, NH_2^+, H_2O, NCHCO), 5.0 (d, 2, NCHS), 3.9 (s, 4, $C_6H_5CH_2N$), 2.6–3.4 (m, 8, $SCH_2C{=}C$, NCH_2CH_2N), 1.9 (s, 18, $CH_3C{=}C$, CH_3CH_2C).

Anal. Calcd for $C_{54}H_{60}N_{10}O_{10}S_2 \cdot 3H_2O$: C, 57.53; H, 5.90; N, 12.43. Found: C, 57.54; H, 6.21; N, 12.71.

The 4 g of the DBED salt of **4** was suspended in 75 ml of water, and 25 ml of 40% H_3PO_4 was added. The mixture was layered with 50 ml of ethyl acetate and shaken vigorously until all the salt dissolved. A final extraction was made with 50 ml of ethyl acetate and the organic layers were collected, washed with water, and evaporated at 40° (15 mm) to obtain a crystalline solid which weighed 2.95 g (32%), mp 175–180°. The ir and nmr spectra were identical with the spectra of authentic **4** prepared from cephalexin.

7β-(D-α-Aminophenylacetamido)-3-methyl-3-cephem-4-carboxylic Acid (Cephalexin) (6) *via* Hetacephalexin (5).—Into a solution of 1 g (0.0025 mol) of **4** in 50 ml of dioxane (purified by running through a column of aluminum oxide) was introduced a stream of dry hydrogen chloride for 5 min at room temperature. The solution was evaporated at 30° (15 mm) to a gum, which was slurried with ethyl acetate and collected. The solid was then dissolved in water (50 ml) and made basic with aqueous sodium bicarbonate solution to pH 4.8. The mixture was filtered, and the filtrate was evaporated at 30° (15 mm) to a glass which was further dried by azeotropic distillation with ethyl acetate. The yield of the sodium salt was 600 mg (63%). The nmr and ir spectra were consistent with the spectra of the acetone condensation product of cephalexin (**5**).

A solution of 1 g (0.0024 mol) of sodium hetacephalexin (**5**) in 5 ml of water was adjusted to pH 3.5 with 6 *N* hydrochloric acid and stirred at room temperature overnight while a stream of nitrogen was bubbled through the solution to remove the acetone formed during the reaction. The white crystalline cephalexin was collected, the filtrate was adjusted to pH 3.5 again and made up to a volume of 5 ml, and the procedure was repeated. The initial crop weighed 350 mg after drying *in vacuo* over P_2O_5. The second crop weighed 240 mg, giving a total yield of 590 mg (70%). The nmr and ir spectra were identical with those of authentic cephalexin.

Cephalexin (6) Prepared Directly from 4.—A solution of 2 g (0.0048 mol) of **4** in 100 ml of peroxide-free dioxane was treated with dry hydrogen chloride for 10 min at room temperature. The solution was evaporated at 35° (15 mm) to a gummy solid. The solid was dissolved in 10 ml of water and filtered, and the pH was raised to 4.5 by the addition of 10% sodium hydroxide solution. The solution was stirred for 48 hr at 30° while a stream of nitrogen was bubbled through the mixture. The white solid was collected and washed with cold water and finally with acetone to yield 550 mg (30%) of pure **6**.

7β-(D-2,2-Dimethyl-3-nitroso-5-oxo-4-phenyl-1-imidazolidinyl)-3-methyl-3-cephem-4-carboxylic Acid (4) from Cephalexin.—To a mixture of 10 g (0.03 mol) of (7-D-α-aminophenylacetamido)-3-methyl-3-cephem-4-carboxylic acid in 100 ml of water was added 10% sodium hydroxide solution until pH 7.8 was attained. To this solution was added 40 ml of acetone, and the reaction mixture was stored overnight. The solvent was evaporated, leaving behind a frothy, amorphous solid which was dissolved in 200 ml of water and acidified to pH 2 with 6 *N* hydrochloric acid, and layered with 200 ml of ethyl acetate. The solution was cooled in an ice bath to 5°, and 2.1 g (0.03 mol) of sodium nitrite was added. After stirring for 0.5 hr, the ethyl acetate was separated, washed with water, and evaporated under reduced pressure to an oil. The oil solidified on slurrying with ether to give 2.5 g of an amorphous solid. During storage overnight, a second crop separated, which was crystalline and weighed 1.2 g. The crops were combined and recrystallized from ethyl acetate and ether to obtain 3.2 g (26%). The analytical sample was recrystallized from boiling methanol: mp 175–180° dec; ir (KBr) 2500–3500 (carboxyl OH), 1780 (β-lactam C=O), 1720 and 1730 (imidazolidinyl C=O and carboxyl C=O), 700 cm^{-1} (C_6H_5–); nmr (DMSO-d_6) δ 7.31 (s, 5, C_6H_5), 5.68 (s, 1, C_6H_5CHN), 5.55 (d, 1, J = 4.5 cps, NCHCO), 5.15 (d, 1, J = 4.5 cps, NCHS), 2.9–3.6 (m, 2, SCH_2), 1.8–2.3 (m, 9, CH_3CH_2CN and $CH_3C{=}$).

Anal. Calcd for $C_{19}H_{20}N_4O_5S \cdot {}^1/_2H_2O$: C, 53.73; H, 4.74; N, 13.17. Found: C, 53.90; H, 4.96; N, 13.48.

6α-(D-2,2-Dimethyl-3-nitroso-5-oxo-4-phenyl-1-imidazolidinyl)-penicillanic Acid Sulfoxide (6 Epimer of 2).—To a solution of 20 g (0.048 mol) of **2** in 500 ml of water made basic to pH 9 by the addition of 10% sodium hydroxide was added 12 g (0.056 mol) of sodium metaperiodate. After stirring for 2 hr at pH 7, the solution was acidified to pH 2 with 40% H_3PO_4 and the crystalline solid was collected, washed with water, and dried *in vacuo* over P_2O_5 to yield 14 g (67%): mp 201° dec; ir (KBr) 2990 and 2950 (CH_3), 1795 (β-lactam C=O), 1735 (imidazolidinyl C=O and carboxyl C=O), 705 (monosubstituted phenyl); nmr ($CDCl_3$ and DMSO-d_6) δ 7.0–7.76 (m, 5, C_6H_5), 5.7 (d, J = 2 Hz, 1, C_6H), 5.6 (s, 1, C_6H_5CH), 4.9 (d, J = 2 Hz, 1, C_5H), 4.3 (s, 1, C_3H), 1.9–2.2 (m, CH_3CH_2CN), 1.65 and 1.3 (2 s, 3, 3, CH_3CH_2CS).

Anal. Calcd for $C_{19}H_{22}N_4O_6S \cdot 2H_2O$: C, 48.51; H, 5.57; N, 11.91. Found: C, 48.47; H, 5.23; N, 11.79.

Registry No.—**1**, 14537-96-3; **2**, 34959-70-1; **2** (6 epimer), 34959-71-2; **3**, 34982-12-2; **4**, 34959-72-3; **4** DBED salt, 34959-73-4; **6**, 15686-71-2.

Synthesis of Compounds Structurally Related to Poison Ivy Urushiol. V.[1a] A Novel Synthesis of 3-*n*-(1′,2′-Dehydro)pentadecylcatechol (3β-Alkylvinylcatechols) *via* Dehydration of a Bis(trimethylsilyl) Intermediate[1b]

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In connection with recent studies[1a] of the role of the side chain in the dermatological activity of 3-alkylcatechols, it became necessary to develop a practical synthesis of 3-*n*-(1′,2′-dehydro)pentadecylcatechol (**1a**), the styrenic analog of the saturated component of poison ivy urushiol, 3-*n*-pentadecylcatechol (3-PDC). A search of the literature revealed that no efficient synthesis of compounds of the general type, 3β-alkylvinylcatechol, had previously been reported.

While the dimethyl (**1b**) and dibenzyl (**1c**) ethers of **1a** can easily be prepared by conventional routes from, respectively, 2,3-dimethoxybenzaldehyde and 2,3-dibenzyloxybenzaldehyde,[2] neither **1b** nor **1c** can be converted to the free dihydroxybenzene derivative, **1a**.[3]

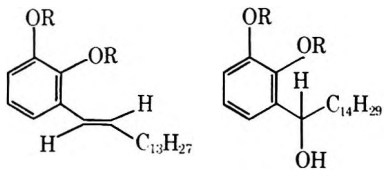
Exploratory experimentation confirmed the results of earlier studies in which it had been found that 3-*n*-

(1) (a) Previous paper in the series (IV): A. P. Kurtz and C. R. Dawson, *J. Med. Chem.*, **14**, 733 (1971). (b) These investigations were supported by Contract PH-43-64-76 with the Division of Biologics Standards of the National Institutes of Health. (c) National Institutes of Health Predoctoral Fellow, 1965–1968.

(2) (a) H. J. Backer and N. H. Haack, *Recl. Trav. Chim. Pays-Bas*, **57**, 225 (1938); (b) B. Loev and C. R. Dawson, *J. Amer. Chem. Soc.*, **78**, 6095 (1956).

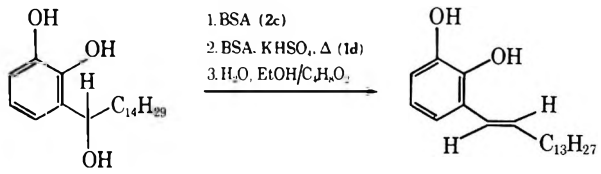
(3) Prior to the development of the synthetic route with which this report is concerned, a series of experiments were conducted testing methods of cleavage of **1b** and **1c** to **1a**. Use of a variety of agents, including $AlCl_3$–chlorobenzene, HBr–HOAc, pyridinium chloride, and others for the cleavage of **1b** gave high yields of polymer when conditions vigorous enough to effect cleavage were employed. Reductive cleavage of **1c** using either Na–1-butanol or hydrogenolysis (10% Pd/C) yielded only the saturated 3-PDC.

(1′-hydroxy)pentadecylcatechol (**2a**)[4] cannot be successfully dehydrated without extensive cyclization or polymerization.[5]



1a, R = H
b, R = CH_3
c, R = CH_2Ph
d, R = $Si(CH_3)_3$

2a, R = H
b, R = CH_2Ph
c, R = $Si(CH_3)_3$



2a **1a**

3-*n*-(1′,2′-Dehydro)pentadecylcatechol (**1a**) was successfully synthesized in the present investigation from **2a**[4] according to the route shown *via* the bis(trimethylsilyl) intermediates **2c** and **1d**. As reported in the Experimental Section, bis(trimethylsilyl)acetamide (BSA)[6] was used first as a reagent to form **2c**, an analog of **2a** having protected phenolic hydroxyl groups, and secondly as a water scavenger during the pyrolytic dehydration of **2c**. It is interesting to note that our mild silylation procedure did not effect etherification of the sterically hindered 1′-hydroxyl group in **2a** (see nmr data for **2c**). Use of BSA as a water scavenger apparently precludes *in situ* hydrolysis of the protecting TMS groups during the dehydration. Concomitant cyclization or polymerization is thus avoided. By this route **1d** was obtained from **2a** in an overall yield of 60%; both **2c** and **1d** were easily purified by fractional distillation. The bis(trimethylsilyl) compound, **1d**, was quantitatively hydrolyzed to the alkylvinylcatechol, **1a**, using aqueous ethanol–dioxane at 100° as given in the Experimental Section.

The success of this synthesis suggests its general applicability to the synthesis of 3β-alkylvinylcatechols, hitherto very elusive compounds.

Experimental Section

Precursors to 3-*n*-(1′,2′-Dehydro)pentadecylcatechol.—A sample of 8.0 g (0.024 mol) of 3-*n*-(1′-hydroxy)pentadecylcatechol (**2a**),[4] mp 90.0–91.0° (lit.[7] mp 89.6–90.5°), was dissolved in 100 ml of anhydrous benzene and stirred under a nitrogen blanket at room temperature. Over a 2-min period, 10.6 g of bis(trimethylsilyl)acetamide (BSA)[6] was added with ice bath cooling as necessary to maintain the temperature of the reaction near 50°. The resulting solution was stirred for about 20 min until the exothermic reaction was complete and allowed to stand under nitrogen for 18 hr. About 1 g of acetamide, mp 68–79°, was filtered off, and the filtrate was evaporated *in vacuo* using an 80° bath to give 17.08 g of a thick oil.

Part (7.25 g) of this oil was cleanly distilled *in vacuo* using a small Vigreux column to give a viscous oil, bis(trimethylsilyl)-3-*n*-(1′-hydroxy)pentadecylcatechol (**2c**): 4.5 g (93% yield); ir (neat) 2.86 (w, sharp), 2.8–3.0 (vw, broad), 3.45 (s, sharp), shoulder 3.53 (s, sharp), 6.29 (w), 6.78 (vs, broad), 7.36 (w, broad), 7.80 (m, broad), 8.01 (vs, sharp), 8.23 (m, broad), 9.0–9.5 (m, very broad), 9.8–10.5 (m, very broad), 10.9 (s, broad), 11.2–12.2 (vs, very broad), 13.0–13.7 (m, very broad); nmr (CCl_4) τ 2.83–3.55 (multiplet, 3 H, aromatic), 5.07 (center of poorly defined triplet, 1 H, benzylic), 7.57 (s, 1 H, hydroxyl), 8.0–9.5 (broad singlet and distorted triplet, 29 H, $C_{14}H_{29}$), 9.78 [center of jagged singlet, 18 H, bis-$Si(CH_3)_3$].

A sample of 8.0 g of the crude (not purified by distillation) **2c** was pipetted into a 125-ml erlenmeyer flask fitted with a gas inlet tube reaching to the bottom and to one side of the flask. While this material was flushed with bubbling nitrogen, 3.4 g of BSA and 0.5 g of powdered $KHSO_4$ were added. With agitation *via* the nitrogen bubbling, the contents of the flask were heated for 30 min using a 150–200° bath. The progress of the dehydration was monitored by observation of frothing and reflux of low-boiling materials. Following this pyrolysis period, 3.4 g further of BSA was added and the contents of the flask were heated for 10 min at 150°. The resulting clear, slightly yellow oil was transferred to a pointed flask and distilled *in vacuo* through a Vigreux column. Following collection of a low-boiling fraction including excess BSA, 2.99 g (60% yield from **2a**) of a clear, slightly yellow oil was obtained, bis(trimethylsilyl(-3-*n*-(1′,2′-dehydro)pentadecylcatechol (**1d**): bp 185–190° (0.1 mm); one spot on tlc analysis (extremely mobile); ir (neat) essentially identical with spectrum for **2c** except no OH bands in the present spectrum (2.86, 2.80, 3.0, 7.36, 9.0–9.5 μ bands absent); nmr (CCl_4) τ 2.8–3.2 (multiplet, 5 H, aromatic and vinyl), 7.4–8.0 (broad resonance, allylic), 8.0–9.3 (broad singlet and distorted triplet, $C_{12}H_{25}$), signals at τ 7.4–9.3 integrated for 27 H, 9.80 and 9.83 (two sharp singlets, 18 H, bis-TMS). A 10.3 μ band in the ir spectrum was diagnostic for predominance of the trans isomer.

3-*n*-(1′,2′-Dehydro)pentadecylcatechol (**1a**).—A sample of 3.18 g of **1d** was dissolved in 30 ml of dioxane containing 10 ml of 95% ethanol. The solution was brought to reflux under nitrogen with stirring. A total of about 15 ml of water was dripped in gradually over 2 hr at a rate slow enough so that the solution never became turbid. Water and ether were added, the phases were separated, and a conventional work-up was performed. A white solid was obtained, 1.95 g, which showed no TMS resonances in the nmr (quantitative hydrolysis). Recrystallization from ligroin gave pure **1a**: 1.75 g; mp 56.5–57.4°; ir (CCl_4) 2.76–3.26 (s, broad), 3.45 (s, sharp), shoulder (3.53 (sharp), 6.13 and 6.24 (pair of medium sharp peaks), 6.78 (vs, broad), 7.2–9.0 (broad band of multiple peaks), 9.35 (w, broad), 10.25 (vs, broad) (diagnostic for trans double bond); no detail in fingerprint region; nmr (CCl_4) τ 3.0–4.1 (multiplet, aromatic and vinyl), 4.29 (broad singlet, hydrolysis), signals at 3.0–4.5 integrated for 7 H, 7.60–8.15 (broad jagged resonance, 2 H, allylic), 8.73 (center of broad singlet, $C_{11}H_{22}$), 9.10 (center of distorted triplet, terminal methyl); signals at 7.6–9.2 integrated for 25 H.

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.12; H, 10.73.

Hydrogenation of **1d** gave bis(trimethylsilyl)-3-*n*-pentadecylcatechol, identical (spectra) with the product of the reaction between 3-PDC and BSA. The hydrogenation required exactly 1 equiv of hydrogen. Similarly, **1a** took up exactly 1 equiv of hydrogen over 10% Pd/C to give 3-PDC, identical in melting point (58–59°) (lit.[8] mp 59–60°) and spectra (ir and nmr) with an authentic sample.

Registry No.—**1a**, 34910-28-6; **1d**, 34910-29-7.

(4) The trihydroxy compound, **2a**, was obtained in the present investigation according to the method of Loev and Dawson (see ref 2b and the Ph.D. Dissertation of B. Loev, Columbia University, 1952). Quantitative hydrogenolysis of 2,3-dibenzyloxy(1′-hydroxy)pentadecylbenzene (**2b**), a precursor of **1c**, at 1 atm over 10% Pd/C gave **2a**. **2b** had been obtained in two steps in an overall yield of 58% from *o*-catechualdehyde according to the method given in ref 2b.

(5) Ortho-allyl and propenyl phenols are very susceptible to cyclization to form dihydrobenzofurans under the influence of heat and/or acidic catalysts. Such reactions are usually accompanied by formation of large amounts of polymer. See (a) D. S. Tarbell, *Chem. Rev.*, **27**, 287 (1940); (b) Q. R. Bartz, R. F. Miller, and R. Adams, *J. Amer. Chem. Soc.*, **57**, 371 (1935); (c) D. S. Tarbell, *Org. React.*, **2**, 1 (1944); (d) C. D. Hurd and L. Schmerling, *J. Amer. Chem. Soc.*, **59**, 107 (1937).

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Simplification of Epoxide and Lactone Proton Magnetic Resonance Spectra Using Tris(dipivalomethanato)europium Shift Reagent[1a]

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The observation by Hinckley[2] that the dipyridine adduct of tris(dipivalomethanato)europium, Eu(DPM)$_3$, caused paramagnetic shifts in the pmr spectrum of cholesterol was closely followed by the discovery that the unsolvated complex was a superior shift reagent.[3] Since then, many articles have appeared describing applications of Eu(DPM)$_3$ to structure determination.[4] While information concerning the extent of paramagnetic shifts for monofunctional compounds is important, data concerning the interactions of shift reagents with polyfunctional compounds are more useful for the structure determination of complex organic compounds. Several groups have reported studies in this area.[5-7] In most of these studies emphasis has been placed on compounds containing sites that complex unequally with Eu(DPM)$_3$. We wish to report our study of the effects of Eu(DPM)$_3$ on the pmr spectra of a series of lactones and epoxides which includes compounds containing two equivalent sites for complexation with Eu(DPM)$_3$. The study of lactones and epoxides is of interest because of their widespread natural occurrence and broad range of physiological activities.

Reference monofunctional compounds studied were 1,2-epoxyoctane (**1**), cyclohexene oxide (**2**), γ-butyrolactone (**3**), and 3aβ,4,5,6,7,7aα-hexahydro-2(3*H*)-benzofuranone (**4**). Difunctional compounds included were the epoxides 1,2,3,4-diepoxybutane (**5**) (isomer mixture) and 1,2,7,8-diepoxyoctane (**6**), and the lactones 4,5-dihydroxyoctanedioic acid bislactone (**7**) and 4,9-dihydroxydodecanedioic acid bislactone (**8**). Compound **1** was prepared from 1-octene by epoxidation with monoperphthalic acid.[8] Compounds **4**, **7**, and **8** were prepared from the corresponding epoxides by the method of Newman and VanderWerf.[9] Chart I summarizes pmr spectral data for representative epoxides and lactones in the presence of Eu(DPM)$_3$. Figure 1 shows the relationship between concentration of epoxide **6** and chemical shift at constant mole ratio of shift reagent to substrate.

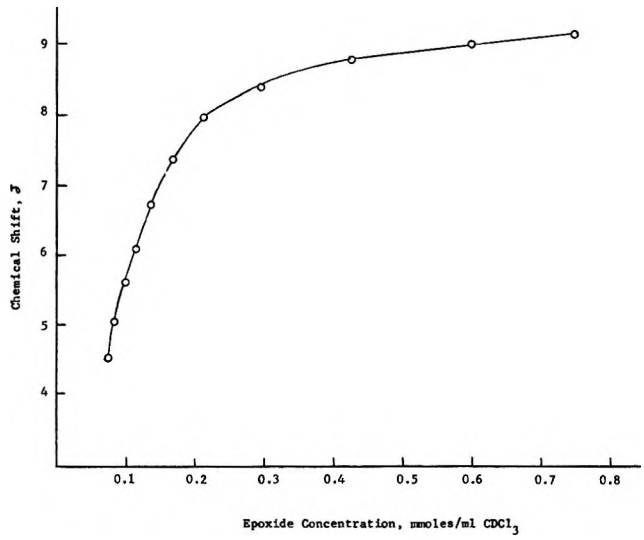
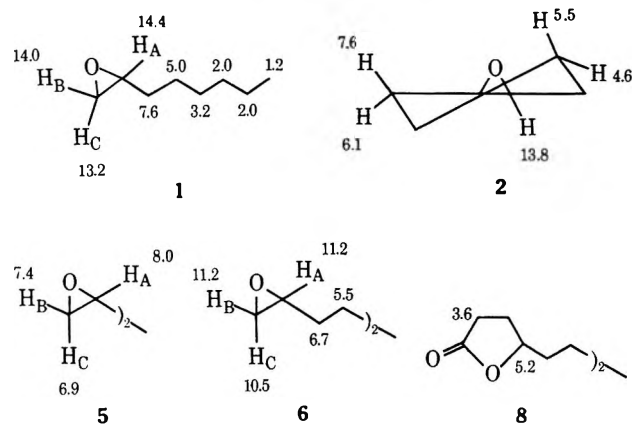


Figure 1.—Chemical shift of methine protons in epoxide **6** as a function of epoxide concentration; Eu(DPM)$_3$:epoxide = 0.5.

CHART I
THE PMR SPECTRA OF EPOXIDES AND LACTONES IN THE PRESENCE OF Eu(DPM)$_3$[a,b]



[a] Epoxide concentration was 1.25 mmol/ml CDCl$_3$; Eu(DPM)$_3$ content, **1**, 0.52 mmol; **2**, 0.19 mmol; **5**, 0.33 mmol; **6**, 0.74 mmol. [b] Lactone concentration was 0.66 mmol/ml CDCl$_3$; Eu(DPM)$_3$ content, 0.13 mmol.

Results and Discussion

Hart and Love[5] have reported the chemical shift of epoxide protons in cyclohexene oxide (**2**) and propylene oxide. Chart I gives more extensive data for **2** which showed sets of signals containing two protons each. The assignments presented were determined by assuming that protons farthest from the epoxide group would be least affected by shift reagent, and by extrapolating to zero Eu(DPM)$_3$ concentration the straight lines produced when the chemical shift of each signal was graphed against Eu(DPM)$_3$ concentration. The data reported[5] for propylene oxide indicated that signals corresponding to H_A and H_B were inseparable. We observed that the corresponding signals[10] in **1** and **5** were resolved while a single peak was still seen for these resonances in compound **6** at the limit of Eu(DPM)$_3$ solubility. The close proximity of the two epoxide groups in **5** could have accounted for the separation of resonances noted. It was expected that similar resolu-

(1) (a) This research was supported in part by Public Health Service Grant No. CA11715 from the National Cancer Institute. (b) David Ross Fellow, 1969–1971. (c) Abstracted in part from the thesis of B. K., 1969.

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(9) M. S. Newman and C. A. VanderWerf, *J. Amer. Chem. Soc.*, **67**, 233 (1945).

(10) 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 228.

tion could be obtained for **6** if the epoxide signals could be shifted beyond δ 11.7. While investigating the latter point we observed an apparently hitherto unreported effect of substrate concentration upon resolution of resonances.

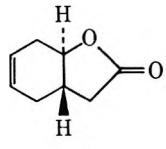
Published data concerning shift reagents has implied that barring effects due to line broadening the resolution of overlapping signals increases as the signals are shifted downfield. However, our data for epoxides **1** and **5** show that resolution of resonances H_A and H_B is achieved at lower chemical shifts when the epoxide concentration is high (1.25 mmol/ml $CDCl_3$) than when the epoxide concentration is low (0.13 mmol/ml $CDCl_3$) although the mole ratio of shift reagent to epoxide was larger (0.92 *vs.* 0.20) in the latter case. This information emphasizes that substrate concentration is as important a factor in the proper use of shift reagents as is the mole ratio of shift reagent to substrate.

Recently, Tomic and coworkers[11] showed that the magnitude of shift experienced by a given set of protons diminished with dilution. Variation over a wide concentration range could not be determined because only one dilution was measured. Compound **6** shows the same overall behavior (Figure 1) upon dilution, with the most pronounced changes occurring at low concentrations. The increased shift caused by dilution could be counterbalanced by adding more shift reagent. The shift observed in the usual experiment is the difference between the downfield shift produced by adding shift reagent and the upfield shift caused by dilution.

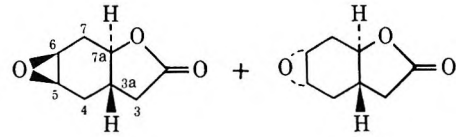
At the concentrations of epoxides and shift reagent used the chemical shift difference ($\Delta\delta = \delta_{Eu} - \delta_{CDCl_3}$) for a given proton varied in proportion to the amount of shift reagent per epoxide group. Thus, at the same concentration of epoxide and shift reagent $\Delta\delta$ for **1** was twice that measured for **6** (3.1 *vs.* 1.6). The same dependence was not seen for the lactones. The effect may be obscured by the much smaller shift experienced by the lactone protons (δ 1–2 at the concentrations studied) due to their weaker association with Eu(DPM)$_3$ compared with epoxides.

Without Eu(DPM)$_3$, only the protons on carbon adjacent to the lactone oxygen were resolved completely; the remaining signals were contained within a broad multiplet. Addition of Eu(DPM)$_3$ caused the signals for protons α to the carbonyl group to experience the greatest shift. These data agree with reports concerning the interaction of Eu(DPM)$_3$ with esters[5] and δ-valerolactones[12] that place the site of complexation at the carbonyl oxygen.

An interesting example of the use of Eu(DPM)$_3$ occurred in the analysis of the reaction products from the epoxidation of **9** with monoperphthalic acid. Column chromatography of the reaction mixture yielded an apparently homogeneous oil on the basis of tlc and spectral data. Elemental analysis established the molecular formula $C_8H_{10}O_3$. However, analysis of the pmr spectrum with Eu(DPM)$_3$ [1.25 mmol of **10**: 0.265 mmol of Eu(DPM)$_3$] showed that the product was a mixture of isomeric epoxylactones **10a** and **10b** in the ratio 6:4. The 7a protons were well resolved (5.4 and 6.6 ppm), and the signal farthest downfield was assigned to the 7a proton which is cis to the epoxide group in compound **10b**. The chemical shift of protons 5 and 6 in **10** is less than that noted for cyclohexene oxide (**2**) measured under comparable conditions. Thus, complexation is occurring at both the lactone and epoxide moieties. The pronounced effect of the epoxide group upon the 7a protons in **10** in the presence of Eu(DPM)$_3$ suggests that this group would be a valuable derivative for studying the structure and stereochemistry of cyclic olefins.



9



10a **10b**

Experimental Section[13]

Preparation of 3aβ,4,7,7aα-Tetrahydro-2(3*H*)-benzofuranone (9).—4,5-Epoxycyclohexene was treated according to the method of Newman and VanderWerf,[9] and gave a 43% yield of crude lactone. An analytical sample was prepared by column chromatography over silicic acid followed by sublimation [45–48° (20 mm)] to give white needles: mp 56.5–58°; nmr δ 5.63 (s, 2, CH=CH), 4.00 (s, 1, CHO), 2.21 (m, 7, CH_2, CH); ir ($CHCl_3$) 5.64 (C=O, γ-lactone), and 6.13 μ (C=C); mass spectrum *m/e* 138 (M^+).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.76; H, 7.31.

Preparation of 3aβ,4,5,6,7,7aα-Hexahydro-5,6-epoxy-2(3*H*)-benzofuranone (10).—To 2 g (0.015 mol) of 3aβ,4,7,7aα-tetrahydro-2(3*H*)-benzofuranone (**9**) was added dropwise with stirring 2.64 g (0.015 mol) of monoperphthalic acid in 23 ml of ethyl ether, and the solution was stirred in the dark at room temperature for 24 hr. A precipitate (1.5 g) of phthalic acid was removed by filtration, and the ether filtrate was mixed with solid potassium carbonate until effervescence ceased. The solution was dried (anhydrous sodium sulfate) and concentrated to give 1.35 g of a mixture containing (nmr) **9** and **10** in the ratio of 80:20. Purification was achieved by column chromatography (silicic acid). Elution with benzene removed **9**, and benzene–chloroform (1:1) removed 400 mg of **10** (18% yield). The sample was homogeneous by tlc, but resisted attempts to crystallize it: nmr δ 3.94 (broad s, 1, HCO, lactone), 3.26 (broad d, separation 4.5 Hz, epoxide), 2.21 (m, 7, CH_2, CH); mass spectrum *m/e* 154 (M^+).

Anal. Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 61.84; H, 6.84.

Data Relating to the Separation of Resonances for H_A and H_B in Compounds 1, 5, and 6.—Under conditions described in Chart I partial separation of resonances was achieved when signals were shifted to δ 10.6 in **1**, and 6.5 in **5**. At larger mole ratio (0.92), but lower epoxide concentration (0.13 mmol/ml $CDCl_3$), resolu-

(11) L. Tomic, Z. Majerski, M. Tomic, and D. E. Sunko, *Chem. Commun.*, 719 (1971).

(12) F. I. Carroll and J. T. Blackwell, *Tetrahedron Lett.*, 4173 (1970).

(13) All melting points are uncorrected. The infrared spectra were measured with a Perkin-Elmer 21 spectrophotometer. Mass spectra were obtained using a Hitachi RMU-6A spectrometer. Pmr spectra were determined at 60 MHz with a Varian A-60A or Jeolco Minimar (JNM-MH-60-II) spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to TMS internal standard. Chloroform-*d* was the solvent for pmr spectra. For studies of shift reagent the sample temperature was maintained at 28 ± 1°. The Eu(DPM)$_3$ content of the solution was increased gradually until the desired resolution was obtained. Solution compositions are expressed as the number of mmoles of Eu(DPM)$_3$ and epoxide added to 1 ml of $CDCl_3$. Unless otherwise noted the term "mole ratio" refers to the fraction Eu(DPM)$_3$/substrate. Physical data are recorded only for new compounds. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Compounds **2**, **3**, **5**, and **6** were obtained commercially, and were used without further purification.

tion was not obtained until the epoxide signals in **5** were shifted to δ 15.

Registry No.—**1**, 2984-50-1; **2**, 286-20-4; **5**, 1464-53-5; **6**, 2426-07-5; **9**, 34905-87-8; **10a**, 34905-88-9; **10b**, 34905-89-0; Eu(DPM)$_3$, 15522-71-1.

Photolysis of 2,6-Di-*tert*-butyl-4-alkylphenols with Polyhalomethanes

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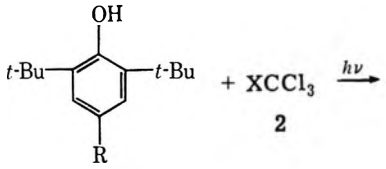
Received August 13, 1971

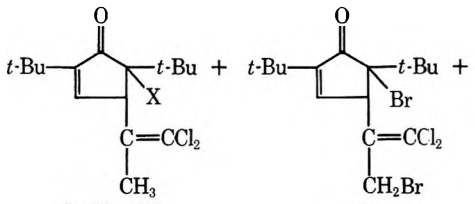
In recent years, a number of studies on photochemical reactions of sterically hindered phenols with various solvents have been published.[1] However, as yet there is little information on the photoreactions of such phenols with polyhalomethanes.

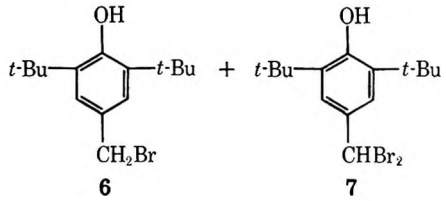
When solutions of 2,6-di-*tert*-butyl-*p*-cresol (**1a**) or 2,4,6-tri-*tert*-butylphenol (**1b**) in either carbon tetrachloride or bromotrichloromethane were irradiated with near-ultraviolet light, two types of photoproducts involving the addition of either a halogen atom or a trichloromethyl radical to the phenol were obtained. The product mixture obtained depended on the structure of the phenol, the solvent used, and, for **1a**, the wavelength of the light used.

The cyclopentenone **3** was the major product of the photolysis of **1a** in carbon tetrachloride when either 300- or 350-nm light was used. When irradiated with 300-nm light in bromotrichloromethane, **1a** gave about



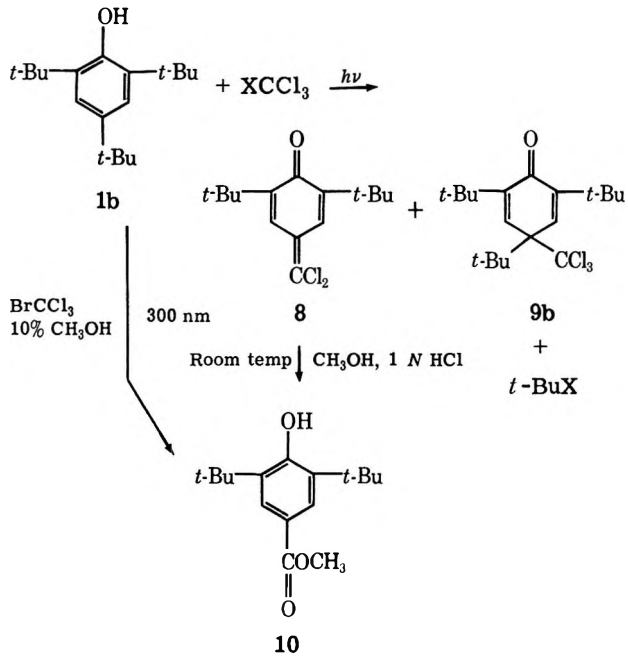
1a, R = CH_3
b, R = *t*-Bu





65 mol % of the cyclopentenones **4** and **5** along with 20 mol % of the α-brominated phenol **7**, but, when irradiated with 350-nm light, **1a** gave more of the α-brominated phenols **6** and **7** (40% total) than the cyclopentenone **4** (25%).

The photolysis of **1b** in either carbon tetrachloride or bromotrichloromethane gave the cyclohexadienones **8** and **9b** as well as a *tert*-butyl halide. The same products were obtained whether 300- or 350-nm light was used, but the use of 350-nm light resulted in a much lower conversion of **1b**. Moreover, **10** was produced either by irradiating **1b** in bromotrichloromethane containing 10% methanol or by stirring a mixture of **8** in methanol containing 1 *N* HCl at room temperature for 1 hr.



The thermal reaction of **1a** or **1b** with bromotrichloromethane at 160° in the dark gave only a low yield of chloroform and black tar. Neither 2,2′-azobis(2-methylpropionitrile) (AIBN) nor benzoyl peroxide increased the rate of reaction of **1a** or **1b** with bromotrichloromethane at 80° in the dark. These results, taken with the abilities of **1** and **2** to absorb light at 300 and 350 nm,[2] probably indicate that the excitation of phenol[3] and the rate of generation of a halogen atom and a trichloromethyl radical are the vital factors in the photochemical reactions of **1** with a halotrichloromethane. Therefore, a short-chain or nonchain radical mechanism, as shown in Scheme I, probably accounts for the first stage of these photolyses.

Since carbon tetrachloride does not absorb light in the 350-nm region, the photolyses of **1a** and **1b** in carbon tetrachloride were probably initiated by the excitation of phenol followed by an energy transfer to the carbon tetrachloride, which decomposed to give a chlorine atom and a trichloromethyl radical. These fragments subsequently reacted with phenol to form products. The mechanism shown in Scheme I is consistent with the relative rates of disappearance of **1a** and **1b**; **1a**, which

(1) (a) H. D. Becker, *J. Org. Chem.*, **32**, 2115 (1967); (b) T. H. Matsuura, Y. Hiromoto, A. Okada, and K. Ogura, *Tetrahedron Lett.*, 3727 (1970).

(2) The optical densities of **1** (0.335 *M* in CH_2Cl_2) and $XCCl_3$ in a quartz tube (i.d. 1.3 cm) are at 300 nm **1a** = 126, **1b** = 1.3, $BrCCl_3$ = 52, CCl_4 = 0.007; at 350 nm, **1a** = 3.0, **1b** = 1.1, $BrCCl_3$ = 0.7, CCl_4 = 0. The spectral distribution of an RPR 350-nm lamp ranges from 307 to 420 nm with the maximum emission at 350 nm.

(3) K. Omura and T. Matsuura, *Tetrahedron*, **26**, 255 (1970).

TABLE I
PHOTOLYSIS OF 2,6-DI-*tert*-BUTYL-*p*-CRESOL (1a)

Solvent	λ, nm	Phenol reacted, %	Products, %[a] 3[b]	4[b]	5[b]	6[b]	7[b,c]	$CHCl_3$[d]	*t*-BuBr[d]	*t*-BuCl[d]
$BrCCl_3$	300	90		30	35		20	45		
	350	80		25		30	10	60		
CCl_4	300	60	35					4		
	350	10	10							

[a] Based on the amount of phenol added. [b] Measured by nmr spectra. [c] Based on the amount of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde, hydrolysis product of 7. [d] Measured by glpc.

TABLE II
PHOTOLYSIS OF 2,4,6-TRI-*tert*-BUTYLPHENOL (1b)

Solvent	λ, nm	Phenol reacted, %	Products, %[a] 8[b]	9[b]	$CHCl_3$[c]	*t*-BuBr[c]	*t*-BuCl[c]
$BrCCl_3$	300	70	35	8	27	26	15
	350	5	trace	3	<1	11	11
CCl_4	300	40	10	25	5		10
	350	2	trace	trace	<1		1

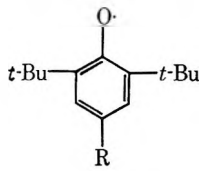
[a] Based on the amount of phenol added. [b] Measured by nmr spectra. [c] Measured by glpc.

SCHEME I

$XCCl_3 \xrightarrow{h\nu} X\cdot + Cl_3C\cdot$

or $1 \xrightarrow{h\nu} 1^*$

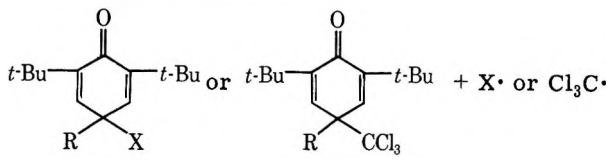
$1^* + XCCl_3 \longrightarrow$

HX or $HCCl_3 + X\cdot$ or $Cl_3C\cdot +$ 

11

$X\cdot + 1 \xrightarrow{k_1} HX + 11$ $\quad Cl_3C\cdot + 1 \xrightarrow{k_2} HCCl_3 + 11$

$11 + XCCl_3 \longrightarrow$

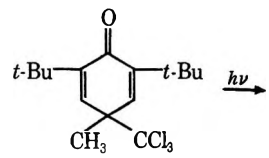


12a, R = CH_3 9a, R = CH_3
b, R = *t*-Bu b, R = *t*-Bu

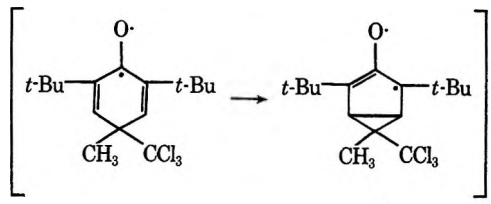
$11 + Cl_3C\cdot \longrightarrow 9$

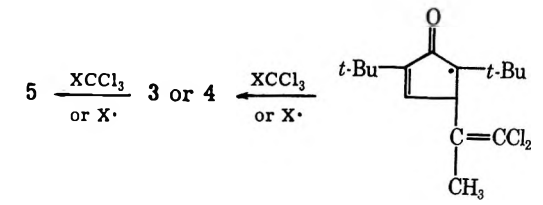
$11 + X\cdot \longrightarrow 12$

SCHEME II



9a





absorbs much more strongly at 350 nm than **1b**, reacted about five times faster with carbon tetrachloride than did **1b** (Tables I and II).

The order of hydrogen atom abstraction from hydrocarbons by the radical species involved in the reactions of Scheme I is known to be $Cl\cdot > Cl_3C\cdot \geq Br\cdot$;[4,5] hence, in carbon tetrachloride $k_1 > k_2$, and a little chloroform was formed. Both **1a** and **1b** would give a cyclohexadienone intermediate, **9a** and **9b**. The courses of the subsequent reactions depend on the nature of R. When R = CH_3 (**9a**), photorearrangement[6] of **9a** would give **3** or **4** and allylic bromination of **4** would give **5** (Scheme II).

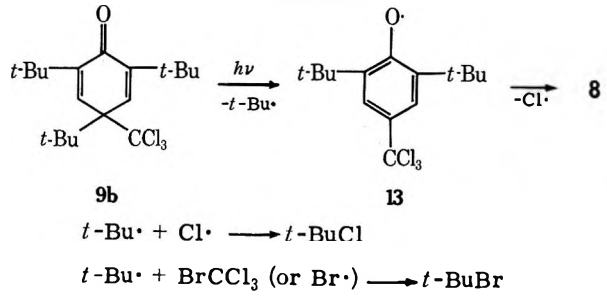
Because the *tert*-butyl group can be cleaved from an aromatic ring,[7] **9b** reacts further from a path different from that for **9a**. It reacts probably *via* expulsion of a *tert*-butyl radical to form a phenoxy radical **13** and subsequently to produce **8** (Scheme III).[8]

Neither **12a** nor **12b** was detected in any of the reaction mixtures, probably because both were photounstable. When **1a** was irradiated in bromotrichloromethane, **12a**, formed along with **9a**, rearranged[9] immediately to form the α-brominated phenols **6** and **7** (Scheme IV).

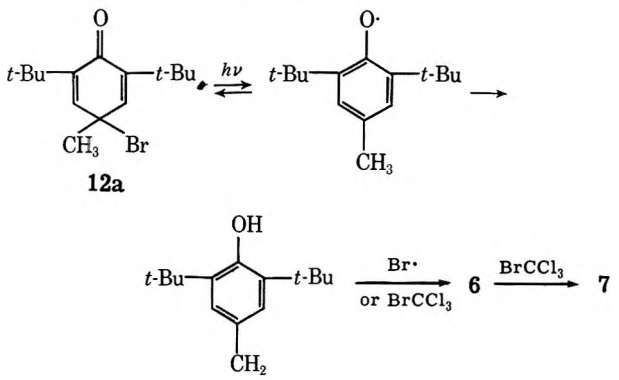
The structures of various photolytic products were deduced from spectroscopic measurements and elemental analyses. The maximum uv absorptions of compounds **3**, **4**, and **5** at 235, 236, and 237 nm, respectively,

(4) C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957, pp 48–50.
(5) J. M. Tedder, *Quart. Rev., Chem. Soc.*, **14**, 344 (1960).
(6) D. J. Patel and D. I. Schuster, *J. Amer. Chem. Soc.*, **90**, 5137 (1968).
(7) T. Matsurra and K. Ogura, *ibid.*, **89**, 3846 (1967).
(8) The acid-catalyzed expulsion of a *tert*-butyl group from **9b** by mixing **9b** with methanol containing 1 *N* HCl at room temperature for 20 hr failed to produce **10**, and only **9b** was recovered.
(9) V. D. Pokhodenko and N. N. Kalibabchu, *Zh. Org. Khim.*, **2**, 1397 (1966).

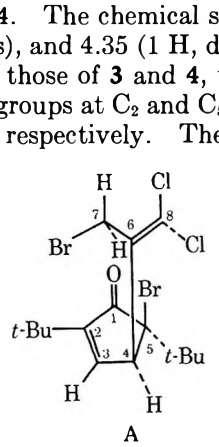
SCHEME III



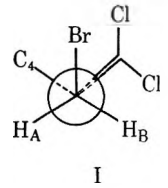
SCHEME IV



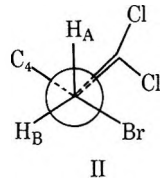
indicate a possible cyclopentenone structure.[10] In the infrared, **3** and **4** have nearly identical spectra with two major bands at 1710 and 1625 cm^{-1} (cyclopentenone carbonyl group and a dichloro-substituted double bond[6]). The nmr spectra (see Experimental Section) of **3** and **4** are also consistent with the assignment of the cyclopentenone structures. The infrared spectrum of **5** is not identical with the spectra of **3** or **4**, but it also shows strong bands at 1710 and 1630 cm^{-1}. However, the nmr spectrum of **5** gives three signals distinctively different from those of **3** and **4**. After investigations of the splittings and the coupling constants of those signals, it was concluded that **5** actually has a cyclopentenone structure similar to the cyclopentenone structures of **3** and **4**. The chemical shifts of δ 1.15 (9 H, s), 1.30 (9 H, s), and 4.35 (1 H, d, J = 3.0 Hz), which are similar to those of **3** and **4**, were assigned to the two *tert*-butyl groups at C_2 and C_5 and to the tertiary hydrogen at C_4, respectively. The two protons at C_7 are non-



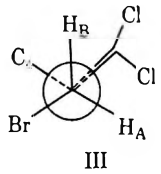
A



I



II



III

equivalent in the three rotomers (I–III); hence, the chemical shifts of δ 3.35 (1 H, J = 11.0 Hz) and 4.25 (1 H, J = 11.0 Hz) can reasonably be assigned to the methylene protons at C_7. The proton at δ 7.30 (1 H, J = 3.0 Hz) is believed to be adjacent to the proton at C_4; hence, it must be the vinyl proton at C_3 in structure A. Although the bromine atom at C_7 would not be expected to directly affect the chemical shift of the vinyl proton at C_3 through the σ bonds, the steric restriction in A would allow the bromine atom to be close enough to affect the vinyl proton at C_3 inductively through space; hence, the chemical shift of the vinyl proton at C_3 appears at a lower field (δ 7.30) in **5** than in **3** and **4**.

The structures of **8** and **9** are fully supported by their spectroscopic data and elemental analyses (see Experimental Section).

Experimental Section[11]

The photolytic reactions were carried out in a Rayonet reactor, Model RPR-100. The RPR 300- and 350-nm lamps were used as light sources without filters. All melting points are uncorrected and were measured with a Thomas-Hoover capillary melting point apparatus. The ultraviolet spectra were recorded on a Cary 14 spectrophotometer. The nmr spectra were determined with a Varian A-60 spectrophotometer with tetramethylsilane as an internal standard. The mass spectra were recorded on a Consolidated Electrodynamic 21-110B mass spectrometer.

General Photolysis Procedure.—A solution of 5 mmol of the desired phenol in 15 ml of polyhalomethane, contained in a quartz tube (i.d. 1.30 cm), was flushed with nitrogen for 5 min and then irradiated with either 300- or 350-nm light for 20 hr. A 1-ml aliquot was analyzed by glpc to determine the amount of volatile products, such as chloroform and *tert*-butyl halides, present. The solvent was removed, and the remainder was analyzed by nmr spectroscopy to determine the molar proportions of various products (Tables I and II).

2,5-Di-*tert*-butyl-5-chloro-4-(2,2-dichloro-1-methylvinyl)-2-cyclopenten-1-one (3).—After the irradiation of **1a** in carbon tetrachloride with 300-nm light, the solvent was removed from the reaction mixture, and the residue was dissolved in absolute ethanol. **3** was obtained after three recrystallizations from ethanol (0.42 g, 42%, white needles): mp 99–101°; ir (KBr) 1710 (cyclopentenone carbonyl group) and 1625 cm^{-1} (C=CCl_2); uv max (CH_2Cl_2) 235 nm (log ϵ 3.99); mass spectrum m/e 336 (M^+ with three chlorines); nmr ($CDCl_3$) δ 1.10 (9 H, s, *t*-Bu), 1.20 (9 H, s, *t*-Bu), 1.60 (3 H, s, CH_3), 4.30 (1 H, d, J = 3.0 Hz, *t*-H), and 6.85 (1 H, d, J = 3.0 Hz, vinyl proton).

Anal. Calcd for $C_{16}H_{23}Cl_3O$ (337.38): C, 56.91; H, 6.82; Cl, 31.53. Found: C, 57.00; H, 6.82; Cl, 31.25.

5-Bromo-2,5-di-*tert*-butyl-4-(2,2-dichloro-1-methylvinyl)-2-cyclopenten-1-one (4).—After the irradiation of **1a** in bromotrichloromethane with 350-nm light, the solvent was removed from the reaction mixture, and the residue was recrystallized three times from ethanol to give **4** as white needles (0.35 g, 23%): mp 126–128°; ir (KBr) 1710 (cyclopentenone carbonyl group) and 1625 cm^{-1} (C=CCl_2); uv max (CH_2Cl_2) 236 nm (log ϵ 3.95); nmr ($CDCl_3$) δ 1.10 (9, H, s, *t*-Bu), 1.20 (9 H, s, *t*-Bu), 1.60 (3 H, s, CH_3), 4.25 (1 H, d, J = 3.0 Hz, *t*-H), and 6.85 (1 H, d, J = 3.0 Hz, vinyl proton).

Anal. Calcd for $C_{16}H_{23}BrCl_2O$ (381.73): C, 50.28; H, 6.02; Br, 20.93; Cl, 18.57. Found: C, 49.95; H, 5.99; Br, 21.01; Cl, 18.72.

The residue which remained after evaporation of the combined filtrates from the recrystallizations of **4** was dissolved in 10 ml of petroleum ether (bp 30–60°) and eluted through a silica gel column (0.05–0.20 mm, 35.0 × 2.5 cm) with additional petroleum ether. The first 50-ml portion of eluate contained mostly **1a**. The second 50-ml portion contained about equal amounts of **1a** and **α-bromo-2,6-di-*tert*-butyl-*p*-cresol (6)**; the presence of **6** was shown by nmr analysis [δ 4.30 (2 H, CH_2Br) and 7.01 (2 H,

(10) R. L. Frank, R. Armstrong, J. Kwiatek, and H. A. Price, *J. Amer. Chem. Soc.*, **70**, 1379 (1948).

(11) The actual yields of various products are based on the actual amount of **1** reacted.

aromatic)], which was consistent with the nmr analysis of an authentic sample of 6.[12]

5-Bromo-2,5-di-*tert*-butyl-4-[1-(bromomethyl)-2,2-dichlorovinyl]-2-cyclopenten-1-one (5).—After the irradiation of **1a** in bromotrichloromethane with 300-nm light, the solvent was removed from the reaction mixture, and the residue was recrystallized five times from absolute ethanol to give **5** (0.28 g, 13.5%) as white needles: mp 180–182°; ir (KBr) 1710 (cyclopentenone carbonyl group) and 1630 cm^{-1} (C=CCl_2); uv max (CH_2Cl_2) 237 nm (log ϵ 4.18); mass spectrum *m/e* 460 (M^+ with two bromines and two chlorines); nmr ($CDCl_3$) δ 1.15 (9 H, s, *t*-Bu), 1.30 (9 H, s, *t*-Bu), 4.35 (1 H, d, J = 3.0 Hz, *t*-H), 7.30 (1 H, d, J = 3.0 Hz, vinyl proton), and 3.35 and 4.25 (2 H, 2 d, $J_{HA} = J_{HB}$ = 11.0 Hz, CH_AH_BBr).

Anal. Calcd for $C_{16}H_{22}Br_2Cl_2O$ (460.74): C, 41.67; H, 4.77; Br, 34.69; Cl, 15.39. Found: C, 41.78; H, 4.84; Br, 34.27; Cl, 15.43.

The residue which remained after evaporation of the combined filtrates from the recrystallizations of **5** was dissolved in 10 ml of petroleum ether and eluted through a silica gel column with additional petroleum ether. The first 20 ml of the petroleum ether fraction contained about 0.01 g of low-melting (35–45°) material, shown by its nmr spectrum to be a mixture of 10% of **1a** and about 90% of a second component. The following spectroscopic data are consistent with the assignment of the **2,5-di-*tert*-butyl-4-methyl-4-(trichloromethyl)-2,5-cyclohexadien-1-one (9a)** structure to the major component of this mixture: ir (neat) 1650 and 1670 cm^{-1} (double strong bands, cyclohexadienone carbonyl group[13]); nmr ($CDCl_3$) δ 1.25 (18 H, s, 2 *t*-Bu), 6.70 (2 H, s, two vinyl protons), and 1.62 (3 H, s, CH_3); mass spectrum *m/e* 336 (M^+ with three chlorines), major fragments at *m/e* (rel intensity) 219 (96), 189 (13), 177 (42), 163 (17), 57 (100), and 41 (37); an intense metastable peak was observed at an apparent mass of 143 which results from the transition of M^+ (336) → M_1^+ (219) + Cl_3C^+ (117). After the elution of the first 20-ml fraction, an additional 100 ml of petroleum ether was added to the column to remove the rest of **1a** and **12a**. Then 50 ml of methylene chloride was passed through the column. Evaporation of the methylene chloride gave a brown tar which was refluxed in 90% ethanol for 30 min. On cooling, white crystals were formed and were identified as **3,5-di-*tert*-butyl-4-hydroxybenzaldehyde** (0.11 g, 10.5%), mp 188–189° (lit.[14] mp 189°). The aldehyde was assumed to result from the hydrolysis of **7** with 90% ethanol.[15] The column was again eluted, this time with 50 ml of methanol, and 0.15 g (8.8%) of **4** was isolated.

2,6-Di-*tert*-butyl-4-(dichloromethylene)-2,5-cyclohexadien-1-one (8).—After the irradiation of **1b** in bromotrichloromethane with 300-nm light, the solvent was removed from the reaction mixture, and the residue was recrystallized five times from absolute ethanol to give **8** as light yellow leaflet crystals (0.30 g, 30%): mp 91–93°; ir (KBr) 1630 (C=O) and 1590 cm^{-1} (conjugated C=CCl_2); uv max (CH_2Cl_2) 323 nm (log ϵ 4.15); nmr ($CDCl_3$) δ 1.40 (18 H, s, 2 *t*-Bu) and 7.30 (2 H, s, two vinyl protons); mass spectrum *m/e* 286 (M^+ with two chlorines).

Anal. Calcd for $C_{15}H_{20}Cl_2O$ (286.91): C, 62.74; H, 6.97; Cl, 24.72. Found: C, 62.59; H, 6.92; Cl, 24.58.

A mixture of **8** in methanol containing 1 *N* HCl was stirred at room temperature for 1 hr. The white precipitate formed was identified as **methyl(3,5-di-*tert*-butyl-4-hydroxy)benzoate (10)**, mp 156–158° (lit.[16] mp 159°).

2,4,6-Tri-*tert*-butyl-4-(trichloromethyl)-2,5-cyclohexadien-1-one (9b).—After the irradiation of **1b** in carbon tetrachloride with 300-nm light, the solvent was removed from the reaction mixture, and the residue was recrystallized three times from absolute ethanol to give **9b** as white needles (0.32 g, 56%): mp 69–71; ir (KBr) 1660 and 1640 cm^{-1} (double strong bands, carbonyl group of cyclohexadienone[13]); uv max (CH_2Cl_2) 248 nm (log ϵ 3.95) and 322 (3.87); nmr ($CDCl_3$) δ 1.24 (9 H, s, *t*-Bu), 1.26 (18 H, s, 2 *t*-Bu), and 6.95 (2 H, s, two vinyl protons).

Anal. Calcd for $C_{19}H_{29}Cl_3O$ (379.38): C, 60.10; H, 7.64; Cl, 28.04. Found: C, 59.95; H, 7.65; Cl, 27.97.

Attempted Thermal Reaction of 2,6-Di-*tert*-butyl-4-alkylphenol with Bromotrichloromethane.—A mixture of 5 mmol of **1a** or **1b** and 15 ml of bromotrichloromethane was sealed in a Pyrex tube and heated at 160°. After 10 hr, the solution was dark brown, but no product, other than some chloroform which was identified by glpc, could be isolated, When a similar mixture was heated at 80° in the presence of either AIBN or benzoyl peroxide, no reaction occurred, even after 2 days.

(12) T. Fujisaki and T. Miyazaki, *Chem. Abstr.*, **35**, 11345*b* (1963).
(13) W. H. Pirkle and G. F. Koser, *J. Amer. Chem. Soc.*, **90**, 3598 (1968).
(14) T. W. Campbell and G. M. Coppinger, *ibid.*, **74**, 1469 (1952).
(15) L. K. Popov, F. M. Egidis, and V. V. Ershov, *Bull. Acad. Sci. USSR*, **4**, 863 (1968).
(16) A. Hausweiler, R. Seydel, and R. Stroh, *Chem. Abstr.*, **55**, 27217*h* (1961).

Registry No.—**1a**, 128-37-0; **1b**, 732-26-3; **3**, 34982-09-7; **4**, 34957-03-4; **5**, 34959-60-9; **8**, 34959-61-0; **9a**, 34959-62-1; **9b**, 34959-63-2.

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The Chemistry of Flavandiones. Reaction with Diazomethane[1a]

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Flavonols **1** are oxidized by periodic acid, 1 mol of oxidant being consumed.[2,3] When methanol is the solvent, the products are the methyl 3-hemiketals of 2-methoxy-3,4-flavandiones **2**.[4] Solutions of these hemiketals are an equilibrium mixture of **2** and the free dione, this being responsible for the solutions' yellow color.

When the hemiketals **2a–d** are mixed with an ethereal solution of diazomethane, they are converted to the epoxides **3**. This formulation is supported by elemental analysis, spectra, and chemical reactivity.

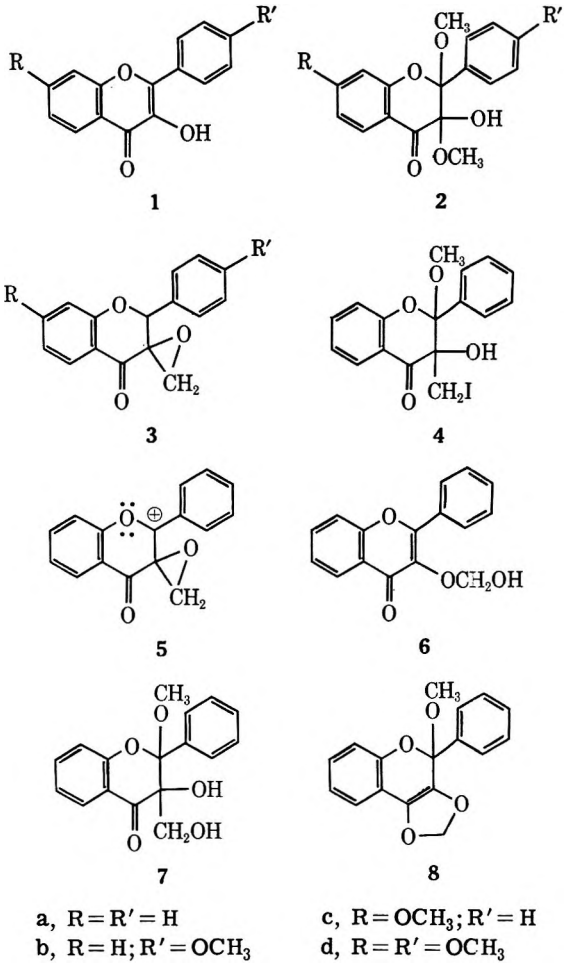
Before the advent of routine ir and nmr spectra, α-diketones were generally believed to form 1,3-dioxoles with diazomethane.[5] Later work by Eistert[6] established that these products were generally epoxides, although exceptions are known.[7] However, the products from diazomethane and **2a–d** all have strong bands in the carbonyl region and this renders a dioxole structure most unlikely.

With monoketones and diazomethane, epoxide formation competes with methylene insertion. This has been observed with α-diketones also. Diazomethane in ether converts phenanthraquinone into an epoxide, but, in the presence of much methanol, a ring-expanded product is found.[8] However, the spectral properties of the diazomethane products from **2a–d** are hardly consistent with those expected for any ring-expanded product. In our case, such a product could be either of a pair of α-diketones or a β-diketone. In the ketone form, any of these diketones would have two bands in

(1) (a) Supported in part by the National Institute of General Medical Sciences, National Institutes of Health, U. S. Public Service (Grant No. 11830). (b) National Science Foundation Undergraduate Research Participant, summer, 1966.
(2) M. A. Smith and B. R. Willeford, *Anal. Chem.*, **26**, 751 (1954).
(3) M. A. Smith, *J. Org. Chem.*, **28**, 933 (1963).
(4) M. A. Smith, R. A. Webb, and L. Cline, *ibid.*, **30**, 995 (1965).
(5) C. D. Gutsche, *Org. React.*, **8**, 364 (1954).
(6) B. Eistert, G. Fink, and R. Wollheim, *Chem. Ber.*, **91**, 2710 (1958).
(7) B. Eistert and L. Klein, *ibid.*, **101**, 391 (1968).
(8) B. Eistert, R. Wollheim, G. Fink, and H. Minas, and L. Klein, *ibid.*, **101**, 84 (1968).

the carbonyl region of the ir spectrum. This is not the case; only a single band is found. Were these α-diketones in an enolic form, a band should be detected in the hydroxyl region of the ir spectra, There are no bands above 3070 cm^{-1} in any of the spectra. Had these enols undergone methylation, this would have doubled the methoxyl analysis.

Therefore, it is clear that the ir spectra of these products are incompatible with both the dioxole and the ring-expanded structures. The ir spectra and the nmr spectra do fit the epoxy structures **3a–d**.



1 2 3 4 5 6 7 8

a, R = R′ = H
b, R = H; R′ = OCH_3
c, R = OCH_3; R′ = H
d, R = R′ = OCH_3

In the earlier work[4] on the flavandione 3-hemiketals **2**, the position of the hemiketal methoxyl was expected to be at C-3, the carbonyl band in the ir spectrum being assigned to a carbonyl at C-4. This was confirmed by measuring the position of the ν_{CO} band with and without a methoxyl at C-7, *i.e*, para to the C-4 carbonyl. A similar study on **3a–d** has established that the oxymethylene group is also at C-3. The relevant data are recorded in Table I. The ν_{CO} for **3c** and **3d**, the pair with methoxyls at C-7, is significantly lower than the ν_{CO} for **3a** and **3b**. A methoxyl group at C-7 would be expected to have a bathochromic effect on the band for a carbonyl at C-4.

TABLE I
CARBONYL STRETCHING FREQUENCIES OF THE EPOXIDES **3a–d**

Compd	ν_{CO}, cm^{-1} [a]
3a, R = R′ = H	1705
3b, R = H; R′ = OCH_3	1703
3c, R = OCH_3; R′ = H	1693
3d, R = R′ = OCH_3	1692

[a] Spectra recorded on a Perkin-Elmer 337 grating spectrophotometer, CCl_4 solution. Calibration was against the 1601-cm^{-1} line of polystyrene.

The epoxy structures **3a–d** receive additional support from the nmr spectra. A three-proton singlet near 3.2 ppm is common to all the spectra of **3a–d**. This is attributed to the 2-methoxyl group. This chemical shift is somewhat upfield from most methoxyl signals but it seems to be characteristic for 2-methoxyl groups in the flavandione compounds (see Table II).

TABLE II
NMR DATA (δ)[a]

	3a	**3b**	**3c**	**3d**
Epoxides				
Aryl[b]	7–8	6.8–8.1	6.5–8.0	6.6–8.0
Aryl OCH_3[d]		4.01	3.88	3.81, 3.88
2-OCH_3[d]	3.19	3.21	3.23	3.21
Oxymethylene[c]	2.62, 3.49	2.65, 3.48	2.61, 3.45	2.62, 3.44
	2a	**2b**	**2c**	**2d**
Flavandione Hemiketals				
Aryl[b]	7–8	7–8	6.6–8	6.6–8
COH[d]	4.73	4.74	4.87	4.78
Aryl OCH_3[d]		3.84	3.87	3.82, 3.85
2-OCH_3 Hemiketal OCH_3 [d]	2.94, 3.03	3.00, 3.07	2.97, 3.10	2.98, 3.07

[a] Varian A-60A, $CDCl_3$, in parts per million from TMS. [b] Complex multiplet. [c] Doublets (J = 6 Hz). [d] Singlets.

The aryl methoxyls of **3b–d** are unexceptional, giving rise to singlets between 3.8 and 3.9 ppm. The methylene protons of the epoxide ring are diastereiomeric. In all cases, these protons appear as a pair of doublets (J = 6 cps), one centered near 3.5 ppm, the other near 2.6.

Chemical evidence for the epoxide formula for **3a** is found in its facile conversion to an iodohydrin **4** by an acetic acid–potassium iodide mixture. The structure of **4** is amply supported by elemental analysis and spectra. Sodium methoxide reacts with **4** to regenerate the epoxide **3a**. The nmr spectrum of the iodohydrin **4** contained a nine-proton aryl multiplet between 6.9 and 7.9 ppm. The 2-methoxyl manifested itself as a singlet at 3.24 ppm, very near an OH singlet at 3.42 ppm. The diasteriomeric methylene protons appeared as a pair of AB doublets at 3.65 and 3.75 ppm (J = 22 cps). The direction of ring opening was as expected. The tertiary nature of the alcohol group in **4** was demonstrated when **4** gave a negative test with Bordwell's chromic acid reagent.[9]

We attempted to isomerize **3a** to an aldehyde with boron trifluoride. This well-known rearrangement[5] had been carried out by Eistert[6] on the epoxides of phenanthraquinone and benzil. In both cases the expected aldehyde was obtained. However, this reagent converts the epoxide **3a** into the corresponding flavonol. The same conversion is effected by aqueous acids. This transformation involves cleavage of the carbon–carbon bond of the epoxide.

(9) F. G. Bordwell and K. M. Wellman, *J. Chem. Educ.*, **39**, 318 (1962).

Several mechanisms can be envisaged to account for this transformation. Protonation of **3** followed by loss of methanol could lead to the carbonium ion **5**. Such a cation should be stabilized by the heterocyclic oxygen as well as the aromatic ring. An attack on the methylene group by water could cleave the carbon–carbon bond and lead to **6**, a hemiacetal of formaldehyde, which would then hydrolyze to flavonol **1**. Alternately, water could open the oxirane ring to the diol **7** which might then undergo fragmentation to flavonol **1**. A third possibility would be a rearrangement of **3** to a dioxole **8** followed by hydrolysis.

Experimental Section

Spectra.—Except for the data reported in Table I, all ir spectra were taken as Nujol mulls on a Perkin-Elmer Infracord. Model 137 (NaCl prism).[10] All nmr spectra were obtained in $CDCl_3$ using a Varian A-60A spectrometer.[10]

All melting points are uncorrected. Analyses were carried out by Schwarzkopf Microanalytical Laboratory.

Diazomethane.—This was prepared from *N,N'*-dimethyl-*N,N'*-dinitrosoterephthalamide (**8**) according to the procedure of Moore and Reed.[11] When running 1-g batches of the flavandione hemiketals **2a–d**, we used 7.2 g of the 70% suspension of **8** in mineral oil, adding this to 120 ml of ether, 18 ml of 2-(2'-ethoxyethoxy)ethanol, and 24 ml of 30% aqueous NaOH. This should produce about a tenfold excess of CH_2N_2. In practice the CH_2N_2–ether was distilled directly into a flask containing **2a–d** suspended in a little ether.

Flavonols (1a–d).—The flavonols **1a** and **1b** were prepared directly from o-hydroxyacetophenone and the corresponding benzaldehydes according to the procedure of Smith, Neuman and Webb.[12] This procedure is erratic for flavonols with methoxyls in the o-hydroxyacetophenone. However, alkaline hydrogen peroxide converts the corresponding 2'-hydroxychalcones into flavonols in yields of 40–50% using essentially the procedure of Algar and Flynn.[13] **1c** and **1d** were made this way.

2-Methoxy-3,4-flavandione Methyl 3-Hemiketals (2a–d).[10]—These were prepared as reported previously.[4] For nmr data, see Table II.

2-Methoxy-3,3-oxymethyleneflavanone (3a).—A 1.0-g sample of **2a** was treated with diazomethane at room temperature over night. The reaction was followed qualitatively by tlc on SiO_2 ($CHCl_3$), **2a** being much less mobile than the epoxide **3a**. Upon standing overnight **2a** had substantially disappeaerd. A trace of a second product was detected but not isolated. Evaporation of the filtered ether solution yielded a mixture of oil and solid. Crystallization from 15 ml of methanol afforded 0.58 g (62%) of **3a**, mp 133–134°.

Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00; OCH_3, 10.99. Found: C, 72.62; H, 5.19; OCH_3, 10.71.

2,4'-Dimethoxy-3,3-oxymethyleneflavanone (3b).—A 1-g sample, treated twice with diazomethane, yielded a tough residue upon evaporation of the solvent. This was crystallized from 20 ml of methanol to give 0.61 g (64%) of rodlike crystals, mp 138–139°.

Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16; OCH_3, 19.88. Found: C, 69.00; H, 5.16; OCH_3, 20.90.

2,7-Dimethoxy-3,3-oxymethyleneflavanone (3c).—A 1-g sample, treated twice with diazomethane, yielded a solid upon evaporation of the solvent. When recrystallized from 15 ml of MeOH, it afforded a 47% yield of white crystals melting at 135–137°. The analytical sample melted at 139–140° (MeOH).

Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16; OCH_3, 19.87. Found: C, 69.13; H, 5.26; OCH_3, 19.34.

2,4',7-Trimethoxy-3,3-oxymethyleneflavanone (3d).—A 1-g sample of **2d** was treated with two portions of diazomethane, tlc indicating incomplete reaction after the first one. Both the starting hemiketal **2d** and the product **3d** have limited solubility in ether. At the end of the second treatment, there was 400 mg of a solid which was **3d** mixed with some polymer. Evaporation of the filtrate from this yielded an oil–solid mixture. This mixture yielded 180 mg (21%) of crystalline **3d**, mp 185–187° from 40 ml of MeOH. The analytical sample melted at 187.5–189°.

Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.69; H, 5.30; OCH_3, 27.20. Found: C, 66.67; H, 5.38; OCH_3, 27.45.

3-Hydroxy-3-iodomethyl-2-methoxyflavanone (4).—A 500-mg sample of **3a** was rapidly converted to **4** in a hot mixture of 15 ml of acetic acid and 750 mg of KI. Tlc (SiO_2, $CHCl_3$) showed that reaction was complete in 10 min. The hot, brown solution was poured into 200 ml of water containing 1 g of sodium bisulfite. A formless solid separated. After drying, it was crystallized from 15 ml of petroleum ether (bp 60–110°), fine crystals separating. The yield of **4** was 450 mg (63%), mp 124–125°, nmr, see discussion. When treated with sodium methoxide in methanol, **4** was converted to the epoxide **3** in high yield.

Anal. Calcd for $C_{17}H_{15}O_4I$: C, 49.80; H, 3.79; I, 30.94. Found: C, 50.00, 50.87; H, 3.28, 3.67; I, 29.39, 30.3.

Conversion of Epoxide to Flavonol. With Boron Trifluoride Etherate.—**2a** (150 mg) was heated at 65° for 1 hr with a mixture of 20 ml of benzene and 2 ml of $BF_3 \cdot Et_2O$. The addition of 60 ml of ether afforded a copious precipitate of flavonol, 70 mg (47%), mp 168–170° (from MeOH).

With Sulfuric Acid.—**2a** (200 mg) was stirred with 40 ml of 50% H_2SO_4 for 1 hr at 100–120°. The resulting yellow solution was filtered through charcoal and diluted with 20 ml of water. After standing, the flavonol (**1a**) was collected by filtration, 120 mg (71%), mp 169°, ir identical with that of an authentic sample.

Registry No.—**1a**, 577-85-5; **2a**, 1603-46-9; **2b**, 1808-05-5; **2c**, 2047-54-3; **2d**, 1808-02-2; **3a**, 34917-93-6; **3b**, 34887-89-3; **3c**, 34887-90-6; **3d**, 34887-91-7; **4**, 34887-92-8; diazomethane, 334-88-3.

(10) The ir and nmr spectra of hemiketal **2a**, epoxide **3a**, and iodohydrin **4** will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-72-2774. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(11) J. A. Moore and D. E. Reed, *Org. Syn.*, **41**, 16 (1961).

(12) M. A. Smith, R. M. Neuman, and R. A. Webb, *J. Heterocycl. Chem.*, **5**, 425 (1968).

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2-Thiocyanobenzimidazoles. The Synthesis of 13*H*-[1,3,5]Thiadiazino[3,2-*a*:5,6-*a'*]-bisbenzimidazole-13-thiones

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We recently reported[1] that 2-thiocyanomethylbenzimidazoles (**1**) cyclized readily to yield 1-imino-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazoles (**2**). These results encouraged us to investigate the utility of 2-thiocyanobenzimidazole (**3**) for the synthesis of novel fused benzimidazole ring systems. Thus, it was hoped that the reaction of **3** with carbon disulfide in basic medium would furnish[2] A. However, the yellow crystalline product isolated in 86% yield from the reaction mixture (reaction time 5 min) showed no exchangeable proton (D_2O) in the nmr but exhibited only aromatic protons, with a one-proton multiplet significantly downfield from the remaining three protons. We have observed similar chemical shifts for 3,4-dihydropyrimido-

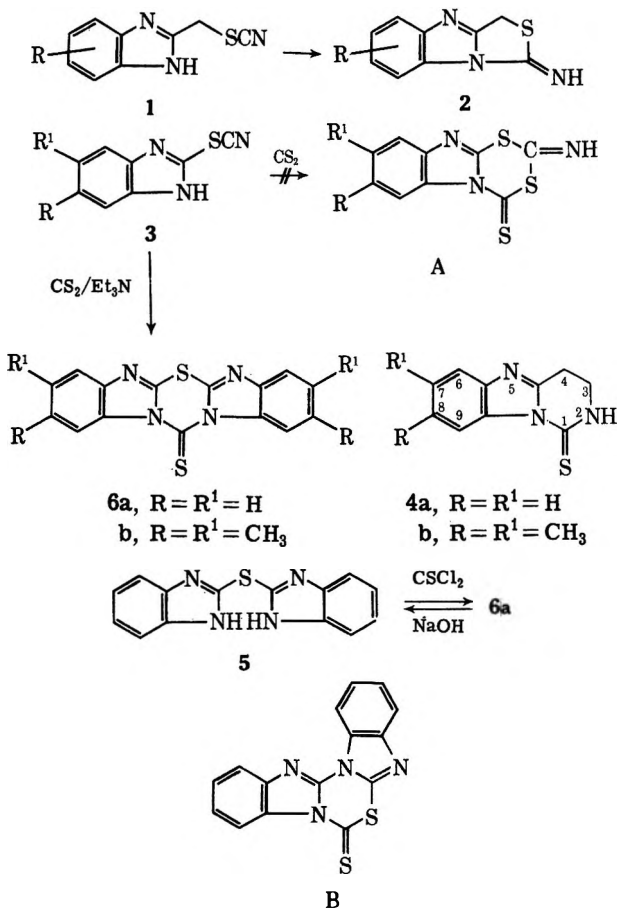
(1) R. D. Haugwitz, B. V. Maurer, and V. L. Narayanan, *Chem. Commun.*, 1100 (1971).

(2) (a) P. G. Sergeev, B. S. Kolychev, and V. S. Kolychev, *J. Gen. Chem. USSR*, **7**, 2863 (1937); *Chem. Abstr.*, **32**, 2940 (1937); (b) M. T. Bogert, *J. Amer. Chem. Soc.*, **25**, 289 (1903).

[3,4-*a*]benzimidazole-1(2*H*)-thiones (**4**) the most downfield signal, namely 9-H, being due to the deshielding effect of the thione function. The ir of the product was devoid of NH absorption but showed a band at 1500 cm^{-1} compatible with a S=CN< moiety. Its mass spectrum showed a molecular ion of M^+ 308 consistent with the formula $C_{15}H_8N_4S_2$, suggestive of two benzimidazole rings linked by CS_2 (structure **6a** or B). Whereas oxidative degradation of the reaction product resulted in ill-defined products and acid hydrolysis led to the recovery of starting material, mild base hydrolysis furnished a white solid which was subsequently identified as dibenzimidazol-2-yl sulfide[3] **5**, obtained by the alkylation of 2-mercaptobenzimidazole with 2-chlorobenzimidazole. Based on the above facts, we have assigned the pentacylic structure **6a** to the product. This was confirmed by synthesizing **6a** from **5** by the interaction of the sodium salt of **5** with thiophosgene.

We have extended this facile one-step synthesis of the pentacyclic system to the preparation of the tetramethyl analog **6b**.

Presently, we are investigating the scope of this interesting cyclization.



Experimental Section

Melting points were determined on a Thomas-Hoover "Uni-Melt" apparatus and are uncorrected. Ir spectra were determined in Nujol. Nmr spectra were obtained on a Varian A-60 instrument. Signals are described as singlet (s) or multiplet (m).

13*H*-[1,3,5]Thiadiazino[3,2-*a*:5,6-*a'*]bisbenzimidazole-13-thione (**6a**).—To a solution of 5 g of 2-thiocyanobenzimidazole in 20 ml of dimethyl sulfoxide, there was added at once 5 ml of carbon disulfide and 5 ml of triethylamine. A yellow solid, deposited after 1 min, was filtered off after 1 hr of standing. The solid was washed with ethanol to yield 3.6 g of **6a**. Two crystallizations from benzene–ethyl ether furnished the pure product: mp 184–185°; nmr ($CDCl_3$) δ 7.26–7.84 (m, 6 H, ArH), 8.93–9.09 (m, 2 H, 1-H, 11-H); mass spectrum *m/e* 308.0187 (M^+). *Anal.* Calcd for $C_{15}H_8N_4S_2$: C, 58.42; H, 2.62; N, 18.17; S, 20.80. Found: C, 58.42; H, 2.75; N, 18.50; S, 21.03.

2,3,9,10-Tetramethyl-13*H*-[1,3,5]thiadiazino[3,2-*a*:5,6-*a'*]bisbenzimidazole-13-thione (**6b**).—To a solution of 1.9 g of 2-thiocyano-5,6-dimethylbenzimidazole in 10 ml of dimethyl sulfoxide was added 2 ml of carbon disulfide and 2 ml of triethylamine. The mixture was allowed to stand at room temperature overnight. The yellow crystals were filtered off, washed with methanol, and crystallized from benzene to yield 0.8 g of **6b**. Recrystallization from benzene yielded the pure product, mp 338–340°, mass spectrum *m/e* 364.0856 (M^+). *Anal.* Calcd for $C_{19}H_{16}N_4S_2$: C, 62.61; H, 4.43; N, 15.37. Found: C, 62.74; H, 4.66; N, 15.46.

3,4-Dihydropyrimido[3,4-*a*]benzimidazole-1(2*H*)-thione (**4a**).—A mixture of 4.6 g of 2-(β-aminoethyl)benzimidazole, 30 ml of dimethyl sulfoxide, 4.6 ml of triethylamine, and 4.6 ml of carbon disulfide was stirred at room temperature for 14 hr. The product that separated upon diluting the reaction mixture with water was crystallized from acetone to yield **4a**: mp 212–213° (lit.[4] mp 216°); nmr (dimethyl sulfoxide-d_6) δ 3.13–3.83 (m, 4 H, $-CH_2-CH_2-$), 7.23–7.92 (m, 3 H, ArH), 8.82–9.02 (m, 1 H, 9-H).

7,8-Dimethyl-3,4-dihydropyrimido[3,4-*a*]benzimidazole-1(2*H*)-thione (**4b**).—A suspension of 6 g of 2-(β-aminoethyl)-5,6-dimethylbenzimidazole dihydrochloride, 6 ml of triethylamine, 6 ml of carbon disulfide, and 40 ml of dimethyl sulfoxide was stirred at room temperature overnight. Water was added and the crude product was filtered off. Crystallization from diglyme gave 3.5 g of pure **4b**: mp 232°, nmr (dimethyl sulfoxide-d_6) δ 2.34 (s, 6 H, CH_3), 2.98–3.78 (m, 4 H, $-CH_2CH_2-$), 7.38 (s, 1 H, 6-H), 8.57 (s, 1 H, 9-H), 10–10.53 (s, 1 H, NH). *Anal.* Calcd for $C_{12}H_{13}N_3S$: C, 62.30; H, 5.66; N, 18.17. Found: C, 61.95; H, 5.94; N, 18.45.

Hydrolysis of 13*H*-[1,3,5]Thiadiazino[3,2-*a*:5,6-*a'*]bisbenzimidazole-13-thione (**6a**).—A mixture of 0.4 g of **6a**, 8 ml of methanol and 2 ml of 10% NaOH was heated on the steam bath for 1 min. By this time, the compound has dissolved and had lost its yellow color. The cooled mixture was filtered and the filtrate was adjusted to pH 7 with 10% HCl. The precipitate was filtered off and dried to yield 0.35 g of crude sulfide **5**. Crystallization from ethanol yielded the pure product, mp 273–275°, the ir of which was identical with that of an authentic sample prepared by the method of Harrison and Ralph.[3]

Synthesis of 6a.—To a suspension of 0.15 g of the sulfide **5** in 20 ml of glyme, there was added 0.03 g of sodium hydride. After 2 hr of stirring at room temperature 0.05 ml of thiophosgene was added to the suspension and the stirring was continued for 2 hr. The mixture was evaporated and the product was extracted with benzene. Two crystallizations from benzene–ethyl ether furnished 0.05 g of **6a**, mp 180–182°, the ir of which was identical with that of the product obtained by the reaction of 2-thiocyanobenzimidazole with carbon disulfide.

Registry No.—**4b**, 34858-78-1; **5**, 2469-66-1; **6a**, 34858-80-5; **6b**, 34858-81-6.

(3) D. Harrison and J. T. Ralph, *J. Chem. Soc.*, 3132 (1965).

(4) K. Nagarajan, V. Rangh Rao, and A. Venkateswalcu, *Indian J. Chem.*, **8**, 126 (1970).

Quaternary Ammonium Salts and Betaines of Thionocarbamic Esters

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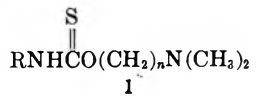
An earlier paper[1] described tertiary aminoalkyl esters of thionocarbamic acids (1) and their isomerism due to

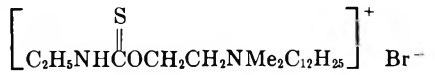
(1) R. A. Bauman, *J. Org. Chem.*, **32**, 4129 (1967).



1

restricted rotation about the N–C bond as revealed by nmr spectroscopy. The present paper is concerned with the behavior of quaternary ammonium salts of these tertiary amines. Examples of aliphatic thionocarbamate quaternaries prepared are **2** and **3** and of

2



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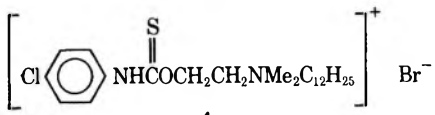
aromatic thionocarbamate quaternaries are **4** and **5**.



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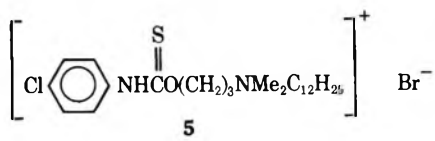

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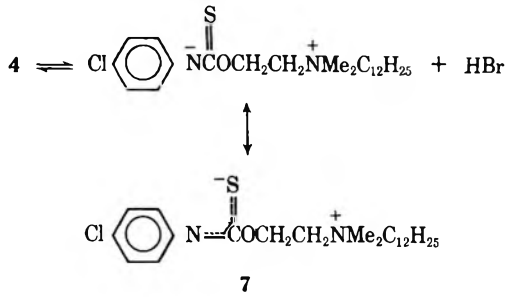
At room temperature an alkyl bromide reacts quantitatively with **1**; the sulfur atom is not attacked. This was shown by comparison of the nmr spectra of these products with those formed from the analogous carbamates where alkylation can occur only on the tertiary nitrogen. In both cases the methyl protons undergo upon quaternization a downfield shift of about 1 ppm and remain a singlet, which would not be the case for the hypothetical product **6** of S-alkylation.

6

Another feature of the nmr spectra (in chloroform-*d*) was a broadening of the signals, perhaps due to the viscosity of the solutions, which made difficult the detection of cis–trans isomerism, except for **2** where two unequal doublets for the carbamate CH_3 were discernible. The aromatic protons in **4** showed an assymmetric broadening, with the downfield pair being most affected.

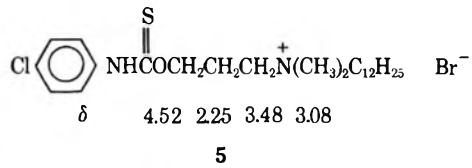
The carbamate proton in the quaternary salts showed a downfield shift of 1–2 ppm compared to the starting amines (measured on equimolar solutions at the same temperature). This appears to be due to a marked increase in the acidity of this proton. Indeed, for **4** this increase in acidity was enough to permit titration to a sharp end point with aqueous sodium hydroxide; **5** showed a shallower break at the end point. Why alkylation of the molecule at a position remote from the carbamate proton should affect the acidity might be explained by the preceding equilibrium, with the negative charge being stabilized both by delocalization and by the positive charge on the quaternary nitrogen. Proof for this hypothesis was obtained by the isolation of several betaines of this type.



7

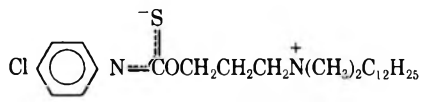
Treatment of compounds **4** and **5** with 1 equiv of methanolic sodium methoxide followed by solvent evaporation at room temperature and crystallization from acetone gave products with the correct elemental analyses, and ir spectra in which the NH absorption had disappeared and a strong characteristic band at 1365 cm^{-1} had been replaced by an equally strong band at about 1080 cm^{-1}. The fingerprint region of the spectrum of the inner salt was completely different from that of the normal quaternary salt.

The nmr spectra of **5** and its betaine **8** were compared in dimethyl sulfoxide. All protons in **8** showed an upfield shift from those in **5**.



δ 4.52 2.25 3.48 3.08

5



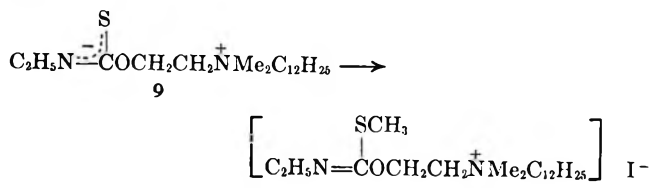
4.12 2.0 3.38 3.02

8

The aliphatic thionocarbamate quaternaries were also readily converted to the inner salts by sodium methoxide; however, these were not stable enough to be recrystallized for analysis. The betaine of **3** was obtained pure by an alternate method of preparation in which an aqueous solution of **3** was passed through a column of Dowex 1-X8 in the hydroxide form. This ordinarily would result in formation of a solution of a quaternary ammonium hydroxide, but here spontaneous crystallization occurred in the eluate to form the inner salt **9**, with an acceptable analysis and an ir spectrum related to that of betaine **7**.

Redissolved in water, **9** gave a strongly basic solution indicating formation of the quaternary hydroxide. Neutralization with 1 equiv of HCl or HBr gave the normal quaternary chloride or bromide. Treatment with HF also gave the quaternary fluoride, as deduced from the ir spectrum of partly dried material, but removal of the water under vacuum also removed HF, and the spectrum reverted to that of the inner salt **9**.

The betaine can be further alkylated at the sulfur atom. For example, **9** when treated with excess methyl iodide gave a single product characterized by elemental analysis, argentimetric titration, ir, and nmr spectroscopy as **10**; no N-alkylation product was found.



9

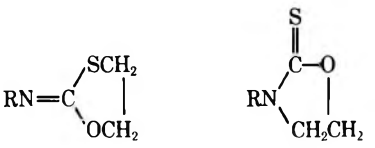
10

With the exception of **8** the betaines prepared are only moderately stable. In a melting point determination the betaine **7** melted sharply to two immiscible liquids. Also when refluxed in benzene for 1 hr it slowly dissolved, and, upon removal of the solvent, two liquid phases remained. The lighter of these was in both cases identified as dimethyldodecylamine. The other phase contained some of the amine as well as two other major products. Separated by their different solubilities in hexane and obtained as pure crystalline compounds, these were isomers of molecular weight 213 (mass spectrometry). The nmr spectrum of each showed a four-proton group typical of the para-substituted benzene ring and two two-proton groups coupled to each other (J = 7 Hz). The two isomers, referred to temporarily as A and B, had different chemical shifts, which are shown in Table I.

TABLE I
CHEMICAL SHIFTS OF THERMAL DEGRADATION PRODUCTS

Isomer	Methylene protons	Benzene protons	N-Alkyl protons
A (11)	3.38, 4.48	6.90, 7.26	
B (14)	4.20, 4.66	7.37, 7.54	
A′ (12)	3.40, 4.36		3.01
B′ (15)	3.84, 4.52		3.22
A″ (13)	3.42, 4.35		1.19, 3.17
B″ (16)	3.78, 4.56		1.24, 3.74

The two structures which conform to these spectra are as follows.



11, R = ClC_6H_4 **14**, R = ClC_6H_4
12, R = CH_3 **15**, R = CH_3
13, R = C_2H_5 **16**, R = C_2H_5

Compound A, the less retentive in both gas and thin layer chromatography, shows very strong absorption at 1640 cm^{-1}, which is interpreted as due to the C=N bond.[2] For compound B the 1640-cm^{-1} band is missing, and the principal absorption bands are very close to those reported for 3-phenyl-1,3-oxazolidine-2-thione.[3] The chemical shifts help establish the structures. It has been found[4] that there is a greater difference in chemical shift between the ortho and meta protons of *p*-chlorophenyl isothiocyanate (and isocyanate) than between the corresponding protons of *p*-chlorothionocarbanilic esters; thus one would expect the aromatic protons of structure **11** to have a greater chemical shift difference than those of **14**. Further, from the nmr data reported for related open-chain[1,5] and cyclic[6] compounds, it appears that resonances for methylene groups attached to O, N, and S occur at increasing field in accordance with their relative electronegativities. This, too, confirms the assignment of A as **11** and B as **14**.

Although the isomeric products from the betaines of **2** and **3** (A′ and B′, and A″ and B″, respectively, in Table I) were not separated on a preparative scale, they could be distinguished in an nmr spectrum of the mixture, and similarly identified from the chemical shifts as the 1,3-oxathiolane-2-imines (**12** and **13**) and the 1,3-oxazolidine-2-thiones (**15** and **16**).

The structural assignments in the aliphatic cases can be further verified by the use of benzene-induced shifts. All the protons of B′ show large positive solvent shifts (δ 0.4–0.9 downfield), whereas in A′ the methylene protons have similar large positive shifts (0.6), but the methyl protons a small shift of 0.05. Also, the methyl protons of B″ have a solvent shift of 0.4, whereas in A″ the shift is only 0.01. Past experience[7] with aromatic solvent-induced shifts of protons near double bonds would make it probable that the protons with the very small shift are located in front of a plane passed perpendicularly through the double-bonded carbon. This procedure identifies A′ as **12** and A″ as **13**.

The thermal decomposition products of the betaines probably represent the results of internal S- and N-alkylation, and thus provide justification for formulating the inner salts with a delocalized negative charge. Approximately the same ratio of products—30% oxazolidinethione **14** and 70% oxathiolane **11**—was obtained when the betaine of **4** was decomposed in benzene and in acetonitrile; for the betaine of **2** the proportions were 78% of **15** and 22% of **12**. This reaction did not occur on refluxing the betaine in methyl or ethyl alcohol, presumably because in protic solvents the compound exists as a normal quaternary ammonium hydroxide rather than as a betaine. The homologous quaternary salt **5** formed a betaine **8** which showed no tendency to eliminate dimethyldodecylamine in refluxing benzene, although one might have expected six-membered rings of structures analogous to **11** and **14**.

The stability of the betaines of the various quaternary salts seems to correlate with the shift in position of the strong infrared absorption band found about 1540 cm^{-1} in the spectra of all thionocarbamic esters examined[4] and recorded in Table II.

TABLE II
INFRARED BAND SHIFT[a] ON BETAINE FORMATION

Quaternary salt	Stability	Absorption band, cm^{-1} Bromide	Betaine	Δ
2	low	1546	1598	52
3	low	1530	1580	50
4	moderate	1522	1560	38
5	high	1534	1534	0

[a] Measured on Nujol mulls.

The synthetic implications of this work are interesting because methods for preparing these particular heterocycles are rare and few examples of the compounds themselves have been recorded. For 3-substituted oxazolidine-2-thiones there is the decomposi-

(2) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 267.
(3) T. Mukaiyama, I. Kuwajima, and K. Mizui, *J. Org. Chem.*, **31**, 32 (1966).
(4) R. A. Bauman, *J. Chem. Eng. Data*, **11**, 274 (1966).
(5) R. Radeglia, S. Scheithauer, and R. Mayer, *Z. Naturforsch. B*, **24**, 283 (1969).
(6) (a) J. L. Richards, D. S. Tarbell, and E. H. Hoffmeister, *Tetrahedron*, **24**, 6485 (1968); (b) F. N. Jones and S. Andreades, *J. Org. Chem.*, **34**, 3011 (1969); (c) K. Pihlaja, *Suomen Kemistilehti B*, **43**, 143 (1970); (d) G. E. Wilson, Jr., M. G. Huang, and F. A. Bovey *J. Amer. Chem Soc.*, **92**, 5907 (1970).
(7) J. D. Connolly and R. McCrindle, *Chem. Ind. (London)*, 379 (1965).

tion of *N*-(2-hydroxyethyl)dithiocarbamate salts,[3,8,9] and for 1,3-oxathiolane-2-ylideneamines there is the reaction of isocyanide dihalides with 2-mercaptoethanol.[10,11] It has been demonstrated here that in the decomposition of thionocarbamate betaines an aryl substituent on the carbamate nitrogen favors S-alkylation, whereas an alkyl substituent favors N-alkylation. We have not studied the possible influence of other solvents or reaction conditions on the product ratio nor the possibility that a preparative method for one or both of these heterocyclic systems might be developed.

Experimental Section

3-Dimethylaminopropyl *p*-Chlorothionocarbanilate.—Two grams of sodium was powdered in 25 ml of xylene. With stirring and warming 8.8 g of 3-dimethylamino-1-propanol was added. When the reaction was over in 3 hr, 13.9 g of *p*-chlorophenyl isothiocyanate was stirred in. After 15 min the stiff paste was diluted with 200 ml of water and acidified with HCl. The precipitate was separated, dried, and crystallized from alcohol (Nuchar) to give 16.5 g (66% of theory) of white crystals. An analytical sample was recrystallized from alcohol, mp 175.5–176°.

Anal. Calcd for $C_{12}H_{18}Cl_2N_2OS$: C, 46.60; H, 5.87; N, 9.06; neut equiv, 309.3. Found: C, 46.44; H, 5.94; N, 8.96; neut equiv, 310.1.

The free base was obtained by neutralization and recrystallization from benzene–hexane, mp 113–115°. The same method was used to prepare the previously reported 2-dimethylaminoethyl esters of methylthionocarbamic,[1] ethylthionocarbamic,[1] and *p*-chlorothionocarbanilic[4] acids.

Quaternary Ammonium Bromides.—Equimolar quantities of an aminoalkyl thionocarbamate and a 1-bromoalkane were mixed neat (for **3**) or in just sufficient acetone or acetonitrile (for **2**, **4**, **5**) for solubility, and were allowed to stand at room temperature for 1 week or longer to obtain substantially quantitative yields. The solidified reaction mixtures were recrystallized from ethyl acetate or acetone. Melting points for the compounds are given in Table III.

TABLE III[a]

MELTING POINTS FOR QUATERNARY AMMONIUM BROMIDES AND BETAINES

Compd	Formula	Mp, °C
2	$C_{20}H_{43}BrN_2OS$	73.5–77.0
3	$C_{19}H_{41}BrN_2OS$	94.0–95.5
4	$C_{23}H_{40}BrClN_2OS$	140.5–142.5
5	$C_{24}H_{42}BrClN_2OS$	150.0–151.0
7	$C_{23}H_{39}ClN_2OS$	116.5–117.0
8	$C_{24}H_{41}ClN_2OS$	157.0–158.0

[a] Satisfactory analytical data (0.4% for C, H, and N) were reported for all compounds. Ed.

Betaines.—The quaternary ammonium bromides **4** and **5** were treated in methanol with 1 equiv of sodium hydroxide or methoxide, and the solvent was removed under vacuum at room temperature. The products, **7** and **8**, were dissolved in acetone with the minimum heating time, filtered from sodium bromide, and allowed to crystallize. Melting points are given in Table III.

2-(Ethylthiocarbamoyloxy)ethyldodecyldimethylammonium Hydroxide Inner Salt (9).—A solution of 12 g of **3** in 200 ml of water was passed through a column packed with 60 g of Dowex 1 X-8 (50–100 mesh) ion exchange resin in OH^- form, collecting 600 ml of eluate at *ca.* 6 ml/min. Crystallization began spontaneously and was completed in the refrigerator. The solid (7 g) was recovered by filtration and washed with ether: mp 118–119° dec; ir (Nujol) 1580 (C=N), 1122, 1054 cm^{-1}.

Anal. Calcd for $C_{19}H_{40}N_2OS$: C, 66.22; H, 11.70; neut equiv, 344.6. Found: C, 66.39; H, 11.75; neut equiv, 344.2.

2-(*N*-Ethyl-*S*-methylisothiocarbamoyloxy)ethyldodecyldimethylammonium Iodide (10).—One gram (2.9 mmol) of **9** was allowed to stand with 1.2 ml (19 mmol) of methyl iodide for 64 hr. At this time the 1577- and 1054-cm^{-1} bands typical of **9** were missing from the infrared spectrum, and there was no absorption at 1545 cm^{-1} as expected of an N-methylated product. The pale yellow liquid solidified in ether to 1.4 g of white solid, which was recrystallized from 6 ml of ethyl acetate: mp 65–69°; ir (Nujol) 1634 (C=N), 1178 cm^{-1}; nmr ($CDCl_3$) δ 2.45 (SCH_3).

Anal. Calcd for $C_{20}H_{43}IN_2OS$: C, 49.37; H, 8.91; I, 26.08. Found: C, 49.11; H, 8.91; I, 26.17.

Thermal Decomposition of 7.—Two grams of the betaine **7** in 25 ml of benzene was refluxed for 1 hr and filtered from a trace of insoluble material. Evaporation of the solvent left two liquid layers, the lighter of which had an infrared spectrum identical with that of dodecyldimethylamine. The heavier liquid, when chromatographed on silica gel (Eastman chromagram plate) with ether, showed two components at R_f 0.6 and 0.8. This liquid was stirred overnight with 100 ml of hexane. The crystals present in the morning were washed with more hexane and dried to 290 mg; this was the component of R_f 0.6. Recrystallization from CCl_4 and benzene–hexane gave colorless prisms: mp 124–125.5°; ir (KBr) 1490, 1468, 1440, 1320, 1291, 1163, 821 cm^{-1}. The ir and nmr data (Table I) lead to assignment of the compound as **3-*p*-chlorophenyl-1,3-oxazolidine-2-thione (14)**.

Anal. Calcd for C_9H_8NOSCl: C, 50.59; H, 3.77. Found: C, 50.53; H, 3.78.

The hexane solution obtained above was evaporated to a viscous oil which was induced to crystallize. Recrystallization from hexane gave 350 mg of white needles: mp 68–69°; ir (KBr) 1640 (broad), 1480, 1113, 1022, 839 cm^{-1}. The spectroscopic data lead to formulation of the compound as **p-chloro-*N*-1,3-oxathiolane-2-ylideneaniline (11)**.[12]

Anal. Calcd for C_9H_8NOSCl: C, 50.59; H, 3.77. Found: C, 50.59; H, 3.91.

Thermal Decomposition of 2-(Methylthiocarbamoyloxy)ethyltetradecyldimethylammonium Hydroxide Inner Salt.—In 25 ml of 0.2 *N* sodium methoxide solution was dissolved 2.2 g (5 mmol) of **2**. The solution was evaporated under vacuum at 30° and the product (admixed with sodium bromide) was characterized as a betaine by its infrared spectrum as compared to that of **9**: ir (Nujol) 1598, 1134, 1075, 1058, 1045, 995, 920 cm^{-1}.

Benzene (25 ml) was added and the mixture was refluxed for 20 min and then filtered hot from sodium bromide. After flash evaporation two liquid phases remained, of which the lighter was tetradecyldimethylamine (ir identification). Sufficient benzene was added to obtain homogeneity, and the solution was then analyzed by gc (4 ft × 0.25 in. column of Apiezon L on Chromosorb W, 178°, thermoconductivity detector). Integration gave a product composition of 78% oxazolidinethione **15** and 22% oxathiolane **12** (nmr identification).

Decomposition of the betaine **9** gave results which were essentially similar, but under the gc conditions used there was a partial overlap of peaks due to dodecyldimethylamine and the oxazolidinethione **16**, so the isomer ratio could not be determined.

Registry No.—**2**, 34524-02-2; **3**, 34523-95-0; **4**, 34916-01-3; **5**, 34916-02-4; **7**, 34916-03-5; **8**, 34916-04-6; **9**, 34916-05-7; **10**, 34934-79-7; **11**, 34916-06-8; **14**, 34916-07-9; 3-dimethylaminopropyl *p*-chlorothiocarbanilate, 34916-08-0; 3-dimethylaminopropyl *p*-chlorothiocarbanilate hydrochloride, 34916-09-1.

Acknowledgments.—The author wishes to thank Messrs. Michael Camara for assistance in the syntheses, Gilbert Suarez for the nmr spectra, Karl Kellenbach for the infrared spectra, and E. Emery for the mass spectra.

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Solvolysis of 1-Bromomethyltriptycene. An Unusually Unreactive Bromide

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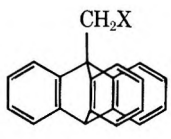
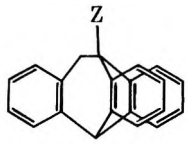
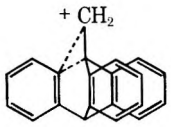
Our interest[2] in the inductive effect of the phenyl group apart from its resonance effect led us to study the solvolysis of the title compound 1-Br. A phenonium ion type of stabilization for the ion 2 logically produced upon solvolysis of 1-Br is precluded geometrically. It was hoped, therefore, that the solvolytic reactivity of 1-Br would reflect rather the inductive influence of these rings upon the stability of 2. Interestingly, deamination of amine 1-NH_2 in acetic acid has recently been shown[3] to give "homotriptycene" derivatives 3 by an astounding 1,2-aryl shift that seemingly demands a σ-bonded precursor such as 4. Whether such a rearrangement would also attend the solvolysis of 1-Br was an additional point of interest in this study.



1, X = cited function
2, X = +



3, Z = OH, OAc



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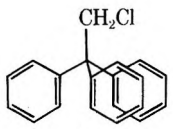


5

The synthesis of 1-Br followed reported procedures used for similar compounds. The synthesis and other relevant reactions are described in the Experimental Section.

Bromide 1-Br was extraordinarily unreactive under typical solvolysis conditions,[4] but reaction in *m*-cresol[5] at elevated temperatures was finally achieved. First-order kinetic behavior was observed to the limit studied (~80%). The kinetic and activation parameter data are collected in Table I. The solvolysis of highly reactive[6] 2-chloro-1,1,1-triphenylethane (5) was studied also for comparison.

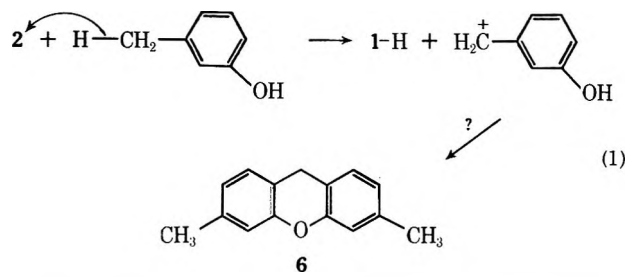
The sole identifiable solvolysis product from 1-Br was 1-methyltriptycene (1-H), isolated in 31% yield. Importantly, however, the solvent-derived product, 3,6-dimethylxanthene (6), was isolated in 16.5% yield.

TABLE I
SOLVOLYSIS DATA IN *m*-CRESOL

Halide	Temp, °C	k_1, sec^{-1} [a]	ΔH^*, kcal mol^{-1}	ΔS^*, eu
1-Br	325[b]	4.47×10^{-5}		
	360	6.25×10^{-5}		
	370	1.01×10^{-4}		
	25[c]	4.13×10^{-19}	35.2	−23.9
5[d]	65[e]	3.65×10^{-5}		
	77	1.11×10^{-4}		
	90	2.97×10^{-4}		
	25[c]	6.15×10^{-7}	20.1	−19.7

[a] Precision ±5%. [b] ±1°. [c] Calculated from data at other temperatures. [d] In the presence of 2,4-lutidine. [e] ±0.2°.

A control experiment showed that 6 was not formed in the absence of 1-Br. Only triphenylethylene was observed as the product from 5. The sluggish behavior of 1-Br, the absence of homotriptycyl products, and the formation of 1-H imply that ion 2 is a highly reactive species formed with considerable difficulty. We suggest that 1-H was formed *via* hydride transfer from the solvent (eq 1), although this is admittedly conjectural. Nonetheless, xanthene 6 does result from *m*-cresol and acids or bases at elevated temperatures[7] and its formation here lends some credibility to an ionic process leading to 1-H.



(1)

6

Homolysis of 1-Br into radicals is also a possible reaction pathway, although the process was insensitive to the presence of oxygen. We feel, moreover, that the kinetic ΔH^* value is too low[8] for such a process (if nonchain) and that the reaction is more likely a heterolytic one.

The remarkable 10^{12}-fold difference in reactivity at 25° between 1-Br and 5 deserves some comment. A minimal value of *ca.* $10^{-2.7}$ per aromatic ring for inductive retardation[9] seems inordinately large.[10] Some of the extra retardation may likely be the result of lost solvent stabilization of 2. A Dreiding model of 2, as depicted in 7, indicated peri-type steric hindrance about the cationic center by the adjacent aromatic hydrogens.

The rearrangement reported[3] with 1-NH_2 may be allowed in its case because no hydride donor was present to trap ion 2. In fact, deamination of 1-NH_2 with nitrosyl chloride[3] gave some unrearranged 1-Cl, pos-

(1) National Science Foundation Trainee, 1968–1970.

(2) J. W. Wilt, H. F. Dabek, Jr., J. P. Berliner, and C. A. Schneider, *J. Org. Chem.*, **35**, 2402 (1970).

(3) S. J. Cristol and D. K. Pennelle, *ibid.*, **35**, 2357 (1970). We thank Professor Cristol for information on this work prior to its publication.

(4) Apropos of this, Cristol and Pennelle[3] reported that 1-Cl was unchanged upon treatment with silver acetate in acetic acid for 24 hr at 210°.

(5) *Cf.* K. B. Wiberg and B. R. Lowry, *J. Amer. Chem. Soc.*, **85**, 3188 (1963). Bromide 1-Br is in fact comparable in reactivity (or lack thereof) to the *bridgehead* halides studied by these workers.

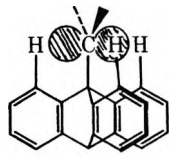
(6) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *ibid.*, **74**, 1113 (1952), studied the corresponding tosylate and developed the basis for understanding in this area.

(7) *Inter alia*, *cf.* C. Graebe, *Ber.*, **16**, 862 (1883); R. Möhlau, *ibid.*, **49**, 168 (1916). See also S. Wawzonek in "Heterocyclic Compounds," Vol. 2, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1951, p 453.

(8) D(C–Br) is normally 65–70 kcal mol^{-1} in the gas phase, much above the ΔH^* value for 1-Br. We seriously doubt that some type of "solvation" phenomenon could lower the enthalpy by 30 kcal mol^{-1}.

(9) The tosylate related to 5 is *ca.* 10^4-fold more reactive in acetolysis (50°) than is neopentyl tosylate,[6] undoubtedly because of anchimeric assistance. The 10^{-12} rate found for 1-Br relative to 5 places 1-Br roughly at 10^{-8} relative to neopentyl tosylate, or *ca.* $10^{-2.7}$ slower per aromatic ring. Because 5 is undoubtedly somewhat slower in solvolysis than its related tosylate, this extrapolation really gives a minimal value for this "inductive retardation."

(10) A value of *ca.* 10^{-1} seems more likely.[2]



7

sibly by capture of 2 prior to rearrangement by chloride ion. In our case, 2 upon formation is surrounded by a potential hydride donor solvent and formation of 1-H is thereby favored, all the more so because eq 1 should be sizably exothermic.

Finally, the relationship of 1-Br to 5 is reminiscent of the similar relationship between 1-triptycyl and triphenylmethyl halides[11] and demonstrates once more the dramatic effect of pinning back the aromatic rings in these compounds.

Experimental Section

General.—Microanalyses were done by Micro-Tech Laboratories, Skokie, Ill., and by M-H-W Laboratories, Garden City, Mich. Spectral data were obtained on Varian A-60A (nmr, $CDCl_3$ solutions) and Beckman IR-5A (ir, KBr discs) instruments.

1-Bromomethyltriptycene (1-Br).—Reaction of yellow 9-bromomethylanthracene, mp 145–147° (lit.[12] mp 137.5–142° dec), anthranilic acid, and isoamyl nitrite in dioxane, as described for similar preparations,[13] led to colorless 1-Br: 39.5% on a 22-mmol scale; mp 217–218.5° from benzene–petroleum ether (bp 30–60°); nmr δ 7.5 (m), 7.0 (m, ArH), 5.37 (s, bridgehead H), 4.85 (s, CH_2Br).

Anal. Calcd for $C_{21}H_{15}Br$: C, 72.63; H, 4.35. Found: 72.61; H, 4.31.

Crude product from this reaction was yellow. Purification was tedious, requiring chromatography on silica gel for final processing. Use of carboxybenzenediazonium chloride[14] as the benzyne precursor in this reaction gave 1-Br contaminated with 1-Cl (82.5:17.5), probably *via* some prior conversion of 9-bromomethylanthracene to its 9-chloro analog by chloride ion displacement. Chloride 1-Cl was apparent from its $-CH_2Cl$ resonance at δ 5.07.[3]

2-Chloro-1,1,1-triphenylethane (5).—The chloride was prepared as reported,[15] mp 99–101° (lit.[14] mp 101.0–101.8°), nmr δ 7.33 (s, ArH), 4.67 (s, CH_2Cl).

Solvolysis Studies.—*m*-Cresol was purified by distillation from zinc dust, bp 50–52° (0.5 mm), homogeneous by glpc. The solvolysis was conducted on *ca.* 0.02 *M* solutions of purified 1-Br in *m*-cresol sealed in Carius tubes, following closely a reported procedure.[5] A Carius tube furnace equipped with a thermocouple for temperature measurement was used. The reactions were carried to ~80% completion and processed as reported.[5] The liberated bromide was titrated potentiometrically at 25° with standard 80% ethanolic silver nitrate (0.010 *M*), using a Leeds and Northrup Model 7402 pH meter. The kinetic data are given in Table I.

The solvolysis product from 1-Br was isolated from the titrated samples by removal of silver bromide by filtration and *m*-cresol by codistillation with water followed by chromatography of the residue on a silica gel column. Elution with petroleum ether (bp 30–60°) gave **3,6-dimethylxanthene** (6): 16.5% based on 1-Br; mp 195–200° (lit.[16] 197.5–203.5°); ir, nmr, and uv spectra agreed with those reported;[16] mass spectrum (70 eV) *m/e inter alia*, 210 (P), 209 (P − 1), 195 (P − CH_3). Elution with benzene–petroleum ether gave **1-methyltriptycene** (1-H, 31% based on consumed 1-Br, melting point, mixture melting point with authentic sample, and nmr spectrum agreed with those reported[3]).

(11) P. D. Bartlett and E. S. Lewis, *J. Amer. Chem. Soc.*, **72**, 1005 (1950).

(12) J. S. Meek, W. B. Evans, V. Godefroi, W. R. Benson, M. F. Wilcox, W. G. Clark, and T. Tiedeman, *J. Org. Chem.*, **26**, 4281 (1961).

(13) E. C. Kornfeld, P. Barney, J. Blankley, and W. Faul, *J. Med. Chem.*, **8**, 342 (1965)

(14) F. M. Logullo, Dissertation, Case Western Reserve University, 1965; B. H. Klanderman and T. R. Criswell, *J. Org. Chem.*, **34**, 3425 (1969).

(15) E. Grovenstein, Jr., *J. Amer. Chem. Soc.*, **79**, 4985 (1957).

(16) J.-B. Chazan and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1384 (1968).

No other characterizable products were eluted. No homotriptycyl products were detected. A control study of *m*-cresol itself at 370° for 6 hr afforded no 6. Degassed reaction conditions showed no difference.

Chloride 5 was solvolyzed analogously. Sealed ampoules containing *ca.* 0.02 *M* solutions of 5 in *m*-cresol with an equimolar amount of redistilled 2,4-lutidine added were held at various temperatures. Processing and chloride determination were as described above. See Table I for further details. From reactions taken to *ca.* 80% completion, the only product isolated (chromatography on silica gel) was **triphenylethylene**, 95% based on consumed 5, mp and mmp with authentic material 67.5–68.5°, coincidental ir and nmr spectra.

Miscellaneous.—Among the triptycenes prepared in this study were those following. Their syntheses followed standard or cited procedures and their properties are briefly reported here for documentation purposes.

1-Diazoacetyltriptycene was yellow: mp 220–222° dec; 89% from 9-triptoyl chloride and diazomethane in ether; λ 4.8, 6.14 ($COCHN_2$); nmr δ 8.02 (m, 3, peri ArH's), 7.45 (m), 7.08 (m, remaining ArH's), 5.80 (s, $-CHN_2$), 5.42 (s, bridgehead H).

Anal. Calcd for $C_{22}H_{14}ON_2$: C, 81.97; H, 4.37; N, 8.69. Found: C, 81.67; H, 4.40; N, 8.41.

1-Chloroacetyltriptycene was colorless: mp 200–202°; 85% from reaction of the diazo ketone above and hydrogen chloride[17] in tetrahydrofuran at 50°; λ 5.82 (CO); nmr δ 7.75 (m, 3, peri ArH's), 7.50 (m), 7.10 (m, remaining ArH's), 5.40 (s, bridgehead H), 4.80 (s, $-CH_2Cl$).

Anal. Calcd for $C_{22}H_{15}OCl$: C, 79.88; H, 4.57. Found: C, 80.07; H, 4.59.

1-Triptycylacetic acid was colorless: mp 298–300°; 10% from the above diazo ketone upon uv irradiation in 20% aqueous tetrahydrofuran;[18] λ 3.3 (broad) 5.82 (COOH); nmr δ 9.6 (broad s, COOH), 7.33 (m), 7.03 (m, ArH), 5.40 (s, bridgehead H), 4.03 (s, CH_2).

Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.23; H, 5.33.

Attempted conversion of the diazo ketone above to this acid using silver benzoate and triethylamine in methanol[19] followed by saponification gave intractable material. Reaction of silver 1-triptycyclacetate with bromine in carbon tetrachloride to form 1-Br seemed partially successful. However, the easier preparation given above made further work on this reaction unnecessary.

Registry No.—1 (X = Br), 34858-83-8; **5**, 33885-01-7; *m*-cresol, 108-39-4; triphenylethylene, 58-72-0; 1-diazoacetyltriptycene, 34887-50-8; 1-chloroacetyltriptycene, 34858-85-0; 1-triptycylacetic acid, 34858-86-1.

(17) W. D. McPhee and E. Klingsberg, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 119.

(18) A. L. Wilds, N. F. Wollsey, J. Van Den Berghe, and C. H. Winestock, *Tetrahedron Lett.*, 4481 (1965).

(19) M. S. Newman and P. F. Beal, III, *J. Amer. Chem. Soc.*, **72**, 5163 (1950).

Intramolecular Addition of 4-Alkynyloxy Radicals

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It was recently reported by Rieke and Cooke, that alkoxy radicals fail to add intramolecularly to alkynes.[1] Analysis of the photolysis products of several 4-alkynyl nitrites has provided us with evidence for the occur-

(1) R. D. Rieke and B. J. A. Cooke, *J. Org. Chem.*, **36**, 2674 (1971).

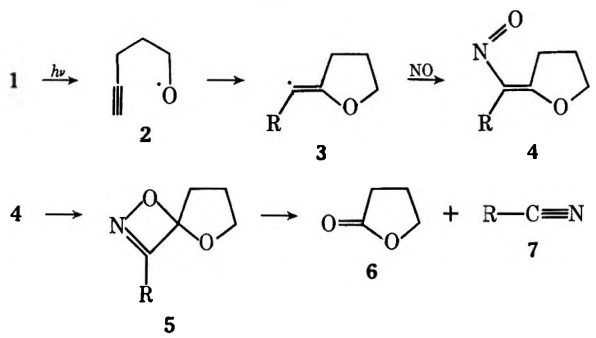
rence of this reaction in low yield. Whereas numerous studies have been devoted to free-radical chemistry of alkenes, little seems to be known on the behavior of alkynes,[2a] particularly toward alkoxy radicals.[3] As an example, the interaction of *tert*-butyl hypobromite or hypochlorite with alkynes leads to an explosive homolytic decomposition which is apparently induced by the triple bond. Abstraction of the propargylic hydrogen by alkoxy radicals is the sole reaction generally observed.[4] However some additions to the triple bond occur in the case of conjugated enynes only.[5] Nevertheless, although hydrogen abstraction is impossible, addition products do not form with phenylacetylene.[4a]

Surprisingly enough, in the case of 4-alkenyloxy radicals the preferred reaction is an intramolecular addition,[6] whereas allylic hydrogen abstraction occurs essentially in intermolecular reactions.[3] On the other hand interesting synthetic reactions could be achieved by intramolecular addition of carbon,[2b,7] and thiyl radicals[9] on alkynes. Accordingly it was of interest to investigate the intramolecular interaction of a nonconjugated triple bond with alkoxy radicals obtained by photolysis of 4-alkynyl nitrites

$$R{-}C{\equiv}C{-}(CH_2)_3{-}O{-}NO$$
1

Results and Discussion

Nitrogen was slowly bubbled through a 0.05–0.1 *M* benzene solution of the nitrites **1**, which was irradiated with a Hanau TQ 81 (70 W) high-pressure lamp equipped with a Pyrex filter. The same compound, identified as γ-butyrolactone by comparison with an authentic sample, was obtained in poor yields (1–6%) from the three nitrites under investigation (R = H, CH_3 or C_6H_5). In order to explain these results we suggest the following scheme.



Irradiation of nitrite **1** yields the alkoxy radical **2** which adds intramolecularly to the triple bond. The vinylic cyclic radical **3** is trapped by nitric oxide to form the nitroso compound **4**. Such nitrosovinylic intermediates have been shown to be unstable by a study of photolytic intramolecular addition of alkyl and chlorine radicals to alkynes in presence of nitric oxide.[10] Indeed, in the present case they fragment into γ-butyrolactone **6** and nitrite **7**. When R = C_6H_5, benzonitrile is detected. This is in agreement with the present mechanism involving an intermediate such as **5**.

In all the cases the other products which are normally expected from the evolution of the alkoxy radical **2**[3] as 4-alkynols (R = H (30–35%), CH_3 (45–50%), and C_6H_5 (50–55%)) were identified besides approximately 25% polymeric material. For R = H 4-pentynal was detected together with four as yet unidentified compounds (less than 10% by vpc). The reaction was very sensitive to experimental conditions. For instance, when the nitrogen flow rate was increased the yield of γ-butyrolactone decreased (when R = H). The use of a Hanau TQ 150 (150 W) lamp lowered the yield of γ-butyrolactone; this could be an explanation for the somewhat different results reported by Rieke and Cooke[1] who used a 450-W lamp. Nitric oxide was bubbled through the solution in order to more efficiently trap **3** and get better yields of **4**; this experiment was unsuccessful since the quantities of γ-butyrolactone formed were not modified. However, this failure might be due to competitive reactions between nitric oxide and the alkyne.[11]

These results strongly support the possibility of intramolecular addition of alkoxy radicals to isolated triple bonds. However, the low yields of cyclic products show that this reaction is more difficult than with a double bond. As a conclusion, we wish to point out that five-membered rings are obtained with substituted alkynes (R = CH_3 or C_6H_5). With monosubstituted alkynes (R = H) no hypothesis on the orientation of the cyclization can be made, as several products need to be identified.

Experimental Section

The ir spectra were measured with a Perkin-Elmer 337 grating ir spectrophotometer. The nmr spectra were obtained on Varian A-60 and HA-100 instruments, chemical shifts were recorded as δ values (parts per million) relative to tetramethylsilane as an internal reference.

4-Pentynol, bp 67° (15 mm) [lit.[12] bp 70–71° (29 mm)], was prepared from tetrahydrofurfuryl chloride according to "Organic Syntheses."[12]

4-Hexynol, bp 78° (13 mm), $n^{18}D$ (1.4602 [lit.[13] bp 85° (20 mm), $n^{18}D$ 1.4604)] was prepared according to a procedure described for 4-undecynol[14] from lithium (7 g), excess of propyne, and 3-bromopropanol yielding 11.4 g of 4-hexynol (46%).

1-Phenyl-1-pentyn-5-ol was prepared according to a procedure described for 5-hexynol[15] using the reaction pathway chloride, iodide, acetate, and alcohol. 5-Chloro-1-phenyl-1-pentyne was prepared in 70% yield (125 g), bp 146° (15 mm), from lithium (8 g), phenylacetylene (112 g), and 3-bromo-1-chloropropane

(2) For a recent review, see M. Julia in "Chemistry of Acetylenes," H. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969: (a) pp 335–354; (b) pp 349–354.

(3) For a review, see C. Walling, *Bull. Soc. Chim. Fr.*, 1609 (1966).

(4) (a) C. Walling, L. Heaton, and D. Tanner, *J. Amer. Chem. Soc.*, **87**, 1715 (1965); (b) J. K. Kochi and P. J. Krusic, *ibid.*, **92**, 4110 (1970).

(5) (a) M. Poutsma and P. Ibarbia, *J. Org. Chem.*, **35**, 4038 (1970); (b) L. Byrd and M. Caserio, *J. Amer. Chem. Soc.*, **92**, 5422 (1970).

(6) (a) J.-M. Surzur, P. Cozzone, and M. P. Bertrand, *C. R. Acad. Sci., Ser. C*, **267**, 908 (1968); (b) R. Rieke and N. Moore, *Tetrahedron Lett.*, 2035 (1969); (c) J.-M. Surzur, M. P. Bertrand, and R. Nouguier, *ibid.*, 4197 (1969); (d) P. Tordo, M. P. Bertrand, and J.-M. Surzur, *ibid.*, 3399 (1970).

(7) (a) H. R. Ward, *J. Amer. Chem. Soc.*, **89**, 5517 (1967). (b) J. K. Crandall and D. J. Keyton, *Tetrahedron Lett.*, 1653 (1969). (c) Intramolecular cyclizations of acetylenic Grignard reagents have also been reported as proceeding possibly by free-radicals intermediates.[8]

(8) (a) H. G. Richey, Jr., and A. Rothman, *Tetrahedron Lett.*, 1457 (1968); (b) J. L. Derocque, U. Beisswenger, and M. Hanack, *ibid.*, 2149 (1969); (c) W. C. Kossa, Jr., T. C. Rees, and H. G. Richey, Jr., *ibid*, 3455 (1971).

(9) (a) J.-M. Surzur, C. Dupuy, M. P. Crozet, and N. Aimar, *C. R. Acad. Sci., Ser. C*, **269**, 849 (1969); (b) H. Kwart and T. J. George, *Chem. Commun.*, 433 (1970).

(10) A. G. Sherwood and H. E. Gunning, *J. Amer. Chem. Soc.*, **85**,, 3506 (1963).

(11) S. F. Reed, Jr., *J. Org. Chem.*, **35**, 3961 (1970).

(12) E. R. H. Jones, G. Eglington, and M. C. Whiting, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 755.

(13) R. Paul, *Bull. Soc. Chim. Fr.*, 109 (1951).

(14) D. Ames, A. Covell, and T. Goodburn, *J. Chem. Soc.*, 5889 (1963).

(15) M. Ohno and A. Hatanaka, *Bull. Inst. Chem. Res., Kyoto Univ.*, **40**, 322 (1962).

(157 g) in 1 l. of liquid ammonia. A mixture of 3-bromo-1-chloropropane (125 g) and sodium iodide (110 g) was refluxed and stirred for 24 hr in 1 l. of dried acetone. The excess of solvent was then distilled and the cooled residue treated with water. The upper layer was washed, dried, and rectified to yield 140 g (74%) of 5-iodo-1-phenyl-1-pentyne, bp 95–100° (0.05 mm). The iodide (43 g) was added while stirring to silver acetate (27 g) in 150 ml of benzene. After refluxing for 6 hr the cooled mixture was filtered and the benzene was evaporated. Distillation gave 25 g (72%) of 5-acetoxy-1-phenyl-1-pentyne, bp 100–105° (0.05 mm). The ester (25 g) was heated at reflux for 2 hr in a solution of potassium hydroxide (12 g) in water (20-ml)–ethanol (50 ml). Ethanol was removed by distillation and the residue was extracted with ether. The ether extract was washed with dilute acid, water, and dried. Distillation gave 11 g (53%), of 1-phenyl-1-pentyn-5-ol: bp 100–104° (0.04 mm), n^{20}D 1.5765 [lit.[16] bp 122° (2 mm), n^{20}D 1.5769]; ir (neat) 3500, 3200, 3080, 3020, 2220, 1600, 1500, 1060, 750, 690 cm^{-1}; nmr (CCl_4) 1.75 (q, J = 6.5 Hz, 2 H) 2.4 (t, J = 6.5 Hz, 2 H), 3.65 (t, J = 6.5 Hz, 2 H), 4.05 (s, 1 H), 7.1 (m, 5 H).

Preparation of 4-Alkynyl Nitrites.—They were prepared, like alkenyl nitrites,[6c] by alkynol esterification with nitrous acid at 0°.[17] Alkynol (0.2 mol) and sodium nitrite (21 g) were dissolved in water (75 ml). Concentrated sulfuric acid (15 g) in water (10 ml) slowly added with vigorous stirring to the solution maintained at 0° with external cooling and swept by a nitrogen stream. The upper layer was dried and 4-alkynyl nitrites $RC{\equiv}C(CH_2)_3$-ONO (1) distilled at temperature below 50°. 1a: (R = H) (70%); bp 35° (25 mm); n^{20}D 1.4168; ir (neat) 3300, 2110, 1640, 1600, 780 cm^{-1}. 1b (R = CH_3) (66%): bp 42° (15 mm); n^{25}D 1.4309; ir (neat) 2210, 1640, 1600, 700 cm^{-1}. 1c (R = C_6H_5) (85%, crude because it decomposed by distillation): ir (neat) 2220, 1640, 1600, 790. [All these compounds have characteristic uv absorption spectra of nitrites[18] between 320 and 380 nm (hexane).]

Photolysis of 4-Alkynyl Nitrites.—The nitrite (0.1–0.05 mol) dissolved in 100 ml of benzene was added during 2 hr to 900 ml of benzene irradiated by an inside Hanau TQ 81 lamp provided with a Pyrex filter. A slow stream of nitrogen was maintained before and during the irradiation. The solution was maintained between 10 and 15° by external cooling. The photolysis was followed by uv spectra and carried to 80% completion. Benzene was removed under reduced pressure at temperature below 50°. The residue was distilled and fractions analyzed by vpc (Carbowax 20M). Compounds were isolated by preparative vpc and identified by comparative spectral analysis with authentic samples. Yields were calculated from the weight of nitrite ester used.

Photolyses were also run in the cavity of an epr (Varian E_3) apparatus irradiated with an SP 500 Philips lamp. Spectra of nitroxides were observed but these spectra were complex and important modification were observed during and after irradiation, not permitting yet, direct verification of the mechanism proposed as in the photolysis of 4-alkenyl nitrites.[6d]

Photolysis of 4-Hexynyl Nitrite.—As described above 9 g (0.07 mol) of the nitrite was irradiated in 1 l. of benzene for 20 hr. Distillation gave 3.7 g, bp 75–90° (13 mm), and undistillable residue, 1.84 g (21%). Only two compounds could be detected by vpc of the distilled fraction; they were identified after vpc preparative and comparison with authentic samples of 4-hexynol (47%) and γ-butyrolactone (6%).

Photolysis of 5-Phenyl-4-pentynyl Nitrite.—An amount of 9.9 g (0.048 mol) was irradiated in 1 l. of benzene for 60 hr. Distillation gave a first fraction, 0.1 g, bp 36–40° (0.05 mm), a second fraction, 1.9 g, bp 110–115° (0.2 mm), and an undistillable residue, 2 g (20%). Only two compounds were detected in the first fraction, identified as γ-butyrolactone (1%) and benzonitrile (1%). 1-phenyl-1-pentyn-5-ol was the major product of the second fraction (57%).

Photolysis of 4-Pentynyl Nitrite.—As above 6.7 g (0.059 mol) of the nitrite was irradiated for 18 hr. Distillation gave fraction 1, 1.8 g, bp 50–65° (13 mm), fraction 2, 0.7 g, bp 60–65° (0.2 mm), and an undistillable residue, 1.6 g (24%). Fraction 1 was composed of 4-pentynol (32%) and traces of 4-pentynal and unreacted nitrite ester. Fraction 2 was composed of six compounds. Two of them were identified as 4-pentynol (6%) and γ-butyrolactone (2%). The photolysis of 4.13 g (0.047 mol) of 4-pentynyl nitrite in 250 ml of benzene as above but with a plunging lamp, Hanau TQ 150 (150 W), gave still two fractions: fraction 1, 0.7 g, bp 32–50° (0.05 mm), fraction 2, 0.7 g, bp 50–80° (0.05 mm), undistillable residue, 1 g (24%), 4-pentynal (4%), 4-pentynol (16%), and traces of nitrite ester composed the first fraction. Six compounds were present in the second fraction, two of them were identified as 4-pentynol (7%) and γ-butyrolactone (traces).

Photolysis of 7.83 g of nitrite ester in 1 l. of benzene with a TQ 81 lamp as above but with a quicker stream of nitrogen gave 4-pentynal (8%) and 4-pentynol (23%) in fraction 1. In fraction 2, the proportion of two unidentified compounds increased but γ-butyrolactone could only be detected. When the stream of nitrogen was replaced by nitric oxide we observed the formation of γ-butyrolactone (2.2%), 4-pentynal (traces), 4-pentynol (10%), four unidentified compounds, and polymeric material (40%).

Registry No.—1a (R = H), 30428-24-1; 1b (R = CH_3), 34886-47-0; 1c (R = Ph), 34886-48-1; 5-chloro-1-phenyl-1-pentyne, 24463-87-4; 5-iodo-1-phenyl-1-pentyne, 34886-50-5; 5-acetoxy-1-phenyl-1-pentyne, 29313-49-3; 1-phenyl-1-pentyn-5-ol, 24595-58-2.

(16) A. S. Atavin and N. V. Egorov, *Khim. Atsetilena, Dokl. Vses. Nauch. Konf., 1965*, 17 (1968) [*Chem. Abstr.*, **71**, 70,019c (1969)].

(17) C. S. Coe and T. F. Doumani, *J. Amer. Chem. Soc.*, **70**, 1516 (1948).

(18) C. H. Purkis and H. W. Thompson, *Trans. Faraday Soc.*, **32**, 1466 (1936).

A Terminology for the Chiral Attributes of Steric Elements[1]

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In a recent analysis of stereoisomerism we concluded[2] that the conventional types of stereoisomerism (the center, axis, plane, "conformational helix," and cis–trans isomerism at double bonds)[3,4] could be reduced to two elements, the center and the line of torsion, and that these elements of stereoisomerism may possess or lack one or both of two distinct chiral characteristics. The first of these determines whether the configuration of the element by itself has to be specified with a chiral descriptor and the second whether the element can contribute to the chirality of a compound. Either of these tests may be thought to be suitable for determining the chiral character of the element. We suggested, at least as a temporary expedient, to call an element chiral if it meets both of these tests, as this would preserve existing practices. The problem of selecting the most useful criterion for a chiral element, however, remained unsolved. We now find that the need for making this difficult choice would be avoided

(1) Supported in part by Grants AM 9105 and K6-AM-14367 from the National Institutes of Health (H. H.), and GB 29021-X from the National Science Foundation (K. R. H.).

(2) H. Hirschmann and K. R. Hanson, *J. Org. Chem.*, **36**, 3293 (1971). This paper should be consulted for the definition of all terms and symbols not explained in this note.

(3) R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, **5**, 385, 511 (1966).

(4) IUPAC Tentative Rules for the Nomenclature of Organic Chemistry. Section E. Fundamental Stereochemistry: *J. Org. Chem.*, **35**, 2849 (1970).

and the discussion of both relevant properties would be facilitated if we had two separate and concise terms to characterize all elements of stereoisomerism that meet one or the other of these tests. Accordingly we propose to call an element *graphochiral*[5] if its configuration, viewed apart from that of any other element of the same molecule, can be specified only by a chiral descriptor, and *pherochiral*[5] if the element would contribute to the chirality of a chiral molecule. Operational definitions of these and of related terms follow. They utilize the same criteria that were presented before[2] and are stated here in a manner applicable to all elements, on the understanding that the atom at a center of stereoisomerism or of prostereoisomerism represents the core of these elements.

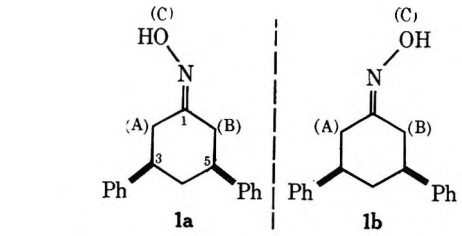
An element of stereoisomerism is graphochiral or agraphochiral, respectively, if its assembly of differentiated atoms ([3], [14])[2] cannot or can be superposed on its mirror image. An element of prostereoisomerism ([8], [16])[2] or an agraphochiral element of stereoisomerism is prographochiral if there are linked to the core two superposable *cf*-ligands ([2], [13])[2] so located that the element would be graphochiral if one of these ligands were considered to be different from all others.

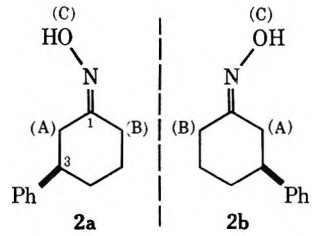
An element of stereoisomerism is pherochiral or apherochiral, respectively, if its assembly cannot or can be superposed on the assembly of corresponding atoms ([5], [15])[2] derived from the reflected model. An element of prostereoisomerism is propherochiral if it should become pherochiral on assuming that one of a pair of equivalent proximal atoms is different from all others in the assembly.

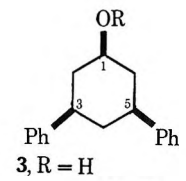
To make the concept fully effective, a correlation is needed between the pherochirality of the individual elements and the chirality of the whole structure. This relationship can be expressed as follows. A compound is chiral if it contains a pherochiral element of stereoisomerism that cannot be paired within the same molecule with another element whose *cf*-ligands can be superposed after a reflection upon the *cf*-ligands of the first.

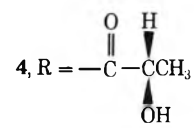
As before,[2] only those elements of stereoisomerism that are both graphochiral and pherochiral are designated as chiral, all others as achiral. The retention of these simpler terms is desirable because in the vast majority of cases an element that meets one test for chirality also meets the other. The exceptions to this rule always involve elements with at least one pair of enantiomeric ligands. Similarly elements of prostereoisomerism are called prochiral, if they are both prographochiral and propherochiral. They are called proachiral if they are "not prographochiral" and/or "not propherochiral." Consequently, there is no conflict between this supplement and any of the statements of the earlier paper.[2]

Application of these new terms will be illustrated by compounds **1**–**4**. In analyzing **1a**[6] one first identifies its elements of stereoisomerism (factorization). These









are the most compact parts of the structure for which one has to define the spatial distribution of the bonds to the individual ligands in order to differentiate the compound from its stereoisomers. The elements of **1a** are two centers C-3 and C-5 which are chiral, and the C=N double bond. To examine this last element one replaces its three *cf*-ligands by three points which are all distinct (A, B, C) as the ligands represented by the points are not superposable. The assembly consisting of C=N and of the three points which we have called the differentiated proximal atoms[2] has a plane of symmetry, as all atoms of the assembly lie in this plane. The element represented by this assembly is, therefore, agraphochiral. As the assembly cannot be superposed on the assembly derived from the enantiomer **1b** with all corresponding atoms coinciding, the double bond is pherochiral. The description of the double bond as agraphochiral and pherochiral brings out the unusual relationship between **1a** and **1b**. They are enantiomers which can be distinguished by a pair of achiral descriptors (*Z* and *E*)[4] because they are also cis–trans isomers. If we merely designate the double bond of **1a** as achiral we would obscure an important difference from **2a**, which derives its chirality only from the chiral center C-3 as its other element of stereoisomerism, the double bond, is both agraphochiral and apherochiral. Factorization of the stereoisomerism of **3** shows three elements which are all centers. Those at C-3 and C-5 are chiral as in **1**, whereas that at C-1 is graphochiral and apherochiral. Therefore, as for the double bond in **1a**, the chirality of C-1 of **3** is incomplete but the combination of properties is the reverse of that found for the double bond. This combination of graphochirality and apherochirality fully characterizes all elements traditionally designated as pseudoasymmetric. As expected for a graphochiral center, it requires a chiral descriptor (*e.g.*, *s*) to specify its configuration without relating it to the configurations of the two other centers. The further conclusion that C-1 is apherochiral is consistent with the achirality of **3**, as any compound with an odd number of pherochiral elements is necessarily chiral. However, it is not essential for a compound to be achiral in order to have such an apherochiral element. The character of C-1 remains un-

(5) The prefix grapho is derived from the Greek verb graphein, to write, which was used by Greek mathematicians in the sense "to describe a figure." The prefix phero is derived from the Greek pherein, to bear, to cause. It seems appropriate as "phore," which is derived from the same root, is used in the same sense in chromophore.

(6) Compound **1** is a close analog of one prepared and resolved by R. E. Lyle and G. G. Lyle, *J. Org. Chem.*, **24**, 1679 (1959), to serve as a first example of what they called "geometrical enantiomorphic isomerism." The term shows how blurred the traditional distinction between geometrical and optical isomerism has become and that a classification of the elements of stereoisomerism requires terms that are mutually exclusive in all situations.

changed, but the plane of symmetry is lost if the hydroxyl group of **3** is esterified (as in **4**) with (*S*)-lactic acid.

In our full paper[2] we summarized the classification of steric centers by a chart which separated centers of stereoisomerism into chiral and achiral and then subdivided the achiral centers into those having and not having chiral configurations. Centers of prostereoisomerism were treated in an analogous manner. This classification brought out pherochiral properties only if the element was also graphochiral (and propherochiral properties only if it was also prographochiral). The present terminology[7] is therefore better balanced and it allows one to focus on the relevant property, as we have illustrated in discussing examples **1**–**4**.

(7) Of the examples listed in Chart 1,[2] Cghij, Cg^+g^-hi, **8a–c,f,g** are graphochiral; tetragonal Xghij, octahedral Xgghgig, **8d, e, h** are agraphochiral. (Of this last group **8d, e, h** can be further classed as prographochiral whereas the two others are not prographochiral.) Cgghi and $Cggh^+h^-$ are prographochiral; tetragonal Xgggh and octahedral Xgggggh are not prographochiral. In the alternative classification Cghij, **8a–e** are pherochiral; Cg^+g^-hi, tetragonal Xghij, **8f–h** and octahedral Xgghgig are apherochiral; Cgghi is propherochiral; $Cggh^+h^-$, tetragonal Xgggh, and octahedral Xgggggh are not propherochiral.

Potential Inhibitors of L-Asparagine Biosynthesis. I. β-Elimination Reactions with β-Hydroxyaspartic Acid Derivatives[1a,b]

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In the course of a study aimed at preparing irreversible inhibitors of the enzyme L-asparagine synthetase we observed a β-elimination reaction with derivatives of β-hydroxyaspartic acids, the results of which form the text of this paper.

In view of the usefulness of the diazoacetate group in the design of irreversible enzyme inhibitors, we attempted to synthesize the *O*-diazoacetyl derivative of both *threo*- (**1a**) and *erythro*-β-hydroxyaspartic acid (**1b**). Initially we began with **1a** since it was readily obtainable,[2] whereas **1b** was more difficult to obtain. Because of contradictory reports[2,3] concerning the stereospecific synthesis of **1a** and **1b**, we used two methods to ascertain their stereointegrity, namely a chemical vanadate test[4] and analysis *via* an automatic amino acid analyzer;[5] both confirmed the stereopurity of **1a** and **1b**.

(1) (a) This work was supported by Grant M-28 from the Health Research and Services Foundation, Pittsburgh, Pa., and Grant CA-11714 from the National Cancer Institute, NIH, Bethesda, Md. (b) Presented in part at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, Medi 26. (c) Taken in part from the M.S. Dissertation of B. S. P., University of Pittsburgh, July 1971.

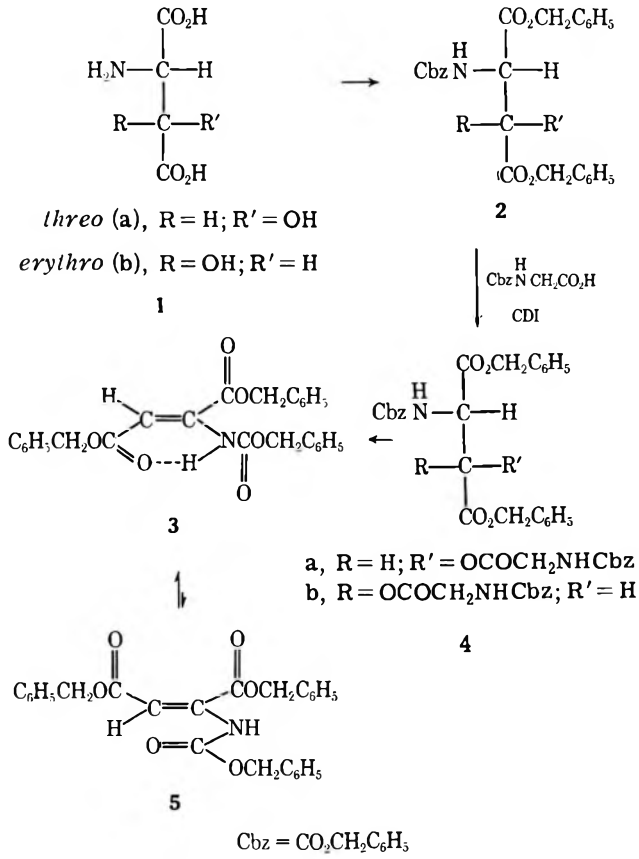
(2) C. W. Jones, III, D. E. Leyden, and C. H. Stammer, *Can. J. Chem.*, **47**, 4363 (1969).

(3) H. Okai, N. Imamura, and N. Izumiya, *Bull. Chem. Soc. Jap.*, **40**, 2154 (1967).

(4) Y. Liwschitz, Y. Robinson, and A. Haber, *J. Chem. Soc.*, 3589 (1962).

(5) Recorded on a Beckman Model 116 A.A.A. The authors thank Mr. J. P. Vergnes, Department of Biochemistry, University of Pittsburgh, for these determinations.

The amino function of **1a** was readily protected by carbobenzoxylation followed by esterification of the carboxyl groups to give **2a**.[6] Esterification of **2a** with carbobenzoxyglycine in the presence of the condensing agent *N,N'*-carbonyldiimidazole (CDI)[7] afforded an oil which, according to tlc, was composed of three components. Separation by preparative tlc afforded starting material, the supposed **4a**, and compound **3**, a product of β elimination. Compound **4a** could not be



crystallized and attempts to prepare an analytical sample failed because of a tendency for it to decompose to **3**. The tentative assignment of the structure for **4a** was based on nmr data [δ 3.88 (d, CH_2 of glycyl, singlet after shaking with D_2O), 5.65 (m, β-H)] and the fact that stirring **4a** in THF with imidazole (this base is a side product of reactions with CDI) readily affords some of compound **3**.

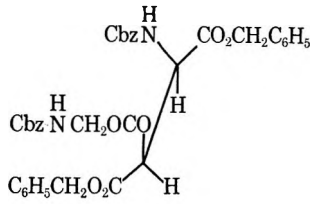
By a scheme similar to that used in the threo series, **2b** was obtained in a 72% overall yield from **1b**. In an attempt to synthesize the coupled product **4b**, similar results were obtained using CDI and carbobenzoxyglycine, namely, small amounts of starting material and unsaturated **3** were obtained and the major product presumably was **4b**. The latter was noncrystalline and attempts to prepare an analytical sample caused some decomposition to **3**. The tentative assignment of the structure for **4b** was based on nmr data [δ 3.92 (d, CH_2 of glycyl) and 5.66 (m, β-H)]. Furthermore, stirring the supposed **4b** in THF with imidazole very slowly (in contrast to the facile **4a**) formed some of **3**. As a control experiment both **2a** and **2b** were separately stirred with imidazole but only

(6) Y. Liwschitz and A. Singerman, *J. Chem. Soc.*, 1696 (1967); H. Okai and N. Izumiya, *Bull. Chem. Soc. Jap.*, **42**, 3550 (1969).

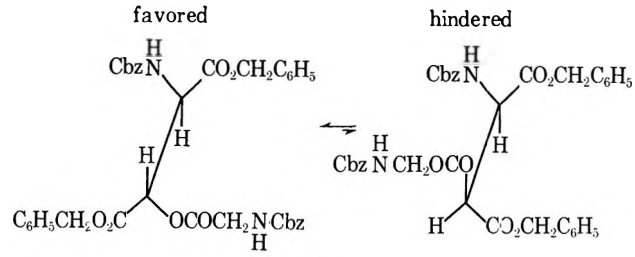
(7) H. A. Staab, *Angew. Chem., Int. Ed. Engl.*, **1**, 351 (1962).

starting material was recovered, thus implicating **4a** and **4b** as the source of **3**.

After several months in the refrigerator, compound **3** (from **4a** and **4b**) showed evidence on tlc for approx-



4a



4b

imately 5% of a lower R_f component. Preparative tlc afforded a small sample of this new compound, whose structure was assigned as the cis isomer **5**. Evidently there is an equilibrium which lies far on the trans isomer (**3**) side. If **3** is dissolved in 15:1 isooctane–methylene chloride and allowed to remain for 1 week in sunlight[8] there is approximately a 25–35% conversion to **5**, and this ratio does not change on heating the mixture to 150°.

Proof for these structures is based on the following evidence. An nmr spectrum of **3** showed signals at δ 5.15, 5.25 (s, 6 H, benzylic), 5.51 (s, 1 H, vinyl), 7.34 (s, 15 H, aromatic), and 9.71 (broad, 1 H, NH), while in the ir (CCl_4) there was a broad NH band at 3.01 (H bonded) and carbonyl absorption at 5.73 and 5.92 μ, the latter band due to the conjugated, H-bonded ester.[9] Furthermore, catalytic hydrogenation (Pt) of **3** gave aspartic acid (identical ir with ir of authentic sample). The cis isomer **5** showed resonance in the nmr at δ 5.00, 5.15 (m, 6 H, benzylic), 6.67 (s, 1 H, vinyl), 6.96 (broad, 1 H, NH, disappears with D_2O), and 7.33 (m, 15 H, aromatic). The ir (CCl_4) spectrum of **5** showed peaks at 2.92 μ (NH) and carbonyl absorption at 5.73 and 5.78 μ.

The data for **3** and **5** deserve brief comment. In **3**, where a six-membered H-bonded ring can exist, the NH is broadened in the ir and further downfield in the nmr, and the H-bonded carbonyl appears at higher wavelength in the ir,[9] when compared to **5**. In **5**, where the carbamate carbonyl can assume a closer proximity to the vinyl hydrogen than the ester carbonyl can in **3**, there is greater deshielding[9,10] of this proton and it appears further downfield in the nmr.

The observation of β elimination with certain amino acid derivatives is well documented.[11] The formation of **3** from **4a** could be explained by a one-step β-elimination mechanism (E2), since in the threo derivative the favored conformation has the leaving groups transcoplanar. However, obtaining **3** from **4b** is not as readily explained. **4b** in its favored arrangement does not have the leaving groups coplanar, and rotation to bring about coplanarity followed by β elimination would afford **5**. There are several possibilities[12] that could explain the formation of **3** from **4b** (cis elimination, E1 or E1cB), but in the absence of further experimental evidence it would be unwise to speculate.

(8) R. E. Lutz, D. F. Hindley, and R. H. Jordan *J. Amer. Chem. Soc.*, **73**, 4647 (1951).

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

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

(11) I. Photaki, *J. Amer. Chem. Soc.*, **85**, 1123 (1963); Y. Liwschitz, A. Singerman, and S. Sokoloff, *J. Chem. Soc.*, 1843 (1968); R. G. Hiskey, R. A. Upham, G. M. Beverly, and W. C. Jones, Jr., *J. Org. Chem.*, **35**, 513 (1970); R. K. Olsen, *ibid.*, **35**, 1912 (1970).

(12) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill, New York, N. Y., 1968, pp 728–736.

(13) G. B. Payne and P. H. Williams, *J. Org. Chem.*, **24**, 54 (1959).

Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are not corrected. Ultraviolet spectra were determined in 95% ethanol on a Beckman DB-G recording spectrophotometer. Infrared absorption spectra were recorded on either a Perkin-Elmer Infracord or a Beckman IR-8 spectrophotometer. Nmr spectra were recorded on a Varian A-60 or A-60D recording spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. Thin layer chromatography and preparative tlc (1.0 mm) were carried out with silica gel GF (Analtech, Inc.) and spots were located with either uv light or by spraying with 3% ceric sulfate in 3 *N* H_2SO_4 and then heating. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Dioxane and tetrahydrofuran (THF) were purified by distillation from $LiAlH_4$. The petroleum ether used had a boiling point range of 30–60°. All concentrations were done under reduced pressure. Prior to concentration all organic layers were dried with anhydrous Na_2SO_4. Mass spectra were determined on an LKB Model 9000 spectrometer at 70 eV.

threo-**β-Hydroxy-DL-aspartic Acid** (**1a**).—Maleic acid was converted[2] to **1a** in a 42% yield, and characterized by conversion to its dimethyl ester: HCl, mp 135–136° (lit.[2] mp 134–135°).

erythro-**β-Hydroxy-DL-aspartic Acid** (**1b**).—Fumaric acid was converted,[2] with much difficulty, to **1b** in a 13–15% yield, and characterized by conversion to its dimethyl ester: HCl, mp 149–150° (lit.[2] mp 152–153°). The difficulty encountered was in the conversion of fumaric acid to *trans*-epoxysuccinic acid.[13] In our hands, the epoxidation never proceeded as smoothly as reported,[13] while the conversion[2] of the epoxide to **1b** consistently (71% yield) gave good results.

Dibenzyl *N*-Carbobenzoxy-*threo*-β-hydroxy-DL-aspartate (**2a**).—This compound was prepared as reported[6] from **1a** in a yield of 88%: mp 90–91° (lit.[6] mp 88°); nmr δ 3.22 (broad, OH, exchangeable with D_2O), 4.6–4.8 (m, 2 H, H-α, H-β), 5.12 (6 H, benzylic $-CH_2$), 5.75 (d, J = 9 Hz, –NH), 7.33 (s, 15 H, phenyls); mass spectrum m/e 463 (M^-).

Dibenzyl *N*-Carbobenzoxy-*erythro*-β-hydroxy-DL-aspartate (**2b**).—*N*-Carbobenzoxy-*erythro*-β-hydroxy-DL-aspartic acid was prepared[6] in a 78% yield from **1b**. This compound (0.50 g, 1.7 mmol) was heated under reflux in CCl_4 (10 ml) containing benzyl alcohol (0.68 ml, 6.8 mmol) and *p*-toluenesulfonic acid (0.05 g) and the H_2O formed was removed *via* a Dean–Stark trap. After 72 hr the reaction solution was allowed to cool to room temperature. The resulting mixture, containing some crystallized product, was concentrated to dryness. The remaining oil was dissolved in $CHCl_3$, the solution was extracted twice with $NaHCO_3$ solution, dilute HCl solution, and H_2O, and the organic layer was dried. The solvent was evaporated and the product was crystallized from EtOAc–petroleum ether, affording 0.72 g (92%) of **2b**. The analytical sample had mp 74.5–75.5°; nmr δ 3.56 (broad, OH, exchangeable with D_2O), 4.57 (m, H_β, doublet after D_2O exchange, J = 2.5 Hz), 4.87 (m, H_α), 5.08 (6 H, benzylic $-CH_2$), 5.83 (d, J = 8 Hz, –NH), 7.30 (15 H, phenyls); mass spectrum m/e 463 (M^-).

Anal. Calcd for $C_{26}H_{25}NO_7$: C, 67.37; H, 5.43; N, 3.02. Found: C, 67.49; H, 5.49; N, 2.90.

Dibenzyl *O*-(*N*-Carbobenzoxyglycyl)-*N*-carbobenzoxy-*threo*-β-hydroxy-DL-asparate (**4a**) **and Dibenzyl 2-Carbobenzoxyamino-**

fumarate (3).—A solution of *N*-carbobenzoxyglycine[14] (0.23 g, 1.1 mmol) in anhydrous THF (1.5 ml) was added dropwise to a solution of *N,N'*-carbonyldiimidazole (CDI, Aldrich Chemical Co., 0.17 g, 1.1 mmol) in THF (2.5 ml) and stirred for 1 hr. To this was then added in one portion, a solution of **2a** (0.50 g, 1.1 mmol) in 2 ml of THF. After 3 days the solution was concentrated to dryness, redissolved in $CHCl_3$, washed twice with 5% HCl solution, saturated $NaHCO_3$ solution, and water and dried. Evaporation of the solvent afforded a syrup (0.61 g) whose tlc ($CHCl_3$) showed three spots. Preparative tlc ($CHCl_3$) of an aliquot (75 mg) of the syrup separated the three components; the one of lowest R_f was shown by comparison ir to be recovered **2a** (10 mg), the middle R_f compound was tentatively assigned (by physical data) as **4a** (10 mg, 11%), and the upper R_f product was identified as the unsaturated **3** (20 mg, 32%). Compound **3** could not be induced to crystallize but an analytical sample was obtained by rechromatographing (1% CH_3OH–$CHCl_3$) on thin layer plates, and the extracted product was washed through a 1:1 charcoal–Celite column with $CHCl_3$. Evaporation of the solvent left a very pale yellow gum (**3**), uv λ_{max} 212 mμ (ϵ 18,400) and 270 (13,900) with a shoulder at 259; mass spectrum *m/e* 445 (M^+), 430, 354 ($-CH_2C_6H_5$), 310 ($-CO_2CH_2C_6H_5$), 248, 140, 107 ($C_6H_5CH_2O^+$), 91 (base peak).

Anal. Calcd for $C_{26}H_{23}NO_6$: C, 70.11; H, 5.20; N, 3.14. Found: C, 70.10; H, 5.27; N, 3.07.

Dibenzyl *O*-(*N*-Carbobenzoxyglycyl-*N*-carbobenzoxy-*erythro*-β-hydroxy-DL-aspartate (4b) and Dibenzyl 2-Carbobenzoxyaminofumarate (3).—The above procedure was followed using CDI (2.30 g, 14.2 mmol) in 10 ml of THF, *N*-carbobenzoxyglycine[14] (2.96 g, 14.2 mmol) in 10 ml of THF, and **2b** (3.30 g, 7.1 mmol) in 10 ml of THF. The reaction mixture was worked up after 2.5 hr, as described above, to give a pale yellow oil (4.4 g). Tlc (1% MeOH–$CHCl_3$) of the oil indicated one major spot, tentatively assigned as **4b**, and traces of starting material (**2b**) and unsaturated **3**. From several purifications by preparative tlc (1.5% MeOH–$CHCl_3$, 0.21 g/three plates) we obtained a fairly pure (not analytical grade) sample of **4b** (0.18 g, 81% yield). Further attempts at purifying **4b** only led to some decomposition to the unsaturated **3**. By the above preparative tlc we obtained a sample of **3** (8 mg, 5%) which was identical in the ir, nmr, and uv with compound **3** as isolated from the reaction with **2a**.

Dibenzyl 2-Carbobenzoxyaminofumarate (3) and Dibenzyl 2-Carbobenzoxyaminomaleate (5).—A solution of **4a** (10 mg), contaminated with a small amount of **3**, in 1 ml of $CHCl_3$ was divided in half and a few crystals of imidazole were added to one portion. After both portions were stirred overnight a tlc examination indicated no change in the ratio of **4a** to **3** in the absence of imidazole, but about a 60–70% conversion to **3** in the presence of imidazole. Similarly, when **4b** contaminated with only a trace of **3** was stirred overnight with imidazole there was only a 20–30% increase in intensity of the spot on tlc corresponding to **3**, whereas in the absence of imidazole there was no change.

A pure sample of **3** (0.22 g), when allowed to remain in a refrigerator for about 3 months, was slowly converted to approximately 5% of the cis isomer **5**. Preparative tlc afforded 10 mg of **5**, which could not be induced to crystallize. An analytical sample of **5** was obtained by chromatography as reported above for **3**, uv λ_{max} 211 mμ (ϵ 20,900) and 267 (14,000). Compound **3** (75 mg) was more readily converted to **5** by dissolving it in 1 ml of CH_2Cl_2, diluting with 15 ml of isooctane, and exposing it to daylight for 7 days. The solvent was removed by evaporation, and tlc of the resulting oil indicated a 25–35% enrichment of **5**: mass spectrum of **5** *m/e* 445 (M^+), 430, 354 ($-CH_2C_6H_5$), 310 ($-CO_2CH_2C_6H_5$), 248, 140, 107 ($C_6H_5CH_2O^+$), 91 (base peak).

Anal. Calcd for $C_{26}H_{23}NO_6$: C, 70.11; H, 5.20. Found: C, 69.92; H, 5.48.

DL-Aspartic Acid from Dibenzyl 2-Carbobenzoxyaminofumarate (3).—To a solution of **3** (0.10 g, 0.22 mmol) in 50% ethanol–dioxane (4 ml) was added 50 mg of PtO_2. The mixture was hydrogenated at 1 atm pressure for 70 min, during which the calculated amount of H_2 was consumed. Removal of the catalyst by filtration and concentration of the filtrate gave a residue which was crystallized from H_2O–ethanol, yielding 12 mg (41%) of DL-aspartic acid (identical in the ir with an authentic sample).

(14) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 2, Wiley, New York, N. Y., 1961, p 891.

Registry No.—**2a**, 16712-81-5; **2b**, 34910-00-4; **3**, 34910-01-5; **5**, 34910-02-6; L-asparagine, 70-47-3.

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Reaction of 3β-Acetoxy-8α,9α-oxido-5α-lanostane with Grignard Reagents[1]

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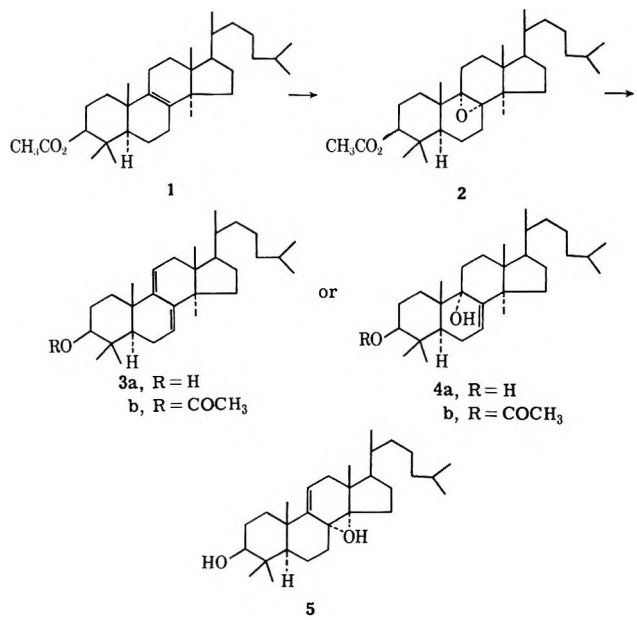
Synthetic degradation of lanosterol has been used to prepare otherwise difficultly accessible 14α-methyl steroids.[2] With the prospect of readily obtaining B/C ring juncture modifications of lanosterol for similar purposes, we decided to explore the oxirane ring opening reactions of an 8α,9α-oxidolanostane with methyl and allyl Grignard reagents. For this purpose dihydrolanosterol acetate (**1**) was oxidized in excellent yield to 3β-acetoxy-8α,9α-oxido-5α-lanostane (**2**).[3]



Methyllithium in ether did not attack the oxirane ring over a period of 19 days. With methylmagnesium iodide in refluxing toluene the product was dihydroagnosterol (**3a**). Allylmagnesium bromide[4] in ether at 25° reacted completely in a few hours with epoxy

(1) Steroids and Related Natural Products. 79. For Part 78 see G. R. Pettit and Y. Kamano, *Experientia*, **28**, in press. This investigation was supported by Public Health Service Research Grants RO1 CA08705-01, R01 CA08705-02, and R01 CA11451-01.

(2) *Cf.* G. R. Pettit and P. Hofer, *Helv. Chim. Acta*, **41**, 2142 (1963); *J. Chem. Soc.*, 4439 1963.

(3) J. Fried, J. W. Brown, and M. Applebaum, *Tetrahedron Lett.*, 849 (1965); I. G. Guest and B. A. Marples, *J. Chem. Soc. C*, 1468 (1971).

(4) H. Felkin and G. Roussi, *Tetrahedron Lett.*, 4153 (1965). The reactivity of allyl Grignard reagents toward epoxide ring-opening is much greater than that of methyl or isopropyl Grignard reagents. The stereochemical course leads to trans diaxial products.

acetate 2. The sole product was formulated as 3β,9α-dihydroxy-5α-lanost-7-ene (**4a**) on the following basis.

Acetylation with pyridine and acetic anhydride under the usual conditions gave a monoacetyl derivative **4b** which still contained a hydroxyl function. Very brief treatment with a trace of mineral acid converted the alcohol **4b** into dihydroagnosteryl acetate (**3b**). The nmr spectrum of alcohol **4a** showed the presence of a trisubstituted olefin. Further support for the olefin was provided by the mass spectrum, which displayed an *m/e* 426 fragment (M − 18). The foregoing would allow the product to be assigned structure **4a** or **5**, of which **4a** is preferred. In this respect the lithium in ethylamine reduction of epoxide 2 gives the α alcohol.[3] Also, the strong vicinal 14α-methyl-8α-hydroxy steric interaction in **5** is absent in **4**.

When no products involving alkylation of the lanostane skeleton were detected the Grignard study was not pursued further. However, the new syntheses of dihydroagnosterol and alcohol **4** were considered potentially useful in approaches to natural products such as batracheotoxinin A.

Experimental Section[5]

Dihydroagnosteryl Acetate (3b).—To a solution of 3β-acetoxy-8α,9α-oxido-5α-lanostane (0.65 g) in dry ether (25 ml) was added (during 5 min) the Grignard reagent (in ether) derived from magnesium turnings (4.9 g) and methyl iodide (28 g). After 20 hr at 25° dry toluene (75 ml) was added and the ether was removed by distillation. The solution was heated under reflux for 11 days, cooled, and poured over crushed ice. The product was isolated using ether to afford a brown grease which slowly solidified. Adsorption on activated alumina (22 g) from solution in benzene and elution with benzene–chloroform (4:1) gave dihydroagnosterol (**3a**, 0.60 g): mp 150–154°; λ_{max}^{EtOH} 236, 243, and 252 mμ. Acetylation gave dihydroagnosteryl acetate, plates from ethanol: mp 167–169°; λ_{max}^{EtOH} 236, 243, and 252 mμ. Acetate **3b** was identical[5] with an authentic specimen.

Reaction between Allylmagnesium Bromide and Oxide 2.—Allylmagnesium bromide was prepared[6] and stored at 0° in a narrow-necked bottle fitted with a septum cap. The assay[7] was 0.66 *M* and 15 ml of the reagent was added to oxide 2 (0.71 g) in dry ether (20 ml, under an atmosphere of dry nitrogen). The reaction mixture was kept at 22° and monitored by tlc upon removal of 0.5-ml aliquots. After 14 hr the mixture was poured into 5% ammonium sulfate (100 ml) at 5°. Ether (25 ml) was used for isolation. The product (0.69 g) was a clear oil which showed one component on tlc. Crystallization from methanol containing one drop of pyridine gave fine needles (0.30 g), mp 132–133°, of a compound formulated as 4a: ν_{max}^{KBr} 3500–3200 cm^{-1}; pmr (pyridine) δ 0.8, 0.88, 0.93, 1.03, 1.12 (ring and side-chain methyl groups), 2.06 (s, 3 protons), 3.5 (broad, 1 proton), 4.25 (1 proton), 5.18 and 5.47 ppm (broad, 1 proton); mass spectrum *m/e* 426 (M$^+$ − 18).

Anal. Calcd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 80.77; H, 11.64.

The product (0.18 g) in pyridine (1.5 ml)–acetic anhydride (1 ml) was kept at 22° for 19 hr. Ether (30 ml) was added and the solution was washed with 2 *N* sodium bicarbonate until effervescence ceased (5 × 15 ml). Drying and solvent removal furnished a colorless solid (0.18 g), one component on tlc, which crystallized as needles from methanol containing one drop of pyridine. The alcohol weighed 0.13 g: mp 170–175° (raised to 171–175° by further recrystallization from the same solvent system); ν_{max}^{KBr} 3580, 1724, and 1230 cm^{-1}; pmr δ 0.675 (C-13 Me), 0.86 (d, *J* = 6.5 Hz, C-26, 27 methyl groups), 0.90, 0.99, 1.18 (C-4, 10, 14α, and 20 methyl groups), 2.03 (3β-OAc), 4.5 (broad, 3α-H), 5.33 ppm (broad, 7-H).

Anal. Calcd for $C_{52}H_{54}O_3$: C, 78.63; H, 11.55. Found: C, 78.98; H, 11.64.

Conversion of Alcohol 4a to Dihydroagnosterol (3a).—Concentrated hydrochloric acid (1 drop) was added to alcohol **4a** (30 mg) in ethanol (5 ml). The ethanol was removed *in vacuo* and the residue was partitioned between ether (15 ml) and water (15 ml). The ether phase was washed with 2 *N* sodium bicarbonate, dried, and evaporated to a white solid (28 mg) which crystallized from ethanol as needles of dihydroagnosterol (**3a**), mp and mp with an authentic sample 150–154°, λ_{max}^{EtOH} 236, 243, and 252 mμ.

Registry No.—**3a**, 2644-75-9; **3b**, 5600-01-1; **4a**, 34910-26-4; **4b**, 34910-27-5.

(5) The introduction to the Experimental Section of an earlier contribution provides a summary of general methods and reagents employed here; see J. C. Knight, G. R. Pettit, and P. Brown, *J. Org. Chem.*, **35**, 1415 (1970).

(6) O. Grummitt, E. P. Budewitz, and C. C. Chudd, *Org. Syn.*, **36**, 61 (1956).

(7) H. Gilman, E. A. Zoellner, and J. B. Dickey, *J. Amer. Chem. Soc.*, **51**, 1576 (1929).

The Camptothecin δ-Lactone[1a]

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As part of an approach to total synthesis of the antineoplastic agent[2a-c] camptothecin (**1**),[2d,e] it became necessary to investigate synthesis of the terpenoid unit,[3] or an appropriate subunit, of the alkaloid. Synthesis of camptothecin by combination of appropriate fragment molecules, involving formation of the pyridone amide bond and condensation with the pyrroloidinoquinoline entity, would require an eight-carbon unit. A δ-lactone precursor of the type depicted by

(1) (a) The research upon which this publication is based was performed pursuant to Contract No. NIH-71-2308 and PH 43-65-94 with Chemotherapy, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare, and by Research Grants CA-11451-02 and CA-10612-04 from the National Cancer Institute and GP 4939 from the National Science Foundation. (b) Part XXVIII of the series Antineoplastic Agents. For part XXVII see G. R. Pettit, L. E. Houghton, N. H. Rogers, R. M. Coomes, D. F. Berger, P. R. Reucroft, J. F. Day, J. L. Hartwell, and H. B. Wood, Jr., *Experientia*, **28**, 381 (1972).

(2) (a) J. M. Venditti and B. J. Abbott, *Lloydia*, **30**, 332 (1967). (b) W. D. DeWys, S. R. Humphreys, and A. Goldin, *Cancer Chemother. Rep.*, **52**, 229 (1968). (c) J. A. Gottlieb, A. M. Guarino, J. B. Call, V. T. Oliverio, and J. B. Block, *ibid.*, **54**, 1461 (1970). (d) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, **88**, 3888 (1966). (e) A. T. McPhail and G. A. Sim, *J. Chem. Soc. B*, 923 (1968). Three total synthesis of camptothecin have recently been reported: G. Stork and A. G. Schultz, *J. Amer. Chem. Soc.*, **93**, 4074 (1971); R. Volkmann, S. Danishefsky, J. Eggler, and D. M. Solomon, *ibid.*, **93**, 5576 (1971); M. C. Wani, H. F. Campbell, G. A. Brine, J. A. Kepler, M. E. Wall, and S. G. Levine, Abstracts, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 12–17, 1971. Recent structure/activity investigations have been summarized by J. A. Beisler, *J. Med. Chem.*, **14**, 1116 (1971); T. K. Liao, W. H. Nyberg, and C. C. Cheng, *J. Heterocycl. Chem.*, **8**, 373 (1971); J. A. Kepler, M. C. Wani, J. N. McNaull, M. E. Wall, and S. G. Levine, *J. Org. Chem.*, **34**, 3853 (1969); M. C. Wani, J. A. Kepler, J. B. Thompson, M. E. Wall, and S. G. Levine, *Chem. Commun.*, 404 (1970).

(3) The terpenoid origin of the nontryptophan portion of the indole alkaloids has been established; see A. R. Battersby, *Pure Appl. Chem.*, **14**, 117 (1967), and A. I. Scott, *Accounts Chem. Res.*, **3**, 151 (1970). Biogenetic linkage of camptothecin to the indole alkaloids has been suggested by E. Wenkert, K. G. Dave, R. G. Lewis, and P. W. Sprague, *J. Amer. Chem. Soc.*, **89**, 6741 (1967). A chemical transformation of the tetrahydrocarboline unit of the indole alkaloids to the camptothecin quinoline unit has been reported: E. Winterfeldt and H. Radunz, *Chem. Commun.*, 374 (1971).

structure **2** seemed attractive and was investigated as follows.

Ethyl α-carbethoxy-γ-ethylglutaconate (**3a**) was known[4] and appeared a suitable first stage for the proposed synthesis. Accordingly, base condensation of diethyl malonate with chloroform and concomitant elimination of hydrogen chloride yielded the sodium salt of tetraethyl 1-propene-1,1,3,3-tetracarboxylate (ethyl α,γ-dicarbethoxy-α-glutaconate),[5] which was ethylated directly to give ethyl α,γ-dicarbethoxy-α-ethylglutaconate.[4] Treatment of the latter compound with 1 molar equiv of sodium ethoxide was reported to yield triester **3a** in 95% yield.[4] However, the decarbethoxylation reaction was accompanied, under a variety of reaction conditions, by the formation of diethyl ethylmalonate. In our hands, this competing mode of reaction could only be suppressed to about 25% of the reaction product. The desired triester **3a** was apparently formed by ethoxide attack at either of the C-3 carbethoxy groups, followed by elimination of ethyl carbonate to yield the resonance-stabilized anion **3b**, while attack at the C-1 carbethoxy group leads to the formation of diethyl ethylmalonate. Attack at the C-1 carbethoxy groups was confirmed by the isolation of the other product, ethyl propiolate, as its trimer triethyl 1,3,5-benzenetricarboxylate.[6] The triester product **3a** was separable, by gas–liquid chromatography, into a major component and two minor components, presumably corresponding to the cis and trans 2 olefins and the 1 olefin. The triester mixture was used as such for the next step, as this involved a base condensation with resultant formation of the resonance-stabilized anion **3b**. The anion structure would be expected, of course, to be independent of the actual olefin isomer or isomer mixture used for its genesis.

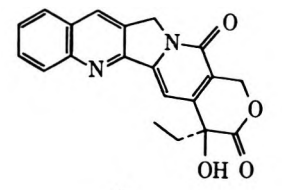
Base condensation of the triester mixture **3a** with formaldehyde gave the desired lactone, diethyl 3-ethyl-5,6-dihydro-2*H*-pyran-2-one-5,5-dicarboxylate (**2**). Formation of neutral lactone **2** would be expected to regenerate base as ethoxide ions, and should, therefore, proceed in the presence of a catalytic amount of base. Indeed, this mechanistic consideration proved to be critical, as the use of 1 molar equiv of sodium ethoxide gave a complex reaction mixture containing virtually no lactone. Increasing the proportion of solvent, ethanol, also gave poorer yields. The reaction was best accomplished in the absence of solvent and with catalytic amounts of sodium ethoxide.

The mass spectrum of lactone **2** showed a weak molecular ion at *m/e* 270 in accord with observed weak or zero molecular ions for substituted diethyl malonates.[7] The spectrum showed similarities to those reported for substituted diethyl malonates in which there was no possibility of a McLafferty rearrangement of the alkyl substituents.[7] The base peak at *m/e* 198 could be obtained by hydrogen rearrangement to give a M − $COOC_2H_4$ ion as well as by initial expulsion of CO_2 from the lactone[8] followed by loss of C_2H_4 (226 → 198). The *m/e* 198 peak showed metastable ion peaks for loss of H_2O (M − 90) followed by loss of 28 (C_2H_4) leading to *m/e* 152, the second most abundant peak, and for loss of 28 (C_2H_4) (M − 100), as expected for ethyl esters. There was a metastable peak for the conversion *m/e* 198 → 125 corresponding to loss of $COOC_2H_5$.

The isomeric lactone, diethyl 5-ethyl-5,6-dihydro-2*H*-pyran-2-one-3,5-dicarboxylate (**4**), was obtained as a minor product from the lactonization reaction *via* attack at C-3 of the triester anion **3b** by formaldehyde. The structure was confirmed by analysis of the nuclear magnetic resonance spectra of the two lactones (**2** and **4**). The vinylic proton of lactone **4** underwent a downfield shift of 62.4 Hz relative to that of lactone **2** due to the electron-withdrawing carbethoxy group at C-5, while the methylene protons of the ethyl group showed a corresponding upfield shift of 31.2 Hz corresponding to the change in environment from allylic to saturated.

Direct hydroxylation of lactone **2** with, *e.g.*, monopersuccinic acid in water, as well as other methods, such as osmium tetroxide or ruthenium tetroxide, were unsuccessful. Generally, lactone **2** was isolated in good recovery. Interestingly, application of the persuccinic acid reaction[9] to isomeric lactone **4** gave only epoxide **5**.

An extensive effort was devoted to developing a means for partial decarboxylation of malonate **2** to provide ethyl ester **6**. However, application of various



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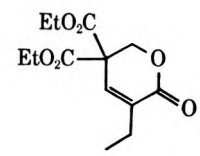

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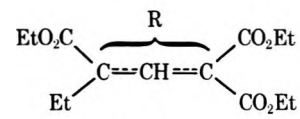
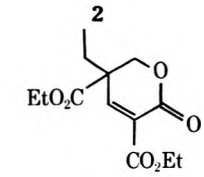


3a, R = H
b, R = −



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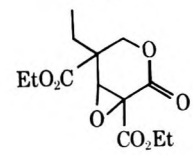

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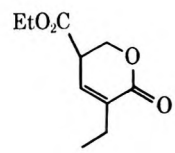

6

acidic and basic reaction conditions led to a variety of different products arising from a facile retroaldol degradation of lactone **2**. Several neutral methods (*e.g.*, dimethyl sulfoxide–sodium cyanide and lithium iodide) offered no regress and other approaches to camptothecin were eventually considered more promising. Nevertheless, the convenient synthesis developed for lactone **2** should prove valuable in evaluating camptothecin E-ring structure/activity relationships.

Experimental Section

Melting points are uncorrected and were recorded on a Kofler melting point apparatus. All organic solvent extracts were

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(5) (a) M. Conrad and M. Guthzert, *Ber.*, **15**, 2841 (1882); (b) C. K. Ingold and E. A. Perren, *J. Chem. Soc.*, 1582 (1921).

(6) The trimerization of ethyl propiolate to aromatic compounds has been described by L. S. Meriwether, E. C. Colthup, G. W. Kennerly, and R. N. Reusch, *J. Org. Chem.*, **26**, 5155 (1961).

(7) J. H. Bowie, D. H. Williams, S. O. Lawesson, and G. Schroll, *ibid.*, **31**, 1792 (1966).

(8) L. Friedmann and F. A. Long, *J. Amer. Chem. Soc.*, **75**, 2832 (1953).

(9) R. Lombard and G. Schroeder, *Bull. Soc. Chim. Fr.*, 2800 (1963).

dried over either anhydrous magnesium sulfate or anhydrous sodium sulfate. The nuclear magnetic resonance (nmr) spectra ($CDCl_3$, TMS internal standard) were recorded by Miss K. Reimer using a Varian A-60 spectrometer. Gas–liquid chromatography was performed with a Varian 1200 instrument (flame ionization detector) using nitrogen as carrier gas. Elemental microanalytical data was provided by Dr. A. Bernhardt, Mikroanalytisches Laboratorium, 5251 Elbach uber Engelskirchen, West Germany. Mass spectral data was obtained by Mr. R. Scott, employing an Atlas CH-4B mass spectrometer equipped with a molecular beam inlet system.

Tetraethyl 1-Pentene-1,1,3,3-tetracarboxylate (Ethyl α,γ-Dicarbethoxy-α-ethylglutaconate).—The following method is a modification of those reported by Ingold and Perren,[5b] for the preparation of the sodium salt of tetraethyl 1-propene-1,1,3,3-tetracarboxylate, and Thole and Thorpe,[4] for the ethylation reaction.

Sodium (46 g, 2 mol) was dissolved in ethanol (absolute, 750 ml). Diethyl malonate (160.2 g, 1 mol) was added over 30 min with heating and stirring and the mixture was heated at reflux for a further 15 min. Heating was stopped and, as soon as reflux had subsided, chloroform (60.5 g, 0.51 mol) was added at a rate sufficient to maintain vigorous reflux (over 15 min). Heating was resumed and the mixture was heated at reflux for 3 hr. The apparatus was arranged for distillation and 110 ml of the solvent was distilled from the reaction vessel.[10] The apparatus was returned to the reflux position, ethyl iodide (85.8 g, 0.55 mol) was added over 10 min, and the mixture was refluxed for a further 36 hr. After cooling the reaction mixture was poured into water (750 ml) and extracted with chloroform (10 × 200 ml). The chloroform layer was washed with potassium hydroxide solution (10%, 5 × 200 ml) and water (5 × 200 ml) and dried, and the solvent was removed under reduced pressure to give an orange oil (203.2 g). Fractionation (Vigreux column) gave tetraethyl 1-pentene-1,1,3,3-tetracarboxylate (46–63%), bp 153–157° (1.5 mm) [reported[4] bp 213° (20 mm)]. The nmr spectrum showed δ 0.88 (3 H, triplet, J = 7.6 Hz, protons on C-5 coupled to C-4 methylene protons), 1.28 and 1.325 (12 H, two triplets, J = 7.1 Hz, methyl protons), 2.22 (2 H, quartet, J = 7.6 Hz, protons on C-4 coupled to C-5 methyl protons), 4.0–4.5 (8 H, complex methylene multiplet), 7.61 ppm (1 H, singlet, vinylic proton on C_2).

Triethyl 3-Ethyl-1(2)-pentene-1,1,3-tricarboxylate (Ethyl α-Carbethoxy-γ-ethylglutaconate) (3a).—Sodium (5.36 g, 0.233 mol) was dissolved in ethanol (absolute, 670 ml) and the solution was cooled to 10°. Tetraethyl 1-pentene-1,1,3,3-tetracarboxylate (83.4 g, 0.233 mol) in ethanol (absolute, 670 ml) was added over 30 min with the temperature maintained between 6 and 10° (immersion in an ice bath), and a deep yellow color appeared. The reaction mixture was stirred for 20 hr at 10° and then poured into chloroform (500 ml) and shaken well with hydrochloric acid (0.6 N, 375 ml). The aqueous layer was extracted with chloroform (3 × 200 ml) and the combined chloroform layer was washed with saturated salt solution (3 × 250 ml), dried, and evaporated under reduced pressure to give a yellow oil (57.5 g). Glc [column, 3% QF_1 on Chromosorb W (60–80 mesh), 5 ft × 0.125 in., Pyrex; flow rate, 12 ml/min; temperature, initial 80°, final 215°, at an average of 3.75° per minute] showed diethyl ethylmalonate (appearance temperature 117–120°) and three peaks with an appearance temperature around 170° in the ratio of 28:26:64. Diethyl ethylmalonate was removed by fractional vacuum distillation and the mixture of isomers of triethyl 3-ethyl-1(2)-pentene-1,1,3-tricarboxylate (**3a**) was used as such for the next step.

Diethyl 3-Ethyl-5,6-dihydro-2*H*-pyran-2-one-5,5-dicarboxylate (2).—Sodium ethoxide (60 mg), triethyl 3-ethyl-1(2)-pentene-1,1,3-tricarboxylate (7.68 g), and paraformaldehyde (0.801 g) were heated to 97° over 60 min (the reaction mixture becoming clear at about 80°) and then maintained at 97° for 3.25 hr. The mixture was cooled and dissolved in ether (50 ml), and the ethereal solution was washed with dilute hydrochloric acid (1 N, 3 × 10 ml) and water (2 × 10 ml), dried, and evaporated under reduced pressure to give an oil (5.96 g). Chromatography on 24 g of silica gel (Merck 0.05–0.2 mm) gave diethyl 3-ethyl-5,6-dihydro-2*H*-pyran-2-one-5,5-dicarboxylate (**2**) (2.15 g) as a colorless oil, eluted with ligroin–benzene (4:1). The nmr spectrum showed δ 1.11 (3 H, triplet, J = 7.4 Hz), 1.28 (6 H, triplet, J = 7.0 Hz), 2.40 (2 H, doublet of quartets, J = 7.4, 7.4, 7.4, 1.4 Hz), 4.26 (4 H, quartet, J = 7.0 Hz), 4.69 [2 H, narrow signal showing small (0.8 Hz) splitting], 6.71 ppm (1 H, narrow signal, $W_{1/2}$ = 3.6 Hz).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.98; H, 6.88.

The mass spectrum showed m/e (rel intensity at 70 and 12 eV, respectively) 271 (M + 1, 13, 2), 270 (M, 1.5, 4), 226 (10, 27), 198 (100, 100), 180 (27, 26), 170 (25, 7), 169 (19, 3), 152 (94, 25), 151 (38, 0), 125 (83, 6), 124 (30, 2); M^+ at 173.3 (calcd for 226 → 198, 173.5), 163.5 (198 → 180, 163.6), 146.0 (198 → 170, 145.9), 143.5 (226 → 180, 143.4), 128.3 (180 → 152, 128.3), 106.8 (270 → 170, 107.0), 101.5 (152 → 124, 101.2).

Further elution of the column gave **diethyl 5-ethyl-5,6-dihydro-2H-pyran-2-one-3,5-dicarboxylate** (**4**, 0.42 g) as a colorless oil. The nmr spectrum showed δ 0.98 (3 H, triplet, J = 7.2 Hz), 1.23 (3 H, triplet, J = 7.0 Hz), 1.35 (3 H, triplet, J = 7.0 Hz), 1.88 (2 H, quartet, J = 7.2 Hz), 4.0–4.5 (6 H, complex multiplet), 7.75 ppm (1 H, singlet).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.65; H, 6.78.

Diethyl 5-Ethyl-3,4-epoxytetrahydro-2*H*-pyran-2-one-3,5-dicarboxylate (5).—A suspension of peroxydisuccinic acid[9] (135 mg) in water (1 ml) was heated and stirred at 50° for 1 hr. The resulting aqueous solution was cooled to 42° and diethyl 5-ethyl-5,6-dihydro-2*H*-pyran-2-one-3,5-dicarboxylate (**4**) (135 mg) was added. The reaction mixture was stirred at 42° for 8 hr, cooled to about 10°, neutralized with sodium bicarbonate, and extracted with ether. The ethereal solution was washed with water (2 × 10 ml), dried, and evaporated under reduced pressure to give a quantitative yield of diester **5**. Recrystallization from ligroin gave colorless crystals: yield 43 mg; mp 50–51°; glc [column, 5% SE-30 on Chromosorb W (60–80 mesh), 5 ft × 0.125 in., stainless steel; temperature, −178°; flow rate, 10 ml/min] retention time 10.5 min relative to starting material 9.5 min. The glc of the mother liquors showed only the one peak corresponding to the isolated solid. The mass spectrum showed a peak at m/e 286 (calcd for $C_{13}H_{18}O_7$, M^+ 286). The nmr spectrum showed δ 1.02 (3 H, triplet, J = 7 Hz), 1.32 (3 H, triplet J = 7 Hz), 1.33 (3 H, triplet, J = 7 Hz), 1.8 (2 H, quartet, J = 7 Hz, exhibiting further splitting), 4.0–4.6 ppm (7 H, complex multiplet).

Anal. Calcd for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.40; H, 6.27.

Registry No.—**2**, 34993-71-0; **4**, 34993-72-1; **5**, 34993-73-2; tetraethyl 1-pentene-1,1,3,3-tetracarboxylate, 34993-74-3.

(10) This removal of a quantity of the solvent was necessary to ensure optimization of the ethylation reaction; otherwise, unethylated material was obtained, as the pyrone, ethyl 6-ethoxy-2*H*-pyran-2-one-3,5-dicarboxylated, *via* elimination of ethanol from tetraethyl 1-propene-1,1,3,3-tetracarboxylate. See M. Guthzeit and O. Dressel, *Ber.*, **22**, 1413 (1889).

Catalytic Deoxygenation of Organic Compounds by Carbon Monoxide. II.[1] Direct Synthesis of Schiff Bases from Aromatic Nitro Derivatives, Aldehydes, and Carbon Monoxide

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The subject of the present communication is a novel synthesis of Schiff bases by intercepting *in situ* deoxygenated nitro derivatives by aldehydes. Thus, in the presence of a group VIII metal catalyst (*e.g.*, rhodium carbonyl), the interaction of benzaldehyde and aromatic nitro compounds under a pressure of

(1) For part I, see A. F. M. Iqbal, *Tetrahedron Lett.*, 3385 (1971).

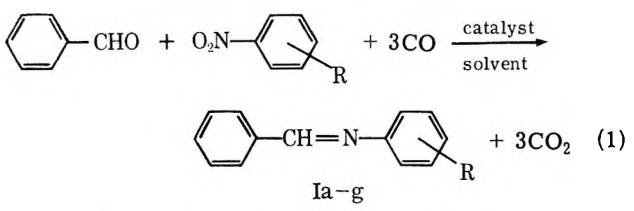
TABLE I

SCHIFF BASES BY THE CATALYTIC CONVERSION OF BENZALDEHYDE AND AROMATIC NITRO COMPOUNDS IN THE PRESENCE OF CARBON MONOXIDE[a]

					Physical constants[f]			
					Ir ($\nu_{C=N}$),[d]	^{1}H Nmr chemical shift, δ, ppm[e]		
Schiff base	R =	Yield, %[b]	Bp, °C (Torr)[c]	Mp, °C[c]	μ[f]	CH=N	Aromatic	CH_3
Ia	H	80	88–92 (0.3)	48–49	6.15	8.28	6.9–8.0	
Ia	H	6[g]	88–92 (0.3)	48–49	6.15	8.28	6.9–8.0	
Ia	H	78[h]	88–92 (0.3)	48–49	6.15	8.28	6.9–8.0	
Ib	*p*-OCH_3	60		71–72	6.15	8.30	6.65–7.95	3.70
Ic	*p*-$N(CH_3)_2$	65		98–99	6.19	8.37	6.5–7.95	2.93
Id	*o*-CH_3	82	94–98 (0.4)		6.12	8.17	6.6–7.95	2.32
Ie	*m*-CH_3	85	90–93 (0.3)		6.15	8.25	6.7–7.95	2.31
If	*p*-CH_3	83	97–100 (0.3)		6.14	8.24	6.8–7.9	2.26
Ig	*p*-Phenyl	84		147	6.16	8.41	7.05–8.05	

[a] Constant conditions: 0.1 mol benzaldehyde, 0.11 mol nitro derivative, 10^{-5} mol hexarhodium hexadecacarbonyl, 50 ml pyridine (solvent), 150 atm carbon monoxide (initial pressure at room temperature), 170°, 3 hr, 0.5-l. rocking stainless steel autoclave. [b] Based on benzaldehyde. [c] Boiling and melting points are uncorrected. [d] Liquids were measured neat, solids in chloroform. [e] Nmr spectra were taken in carbon tetrachloride. [f] Observed physical constants are identical with those of authentic samples, easily synthesized by applying the standard procedure [see, for example, A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., London, 1956, p 653] for condensation of aldehydes with corresponding amines. [g] Yield obtained on substituting pyridine by 50 ml of benzene. [h] In dry *N*-methylpyrrolidine as solvent (at 70°, 50 atm, 6 hr).

carbon monoxide eventuated in the formation of the corresponding azomethines in high yields (eq 1).



Carbon monoxide apparently functions here solely as a deoxygenating agent. All reactions were carried out in a stainless steel autoclave, using dry pyridine as solvent and hexarhodium hexadecacarbonyl as catalyst. The Schiff bases were obtained by fractional distillation or, where necessary, by fractional crystallization of the pyridine-free reaction mixture. The identity of the azomethine compounds has been ascertained by derivatization, as well as by ir and nmr spectroscopic comparison with authentic samples.

Some results and reaction conditions have been summarized in Table I. Only 5–7% Schiff base formation takes place in benzene, while over 80% yield of the same is obtained in pyridine solvent. Anhydrous *N*-methylpyrrolidine, for example, enables successful operation under essentially mild conditions (70°, 50 atm CO). Analogous enhancement of the catalytic activity of rhodium carbonyls by the addition of tertiary amines has been noted previously.[1]

Azomethine yields from dimethylamino- and methoxy-substituted nitrobenzenes are distinctly lower. However, in view of the paucity of data and manipulative losses, particularly during work-up of the latter compounds, substituent effects are not easy to interpret. Some trends may seem apparent; nonetheless, it would be premature to make any generalizations. While exclusively rhodium carbonyl has been listed in Table I, under analogous conditions, iron pentacarbonyl, triruthenium dodecacarbonyl, and dicobalt octacarbonyl likewise catalyze the formation of Schiff base by the present route. In the absence of any one of these metals, no formation of the corresponding azomethine derivative was observed under the given conditions.

A reasonable explanation for Schiff bases would be eq 2. This is unlikely, since intermediacy of amines is

$$ArNO_2 \longrightarrow ArNH_2 \xrightarrow{PhCHO} ArN{=}HCPh \qquad (2)$$

precluded by the absence of water[1] or of sufficiently high pressures of hydrogen.[2] The formation of aryl isocyanate by reductive carbonylation[5] of aromatic nitro compounds would, on the other hand, suggest the following route[6] (eq 3).

$$ArNO_2 \longrightarrow ArNCO \xrightarrow{PhCHO} ArN{=}HCPh \qquad (3)$$

However, control experiments with nitrobenzene and ethanol, in place of benzaldehyde, under conditions of azomethine formation yielded but small amounts of the corresponding urethane (<10%) and urea (<5%) derivatives. The major product, as expected,[1] was aniline (*ca.* 45%), which could not have originated in phenyl isocyanate since no water was present. While consequently the isocyanate route (eq 3) may at best account for a minor portion of Schiff base, we believe that the preponderant mechanism incorporates the following sequence of reactions.

$$ArNO_2 + 2CO \xrightarrow{\text{Catalyst}} [Ar\text{–}\overline{N}] + 2CO_2$$
II

II + Ar'CHO ⟶ Ar'CH(O)—NAr
IIIa

IIIa ⇌ Ar'CH=NAr(O)
IIIb

$$III + CO \longrightarrow Ar'CH{=}NAr + CO_2$$

(2) At low partial pressures of hydrogen the corresponding 1,3-diarylureas are formed[3,4] along pathways independent of intermediate amine.

(3) A. F. M. Iqbal, submitted for publication.

(4) F. L'Eplattenier, P. Matthys, and F. Calderazzo, *Inorg. Chem.*, **9**, 342 (1970).

(5) W. B. Hardy and R. P. Bennett, *Tetrahedron Lett.*, 961 (1967).

(6) H. Staudinger and R. Endle, *Ber.*, **50**, 1042 (1917).

The first step is considered to involve the catalytic deoxygenation of the nitro compound to a nitrene (II), discrete or complexed, whose subsequent addition to the carbonyl compound, present in solution, would furnish the oxazirane IIIa, and correspondingly the isomeric nitrone IIIb.

The intermediacy of nitrene and nitrenoid intermediates has been invoked by previous investigators[4,7,8] in an attempt to rationalize the formation of an array of products from catalytic coversions of nitro compounds with carbon monoxide. Even in formation of isocyanates,[5] nitrene intervention is made very probable by the analogous reaction of azides.[9] One might thus expect *in situ* trapping of the reactive intermediate by aldehyde (*vide supra*) to prevail over transformation to isocyanate and subsequent reaction (eq 3). As additional persuasive evidence for the first two steps may be cited the formation of Schiff bases by thermolysis of phenyl azide in aldehydes or ketone, reported by Neiman, *et al.*[10,11] The expected nitrone or oxazirane, however, remained elusive in these latter reactions. This fact is ascribed by the authors to probable oxidation of excess carbonyl compound by the oxygenated intermediates, which in the process become reduced to Schiff base.

Once formed, III can be reduced by carbon monoxide in the presence of rhodium carbonyl to the Schiff base I, as could also be verified experimentally.[12]

Experimental Section

Materials.—Commercial carbon monoxide was used without further purification. Benzaldehyde and various nitro compounds were freshly distilled prior to reaction. Hexarhodium hexadecacarbonyl was prepared by the reductive carbonylation of rhodium chloride in the presence of iron pentacarbonyl.[14] Pyridine and *N*-methylpyrrolidine were additionally dried and distilled over potassium hydroxide. Authentic samples of Schiff bases for comparison of physical constants were synthesized by usual condensation[2] of benzaldehyde with corresponding amines.

General Procedure for Schiff Bases.—All reactions were carried out in a stainless steel autoclave of 500-ml capacity, heated by an external rocking electric oven. Only one experiment, with benzaldehdye and *p*-nitrobiphenyl, will be described here to exemplify the general procedure adopted; the effect of varying conditions can be seen from the data presented in Table I. A solution of benzaldehyde (0.1 mol), *p*-nitrobiphenyl (0.11 mol), and hexarhodium hexadecacarbonyl (10^{-5} mol) in 50 ml of anhydrous pyridine was allowed to react with carbon monoxide (150 atm). The content of the autoclave was heated during 40 min to 165–170° and held at this temperature for 3 hr. After cooling, the autoclave was discharged and pyridine was evaporated from the mixture under vacuum. The residue was swirled with *ca.* 40–50 ml of methanol and filtered to give in 84% yield substantially pure crystals of *N*-benzylidene-*p*-phenylaniline (Ig), mp 147°. Identity of the compound was confirmed by mixture melting point, ir, and nmr spectroscopic comparison with an authentic sample. Yields and physical properties of further azomethine derivatives are compiled in Table I.

(7) J. E. Kmiecik, *J. Org. Chem.*, **30**, 2014 (1965).
(8) T. Kajimoto and J. Tsuji, *Bull. Chem. Soc. Jap.*, **42**, 827 (1969).
(9) R. P. Bennett and W. B. Hardy, *J. Amer. Chem. Soc.*, **90**, 3295 (1968).
(10) L. A. Neiman, V. I. Maimind, and M. M. Shemyakin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1498 (1962).[11]
(11) Compare also *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1831 (1964).
(12) For example, α-phenyl-*N*-phenylnitrone[13] was smoothly deoxygenated by hexarhodium hexadecacarbonyl at 150° and 130 atm carbon monoxide pressure to *N*-benzylideneaniline.
(13) O. H. Wheeler and P. H. Gore, *J. Amer. Chem. Soc.*, **78**, 3363 (1956).
(14) B. L. Booth, M. J. Else, R. Fields, H. Goldwhite, and R. N. Haszeldine, *J. Organometal. Chem.*, **14**, 417 (1968).

Registry No.—Ia, 538-51-2; Ib, 783-08-4; Ic, 889-38-3; Id, 5877-55-4; Ie, 5877-58-7; If, 2272-45-9; Ig, 13924-28-2; carbon monoxide, 630-08-0.

Conformational Preference of *cis*-8-Oxabicyclo[4.3.0]non-3-ene

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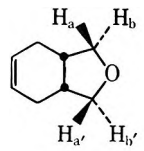
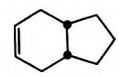
Received January 25, 1972

cis-8-Oxabicyclo[4.3.0]non-3-ene (**1**) has found occasional use as a model of *cis*-bicyclo[4.3.0]non-3-ene (**2**), primarily due to the ease of preparing **1**.[2] As part of our effort to test the validity of using an oxygen-containing molecule as a model for its carbocyclic analog,[3] we examined the ground-state conformation of **1**.



1

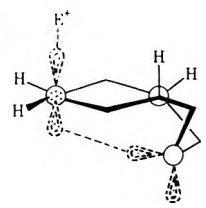


2

Using results based on the steric course of epoxidation, previous investigations have suggested that **5** is the preferred ground-state conformer of **2**[4] (Scheme I[5]). We have examined the products from epoxidation of **1** and find a fortuitously similar product ratio (Scheme I). These data would appear to support, based on steric data alone, conformer **8** as the ground-state conformer. Furthermore, this would be consistent with the steric course of oxymercuration and the oxygen participation noted for this reaction.[6] However, the nmr spectrum of **1** is better accommodated by conformer **9**.

The spectrum of **1** exhibited a multiplet for the pro-

(1) NDEA Predoctoral Fellow, 1968–1971. Abstracted, in part, from the Ph.D. Thesis of Rodney D. Otzenberger, Montana State University, 1971.
(2) (a) E. L. Eliel and C. Pillar, *J. Amer. Chem. Soc.*, **77**, 3600 (1955); (b) B. Rickborn and S. Y. Lwo, *J. Org. Chem.*, **30**, 2212 (1965).
(3) (a) B. P. Mundy, A. R. DeBernardis, and R. D. Otzenberger, *ibid.*, **36**, 3830 (1971); (b) B. P. Mundy and R. D. Otzenberger, *ibid.*, **37**, 677 (1972).
(4) J. C. Jallageas and E. Casadevall, *C. R. Acad. Sci., Ser. C*, **268**, 449 (1969).
(5) We did not analyze the epoxides, but rather compared the alcohols resulting from lithium aluminum hydride reduction of the epoxide mixture. The stereochemistry of the alcohols had been previously assigned,[3b] and the known stereospecificity of reductive opening of the epoxide moiety assured us that we were analyzing an alcohol mixture representative of the epoxide mixture.
(6) See ref 3b. The stereospecificity and oxygen participation is best explained by invoking an intermediate for reactions proceeding *via* carbonium ion intermediates.



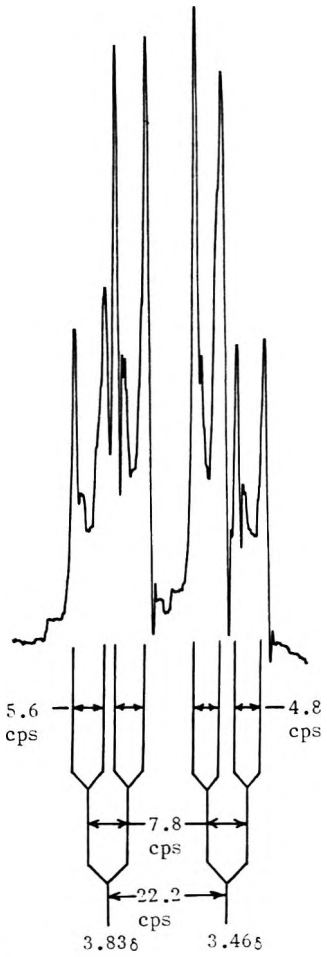
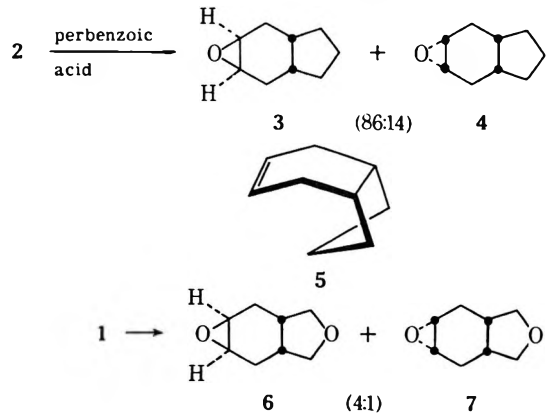
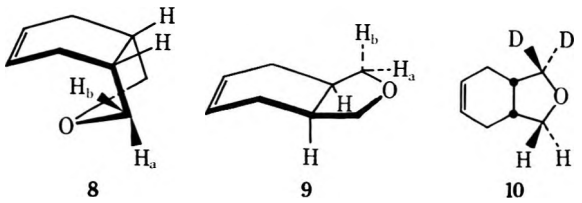


Figure 1.—Partial nmr spectrum of *cis*-8-oxabicyclo[4.3.0]-non-3-ene.

SCHEME I
STERIC COURSE OF EPOXIDATION[5]



tons adjacent to the ether oxygen. The spectrum of *cis*-8-oxabicyclo[4.3.0]7,7-dideuterionon-3-ene (**10**) ex-



hibited the *same* multiplet, but with only half the "intensity." This requires that H_a and $H_{a'}$ share equivalent magnetic environments, as must H_b and $H_{b'}$. An analysis of the coupling of these protons with each other and with the protons at the ring juncture (Figure 1) suggests that **9** will be the stable conformer.

A very simple ABX pattern for the spectrum of **1** can be analyzed. Protons H_a ($H_{a'}$) and H_b ($H_{b'}$) exist in different magnetic environments, leading to different chemical shifts of δ 3.46 and 3.83, respectively. H_a couples with H_b to give a coupling constant of $J = 7.8$ cps. The only other coupling available now can be between the proton at the ring juncture. At this point we face interpretative problems because coupling constant–dihedral angle relationships have not been well studied for heterocyclic systems. However, we will assign the larger coupling constant to the trans coupling of H_b with the ring juncture proton. Additional chemical evidence supports the necessary conformation, **9**, resulting from this assignment. If **8** were the ground-state conformer, proton H_b would be expected to be upfield from H_a because it would be influenced by the shielding cone of the alkene system. Another argument for **9** being the ground-state conformer might be suggested from the simple suggestion that in **8** there would be extensive repulsion of the π electrons with the nonbonding electrons of oxygen. The effects of interacting dipoles of oxygen heteroatoms has been well documented in the field of carbohydrate chemistry.[7]

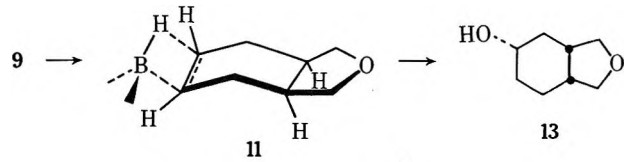
Although the use of molecular models does not always solve conformational problems, their use can be instructive in the sense that certain conformations are readily noted to be improbable. Space-filling models are particularly useful in this study and it can be readily suggested that only two conformations, **8** and **9**, are reasonable, both maintaining a boat conformation of the cyclohexene moiety. As we have already noted, nmr evidence is consistent with, but does not prove, the assumption that **9** is the ground-state conformer. We next sought chemical evidence to substantiate our assignment.

Buttressing our argument for **9** being the ground-state conformer are the results from our studies related to the steric course of hydroboration. Because the transition state for hydroboration has a structure similar to that of the reactants, it has been suggested that the stereochemistry of the reaction products can be correlated with the ground state of the reactants.[8] Brown[8c] has convincingly argued that the observed high reactivity for diborane addition is most consistent with a low activation energy, and with thujopsene has suggested that the energy of interconversion of conformations would be greater than the energy of activation for diborane addition. Although we do not have the necessary thermodynamic data, we suggest that, in our fused ring system, conformational interconversions might be also expected to be higher than the activation energy for diborane addition. With this reasonable assumption we can consider transition states **11** and **12**, resembling **9** and **8**, respectively. The ex-

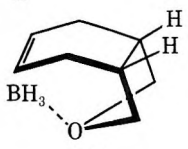
(7) See, for example, R. V. Lemieux in "Molecular Rearrangements," Vol. 2, P. de Mayo, Ed., Interscience, New York, N. Y., 1964, Chapter 12.

(8) (a) F. Frinquelli and A. Taticchi, *J. Chem. Soc. C*, 2011 (1971); (b) J. Klein and D. Lichtenbert, *J. Org. Chem.*, **35**, 2654 (1970); (c) S. P. Acharya and H. C. Brown, *ibid.*, **35**, 3874 (1970).

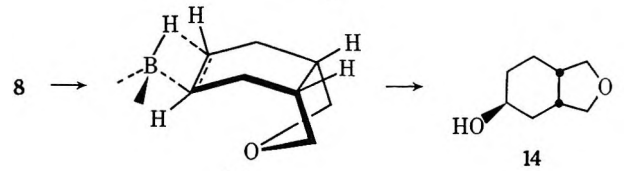
pected major product resulting from **11** would be **13**[9] and from **12** would be **14**.[10] We find **13** to make up 72% of the reaction product after addition of diborane. The apparent insensitivity of **1** to steric demands of the reactants is most consistent with **9** being the ground-state conformer.[11]



11 **13**



15



12 **14**

Diborane is known to complex with tetrahydrofuran.[12] That our results from diborane addition are not merely a reflection of simple coordination with the ether oxygen of **1**, followed by a rapid transfer to the π system, can best be seen by examining space-filling models. Steric crowding around the π system of **8** is so great that it precludes the possibility of addition, as might be suggested by **15**. If complexing were to occur, it would most certainly have to take place on the other face of the tetrahydrofuran moiety. This brings us to another argument against an intermediate such as **15**. Since the reaction is carried out in an ether, a consideration of the high reactivity of diborane with alkene bonds coupled with the necessary and unfavorable competition of solvent and the oxygen of **1** would suggest that preferential complexing, as in **15**, is not reasonable.

The results of this work, coupled with our previous investigations relating to the directive[3a] and electronic effects of the oxygen heteroatom,[3b] clearly demonstrate that there can be serious consequences resulting from the use of heterocyclic molecules as models for the carbocyclic analogs.

(9) Attack of the other side of the π system would be less favorable due to interference of the protons at the ring juncture. Being in a boat, this interaction would be of critical importance, similar to that found in the lack of endo addition to nonbornene.

(10) Space-filling models clearly indicate that in conformation **12** there is no possibility of attack from the other side of the π system.

(11) We find an almost identical product ratio after the addition of disiamylborane.

(12) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 42.

Experimental Section

The nmr spectra were recorded on a Varian A-60 instrument, using deuteriochloroform as solvent and tetramethylsilane as standard.

Epoxidation of *cis*-8-Oxabicyclo[4.3.0]non-3-ene (1).—To 5 ml of chloroform containing 5 mmol of perbenzoic acid[13] was added 0.5 g of **1**. The reaction mixture was maintained at 0° for 3 days, after which it was washed with a solution of 10% bicarbonate. The chloroform solution was dried and reduced in volume to yield 0.56 g of crude product. Distillation yielded 240 mg of a water-clear liquid, bp 94–98° (9 mm). The epoxide mixture was immediately reduced with 20 mg of lithium aluminum hydride in 10 ml of dry tetrahydrofuran. The known alcohols[3b] resulting from this procedure were analyzed by analytical glc.

Synthesis of *cis*-8-Oxabicyclo[4.3.0]7,7-dideuteriononon-3-ene (10).—Following the method of Bailey,[14] 7.7 g of *cis*-1,2,3,6-tetrahydrophthalic anhydride in 40 ml of anhydrous tetrahydrofuran were slowly added to a cooled solution prepared from 2.0 g of sodium borohydride in 10 ml of tetrahydrofuran. After 1 hr, 20 ml of 6 *M* hydrochloric acid was cautiously added to the reaction mixture. After the addition had been completed, the reaction mixture was extracted with dichloromethane. The combined extracts were dried, filtered, and distilled, yielding 1.7 g of product, bp 129–132° (10 mm). This lactone was taken directly onto the next step, where 0.5 g of lithium aluminum deuteride and 30 ml of anhydrous tetrahydrofuran reduced it to the 1,4-diol (0.75 g). Cyclization by the method of Eliel[2a] was affected with 1 g of *p*-toluenesulfonyl chloride in 10 ml of pyridine. The product, identical by glc with **1**, exhibited an nmr spectrum identical with that of **1**, except that the portions of the spectrum assigned to the protons at C-7 and C-9 exhibited only half the intensity.

Hydroboration of *cis*-8-Oxabicyclo[4.3.0]non-3-ene (1).—To a reaction mixture prepared from 1.5 g of sodium borohydride and 3.6 g of **1** in 17 ml of anhydrous diglyme was slowly added 3 ml of a freshly distilled sample of boron trifluoride etherate. The reaction mixture was maintained at 20° and under a nitrogen atmosphere during the addition. After stirring for 30 min, 3.5 ml of 2 *N* sodium hydroxide was slowly added. This was followed by the slow addition of 3.5 ml of 30% hydrogen peroxide. After stirring for an additional 1 hr the reaction mixture was extracted with ether, and the resulting crude alcohol mixture was compared with the known products[3b] by analytical glc.

Registry No.—**1**, 3471-41-8; **10**, 34959-69-8.

Acknowledgments.—We acknowledge the support of the Endowment and Research Foundation of Montana State University and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. Helpful discussions with Dr. Arnold Craig have also been appreciated.

(13) G. Braun, "Organic Syntheses," Collect. Vol. I., Wiley, New York, N. Y., 1941, p 431.

(14) D. M. Bailey and R. E. Johnson, *J. Org. Chem.*, **35**, 3574 (1970).

See Editorial, *J. Org. Chem.*, **37**, No. 13, 4A (1972).

Heterocyclic Studies. 36. Acyldiazepinium Intermediates in Thermal Reactions of Diazabicyclo[3.2.0]heptenones†[1]

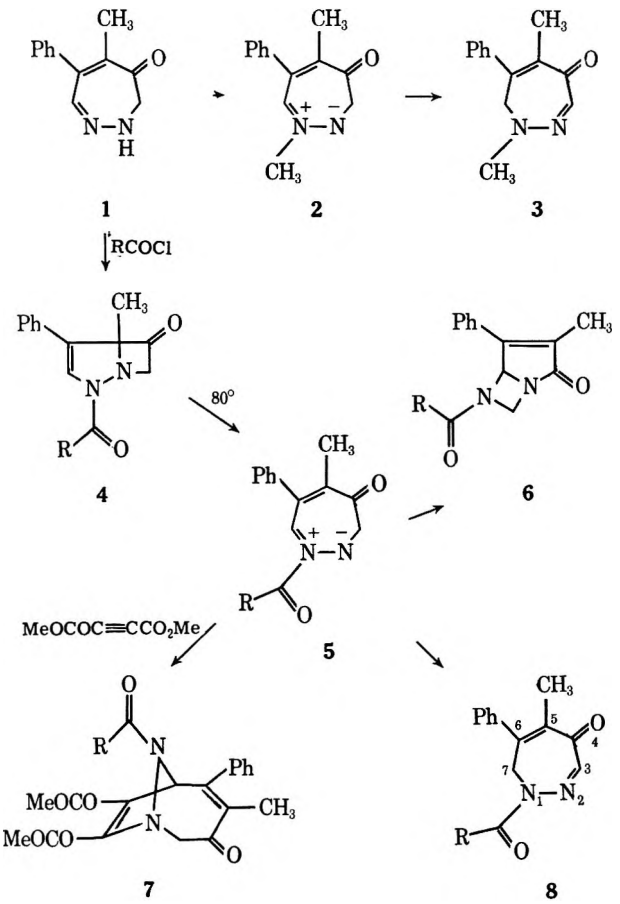
Summary: The bicyclic ketones **4** undergo thermal ring opening to acyldiazepinium betaines **5** which can be trapped by 1,3 cycloaddition; rearrangement of **5** gives the bicyclic lactams **6** and 1-acyl-1,7-dihydrodiazepinones **8**.

Sir: Methylation of the 2,3-dihydrodiazepinone **1** at N-1 gives the betaine **2**,[2] but the corresponding 1-acyl derivatives of **1** exist entirely as the 2-acyl-1,2-diazabicyclo[3.2.0] ketones **4**.[3] This difference in structure can be attributed to the poor stabilization of positive charge in the acyl betaine **5**, as compared to **2**. The facile formation of cycloaddition products from **2**[2] prompted us to examine whether acyl betaines could be produced from the acylbicyclic ketones and trapped at elevated temperatures. On heating **4a** or **4b** at 80° in excess dimethyl acetylenedicarboxylate, the crystalline adducts **7a** and **7b** were in fact obtained in yields of 55 and 30%, respectively (Scheme I). The spectra of these products were fully consistent with the bicyclo[4.2.1] structures and resembled those of the methyl betaine adduct,[2] although the methylene protons were nonequivalent in **7a** and **7b** [for **7a**, δ_A 5.20, δ_B 5.35 (J_{AB} = 4.2)].[4]

Thermal isomerization of the benzoyl ketone **4** in the absence of dipolarophile involves an unusual rearrangement leading in 75% yield to the bicyclic lactam **6b**.[5] The isolation of the acyl–azomethine imine adducts **7** indicates the accessibility of the acyl betaine at moderate temperature and strongly suggests that **5b**, rather than the intermediates previously postulated,[6] is the precursor of **6b**. This behavior, however, appeared to be in marked contrast to the thermal reaction of the methyl betaine **2**, which undergoes sigmatropic hydrogen migration to the 1-methyl-1,7-dihydrodiazepinone **3**.[7]

To examine this point, the acetyl bicyclic ketone **4a** was heated in benzene solution at 80°. The nmr spectrum of the resulting mixture showed peaks corresponding to the lactam **6a** and the acetyldihydrodiazepinone **8a**, in a ratio of 2:1, accounting for over 90% of the total integral. The two products were then isolated by crystallization, the less soluble yellow minor product **8a** crystallizing first. Structure **6a** is based on the very close correspondence of spectra with those of **6b** and the characteristic reaction of the methylene diamine ring of **6a** with acidic methanol to give the 5-acetamido-1-methoxymethylpyrrolone, analogous to the well-characterized methanolysis product of **6b**.[5]

Scheme I



In **4–8**,
a, R = CH_3
b, R = C_6H_5

The contrasting results with the methyl and acyl betaines thus reflect merely a difference in product distribution. Reexamination of the reaction product from pyrolysis of **4b** by nmr, after removing a first crop of **6b**, showed a trace (maximum ~8%) of **8b**. The role of the substituent in the partition of the acyl betaines between products **6** and **8**, and the pathway from **5** to **6** are now being studied.

The 1-acetyl-1,7-dihydrodiazepinone structure **8a** follows from the close correspondence of properties with those of the 1-methyl derivative **3** (including the characteristic low ir C-4 carbonyl frequency, ν^{CHCl_3} 1622

† Attention is called to the possibility of including supplementary data [*e.g.*, see footnote 4 of this communication and editorial, *J. Org. Chem.*, **37**, No. 13, 4A (1972)]: F. D. G.

(1) Supported by Grant GP-9322 from the National Science Foundation.

(2) O. S. Rothenberger, R. T. Taylor, D. L. Dalrymple, and J. A. Moore, *J. Org. Chem.*, **37**, 2540 (1972).

(3) J. A. Moore, F. J. Marascia, R. W. Medeiros, and R. L. Wineholt, *ibid.*, **31**, 34 (1966).

(4) Complete experimental details on all compounds described in this communication will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 16th Street, N.W., Washington, D. C. 20036, by referring to code number JOC-72-2796. Remit $3.00 for photocopy or $2.00 for microfiche.

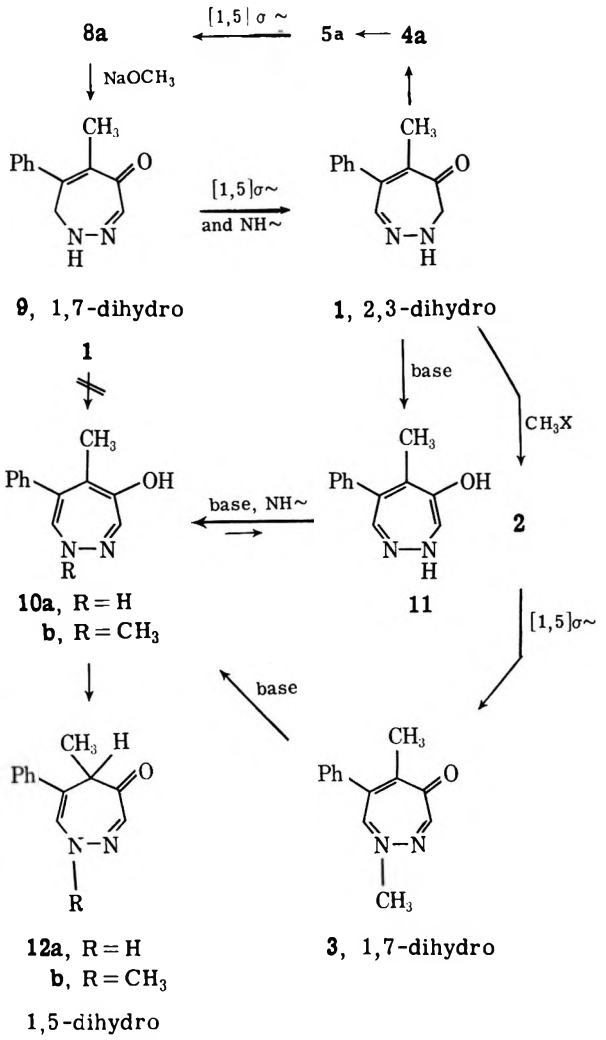
(5) J. M. Eby and J. A. Moore, *ibid.*, **32**, 1346 (1967).

(6) J. A. Moore, R. L. Wineholt, F. J. Marascia, R. W. Medeiros, and F. J. Creegan, *ibid.*, **32**, 1353 (1967).

(7) M. G. Pleiss and J. A. Moore, *J. Amer. Chem. Soc.*, **90**, 4738 (1968).

cm^{-1}) and its further transformations. Base-catalyzed methanolysis of **8a** at 25° gave the deacetylated 1,7-dihydrodiazepinone **9** (Scheme II) ($\nu_{C=O}^{Chf}$ 1605

SCHEME II



cm^{-1}) as very pale yellow crystals, mp 119–121°, then 148–150°. The double melting point reflects conversion to the 2,3-dihydrodiazepinone **1** (mp 152°). This isomerization occurred rapidly at 20° in stronger base and obeyed clean first-order kinetics on heating at 80° in neutral solution ($k_1^{CDCl_3}$ 2 × 10^{-5} sec^{-1}; k^{CD_3OD} 9 × 10^{-5} sec^{-1}). No deuterium incorporation occurred at C-3 in CD_3OD. The transformation **9** → **1** thus involves a 1,5-sigmatropic shift of hydrogen from C-7 to C-3, in the reverse direction to that of the 2,3-dihydrobetaines **2** and **5**.[8] The faster rate in CD_3OD, in contrast to the rearrangement of **2** to **3** which is slightly faster in $CHCl_3$ than in CH_3OH,[7] is consistent with the fact that proton transfer, in addition to sigmatropic hydrogen migration, is required in the reaction **9** → **1**.

Tautomeric Relationships in the 1,2-Dihydrodiazepin-4-one System.—The NH 1,7-dihydro compound **9** is the third of three possible unsubstituted tautomers in this series; all have been isolated in crystalline form. The NH 1,5-dihydrodiazepinone **12a** is obtained from the 2,3-dihydro isomer by base-catalyzed equilibration *via* the enols **10a** and **11** and is the more stable of the two ketones.[9] Furthermore, the 1-methyl-1,7-diazepinone **3** is converted completely to the 1-methyl derivative **12b** by base *via* the enol **10b**.[9] It is remarkable, therefore, that isomerization of **9**, even in the presence of base, gives exclusively the 2,3-dihydro tautomer and none of the more stable **12a**.

This combination of interconversions by sigmatropic rearrangements and enolizations establish the stability order 1,7 < 2,3 < 1,5 in this multitautomer system. The 1,7-dihydro system is accessible only when this stability sequence is reversed by the formation of 1-substituted 2,3-dihydrobetaines; it can be predicted that a 2-substituted 1,7-dihydrobetaine would undergo extremely rapid rearrangement to a 2-substituted 2,3-dihydro derivative.

(8) The same process was observed previously in the base-catalyzed conversion of the 7-methoxy-1-benzoyl-1,7-dihydrodiazepinone to the 7-methoxy-2,3-dihydrodiazepinone, but was not recognized as such, and was represented as a series of prototropic rearrangements: R. L. Wineholt, E. Wyss, and J. A. Moore, *J. Org. Chem.*, **31**, 48 (1966).

(9) M. G. Pleiss and J. A. Moore, *J. Amer. Chem. Soc.*, **90**, 1369 (1968).

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RECEIVED JUNE 2, 1972

Thallium in Organic Synthesis. XXXVI. A New Synthesis of Allenic Esters†

Summary: α-Alkyl-β-keto esters can be converted in a single step into allenic esters by initial reaction with hydrazine (giving the 5-pyrazolones *in situ*) followed by oxidation by thallium(III) nitrate.

Sir: There has been much recent interest in the synthesis[1] and reactions[2] of allenic acids and esters. Available synthetic methods include addition of Wittig reagents to ketenes[3] or acid chlorides,[4] reaction of propargyl alcohols with nickel carbonyl,[5] and basic isomerization of acetylenes.[6] We now report a simple synthesis of allenic esters from α-alkyl-β-keto esters.

Our recently reported new synthesis of α,β-acetylenic esters[7] by thallium(III) nitrate (TTN)[8] oxidation of 3-substituted 5-pyrazolones (**2**, R_3 = H) involves, in a formal sense, the dehydration of a β-keto ester. We have now found that α-alkyl-β-keto esters (**1**) are converted under the same conditions to allenic esters (**6**). Thus, the β-keto ester is first converted to a 3,4-disub-

† Part XXXV: A. McKillop, J. D. Hunt, and E. C. Taylor, *J. Org. Chem.*, in press.

(1) S. C. Sandler and W. Karo, "Organic Functional Group Preparations," Vol. 2, Academic Press, New York, N. Y., 1971.

(2) M. Caserio in "Selective Organic Transformations," Vol. 1, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1970, p 239.

(3) W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1966).

(4) (a) H. J. Bestmann, G. Graf, H. Hartung, S. Kalewa, and E. Vilsmaier, *Chem. Ber.*, **103**, 2794 (1970); (b) H. J. Bestmann and H. Hartung, *ibid.*, **99**, 1198 (1966).

(5) E. R. H. Jones, G. H. Whitham, and M. C. Whiting, *J. Chem. Soc.*, 4628 (1957).

(6) G. Eglington, E. R. H. Jones, G. H. Mansfield, and M. C. Whiting, *ibid.*, 3197 (1954).

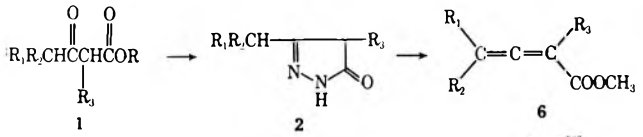
(7) E. C. Taylor, R. L. Robey, and A. McKillop, *Angew. Chem., Int. Ed. Engl.*, **11**, 48 (1972).

(8) A. McKillop, J. D. Hunt, E. C. Taylor, and F. Kienzle, *Tetrahedron Lett.*, 5275 (1970).

stituted 5-pyrazolone (2, R_3 = alkyl) by addition of 1 equiv of hydrazine, and then a solution of 2 equiv of TTN in methanol is added to a suspension or solution of the pyrazolone in methanol. The reaction mixture is stirred at room temperature for 30 min and the precipitated thallium(I) nitrate removed by filtration. The filtrate is poured into water, which is extracted with chloroform, and the extracts are dried (Na_2SO_4) and filtered through a short column of Florisil. Evaporation of the solvent followed by distillation gives the pure allenic ester. Representative conversions are given in Table I.

TABLE I

SYNTHESIS OF ALLENIC ESTERS FROM β-KETO ESTERS WITH TTN/CH_3OH

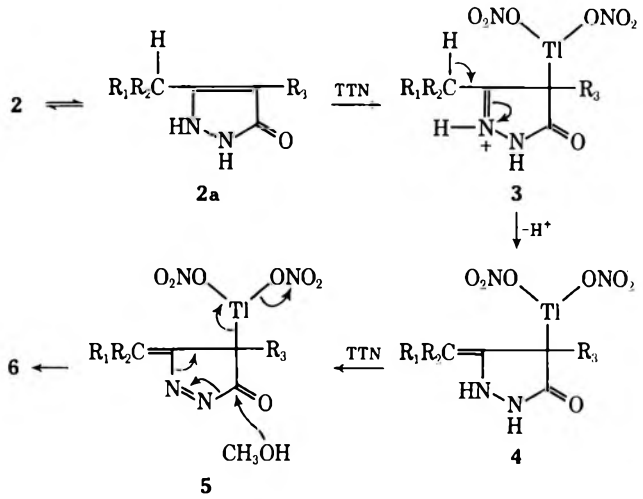


R_1	R_2	R_3	Yield, %[b,c]
H	H	CH_3	50
H	H	CH_2CH_3	48
H	H	$CH(CH_3)_2$	54
H	H	$(CH_2)_4CH_3$	70
CH_2CH_3	H	CH_3	55
CH_2CH_3	H	CH_2CH_3	61

[a] Based upon the intermediate 5-pyrazolone. [b] Yield after distillation. [c] Identity of products established *via* spectral and analytical data.

This reaction, like that of β-keto esters to α,β-acetylenic esters,[7] formally represents the dehydration of the precursor α-substituted β-keto ester. In fact, isolation of the intermediate 5-pyrazolone is unnecessary, and allenic esters can be formed in a single operation by initial addition of hydrazine to a methanol solution of the α-substituted β-keto ester followed by addition of TTN in methanol. In this manner, ethyl 2-isopropylacetoacetate was converted to 3-carbomethoxy-4-methyl-1,2-pentadiene [6, $R_1 = R_2 = H$; $R_3 = CH(CH_3)_2$] in 63% yield.

The conversion of 5-pyrazolones to allenic esters can be explained by electrophilic thallation of the enamine (3-pyrazolin-5-one) tautomer[9] (2a) of the 5-pyrazolone (2), followed by proton loss to give the alkylidene pyrazolidone (4). Subsequent oxidation to 5 and solvolysis by methanol would give the observed allenic ester (6).[10]



The ready availability of monoalkylated β-keto esters[13] and their facile (and usually quantitative) conversion to 5-pyrazolones[14] make this route to allenes particularly appealing. Further work in this area is in progress.

(9) A. R. Katritzky and J. M. Lagowski, *Advan. Heterocycl. Chem.*, **2**, 28 (1963).

(10) Although 5-pyrazolones have been mercurated in the 4 position[11] and oxidized to diazacyclopentadienones by lead tetraacetate,[12] no conversions analogous to those reported here are known.

(11) (a) W. Schrauth and H. Bauerschmidt, *Ber.*, **47**, 2736 (1914); (b) R. H. Kent and J.-P. Anselme, *Can. J. Chem.*, **46**, 2322 (1968).

(12) B. T. Gillis and R. Weinkam, *J. Org. Chem.*, **32**, 3321 (1967).

(13) E. C. Taylor, G. H. Hawks, and A. McKillop, *J. Amer. Chem. Soc.*, **90**, 2421 (1968).

(14) R. H. Wiley and P. Wiley, "Pyrazolones, Pyrazolidones, and Derivatives," Vol. 20 in the series "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience, New York, N. Y., 1964.

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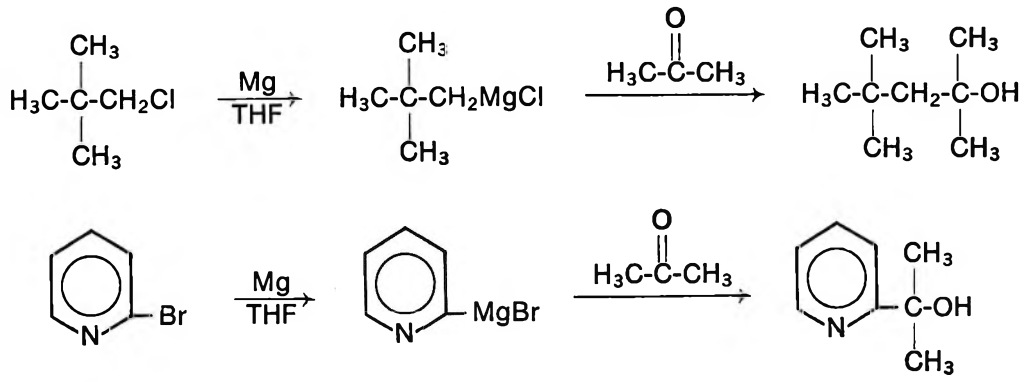
Grignard Reactions



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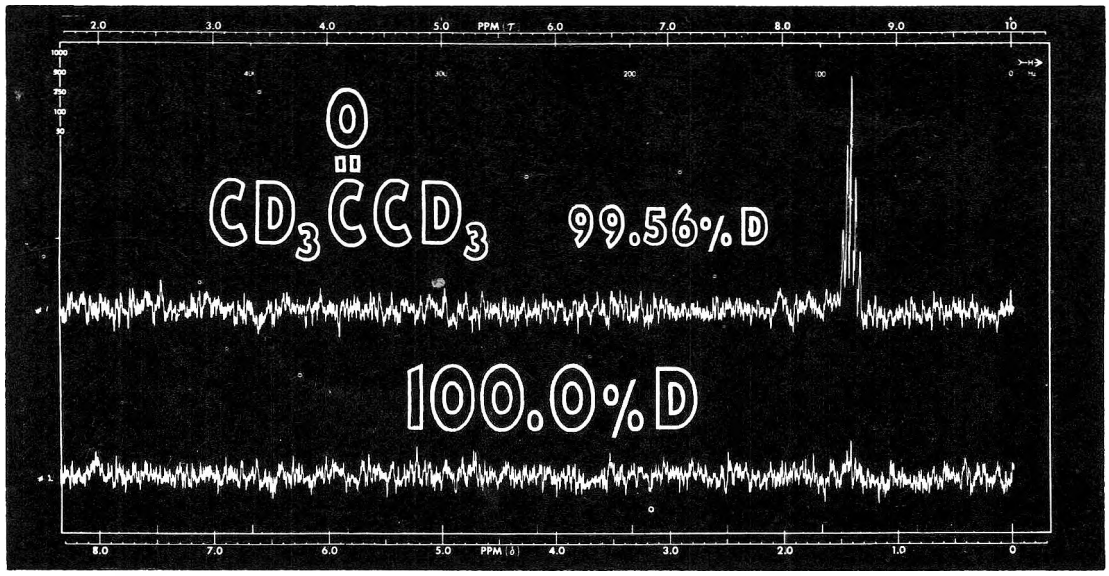

Nuclear magnetic resonance spectroscopy (nmr) is an extremely useful tool for the organic chemist; however, a prime experimental difficulty of this technique is the requirement for solvents which dissolve a wide range of compounds but which have minimal spectral absorptions. Carbon tetrachloride and carbon disulfide should be ideal choices because they have no nmr absorptions. However, they dissolve only a limited range of compounds and nmr spectra are usually obtained by using proton-containing or conventional deuterated solvents. As a result, nmr spectra often are partially masked by solvent absorptions or spinning sidebands. In addition, the availability of Fourier Transform accessories which enable nmr experiments on very dilute solutions compounds the difficulty of choosing the appropriate solvent.

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