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Photochemical Transformations of Phthaloyl Dixanthates and Phthaloic Bisdithiocarbamic Anhydrides

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Received March 31, 1970

The reaction of phthaloyl dichloride with potassium *O*-alkyl xanthates gave rise to the corresponding unsymmetrical phthaloyl dixanthates. Treatment of phthaloyl dichloride with dithiocarbamates, on the other hand, gave the symmetrical bisdithiocarbamic anhydrides. Photolysis of unsymmetrical phthaloyl dixanthates in benzene solution gave chiefly *trans*-biphthalyl, whereas symmetrical phthaloic bisdithiocarbamic anhydrides gave a mixture of *trans*-biphthalyl and the corresponding thiuram disulfides. No benzocyclobutenedione could be isolated from these runs. The thermal decomposition of unsymmetrical phthaloyl dixanthates yielded a mixture of several products, consisting of *trans*-biphthalyl, thiophthalic anhydride, carbonyl sulfide, and the corresponding *O,S*-dialkyl xanthates.

Photolysis of acyl xanthates are reported to give rise to the corresponding alkyl xanthates.[2] It has been shown that in these reactions the CO–S bond of the acyl xanthates undergoes homolytic fission giving rise to acyl and xanthate radicals. These acyl radicals are decarbonylated at appropriate temperatures to give alkyl radicals which then combine with xanthate radicals giving rise to the corresponding alkyl xanthates. By taking advantage of the fact that primary acyl radicals are decarbonylated only slowly, it has been possible to synthesize α diketones through the photolysis of the corresponding xanthates. Thus, the photolysis of di-*O*-ethyl *S,S*-glutaryl xanthate, for example, has been shown to give a satisfactory yield of cyclopentane-1,2-dione.[2] As aroyl xanthates are also reasonably stable at room temperatures, we argued that the photolysis of a xanthate such as symmetrical di-*O*-alkyl *S,S*-phthaloyl dixanthate (IV) should lead to the formation of benzocyclobutenedione, through the intramolecular coupling of the intermediate aroyl radical.

Acyl and aroyl xanthates are conveniently prepared by the treatment of potassium *O*-alkyl xanthates with the corresponding acid chlorides in acetone solution at low temperatures.[2] In a preliminary communication,[3] we have shown that the reaction of potassium *O*-ethyl xanthate with phthaloyl dichloride in acetone solution does not give rise to the expected symmetrical di-*O*-ethyl *S,S*-phthaloyl dixanthate (IVb), but the unsymmetrical phthaloyl dixanthate (VIb) (Scheme I). In the present investigation, we have examined the reactions of several potassium alkyl xanthates with symmetrical phthaloyl dichloride (I) with a view to studying the nature of the products formed in these cases.

Treatment of potassium *O*-methyl xanthate with I in ether solution around 0° gave a 78% yield of a product, identified as unsymmetrical di-*O*-methyl *S,S*-phthaloyl dixanthate (VIa), mp 120°. The identity of this product was confirmed on the basis of analytical results and spectral data. The infrared spectrum of VIa showed a carbonyl absorption at 1780 cm^{-1}, characteristic of γ-lactones. The nmr spectrum of VIa showed a multiplet centered around τ 2.86 (4 H) due to the phenyl protons and a singlet at τ 6.31 (6 H) due to the methoxyl protons. The multiplet due to the aromatic protons showed a characteristic ABCD pattern, as would be expected for the unsymmetrical structure VIa. Further evidence concerning the unsymmetrical structure VIa for this xanthate was derived from its conversion to phthalide, on treatment with Raney nickel.

The reason why the unsymmetrical phthaloyl dixanthate VIa is formed from the reaction of I with potassium *O*-methyl xanthate was not very apparent. Knapp[4] had reported that an unsymmetrical diphenyl dithiolphthalate is formed when I is treated with a mixture of phenyl thiolacetate and anhydrous aluminum chloride. The formation of the unsymmetrical isomer has been explained in terms of the reaction of the unsymmetrical phthaloyl dichloride (II), which is assumed to be formed from I, under the influence of aluminum chloride.[5] However, it is very doubtful that

(1) To whom correspondence shoud be addressed.

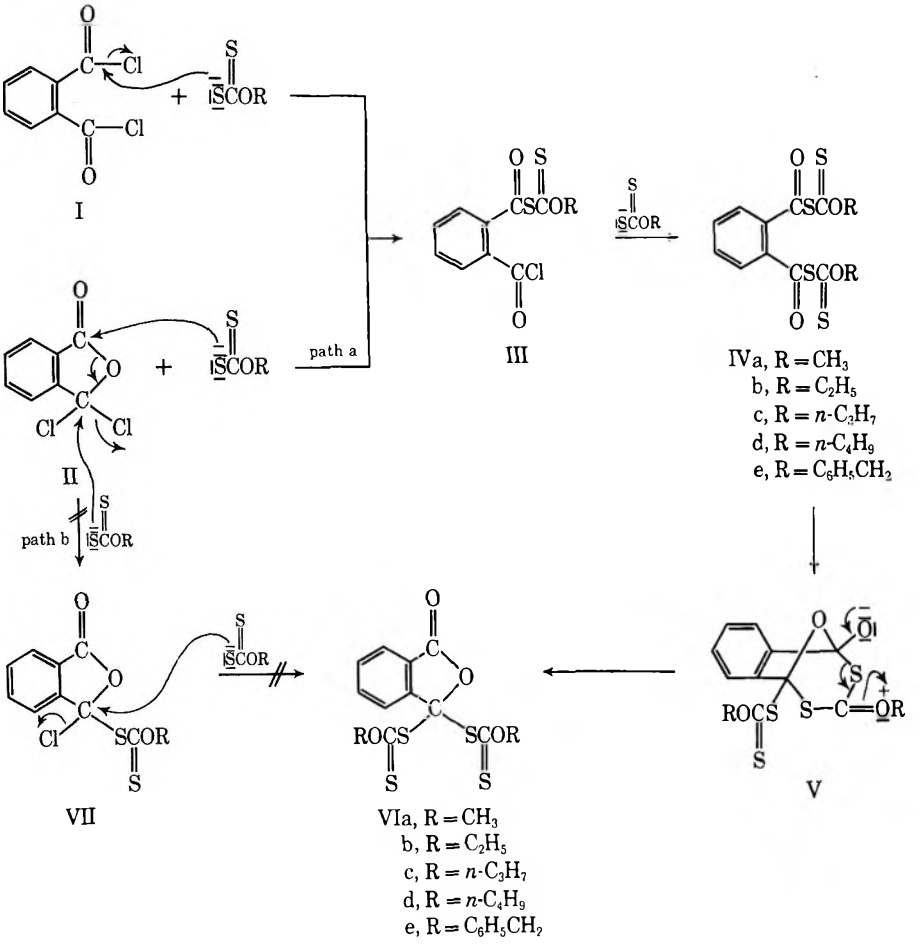
(2) D. H. R. Barton, M. V. George, and M. Tomoeda, *J. Chem. Soc.*, 1967 (1962).

(3) A. Shah, S. N. Singh, and M. V. George, *Tetrahedron Lett.*, 3983 (1968).

(4) W. Knapp, *Monatsh. Chem.*, **58**, 176 (1931); *Chem. Abstr.*, **26**, 436 (1932).

(5) E. Ott, "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 528.

SCHEME I



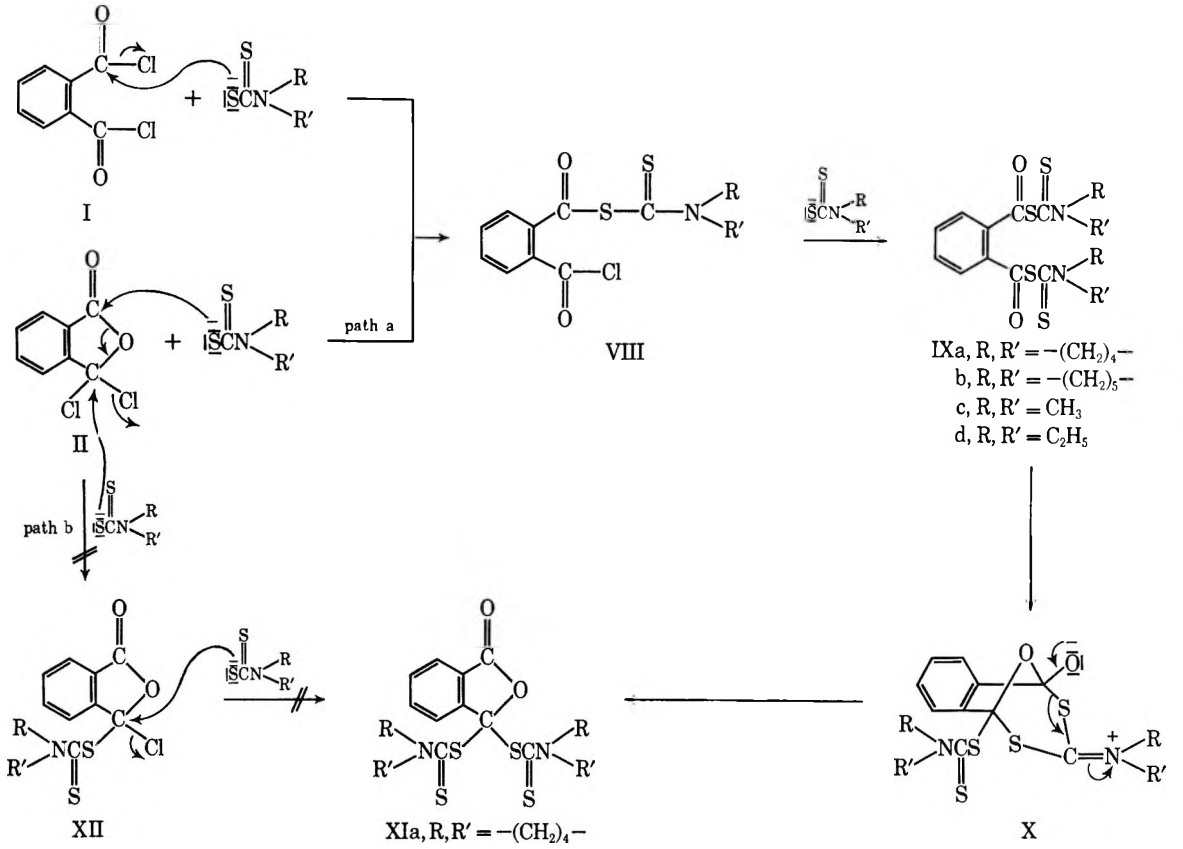
in the reaction of I with potassium *O*-methyl xanthate, the acid chloride is undergoing isomerization to the unsymmetrical derivative, especially in the absence of any catalyst such as aluminum chloride. A more probable explanation for the formation of VIa is indicated in Scheme I. In this scheme, we assume that the alkyl xanthate reacts with I to give the symmetrical di-*O*-methyl *S*,*S*-phthaloyl dixanthate (IVa), which undergoes an intramolecular rearrangement to the unsymmetrical isomer VIa, through the bicyclic 3,2,1 transition state V.[6] With a view to finding out whether the symmetrical dixanthate IVa is initially formed in the reaction, as shown in Scheme I, we have examined the absorption spectrum of the product mixture, soon after mixing together the symmetrical phthaloyl dichloride and potassium *O*-methyl xanthate in a 1:2 ratio in ether solution around 0°. The absorption spectrum was characterized by the presence of two maxima at 288 mμ (ε 19,700) and 394 (70), respectively. Of these, the weak absorption around 394 mμ is characteristic of all acyl and aroyl xanthates containing the C(=O)SC(=S)OR chromophore.[2] It was further observed that the absorption maximum at 394 mμ of a freshly formed solution of the dixanthate IVa disappeared after a few hours, and a new absorption maximum was observed at 364 mμ (ε 95), characteristic of the unsymmetrical dixanthate VI.[3] These findings are in support of the view that the symmetrical dixanthate IVa is actually formed at first, which then rapidly isomerizes to the unsymmetrical derivative VIa.

Our next objective was to examine the reaction of II with potassium *O*-methyl xanthate, with a view to studying the mode of this reaction. Treatment of an acetone solution of II with excess of potassium *O*-methyl xanthate around 5° gave a 70% yield of the unsymmetrical dixanthate VIa. The formation of VIa could be by the attack of the nucleophile on the carbonyl carbon (path a) or by a direct displacement on the carbon atom, attached to the chlorine atoms (path b), as shown in Scheme I. With a view to distinguishing between these two possible modes of reactions, we have examined the uv spectrum of the product mixture, immediately after mixing together II and potassium *O*-methyl xanthate in a 1:2 ratio in ether solution. If the reaction is proceeding through path a, then one would expect the initial formation of the symmetrical dixanthate IVa, which can be characterized by the absorption maximum at 394 mμ.[2] On the other hand, if path b is the preferred mode, then one would expect the formation of VIa directly. The uv spectrum of an ether solution of the product mixture, on treatment of II with potassium *O*-methyl xanthate, showed an absorption maximum at 394 mμ (ε 94), indicating thereby that the symmetrical dixanthate IIa is initially being formed in this reaction, which then undergoes thermal isomerization as shown in Scheme I.

With a view to finding out whether the symmetrical dixanthates of type IV (Scheme I) can be stabilized by changing the alkyl substituent on the xanthate,

(6) For some examples of reactions in which such bicyclic 3,2,1 transition states have been suggested, see (a) M. S. Newman and C. Courduvelis *J. Amer. Chem. Soc.*, **86**, 2942 (1964); **88**, 781 (1966); (b) M. S. Newman, N. Gill, and B. Darre, *J. Org. Chem.*, **31**, 2713 (1966).

SCHEME II



we have examined the reactions of I with different *O*-alkyl xanthates. Treatment of I with potassium *O*-*n*-propyl xanthate, for example, gave a 50% yield of di-*O*-*n*-propyl *S*,*S*-phthaloyl dixanthate (VIc), mp 81–82°. The same dixanthate was obtained in a 60% yield, on treatment of the unsymmetrical phthaloyl dichloride with potassium *O*-*n*-propyl xanthate. Similarly, the reactions of I with potassium *O*-*n*-butyl xanthate and potassium *O*-benzyl xanthate gave in each case the corresponding unsymmetrical dixanthates VId and VIe, respectively, in yields ranging between 65 and 82%. Both the unsymmetrical dixanthates VId and VIe were also obtained in 66 and 70% yields, respectively, when II was treated with the corresponding potassium *O*-alkyl xanthates.

In our further efforts at preparing the symmetrical dixanthates of type IV, we have examined the reactions of I with a few dithiocarbamates. The reaction of I with pyrrolidinedithiocarbamate, for example, gave a 68% yield of a product, mp 140–141°, identified as symmetrical phthaloic bis(pyrrolidinedithiocarbamic anhydride) (IXa) (Scheme II). The identity of IXa was confirmed on the basis of analytical results and spectral data. The infrared spectrum of IXa showed a characteristic absorption band at 1675 cm^{-1} due to the C=O group and a band at 1471 cm^{-1} due to the C=S group. The ultraviolet absorption spectrum of IXa was characterized by two absorption maxima at 290 mμ (ε 31,100) and 410 (400). The absorption characteristics of IXa are quite similar to those of the analogous benzoic piperidinedithiocarbamic anhydride.[7] The nmr spectrum of IXa showed two broad singlets at τ 7.83 (8 H) and 6.1 (8 H). Of these, the peak at τ 7.83 is assigned to the methylene protons away from the nitrogen atoms, whereas the one at τ 6.1 is due to the methylene protons adjacent to the nitrogen atoms of the pyrrolidine rings. The aromatic protons appeared as a multiplet centered around τ 2.31 (4 H), characteristic of an A_2B_2 system.

Further evidence concerning the symmetrical structure for IXa was derived by its conversion to *o*-phthalaldehyde, on treatment with Raney nickel.

In the formation of the unsymmetrical dixanthate VIa from the reaction of I and potassium *O*-methyl xanthate, we had suggested that initially the symmetrical dixanthate IVa is being formed which then isomerizes to VIa. It would be reasonable therefore to assume that the symmetrical phthaloic bis(pyrrolidinedithiocarbamic anhydride) (IXa) should also be capable of undergoing thermal isomerization to an unsymmetrical derivative. Refluxing a solution of IXa in dry benzene for 1 hr gave a 70% yield of a product, mp 161–162°, and identified as unsymmetrical phthaloic bis(pyrrolidinedithiocarbamic) anhydride (XIa). The identity of XIa was confirmed on the basis of analytical data and spectral evidences. The infrared spectrum of XIa showed a strong absorption band at 1786 cm^{-1} due to the C=O group present in a γ-lactone ring.

The uv spectrum of XIa was characterized by the presence of two absorption maxima at 284 mμ (ε 14,900) and 330 (90). The nmr spectrum of XIa showed two broad singlets at τ 7.82 (8 H) and 6.36 (8 H), due to the methylene protons of the pyrrolidine rings. The aromatic protons appeared as a multiplet centered around τ 2.52 (4 H) and characteristic of an ABCD pattern.

(7) E. H. Hoffmeister and D. S. Tarbell, *Tetrahedron*, **21**, 35 (1965).

The transformation of the symmetrical phthaloic bis(pyrrolidinedithiocarbamic anhydride) (IXa) to the unsymmetrical isomer XIa may also be proceeding through a bicyclic 3,2,1 transition state (X) as shown in Scheme II. By taking advantage of the fact that IXa shows a characteristic absorption band around 410 mμ, it has been possible to study the kinetics of the isomerization of IXa spectrophotometrically. Table I summarizes the rate data for three different

TABLE I
FIRST-ORDER RATE CONSTANTS FOR THE ISOMERIZATION OF IXa TO XIa

Solvent	Temp, °C	k_1 (sec^{-1})
Benzene	40	2.18×10^{-5}
Benzene	45	4.63×10^{-5}
Benzene	50	6.55×10^{-5}

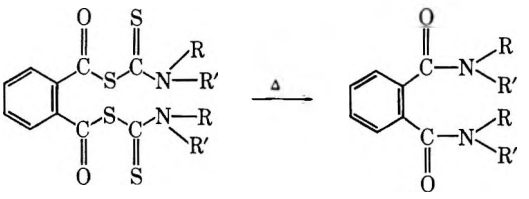
temperatures, 40, 45, and 50°. These results show that the isomerization of IXa to XIa obeys the first-order rate law and the value for $\Delta H_a = 22$ kcal mol^{-1}. The calculated entropy of activation at 50°, $\Delta S_{50°} = -9.7$ eu, suggests an ordered transition state for the isomerization of IXa, in agreement with the suggested mechanism.

Our next objective was to study the reaction of the unsymmetrical phthaloyl dichloride (II) with aminedithiocarbamates with a view to understanding the mode of these reactions. Treatment of an acetone solution of II with pyrrolidinedithiocarbamate gave a 60% of the symmetrical phthaloic bis(pyrrolidinedithiocarbamic anhydride) (IXa). The formation of the symmetrical isomer IXa in this reaction clearly indicates that the preferred mode of attack of the nucleophile is on the carbonyl carbon of II and not on the carbon atom attached to the halogen atoms (Scheme II). This is analogous to the reaction of *O*-alkyl xanthates with II proceeding through path a, as shown in Scheme I.

In continuation of our studies, we have examined the reactions of a few other aminedithiocarbamates with both I and II. The reactions of I with piperidinedithiocarbamate, dimethylaminedithiocarbamate, and diethylaminedithiocarbamate gave the corresponding symmetrical phthaloic aminedithiocarbamic anhydrides IXb, IXc, and IXd in yields ranging between 50 and 76%. Symmetrical phthaloic aminedithiocarbamic anhydrides IXa and IXb were also obtained when II was treated with the corresponding aminedithiocarbamates.

It was mentioned earlier that the symmetrical phthaloic bis(pyrrolidinedithiocarbamic anhydride) (IXa) undergoes isomerization to the unsymmetrical derivative XIa on refluxing in benzene solution for 1 hr. Our attempts at bringing about similar isomerizations of the symmetrical phthaloic aminedithiocarbamic anhydrides IXb, IXc, and IXd to the corresponding unsymmetrical derivatives were, however, unsuccessful. In each case, the compound decomposed with the loss of carbon disulfide to the corresponding phthalamide, as shown in Scheme III. Thus, on refluxing, a benzene solution of IXb for 1 hr gave a 90% yield of phthaloyl dipiperidide (XIIb).[8] Similarly, IXc and

SCHEME III



IXb, R, R′ = $-(CH_2)_5-$
c, R = R′ = CH_3
d, R = R′ = C_2H_5

XIIb, R,R′ = $-(CH_2)_5-$
c, R = R′ = CH_3
d, R = R′ = C_2H_5

IXd, on refluxing in benzene for 1 hr, gave *N,N,N′,N′*-tetramethylphthalamide (XIIc)[8] and *N,N,N′,N′*-tetraethylphthalamide (XIId),[9] respectively.

Our next aim was to study the reaction of I with a mixture of nucleophiles, with a view to preparing mixed xanthates and aminedithiocarbamic anhydrides. Treatment of an ether solution of I and a mixture of potassium *O*-methyl xanthate and piperidinedithiocarbamate in equimolar proportions gave a mixture of products consisting of 25% of the unsymmetrical dixanthate VIa and 45% of the symmetrical aminedithiocarbamic anhydride IXb. None of the mixed xanthate could be isolated from this run.

In an earlier communication,[3] we had reported the thermal and photochemical transformations of an unsymmetrical phthaloyl dixanthate such as VIb. In the present studies we have examined both the thermal and photochemical reactions of few unsymmetrical phthaloyl dixanthates such as VIa, VIc, VId, and VIe with a view to studying the nature of the products formed in these reactions.

Photolysis of VIa in benzene solution at room temperature gave a 38% yield of *trans*-biphthalyl (XXI), mp 352–54°, as the only isolable product. Under similar conditions, the photolysis of other unsymmetrical phthaloyl dixanthates such as VIc, VId, and VIe gave XXI in yields ranging between 34 and 41%. The formation of XXI in the photolysis of unsymmetrical phthaloyl dixanthates suggests that in all these cases the fragmentation may be taking place through a C–S bond fission giving rise to the radical intermediate XIII, which then gives rise to the carbene intermediate XIV through a second C–S bond fission. Dimerization of XIV would lead to *trans*-biphthalyl (XXI) (Scheme IV). It has not been possible to isolate either benzocyclobutenedione (XVII) or other dimeric products such as XVIII, XIX, or XX from these reactions.[10] A similar type of photochemical transformation involving a C–S bond fission is reported in the case of 9,9-dixanthogenyl xanthene.[11]

It is interesting to note that the C–S bond fission of the type postulated for the fragmentation of acyl and aroyl xanthates[2] has also been suggested for the photolysis of dithiocarbamic anhydrides.[7,12] Thus, in the photolysis of benzoic piperidinedithiocarbamic anhydride,[7] a mixture of products such as benzoic acid, benzoyl piperidide, benzoyl cyclopentamethylenethio-

(8) For an earlier report on the thermal decomposition of IXb, see J. von Braun and W. Kaiser, *Ber.*, **55**, 1305 (1922).

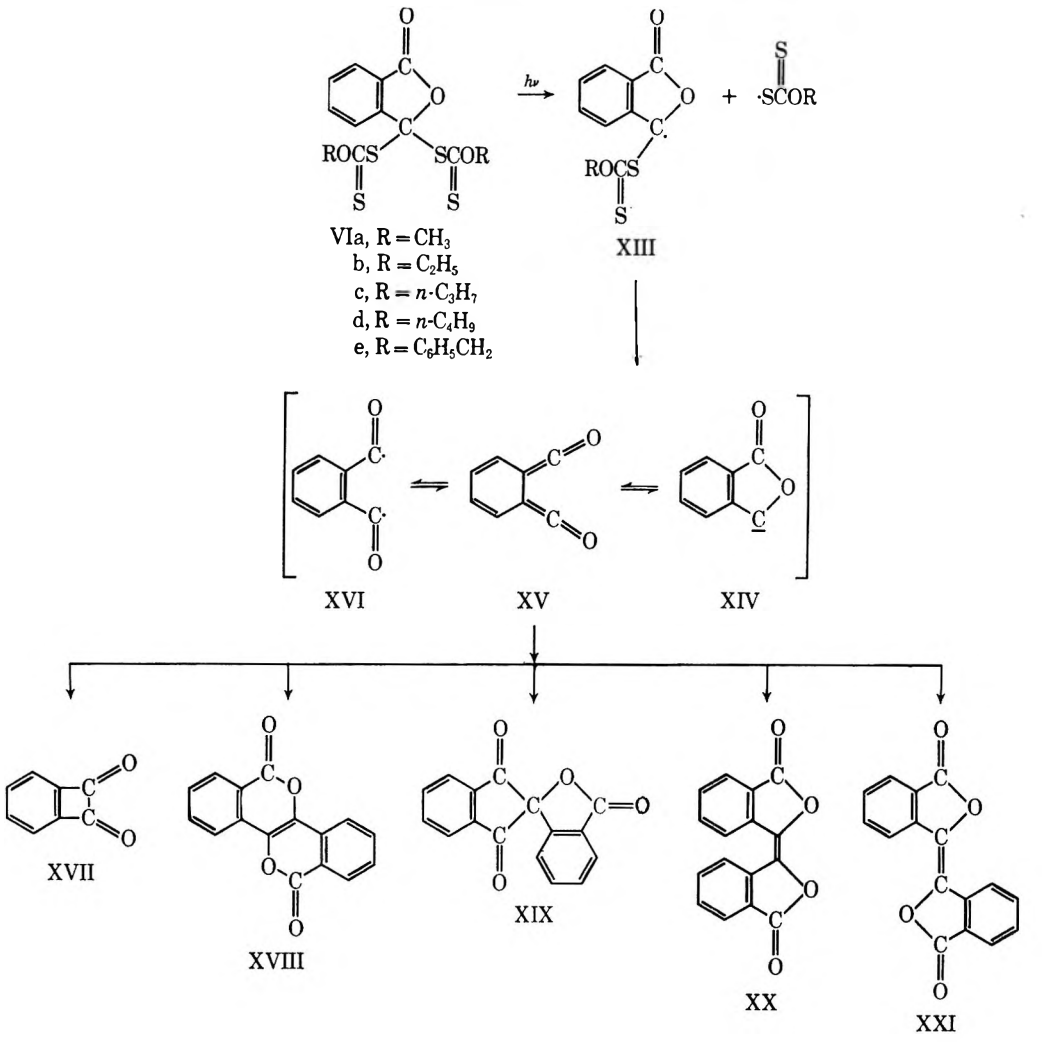
(9) P. B. Corbiere, French Patent 866,229 (1941); *Chem. Abstr.*, **43**, 5038 (1949).

(10) For the formation of several dimeric products in the photolysis of benzocyclobutenedione, see (a) R. F. C. Brown and R. K. Solly, *Tetrahedron Lett.*, 169 (1966); (b) H. A. Staab and J. Ipaktschi, *ibid.*, 583 (1966).

(11) A. Schönberg and U. Sodtke, *ibid.*, 4977 (1967).

(12) E. H. Hoffmeister and D. S. Tarbell, *Tetrahedron*, **21**, 2857 2865 (1965).

SCHEME IV



carbamyl disufide, and cyclopentamethylene thiuram bisulfide are formed. A free-radical mechanism has been suggested to account for the formation of these products.

In the present investigation we have examined the photolysis of a few symmetrical phthaloic bisaminedithiocarbamic anhydrides with a veiw to studying the nature of the products formed in these reactions. The photolysis of symmetrical bis(pyrrolidinedithiocarbamic anhydride) (IXa), for example, gives rise to a mixture of *trans*-biphthalyl (XXI, 30%) and pyrrolidyl thiuram disulfide (XXIIIa, 75%). The formation of both XXI and XXIIIa can be explained on the basis of C–S bond fission in IXa, giving rise to the radical intermediates XVI and XXII, respectively (Scheme V). The diradical species can isomerize to the carbene intermediate XIV, which then undergoes dimerization to give *trans*-biphthalyl (XXI). The formation of the thiuram disulfide XXIIIa may arise through the dimerization of the radical species XXII.

Similarly, the photolysis of other symmetrical phthaloic bisaminedithiocarbamic anhydrides such as IXb, IXc, and IXd gave, in each case, *trans*-biphthalyl and the corresponding thiuram disulfides, XXIIIb, XXIIIc, and XXIIId, respectively.

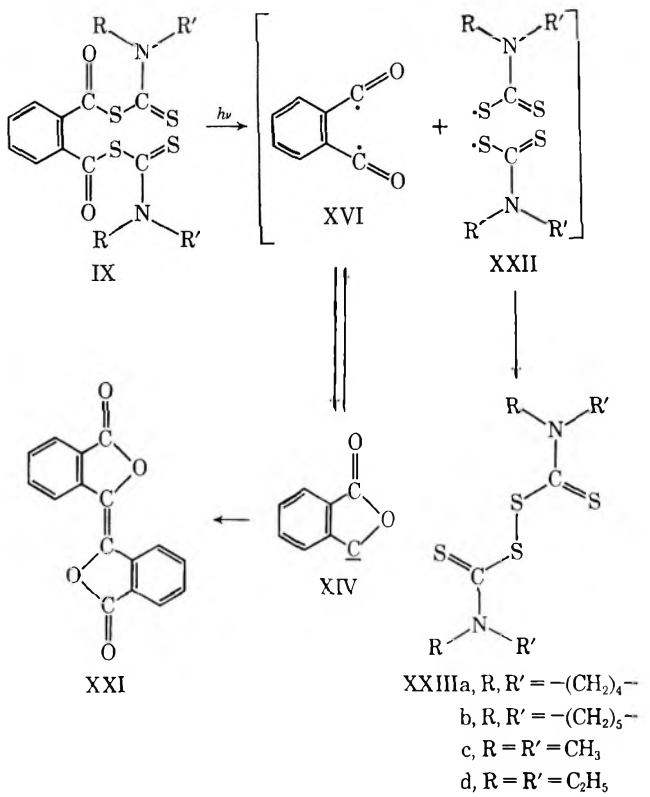
It is noteworthy that the photolysis of unsymmetrical phthaloic bis(pyrrolidinedithiocarbamic) anhydride (XIa) also gives rise to a mixture of *trans*-biphthalyl (XXI, 50%) and pyrrolidyl thiuram disulfide (XXIIIa, 75%). The formation of *trans*-biphthalyl from XIa suggests that both XIa and the unsymmetrical phthaloyl dixanthates undergo similar type of fragmentation reactions (Scheme IV).

Thermal decomposition of acyl xanthates are reported to give rise to a mixture of products.[2,13,14] Thus, ethyl phenylacetyl xanthate, for example, decomposes on heating to give a mixture of ethyl phenylacetate and carbon disulfide and a mechanism involving a four-membered, cyclic transition state has been suggested for this reaction.[2] During the present investigation, we have examined the thermal decomposition of several umsymmetrical phthaloyl dixanthates with a view to studying the nature of the products formed in these reactions. Heating unsymmetrical di-*O*-methyl phthaloyl dixanthate (VIa) to around 230–240° for about 30 min, for example, gave rise to a mixture of products which include thiophthalic anhydride (XXV, 68%), *O,S*-dimethyl xanthate (XXVIa, 30%), and carbonyl sulfide (XXVII, 76%), identified through its piperidinium salt[15] (Scheme VI).

Similarly, the thermal decompositions of unsym-

(13) G. Bulmer and F. G. Mann, *J. Chem. Soc.*, 677 (1945).
(14) T. Taguchi and M. Nako, *Tetrahedron*, **18**, 245 (1962).
(15) J. Parrod, *C. R. Acad. Sci., Ser. C*, **234**, 1062 (1952); *Chem. Abstr.*, **47**, 1606 (1953).

SCHEME V



metrical phthaloyl dixanthates VIc, VId, and VIe gave rise to a mixture of thiophthalic anhydride, carbonyl sulfide, and the corresponding *O,S*-dialkyl xanthates (XXVIc–e). It is interesting to note that in the decomposition of unsymmetrical phthaloyl dixanthates such as VIb, VIc, and VId, small amounts of *trans*-biphthalyl (XXI) could also be isolated. The formation of XXI in the thermal decomposition of these dixanthates suggests that a minor mode of decomposition is through the carbene intermediate XIV which dimerizes to give *trans*-biphthalyl. The exact nature of the pyrolytic decomposition of the unsymmetrical phthaloyl dixanthates is not very clearly understood. A probable mechanism, which accounts for the formation of products such as carbonyl sulfide (XXVII), thiophthalic anhydride (XXV), and *O,S*-dialkyl xanthates (XXVIa–e), is one which involves a cyclic concerted process as shown in Scheme VI. The formation of phthalic thioanhydride may be through a rearrangement of the initially formed thionphthalic anhydride (XXIV).[16]

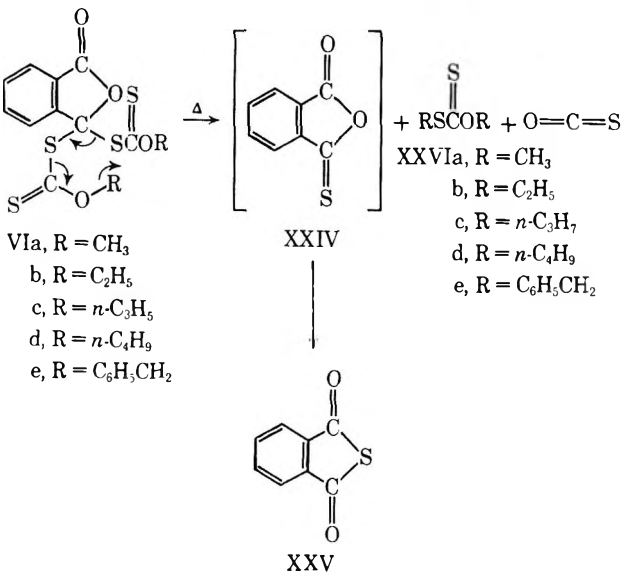
In contrast to the thermal decomposition of unsymmetrical phthaloyl dixanthates, the dithiocarbamic anhydrides give chiefly the corresponding amides and carbon disulfide.[7,8,12]

Experimental Section

All melting points are uncorrected and were taken on a Koffler hot stage. Ir spectra were determined on a Perkin-Elmer Model 137 Infracord spectrometer and uv spectra were determined on a Beckman DB spectrophotometer. Nmr traces were recorded on a Varian HR-100 spectrometer, using tetramethylsilane as internal standard. All irradiation experiments were carried out using a Hanovia, medium-pressure, mercury lamp (450 W). Kinetic studies were carried out spectrophotometrically, using a Beckman DU spectrophotometer.

(16) C. M. Sharts and D. W. Fong, *J. Org. Chem.*, **32**, 3709 (1967).

SCHEME VI



Potassium *O*-methyl xanthate, mp 185–186°, potassium *O*-*n*-propyl xanthate, mp 237–238°, potassium *O*-*n*-butyl xanthate, 261–262°, and potassium *O*-benzyl xanthate, mp 179–180°, were prepared by reported procedures.[17] Dimethylaminedithiocarbamate,[18] mp 136°, and diethylaminedithiocarbamate,[15] mp 81°, pyrrolidinedithiocarbamate,[12] mp 152°, and piperidinedithiocarbamate,[7] mp 169–170°, were prepared by standard procedures. Symmetrical phthaloyl dichloride, bp 132–133° (10 mm), and unsymmetrical phthaloyl dichloride, mp 87–88°, were prepared by reported procedures.[5]

Unsymmetrical Di-*O*-alkyl *S,S*-Phthaloyl Dixanthates.—In a typical run, 0.09 mol of potassium *O*-alkyl xanthate was slowly added to a solution of 0.02 mol of symmetrical phthaloyl dichloride in 30 ml of diethyl ether, maintained around 5°. The mixture was stirred for 30 min and then was treated with water to remove any unchanged potassium *O*-alkyl xanthate. Removal of the solvent under vacuum gave the product which was recrystallized from a mixture (1:1) of methylene chloride and petroleum ether (bp 40–60°). Table II summarizes the percentage yields and the physical data of the different unsymmetrical di-*O*-alkyl *S,S*-phthaloyl dixanthates.

Treatment of Di-*O*-methyl *S,S*-Phthaloyl Dixanthate (VIa) with Raney Nickel.—A mixture of VIa (0.4 g, 0.001 mol) and Raney nickel (2 g) was refluxed in acetone (20 ml) for 8 hr. Removal of the unchanged nickel and the solvent gave 0.1 g (62%) of phthalide, which melted at 75°, after recrystallization from methylene chloride. There was no depression in the melting point when mixed with an authentic sample.[19]

Photolysis of Di-*O*-alkyl *S,S*-Phthaloyl Dixanthates.—In a typical run, a solution of di-*O*-methyl *S,S*-phthaloyl dixanthate (1.5 g, 0.004 mol) in benzene (200 ml) was irradiated for 1 hr at room temperature. Removal of the solvent gave a product which on treatment with methylene chloride gave 0.22 g (38%) of *trans*-biphthalyl (XXI), which melted over the range 352–354° (lit.[10a] mp 352–354°), on recrystallization from acetic acid. The ir spectrum (KBr) of XXI showed a strong absorption band at 1789 cm^{-1} due to a carbonyl group (γ-lactone). The uv spectrum of XXI (CH_2Cl_2) was characterized by the following absorption maxima: 250 mμ (ε 13,900) (shoulder), 260 (18,000), 272 (18,800) (shoulder), 292 (9300), 294 (42,00), 307 (16,600), 316 (11,100), 325 (13,000), 363 (36,200), 376 (30,300), and 382 (26,400).

Anal. Calcd for $C_{16}H_8O_4$: C, 72.70; H, 3.01. Found: C, 72.68; H, 3.34.

Similarly, the photolyses of VIc, VId, and VIe in benzene solution gave *trans*-biphthalyl (XXI) as the only isolable product in each case, in yields ranging between 34 and 41%.

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TABLE II
UNSYMMETRICAL DI-*O*-ALKYL *S,S*-PHTHALOYL DIXANTHATES

Compd	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Infrared, cm⁻¹ (KBr) C=O (γ-lactone)	Infrared, cm⁻¹ (KBr) C=S	Uv, λmax, mμ (ε)
VIa	78	119–120	41.61	2.89	41.90	2.72	1780	1040	288 (22,100), 364 (100)
VIc	50	81–82	47.75	4.47	47.75	4.45	1782	1030	288 (31,900), 366 (120)
VId	88	60–61	50.23	5.10	50.33	5.22	1770	1030	290 (25,000), 366 (130)
VIe	65	124–125	57.83	3.61	57.87	3.76	1785	1020	290 (25,500), 368 (100)

Thermal Decomposition of Di-*O*-alkyl *S,S*-Phthaloyl Dixanthates.—In a typical run, 2 g (0.005 mol) of di-*O*-methyl *S,S*-phthaloyl dixanthate was heated around 230–240° for 20 min in a 10-ml round-bottomed flask, provided with a nitrogen inlet and a condenser. The gaseous products were bubbled through a 10% solution of piperidine in diethyl ether. The precipitated piperidinium salt was filtered and recrystallized from a mixture (1:1) of methylene chloride and diethyl ether to give 1 g (76%) of piperidinium 1-piperidinecarbothiolate, mp 112°, which showed no depression in its melting point when mixed with an authentic sample.[15]

The pyrolyzed residue was treated with petroleum ether (bp 60–80°) to give 0.65 g (68%) of thiophthalic anhydride (XXV), mp 110° (mmp). The petroleum ether-soluble fraction was chromatographed over alumina to give 0.2 g (30%) of *O,S*-dimethyl xanthate (XXVIa), identified through a comparison of its ir spectrum with that of an authentic sample.[20]

Di-*O*-*n*-propyl *S,S*-phthaloyl dixanthate (1 g, 0.002 mol) was heated around 230–240° for 30 min under a stream of nitrogen and the evolved gases were bubbled through a 10% solution of piperidine in ether. The precipitated salt on recrystallization from a mixture (1:1) of methylene chloride and ether gave 0.25 g (43%) of piperidinium 1-piperidinecarbothiolate, mp 112° (mmp). Work-up of the pyrolyzed residue as in the previous case gave 0.02 g (6%) of *trans*-biphthalyl, mp 352–354° (mmp), 0.27 g (67%) of thiophthalic anhydride, mp 110° (mmp), and 0.3 g (70%) of *O,S*-di-*n*-propyl xanthate (XXVIc), identified by comparison of its infrared spectrum with that of an authentic sample.[21]

Similarly, heating VId (2 g, 0.004 mol) around 230–240° for 30 min gave carbonyl sulfide which when absorbed in an ether solution of piperidine gave 0.35 g (32%) of piperidinium 1-piperidinecarbothiolate, mp 112° (mmp). Work-up of the pyrolyzed residue as in the earlier cases gave 0.15 g (25%) of *trans*-biphthalyl, mp 352–354° (mmp), 0.12 g (16%) of thiophthalic anhydride, mp 110° (mmp), and 0.5 g (52%) of *O,S*-di-*n*-butyl xanthate (XXVId), identified by a comparison of its infrared spectrum with that of an authentic sample.[22]

In a separate run, 2 g (0.004 mol) of VIe was heated around 230–240° for 30 min and the carbonyl sulfide that was evolved was absorbed in 10% piperidine in ether to give 0.8 g (83%) of piperidinium 1-piperidinecarbothiolate, mp 112° (mmp). The pyrolyzed residue, on work-up as in the previous cases gave 0.32 g (50%) of thiophthalic anhydride, mp 110° (mmp), and 0.7 g (63%) of *O,S*-dibenzyl xanthate (XXVIe), identified through a comparison of its ir spectrum with that of an authentic sample.[20]

Reaction of Unsymmetrical Phthaloyl Dichloride with Potassium *O*-Alkyl Xanthates.—In a typical run, 0.59 g (0.004 mol) of potassium *O*-methyl xanthate was treated with a solution of 0.3 g (0.001 mol) of II in acetone (10 ml) around 0°. Removal of the solvent under vacuum gave a product which was extracted with methylene chloride. The methylene chloride extract was washed with water and dried over anhydrous sodium sulfate, and the solvent removed under vacuum to give 0.35 g (70%) of unsymmetrical di-*O*-methyl *S,S*-phthaloyl dixanthate, which melted at 119–120° (mmp), on recrystallization from a mixture (1:1) of methylene chloride and petroleum ether (bp 40–60°).

Similarly, the reactions of potassium *O*-*n*-propyl xanthate, potassium *O*-*n*-butyl xanthate, and potassium *O*-benzyl xanthate with II gave the unsymmetrical xanthates VIc, mp 81–82° (60%), VId, mp 60–61° (66%), and VIe, mp, 124–125° (70%).

Phthaloic Bis(pyrrolidinedithiocarbamic anhydride) (IXa).—A solution of 6.5 g (0.03 mol) of pyrrolidinedithiocarbamate in ether (50 ml) was gradually added to an ether solution of I (2.5 g, 0.012 mol in 50 ml) at 5°, over a period of 30 min. The reaction mixture was washed with water to remove any unchanged pyrrolidinedithiocarbamate, and the ether solution was dried over anhydrous sodium sulfate. Removal of the solvent under vacuum gave a product which was recrystallized from a mixture (1:1) of ether and methylene chloride to give 3.5 g (68%) of symmetrical phthaloic bis(pyrrolidinedithiocarbamic anhydride) (IXa), mp 140–141°. The ir spectrum (KBr) of IXa showed absorption bands at 1675 (C=O) and 1471 cm⁻¹ (C=S). The uv spectrum (CH_2Cl_2) of IXa was characterized by the following absorption maxima: 290 mμ (ε 31,100) and 410 (400).

Anal. Calcd for $C_{18}H_{20}N_2O_2S_4$: C, 50.94; H, 4.72; N, 6.60. Found: C, 51.24; H, 4.70; N, 6.61.

Treatment of Symmetrical Phthaloic Bis(pyrrolidinedithiocarbamic anhydride) with Raney Nickel.—A mixture of 0.42 g (0.001 mol) of IXa and 2 g of Raney nickel in 25 ml of alcohol was stirred under reflux for 8 hr. Removal of the solvent and unchanged nickel gave a residue which on treatment with a solution of 2,4-dinitrophenylhydrazine gave 0.12 g (30%) of *o*-phthalaldehyde 2,4-dinitrophenylhydrazone, mp 265° (lit.[23] mp 270°), after recrystallization from ethanol

Anal. Calcd for $C_{20}H_{14}N_8O_8$: C, 48.58; H, 2.83; N, 22.76. Found: C, 48.83; H, 3.00; N, 22.55.

Photolysis of Symmetrical Phthaloic Bis(pyrrolidinedithiocarbamic anhydride) (IXa).—A solution of (0.8 g, 0.002 mol) of IXa in dry benzene (175 ml) was irradiated for 1 hr around 5°. Removal of the solvent under vacuum gave a residue which on treatment with methylene chloride gave 0.07 g (30%) of *trans*-biphthalyl, mp 352–354° (mmp), after recrystallization from acetic acid.

Removal of the solvent from the methylene chloride- soluble fraction gave 0.35 g (75%) of pyrrolidyl thiuram disulfide (XXIIIa), mp 144°, on recrystallization from a mixture (1:1) of ether and methylene chloride. There was no depression in the melting point of XXIIIa when mixed with an authentic sample.[12]

Thermal Isomerization of Symmetrical Phthaloic Bis(pyrrolidinedithiocarbamic anhydride) (IXa) to the Unsymmetrical Derivative XIa.—A solution of 0.5 g (0.001 mol) of IXa in dry benzene (25 ml) was refluxed for 1 hr. Removal of the solvent under vacuum gave 0.35 g (70%) of unsymmetrical phthaloic bis(pyrrolidinedithiocarbamic) anhydride (XIa), which melted at 161–162°, after recrystallization from a mixture (1:1) of methylene chloride and petroleum ether (bp 40–60°). The infrared spectrum of XIa showed an absorption band at 1786 cm⁻¹ (C=O, γ-lactone). The uv spectrum (CH_2Cl_2) was characterized by the following absorption maxima: 284 mμ (ε 14,900) and 330 (90). The nmr spectrum ($CDCl_3$) of XIa showed two multiplets at τ 6.36 (8 H) and 7.82 (8 H), respectively, due to the methylene protons of the pyrrolidine ring. Of these two multiplets, the one at τ 6.36 is assigned to the methylene protons near to the nitrogen atoms, whereas the multiplet at τ 7.82 is assigned to the methylene protons away from the nitrogen atoms. The aromatic protons appeared as a separate multiplet centered around τ 2.52 (4 H) and characteristic of an ABCD pattern.

Anal. Calcd for $C_{18}H_{20}N_2O_2S_4$: C, 50.94; H, 4.71; N, 6.60. Found: C, 50.64; H, 4.60; N, 6.55.

Photolysis of Unsymmetrical Phthaloic Bis(pyrrolidinedithiocarbamic) anhydride (XIa).—A solution of XIa (0.7 g, 1.6 mmol) in benzene (175 ml) was irradiated for 1 hr. Removal of the solvent under vacuum gave a residue which was treated with methylene chloride to give 0.11 g (50%) of *trans*-biphthalyl, mp 352–354° (mmp), after recrystallization from acetic acid.

(20) B. Fetkenheuer, H. Fetkenheuer, and H. Lecus, *Ber.*, **60**, 2528 (1927); *Chem. Abstr.*, **22**, 1136 (1928).

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The methylene chloride soluble portion gave 0.33 g (70%) of pyrrolidyl thiuram disulfide (XXIIIa), mp 144–145° (mmp), after recrystallization from a mixture (1:1) of methylene chloride and petroleum ether (bp 40–60°).

Reaction of Unsymmetrical Phthaloyl Dichloride with Pyrrolidinedithiocarbamate.—Treatment of a solution of 3 g (0.013 mol) of pyrrolidinedithiocarbamate in acetone (25 ml) with an acetone solution of II (1 g, 0.005 mol in 25 ml) around 5° and work-up in the usual manner gave 1.2 g (60%) of symmetrical phthaloic bis(pyrrolidinedithiocarbamic anhydride) (IXa), mp 140–141° (mmp), after recrystallization from methylene chloride.

Symmetrical Phthaloic Bis(piperidinedithiocarbamic anhydride) (IXb).—Treatment of a mixture of 10 g (0.04 mol) of piperidinedithiocarbamate and 3.8 g (0.018 mol) of I in ether (100 ml) around 5° and work-up as in the case of IXa gave 5.7 g (68%) of symmetrical phthaloic bis(piperidinedithiocarbamic anhydride) (IXb), which melted at 132–133° (lit.[8] mp 123°), after recrystallization from a mixture (1:1) of ether and methylene chloride. The ir spectrum (CCl_4) of IXb showed absorption bands at 1684 (C=O) and 1471 cm^{-1} (C=S). The uv spectrum (CH_2Cl_2) of IXb was characterized by the following absorption maxima: 296 mμ (ε 18,700) and 410 (500). The nmr spectrum ($CDCl_3$) of IXb showed two broad singlets centered around τ 5.89 (8 H) and 8.27 (12 H), due to the methylene protons situated near the nitrogen atoms and those situated away from the nitrogen atoms in the piperidine rings, respectively. In addition, the spectrum showed a symmetrical multiplet centered around τ 2.5 (4 H), due to the aromatic protons, characteristic of an A_2B_2 pattern.

Anal. Calcd for $C_{20}H_{24}N_2O_2S_4$: C, 53.09; H, 5.31; N, 6.19. Found: C, 53.23; H, 5.22; N, 6.30.

Treatment of IXb with Raney Nickel.—A mixture of IXb (0.4 g, 0.8 mmol) and Raney nickel (2 g) in ethanol (20 ml) was refluxed for 10 hr. Removal of the solvent and unchanged nickel gave a product which on treatment with a solution of 2,4-dinitrophenylhydrazine gave 0.12 g (30%) of *o*-phthaldehyde 2,4-dinitrophenylhydrazone, mp 265° (mmp), after recrystallization from ethanol.

Photolysis of Symmetrical Phthaloic Bis(piperidinedithiocarbamic anhydride) (IXb).—A solution of 1.5 g (0.003 mol) of IXb in dry benzene (175 ml) was irradiated for 1 hr at 5°. Removal of the solvent under vacuum gave a product which on treatment with methylene chloride gave 0.2 g (46%) of *trans*-biphthalyl, mp 352–354° (mmp), after recrystallization from acetic acid.

Removal of the solvent from the methylene chloride soluble fraction gave 0.4 g (40%) of cyclopentamethylene thiuram disulfide (XXIIIb), mp 130° (mmp). The identity of XXIIIb was further confirmed by a comparison of its infrared spectrum with that of an authentic sample.[24]

Attempted Isomerization of IXb.—A solution of 0.5 g (0.001 mol) of IXb in benzene (25 ml) was refluxed for 45 min. Removal of the solvent under vacuum gave a product which was recrystallized from a mixture (1:1) of methylene chloride and petroleum ether (bp 40–60°) to give 0.3 g (90%) of phthaloyl dipiperidide, mp 65–66° (lit.[8] mp 54°). The infrared spectrum of this product showed an absorption band at 1640 cm^{-1}, characteristic of an amide carbonyl group.

Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 72.00; H, 8.00; N, 9.33. Found: C, 72.38; H, 8.31; N, 8.95.

Reaction of Unsymmetrical Phthaloyl Dichloride with Piperidinedithiocarbamate.—A solution of 2 g (0.008 mol) of piperidine)dithiocarbamate in acetone (20 ml) was treated with an acetone solution of II (0.8 g, 0.004 mol) around 5°. Work-up of the mixture as in the earlier cases gave 0.75 g (44%) of symmetrical phthaloic piperidinedithiocarbamate, mp 132–133° (mmp).

Symmetrical Phthaloic Bis(dimethylaminedithiocarbamic anhydride) (IXc).—Treatment of a mixture of 6 g (0.036 mol) of dimethylaminedithiocarbamate with 3 g (0.014 mol) of I in ether (150 ml) around −30° and work-up as in the earlier cases gave 2.7 g (50%) of symmetrical phthaloic bis(dimethylaminedithiocarbamic anhydride) (IXc), mp 115–116° (lit.[8] mp 107°), after recrystallization from methylene chloride. The ir spectrum of IXc showed absorption bands at 1686 (C=O) and 1493 cm^{-1} (C=S). The uv spectrum (CH_2Cl_2) of IXc was characterized by the following absorption maxima: 290 mμ (ε 32,900) and 410 (600).

Anal. Calcd for $C_{14}H_{16}N_2O_2S_4$: C, 45.16; H, 4.30; N, 7.52. Found: C, 45.41; H, 4.40; N, 7.40.

Photolysis of Phthaloic Bis(dimethylaminedithiocarbamic anhydride) (IXc).—Irradiation of a solution of 1 g (0.002 mol) of IXc in benzene (175 ml) for 1 hr at 5° and work-up of the reaction as in the earlier cases gave 0.13 g (37%) of *trans*-biphthalyl, mp 352–354° (mmp), and 0.3 g (48%) of tetramethyl thiuram disulfide (XXIIIc), mp 154° (mmp).

Attempted Isomerization of IXc.—A solution of 0.5 g (0.001 mol) of IXc in dry benzene (25 ml) was refluxed for 1 hr. Removal of the solvent under vacuum and recrystallization of the product from a mixture (1:1) of methylene chloride and petroleum ether (bp 40–80°) gave 0.25 g (83%) of *N,N,N′,N′*-tetramethylphthalamide, mp 121–122° (lit.[8] mp 121–122°). The ir spectrum of this product showed an absorption band at 1640 cm^{-1}, characteristic of an amide carbonyl group.

Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.45; H, 7.27; N, 12.72. Found: C, 65.11; H, 7.10; N, 12.80.

Symmetrical Phthaloic Bis(diethylaminedithiocarbamic anhydride) (IXd).—A solution of diethylaminedithiocarbamate (4.5 g, 0.02 mol) in ether (75 ml) was treated with an ether solution of I (2 g, 0.01 mol, in 50 ml) around 30°. The reaction mixture was worked up in the usual manner to give 3.2 g (76%) of IXd, mp 86–87°, after recrystallization from methylene chloride. The ir spectrum (KBr) of IXd showed absorption bands at 1686 (C=O) and 1476 cm^{-1} (C=S). The uv spectrum (ethanol) of IXd was characterized by the following absorption maxima: 290 mμ (ε 24,300) and 410 (250). The nmr spectrum ($CDCl_3$) of IXd showed a triplet centered around τ 8.69 (12 H) due to the methyl protons and a quartet centered around τ 6.1 (8 H) due to the methylene protons. In addition, the spectrum showed a multiplet centered around τ 2.37 (4 H) due to the aromatic protons, characteristic of an A_2B_2 pattern.

Anal. Calcd for $C_{18}H_{24}N_2O_2S_4$: C, 50.46; H, 5.6; N, 6.54. Found: C, 50.23; H, 5.6; N, 6.72.

Photolysis of Symmetrical Phthaloic Bis(diethylaminedithiocarbamic anhydride) (IXd).—A solution of 1 g (0.002 mol) of IXd in 175 ml of dry benzene was irradiated for 1 hr at 5°. Removal of the solvent under vacuum gave a product which was treated with methylene chloride to give 0.1 g (33%) of *trans*-biphthalyl, mp 352–354° (mmp).

Removal of the solvent from the methylene chloride soluble portion gave 0.2 g (34%) of tetraethyl thiuram disulfide (XXIIId), mp 71–72°, after recrystallization from methylene chloride. There was no depression in the melting point of XXIIId when mixed with an authentic sample.[24,25]

Attempted Isomerization of IXd.—A solution of 0.5 g (0.001 mol) of IXd in dry benzene (25 ml) was refluxed for 1 hr. Removal of the solvent under vacuum and recrystallization of the product from a mixture (1:1) of methylene chloride and petroleum ether (bp 40–60°) gave 0.22 g (64%) of *N,N,N′,N′*-tetraethylphthalamide, mp 39–40° (lit.[9] mp 38°). The ir spectrum of the product showed an absorption band at 1645 cm^{-1}, characteristic of an amide carbonyl group.

Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.56; H, 8.75; N, 10.21. Found: C, 69.72; H, 8.55; N, 10.00.

Reaction of Symmetrical Phthaloyl Dichloride with a Mixture (1:1) of Potassium *O*-Methyl Xanthate and Piperidinedithiocarbamate.—To a solution of 4 g (0.02 mol) of I in ether (25 ml), maintained at 5°, was added an ether solution (50 ml) of a mixture of potassium *O*-methyl xanthate (3 g, 0.02 mol) and piperidinedithiocarbamate (5 g, 0.02 mol), over a period of 30 min. Removal of the solvent under vacuum gave a residue which was washed with water to remove all unchanged xanthate and piperidinedithiocarbamate. Treatment of this residue with ether (50 ml) gave an ether-soluble portion, which on recrystallization from a mixture (1:1) of methylene chloride and petroleum ether (bp 40–60°) gave 4.0 g (45%) of symmetrical phthaloic bis(piperidinedithiocarbamic anhydride) (IXb), mp 143–144° (mmp).

Removal of the solvent from the ether-soluble portion gave a product which was recrystallized from methylene chloride to give 1.7 g (25%) of unsymmetrical di-*O*-methyl *S,S*-phthaloyl dixanthate (VIa), mp 119–120° (mmp). None of the mixed product could be isolated from this run.

Registry No.—VIa, 27193-06-2; VIc, 27193-07-3; VId, 27193-08-4; VIe, 27193-09-5; IXa, 27193-10-8;

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(25) M. Grodzki, *Ber.*, **14**, 2756 (1881).

IXb, 27193-11-9; IXc, 27193-12-0; IXd, 27193-13-1; XIa, 27193-14-2; XXI, 482-23-5; XXIIIa, 496-08-2.

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Organic Disulfides and Related Substances. 31. Possible Anchimeric Involvement of an Ortho Carboxylate Moiety in Disproportionation of Unsymmetrical *o*-Carboxyphenyl Disulfides[1]

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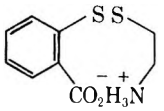
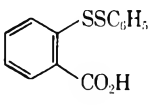
Disproportionation of 2-(phenyldithio)benzoic acid (**2**) to phenyl disulfide and 2,2′-dithiodibenzoic acid is much faster for the salt than for the acid. Among the facts which suggest that the *o*-carboxylate moiety of the salt anchimerically facilitates disproportionation are the following: an increase in rapidity with increasing pH near pH 7; decreased rapidity for the meta isomer; lack of a marked effect of dilution; inhibition of disproportionation by *N*-ethylmaleimide (through trapping of benzenethiolate ion) but acceleration by addition of thiolate ion; accordance with expectation as to the relative rapidity of disproportionation of other dithiobenzoic acids; and, evidence for existence and consistent reactions of *o*-sulfenobenzoic acid anhydride (**5a**) as an unstable intermediate generated by anchimeric displacement of benzenethiolate ion by the *o*-carboxylate moiety.

o-(2-Protoaminoethyldithio)benzoate (**1**) is active as an antiradiation drug.[2] That the methyl ester, the



1



2

meta isomer, and the para isomer of **1** showed no significant antiradiation activity[2a] led us to suspect anchimeric involvement of the carboxylate moiety of **1** with the disulfide linkage. In a similar vein, inactivity of the cyclohexyl analog of **1**[2b] is understandable, since this analog is believed to have trans substituents, which should resist anchimeric involvement. This suspicion of anchimeric involvement was strengthened during work with a phenyl counterpart (**2**) of **1**, since the sodium salt of **2** (**3**) disproportionated far more readily to the two symmetrical disulfides than did **2** itself (eq 1).[3]

$$2 + OH^- \xrightarrow{-H_2O} o\text{-}\bar{O}_2CC_6H_4SSC_6H_5 \rightleftharpoons {}^1/_2(o\text{-}\bar{O}_2CC_6H_4S)_2 + {}^1/_2(C_6H_5S)_2 \quad (1)$$

3

This paper further supports the probability of such an anchimeric involvement in the reaction of eq 1.

The extent of disproportionation of **2** proved to be highly dependent on the pH of the solution (Table I). At pH 14 disproportionation is 95% complete in 0.6 hr (calculated as usual).[4] Attack of the hydroxyl ion on the disulfide bond may be a major path of reaction at high pH.[5] At much lower values of pH, on the other hand, the notable increase in disproportionation with increasing pH points toward increasing anchimeric involvement of carboxylate ion with the disulfide moiety. For example, with a 24-hr reaction period, Table I shows that for the pH sequence 6.4, 6.8, 7.6, and 8.5, the sequence in "disproportionation, %" was 13, 14, 46, and 70.

TABLE I

pH DEPENDENCE OF THE DISPROPORTIONATION OF DISULFIDE **2**[a]

pH[b]	Time, hr	%[c]	pH[b]	Time, hr	%[c]
14	0.6	95	6.8	164	31
8.5	48	81	6.8	73	31
8.5	24	70	6.8	56	26
8.5	3	39	6.8	24	14
8.5	2	32	6.4	216	25
7.6	24	46	6.4	44	17
7.6	24	45[d]	6.4	24	13
7.6	24	39[e]	6.4	18	12
7.6	24	3[f]	6.4	2	3
7.6	24	39[g]	6.4	24	100[h]
			i	*i*	<2

[a] In 10 ml of H_2O (except as noted) at 25–26°; solutions resulted in each instance. [b] Measured both before and after the reaction; not more than 0.4 pH unit change in 216 hr and no change in 72 hr. [c] "Disproportionation, %"; see ref 4. [d] Containing 10 mol % of *N*-ethylmaleimide (**4**). [e] Containing 31 mol % of **4**. [f] Containing 115 mol % of **4**. [g] In 100 ml of H_2O. [h] Containing 10 mol % of $C_6H_5S^-Na^+$ (**6**). [i] After being dissolved completely in 10 ml of AcOH and heated for 119 hr at 100°, **2** was recovered unchanged.[3]

Disproportionation reactions of disulfides can be homolytic, heterolytic, or some combination of these pathways.[6] Although **2** also may be subject to light-induced disproportionation,[3] the carboxylate-assisted re-

(1) (a) Paper XXX: L. Field and P. R. Engelhardt, *J. Org. Chem.*, **35**, 3647 (1970). (b) This investigation was supported by Public Health Service Research Grant AM11685 from the National Institute of Arthritis and Metabolic Diseases. (c) Abstracted from the Ph.D. Dissertation of P. M. G., Jr. (Vanderbilt University, May 1970), which may be consulted for further details. (d) Reported in part at the Southeastern Region Meeting of the American Chemical Society, Tallahassee, Fla., Dec 1968, Abstracts, p 98, and at the IVth Symposium on Organic Sulfur, Venice, Italy, June 1970.

(2) (a) R. R. Crenshaw and L. Field, *J. Org. Chem.*, **30**, 175 (1965); (b) L. Field and P. M. Giles, Jr., *J. Med. Chem.*, **13**, 317 (1970).

(3) L. Field and P. M. Giles, Jr., *J. Org. Chem.*, **36**, 309 (1971).

(4) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Amer. Chem. Soc.*, **83**, 4414 (1961).

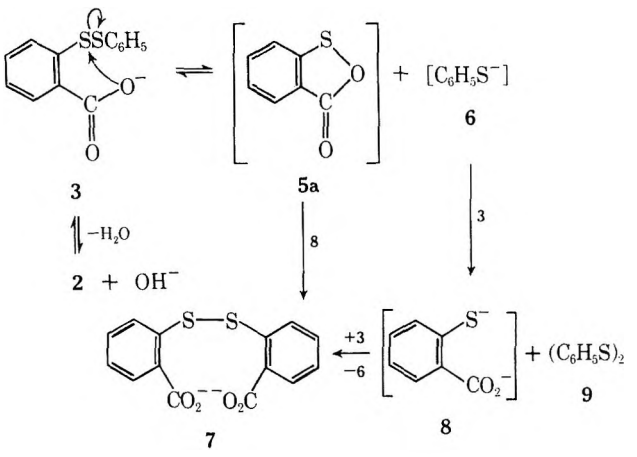
(5) For a discussion of the effect of base on symmetrical disulfides and of the resistance of sodium 2,2′-dithiodibenzoate to attack by OH^- even at high pH, however, see J. P. Danehy and K. N. Parameswaran, *J. Org. Chem.*, **33**, 568 (1968).

(6) L. Field, T. F. Parsons, and D. E. Pearson, *ibid.*, **31**, 3550 (1966).

action seems likely to involve mainly heterolytic cleavage, since all of the studies described in this paper were done in the dark.

Scheme I outlines the best rationalization that has

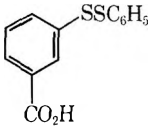
SCHEME I



occurred to us for the disproportionation of 2, after an accumulation of experiments designed to test possibilities. Scheme I resembles one proposed earlier in which an anchimeric effect of a β-amino moiety was invoked.[7] We regard Scheme I as a formulation of several processes likely to play a role and not as a detailed exposition of mechanism. The reactions involved in the disproportionation of 2 undoubtedly are quite complex in their dependence on ionization and displacement equilibria; for example, the effect of the increase in pH mentioned above may result partly from an increase in the amount of thiolate ion relative to that of thiol. Even so, the experimental facts which have emerged in testing consequences of Scheme I have predictive value *per se*, quite apart from the support they seem to lend to the general credibility of Scheme I. Some experiments suggested during the evolution of Scheme I are outlined in the sections which follow, along with a discussion of their predictive value and their apparent consistency with Scheme I.

(1) A pH dependence like that seen in Table I would be expected in Scheme I.

(2) The meta isomer of 2 should be less susceptible to disproportionation, at least to the extent that its disproportionation fails to be initiated *via* an anchimeric effect. At pH 6.8, the salt of **10** is 10% disproportionated in 24 hr (14% for 2) and 18% after 73 hr (31% for 2). That differences are not greater may result from



10

the known considerably greater susceptibility of *m*-carboxyphenyl disulfides to attack by hydroxyl ion,[5] which of course would lead to thiolate ion.

(3) Since the conversion of **3** to **5a** is intramolecular, the extent of disproportionation should not be much affected by concentration if this step is slow relative to the thiolate interchange. When the disproportionation of 2 at pH 7.6 was carried out at one-tenth the usual concentration, the extent of disproportionation decreased only from 46 to 39% (see Table I).

(4) Trapping of the thiolate ion **6** should greatly inhibit disproportionation, since **6** has a chain-propagating function in Scheme I. A similar function for the dianion **8** seems likely, although it should be less important because of the lower acidity of **8** (pk_{SH} 8.20 contrasted with pK_{SH} 6.62 for **6**);[5] facile protonation of the thiolate ion of **8** thus should reduce its relative availability.

When 10 mol % of *N*-ethylmaleimide (**4**) was added at pH 7.6 (Table I), the disproportionation of 2 (46%) was not affected (45%), but 31 mol % of **4** began to cause an effect (39%) and 115 mol % virtually shut down the disproportionation (3%). Thiolate ion thus certainly seems to be implicated in the disproportionation of 2.

As an incidental matter, this effect with the imide **4** led us to try it with disproportionations studied earlier of aminoalkyl aryl disulfide hydrochlorides[6] and of 2-(*n*-decylamino)ethyl benzyl disulfide hydrochlorides.[7] The first of these evidently involves either a lack of marked dependence on thiolate–disulfide interaction or ineffective trapping, since the results were quite different from those with 2. For example, we observed for 2-(phenyldithio)ethylamine hydrochloride (**11**), 80% disproportionation without **4** and 71% with 100 mol %

$C_6H_5SS(CH_2)_2NH_3^+Cl^-$
11

p-$CH_3C_6H_4CH_2SS(CH_2)_2NH_2^+$-$n$-$C_{10}H_{21}Cl^-$
12

of **4** (160 hr, 68°). With *p*-methylbenzyl 2-(*n*-decylamino)ethyl disulfide hydrochloride (**12**), results were more as expected, 35% without **4** and only 1% with 100 mol % of **4** (100°, 480 hr).

The results in Table I for the early phases of reactions seem consistent with first-order reactions, as did those with **11** and **12** (for which the significance still is uncertain),[6,7] but the different effects of **4** imply that the disproportionation of 2 may differ from that of **11**, although perhaps not from that of **12**.

(5) Addition of the thiolate ion **6** should accelerate disproportionation. Table I shows that disproportionation increased from 13 to 100% when 10 mol % of 6 was added (pH 6.4, 24 hr).

(6) The *p*-chlorophenyl analog of 2 (**13**) might be expected to disproportionate more rapidly than 2, if the generation of thiolate ion **6** were rate determining, since Parker and Kharasch report that "the greater the anionic stability of the displaced mercaptide ion, the more susceptible to scission is the parent disulfide,"[8] and since *p*-chlorothiophenol has a pK_{SH} of 5.9 in water, compared with 6.62 for thiophenol.[9] Conversely, 2-(*n*-butyldithio)benzoic acid (**14**) should react less rapidly than 2 (1-butanethiol has a pK_{SH} of 11.51).[9]

n-Butyl disulfide was isolated in 40% yield using the sodium salt of **14** (24 hr, 25°, pH 8.5; Table I shows that **3** underwent 70% disproportionation under these conditions). The sodium salt of the *p*-chlorophenyl analog

(7) M. Bellas, D. L. Tuleen, and L. Field, *J. Org. Chem.*, **32**, 2591 (1967).

(8) A. J. Parker and N. Kharasch, *J. Amer. Chem. Soc.*, **82**, 3071 (1960).

(9) J. P. Danehy and K. N. Parameswaran, *J. Chem. Eng. Data*, **13**, 386 (1968).

13 was 90% disproportionated under the same conditions.

At first, the stability of the aminoalkyl disulfide 1 seemed to contradict the views above. The remainder of this section deals with experiments carried out in an effort to clarify this point. 2-Aminoethanethiol has the rather low pK_{SH} of 8.23;[9] 1 might therefore be thought to undergo disproportionation not a great deal less rapidly than 2. However, disulfide 1 was only 1% disproportionated under conditions which resulted in 46% disproportionation of 2 (pH 7.6, 24 hr, 25°). Furthermore, 1 is less reactive than its hydrochloride,[2a] not more so. We are inclined to attribute these paradoxes to anomalies with 1. In part, a tight ion-pair involvement of the carboxylate ion of 1 with an ammonium moiety may hinder its usual anchimeric function. In part also, since 2 undergoes an essentially irreversible reaction driven by sparing solubility of phenyl disulfide (9) in water (*vide infra*), the reversible reaction of 1 may be slowed relative to that of 2 by accumulation of 15 (eq 2), which is soluble.

$$\underset{15}{(o\text{-}\bar{O}_2CC_6H_4S)_2(H_3\overset{+}{N}CH_2CH_2S)_2} \rightleftharpoons 2\,\underset{1}{o\text{-}\bar{O}_2CC_6H_4SSCH_2CH_2NH_3^+} \quad (2)$$

With respect to this matter of reversibility, it is true that the disproportionation of 2 does not readily go to completion at pH 6.4–8.5 (although it does do so at higher pH). This result *could* indicate attainment of equilibrium, but it seems more likely to be caused by an accumulation of a species such as 7 in such concentration as to compete with 3 for thiolate ions (6). In this respect therefore, 2 resembles 1 except that only one soluble symmetrical disulfide is accumulating rather than two, as a competitor for thiolate ions. To test these points, examination of the extent of reversibility within Scheme I and eq 2 was desirable. The equilibrium with 2 (Scheme I) was examined by approaching the reaction of Scheme I from the product side. When typical amounts of 7 and 9 were maintained in water at 25° for 24 hr at pH 7, *i.e.*, under conditions for 14–46% disproportionation of 2, only 7 and 9 could be isolated, although tlc (after acidification) did suggest the presence of a trace of 2. Thus, although the possibility of an equilibrium cannot be ignored, the precipitation of 9 surely tends to force 3 toward 7 and 9.

The slower disproportionation of 1 than of its hydrochloride was tentatively attributed earlier to the solubility of the disproportionation product formed by 1 (*i.e.*, cystamine 2,2′-dithiodibenzoate, 15);[2a] the hydrochloride leads to only one soluble product, cystamine dihydrochloride, since the other (2,2′-dithiodibenzoic acid) precipitates. To confirm the supposed reversibility of eq 2, the salt 15 was heated in water until reaction was complete. The sparingly soluble 1 then could be separated in 41% yield, permitting the estimate that K for eq 2 approximates 2 (the statistical value is 4).[10]

(7) *o*-Sulfenobenzoic acid anhydride (5a), in common with sulfenyl species in general, should be highly reactive and unstable, although it might persist long enough for its existence to be corroborated; 5a has been proposed as an intermediate in the oxidation of 2,2′-dithiodibenzoate ion.[11] A few sulfenyl carboxylates having the moiety –SOC(O)– are known.[12] Most are quite unstable and exhibit ir absorption at 1710–1780 cm^{-1}.[12b]

The preparation of a red oil (5b) that appeared to be largely 5a was achieved as shown by eq 3. During 0.5

$$o\text{-}HO_2CC_6H_4SH + Cl_2 \longrightarrow [o\text{-}HO_2CC_6H_4SCl] \xrightarrow{Et_3N} \mathbf{5b} + Et_3NH^+Cl^- \quad (3)$$

hr after preparation, this oil (5b) oxidized iodide to iodine (86% of expectation), showed strong ir absorption appropriate for 5a at 1790 cm^{-1}, and had a mass spectrum peak at m/e 152 of relative abundance 25% (calcd for 5a, 152). The oil contained no chlorine, thus eliminating a sulfenyl chloride as a cause of its reactions. Sulfenyl character nevertheless could be demonstrated by conversion of 5b by thiophenol to 2 (81%), and by the dianion 8 (after acidification) to the conjugate acid of 7 (29%); these reactions also support the feasibility of the two similar processes in Scheme I. After 0.5 hr 5b began to stiffen, and both the ir band at 1790 cm^{-1} and the peak at m/e 152 began to shrink. After 24 hr, 5b had solidified. Repeated recrystallization then gave red solid (16) with a constant melting point of 110–114°. The 16 (in solution) no longer oxidized iodide to iodine; it had ir absorption at 1680 cm^{-1} but not at 1790 cm^{-1}, a mass spectrum peak of relative abundance only 1% at m/e 152, and an elemental analysis roughly consistent with a polymer of 5a; unfortunately, sparing solubility of 16 precluded determination of its molecular weight.

Experimental Section[13]

Materials.—Disulfides 1,[2a] 2,[3] 14,[3] and 15,[2a] and *o*-carboxyphenyl *o*-carboxybenzenethiolsulfonate[3] were prepared according to established procedures. Disulfide 11 was kindly provided by Dr. T. F. Parsons[6] and disulfide 12 by Dr. M. Bellas.[7] *o*-Mercaptobenzoic acid was recrystallized from EtOH–H_2O,[14] mp 165–166° (lit.[14] mp 163–164°). All other materials were used as purchased. The pK_a of disulfide 2 determined by titration using a Model 72 Beckman pH meter was 6.5 in 3:7 EtOH–H_2O and 8.0 in 1:1 EtOH–H_2O. The mass spectrum of 2 was as follows: m/e (rel intensity) 264 (6), 263 (8), 262 (46), 155 (6), 154 (12), 153 (100), 152 (37), 136 (10), 111 (3), 110 (8), 109 (65), 108 (46), 107 (21), 98 (19), 82 (10), 77 (12), 69 (31), 65 (35), 63 (12), 51 (17), 50 (12), 45 (17).

Preparation of 3-(Phenyldithio)benzoic Acid (10).—A solution of *m*-mercaptobenzoic acid[2a] (0.77 g, 5 mmol) and phenyl benzenethiolsulfonate[15] (1.25 g, 5 mmol) in EtOH (25 ml) was heated (reflux, 4 hr). Water (100 ml) was added, the solution was extracted with three 50-ml portions of Et_2O, and the combined ethereal extracts were dried ($MgSO_4$). Solvent was removed to give crude 10, 1.30 g (99%), mp 160–170°. Repeated recrystallization of 10 from MeOH–H_2O and from Et_2O–hexane gave 10

(10) L. Haraldson, C. J. Olander, S. Sunner, and E. Varde, *Acta Chem. Scand.*, **14**, 1509 (1960).

(11) J. P. Danehy and M. Y. Oester, *J. Org. Chem.*, **32**, 1491 (1967).

(12) (a) A. J. Havlik and N. Kharasch, *J. Amer. Chem. Soc.*, **78**, 1207 (1956); (b) R. E. Putnam and W. H. Sharkey, *ibid.*, **79**, 6526 (1957); (c) J. H. Uhlenbroek and M. J. Koopmans, *Recl. Trav. Chim. Pays-Bas*, **76**, 666 (1957).

(13) Melting points are corrected. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Mass spectra were obtained with an LKB Model 9000 instrument, operating at 70 eV using the direct-inlet system, which was obtained through Science Development Program Grant GU-2057 from the National Science Foundation; we are indebted to Mr. C. Wetter for these spectra. Ir spectra were obtained using a Beckman Model IR-10 with films of liquids and KBr pellets of solids. Solvents were evaporated under reduced pressure with a rotary evaporator. Eastman Chromagram sheet type 6060 (silica gel) was used for tlc (developed at 25° with 9:1 $CHCl_3$–EtOH and then exposed to I_2 vapor in a sealed container).

(14) C. F. H. Allen and D. D. MacKay, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 580.

(15) L. Field and T. F. Parsons, *J. Org. Chem.*, **30**, 657 (1965).

having mp 170–175°: tlc showed only one spot (R_f 0.13); ir (KBr) 3300–2300, 1690, 1590, 1565, 1440, 1300, 900, 740, 720, and 550 cm^{-1}; mass spectrum *m/e* (rel intensity) 264 (10), 263 (17), 262 (100), 198 (6), 155 (6), 154 (9), 111 (3), 110 (12), 109 (64), 77 (8), 69 (17), 65 (30), 51 (9), 45 (8) (*note the absence of m/e 152 which is found in the mass spectrum of* **2**).

Anal. Calcd for $C_{13}H_{10}O_2S_2$: C, 59.51; H, 3.84; S, 24.45. Found: C, 59.71; H, 3.91; S, 24.66.

Preparation of 2-(4-Chlorophenyldithio)benzoic Acid (13).—A solution of *p*-chlorothiophenol (1.45 g, 10 mmol) and *o*-carboxyphenyl *o*-carboxybenzenethiolsulfonate (3.38 g, 10 mmol)[3] was stirred for 1 hr at 25° in 95% EtOH (50 ml). A white solid began to separate after 0.25 hr. Cooling (*ca.* 0°) and filtration gave 2.60 g (88%) of **13** having mp 195–197°. Recrystallization from EtOH–H_2O gave **13** having a constant melting point of 204–206°: tlc gave only one spot (R_f 0.05); ir (KBr) 3200–2300, 1670, 1590, 1560, 1465, 1420, 1315, 1270, 1260, 815, 740, 690, and 640 cm^{-1}.

Anal. Calcd for $C_{13}H_9ClO_2S_2$: C, 52.61; H, 3.06; Cl, 11.95; S, 21.61. Found: C, 52.89; H, 3.11; Cl, 12.01; S, 21.33.

Studies of Disproportionation.—Carefully weighed samples of disulfide **2** (*ca.* 1 mmol) were dissolved in 10 ml of H_2O containing an exactly equivalent amount of NaOH (*ca.* 1 mmol) in 10-ml flasks. The pH of the solution was measured using pHydrion paper (accuracy of ±0.1 pH unit) and was adjusted to the value given in Table I. The flasks were wrapped with aluminum foil for protection from light. They were kept at 25–26° for the time intervals designated in Table I, after which they were chilled in ice and the pH was measured again. "Disproportionation, %" was determined by isolating phenyl disulfide (**9**) formed using filtration (identity and purity were established by melting point, ir, and tlc after recrystallization from hexane) and then by calculation as usual;[4] the results are given in Table I. The disproportionation of the meta isomer **10** was measured similarly, as was that of 2-(*n*-butyldithio)benzoic acid (**14**; *n*-butyl disulfide was isolated by extraction with Et_2O and was identified by ir and tlc) and of 2-(4-chlorophenyldithio)benzoic acid (**13**; *p*-chlorophenyl disulfide was isolated by filtration, recrystallized from hexane, and identified by melting point, ir, and tlc). Disulfide **1** (*ca.* 1 mmol) was dissolved in 10 ml of H_2O (100°) in a 10-ml foil-wrapped flask, and the solution was cooled quickly to 25°; a relatively small amount of the solid **1** precipitated. After 24 hr at 25°, chilling (0°) and filtration gave unchanged **1** in *ca.* 99% yield (identified by melting point and ir). Disproportionation of **11** and **12** were determined essentially as reported earlier,[6,7] with or without dissolved **4**; the symmetrical disulfides were characterized by ir and melting point; "disproportionation, %" was calculated as usual.[4]

Equilibration Studies.—Cystamine 2,2′-dithiodibenzoate (**15**) (0.41 g, 0.90 mmol) in H_2O (10 ml) was heated at 100° for 72 hr. The solution was cooled (0°), and crude **1** (very sparingly soluble) was separated by filtration. Recrystallization from H_2O (100°) gave 0.17 g (41%) of material identical with authentic **1** by ir, mp 202–204° dec (lit.[2a] mp 205° dec and 198–200° dec). After 144 hr, an identical sample of **15** again yielded 0.17 g (0.74 mmol) of **1** thus confirming that equilibrium had been achieved in 72 hr; hence K for eq 2[10] = $[1]^2/[15][15] = [0.74]^2/[0.90 - 0.5\cdot(0.74)]^2$ = *ca.* 2.

In the study of the reversibility within Scheme I, phenyl disulfide (**9**, 1.09 g, 5.0 mmol) was suspended in a solution of salt **7** (1.75 g, 5.0 mmol) in H_2O (100 ml). After 24 hr (pH 7, 25°), disulfide **9** was isolated by filtration (1.03 g, 95% recovery, identified by melting point and ir). The filtrate was acidified (pH 1, 10% HCl) and extracted (Et_2O). Tlc showed two spots, R_f 0.00 and 0.19, the former corresponding to the conjugate acid of **7** and the latter to a trace of disulfide **2** (**2** being done concurrently).

Possible Existence of 5a. A. Preparation of 5b.—*o*-Mercaptobenzoic acid (5.00 g, 32.4 mmol) was suspended in CH_2Cl_2 (70 ml) and cooled to 0°. Chlorine (1.61 ml, 2.62 g, 35 mmol) was added slowly (0.5 hr) with stirring. Dry N_2 then was swept through the solution until no HCl or Cl_2 was evident. Triethylamine (4.55 ml, 3.28 g, 32.4 mmol) in CH_2Cl_2 (50 ml) was added (0.25 hr). After 3 hr at 0° the solution was washed twice with 100-ml portions of cold H_2O [triethylammonium chloride was recovered from the H_2O wash (3.34 g, 75% yield), identical with authentic material by melting point (253–255°) and ir], and the organic layer was dried ($CaSO_4$). Evaporation of the solvent below 25° gave a red oil (**5b**), presumed to be largely **5a**: 4.59 g (93%); ir 1790 cm^{-1} (C=O); negative Beilstein test. A sample of **5b** (0.1900 g, 1.25 mequiv if pure **5a**) liberated 1.08 mequiv of I_2 (86%) when treated with excess KI in a modification of the procedure of Kharasch and Wald;[16] this technique has been used for the assay of sulfenyl carboxylates.[12a,16] The mass spectrum of **5b** (peaks above *m/e* 152 were small) was as follows: *m/e* (rel intensity, assignment) 154 (1), 153 (3), 152 (25, $C_7H_4O_2S$), 104 (100, C_7H_4O), 96 (20), 95 (6), 77 (11), 76 (76, C_6H_4), 75 (16), 74 (20), 73 (9), 70 (21), 69 (30), 63 (6), 62 (5), 61 (5), 58 (5), 50 (60), 49 (9), 48 (16); ir (NaCl plates) 3500–2300, 1790, 1700, 1590, 1440, 1270, 1220, 1150, 1020, 990, 890, and 750 cm^{-1}.

The solidified oil which resulted after **5b** had stood at *ca.* 25° for *ca.* 24 hr was recrystallized repeatedly (Et_2O–hexane and MeOH–H_2O) to give material **16** having a constant melting point of 110–114°. A sample of **16** did not liberate I_2 from KI; the ir and mass spectra are mentioned in the discussion.

Anal. Calcd for polymer of $C_7H_4O_2S$: C, 55.25; H, 2.65; S, 21.08. Found: C, 54.56; H, 3.82; S, 20.16.

B. Reaction of 5b with Thiols.—The red oily **5b** (4.03 g, 26.6 mmol if pure **5a**) was stirred with thiophenol (2.69 ml, 26.2 mmol) in EtOH (50 ml). Water (100 ml) was added after 1 hr; solid **2** which precipitated amounted to 5.63 g (81%, based on thiophenol), mp 190–195° dec. Recrystallization from Et_2O–pentane and from EtOH–H_2O gave **2** with a constant melting point of 198–199° dec (identical with authentic **2** by ir and tlc) (lit.[3] mp 197–198.5° dec).

Another sample of **5b** (1.92 g, 12.6 mmol if pure **5a**) was added in one portion with stirring to H_2O (50 ml) containing the dianion **8** [2.52 g, 12.6 mmol, prepared by neutralizing *o*-mercaptobenzoic acid (12.6 mmol, in MeOH) with NaOMe (25.2 mmol, in MeOH) and carefully removing the solvent]. After the mixture had been stirred at 25° for 0.25 hr, acidification (pH 1, 10% HCl) gave a mixture of *o*-mercaptobenzoic acid and 2,2′-dithiodibenzoic acid, which was separated by fractional recrystallization from EtOH–H_2O. The 2,2′-dithiodibenzoic acid produced (1.10 g, 29%) had mp and mmp 285–290° dec (identical with authentic material by ir) (lit.[17] mp 287–288°). A sample of *o*-mercaptobenzoic acid alone did not react under comparable conditions in a control experiment (tlc and melting point unchanged).

Registry No.—**2**, 26929-62-4; **5**, 27396-44-7; **10**, 27396-45-8; **13**, 27396-46-9.

Acknowledgment.—Thanks are due to Professor J. P. Danehy of the University of Notre Dame and to Professor L. C. Hall of Vanderbilt University for helpful comments and suggestions.

(16) N. Kharasch and M. M. Wald, *Anal. Chem.*, **27**, 996 (1955).
(17) W. G. Prescott and S. Smiles, *J. Chem. Soc.*, **99**, 640 (1911).

N-Benzylisoquinolinium 4-Dithiocarboxylate Adducts from N-Benzylisoquinolinium Halides and Carbon Disulfide[1]

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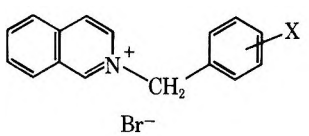
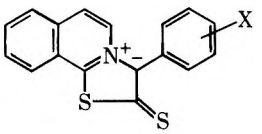
N-Benzylisoquinolinium halides, when combined with carbon disulfide in alkaline aqueous dioxane, give both the mesoionic cycloadducts first described by Kröhnke and Steuernagel[3] and products identified as *N*-benzylisoquinolinium 4-dithiocarboxylates. The derivation of this structural assignment through physical methods and deuterium-labeling experiments and a plausible rationale for the formation of these novel adducts are presented.

Mesoionic adducts derived from *N*-benzylisoquinolinium bromides (**1**) and carbon disulfide in alkaline aqueous dioxane are 3-phenylthiazolo[2,3-*a*]isoquinolinium-2-thione betaines (**2**).[3-5]

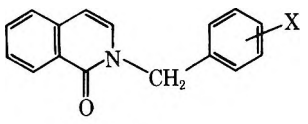


1



2

It was observed[3] that the isolated yields of the betaine **2** increased as the substituent became more electronegative; from **1** (4′-X = Cl, CH=CH_2, CN, NO_2) the yields of the corresponding adducts **2** were 20, 34, 40, and 66% of theory. In the chlorobenzyl case, an anticipated[6] side product, *N*-(4-chlorobenzyl)isoquinolone (**3**), was obtained in low yield.[3]



3

In the course of studies directed toward reducing the mechanistic ambiguities associated with this cycloaddition process, we prepared and subjected a series of substituted benzylisoquinolinium salts to the reaction conditions. Eleven representatives of a new class of adducts were obtained. This manuscript describes the structural elucidation of these hitherto unexamined products.

Results

An *N*-benzylisoquinolinium halide, carbon disulfide, and aqueous alkaline dioxane react to give the corresponding mesoionic adduct **2**, *N*-benzylisoquinolone (**3**), and a third major product having a molecular formula relative to the isoquinolinium starting material corresponding to loss of hydrogen halide and gain of carbon disulfide.

The new adducts had prominent mass spectrometric fragmentation ions at *m/e* 172 ($C_{10}H_6NS$), 128 (C_9H_6N), M − 76 (loss of carbon disulfide), and at values corresponding to substituted tropylium ions (*e.g.*, 169 and 171 from the 4-bromobenzyl product). The elemental compositions for these fragments were confirmed by high resolution data. The mass spectrum of the adduct derived from *N*-(4-bromobenzyl-α-d_2)isoquinolinium bromide contained the intense tropylium ion peaks at *m/e* 171 and 173 and molecular ions at 375 and 377, thus demonstrating complete retention of the deuterium labels.

The ultraviolet spectra of the new adducts typically exhibited λ_{max} 236 nm (log ϵ 4.5) and 335 (4.0) in ethanol, values in close agreement with those appropriate for *N*-benzylisoquinolinium systems[7] (Figure 1).

The mass and ultraviolet spectra thus provide sound grounds for assigning the new adducts as *N*-benzylisoquinolinium dithiocarboxylates.

The correct position of the dithiocarboxylate group on the isoquinolinium nucleus was uncovered through deuterium-labeling experiments.

1-Deuterio-, 4-deuterio-, and 8-deuterioisoquinolinium salts in the 4-bromobenzyl series were synthesized and converted to products. Mass spectrometric analyses (Table I) of the new adducts indicated that most of the 1-deuterium label was lost during the process; all of the 4-deuterium label was eliminated; none of the 8-deuterium tag was removed.

TABLE I

DEUTERIUM ANALYSES IN ISOQUINOLINES AND DITHIOCARBOXYLATE ADDUCTS

Label in isoquinoline	% of d_1 in isoquinoline[a]	% of d_1 in derived adduct **4** (X = 4′-Br)[a]
1	93[b]	1.4
4	96.4	0.3
8	50.2	52.0

[a] Except as noted, by mass spectrometry. [b] By nmr.

Exchange experiments were used to learn when exchange at C_1 occurred: in alkaline deuterium oxide–dioxane, the salt **1** (X = 4′-Br) incorporated 86% of one deuterium atom at C_1 in 4 min; the 1-deuterio salt (**1**, X = 4′-Br, H_1 = D) in aqueous alkaline dioxane–carbon disulfide incorporated 60% of one hydrogen at C_1 in 4 min; and the unlabeled adduct, resubmitted to deuterated media under the reaction conditions for 9.5 hr, gave no detectable d_1 component in the reisolated product. Thus the exchange at C_1 is a reaction of the *N*-benzylisoquinolinium salt, and the dithiocarboxylate

(1) Supported initially by Public Health Service Research Grants GM 14381 and GM 16576, and currently by the National Science Foundation Grant GP 9259.

(2) National Institute of General Medical Sciences Predoctoral Fellow, 1969–present.

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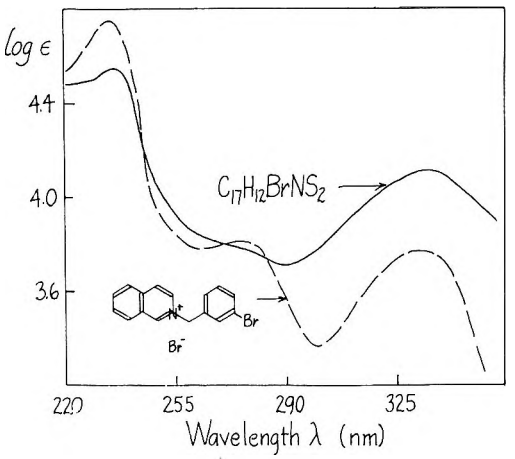
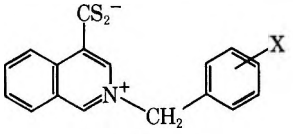


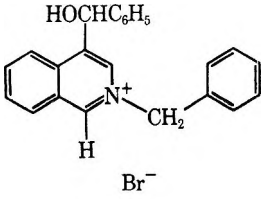
Figure 1.—Ultraviolet absorption spectra in ethanol for *N*-(3-bromobenzyl)isoquinolinium bromide (– – –) and the derived $C_{17}H_{12}BrNS_2$ adduct (——).

group in the new class of adducts must be located at C_4. The structure is thus assigned as **4**.



4

The nmr spectra of these adducts provide valuable confirmatory evidence. In trifluoroacetic acid, the unsubstituted adduct (**4**, X = H) has absorptions at δ 6.0 (s, 2), 7.6 (s, 5), 8.4 (m, 5), and 9.7 (s, 1). Similar spectra were obtained in hexafluoroacetone. Interpretation of these data in terms of structure **4** follows at once from literature precedent for isoquinolines[8,9] and for the very similar isoquinolinium salt **5**,[10–13] which in trifluoroacetic acid has corresponding absorptions at 6.0 (s, 2), 7.50 (s, 5), 8.2 (m, 4), 8.87 (s, 1), and 9.68 (s, 1), assigned respectively to the methylene, phenyl, $H_{5,6,7,8}$, H_3, and H_1.

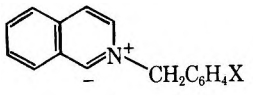


5

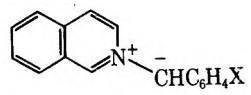
A still more conclusive conformation has been secured through an X-ray single-crystal structure determination on **4** (X = 4′-Br).[14]

Discussion

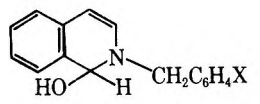
A reaction scheme in conformity with the labeling results given above may be easily constructed. The most accessible conjugate base of the *N*-benzylisoquinolinium salt is not **7** but rather **6**, produced through abstraction of H_1; the pseudobase **8** of the isoquinolinium salt behaves as an enamine sufficiently reactive to attack carbon disulfide nucleophilically. Base-catalyzed 1,4 elimination of water from the 1,4-dihydroisoquinolinium intermediate so produced (**9**) gives the isolable adduct **4**.



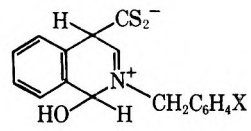
6



7



8



9

The apparent discrepancy between the labeling results, which provide no basis for postulating reversible formation of the 1,3-dipolar intermediate **7**, and the obtention of mesoionic compounds **1**, which can be most promptly rationalized[15,16] in terms of cycloadditions between **7** and carbon disulfide, followed by an oxidation, will be considered in another context.[17]

Experimental Section

Except when noted otherwise, nmr spectra were determined at 60 MHz as solutions in $CDCl_3$ using a Varian spectrometer; mass spectrometric data were obtained at the Battelle Memorial Institute High Resolution Mass Spectrometry Center, Columbus, Ohio, and by Mrs. Mary Mitchell on a CEC 21-110 at the University of Oregon; elemental analyses were done by J. Nemeth and associates, Urbana, Ill., and by Chemalytics, Tempe, Ariz.; melting points were determined on a "Kofler" micro hot state.

4-Chlorobenzyl Bromide.—A 500-ml three-necked flask fitted with a thermometer and gas inlet and outlet tubes was charged with 14.9 g of 4-chlorobenzyl alcohol (Aldrich) in 300 ml of benzene. Hydrogen bromide was bubbled into the cooled solution. The reaction temperature rose to 11°, and, when it subsequently fell to 5°, the addition was terminated. Sodium sulfate was added, the mixture was stirred overnight, and, upon filtration and concentration, a white solid was obtained. Recrystallization of this solid from petroleum ether (bp 30–60°) gave 16.8 g (78%) of 4-chlorobenzyl bromide, mp 50–52° (lit.[18] mp 51°). This lachrymator had nmr singlets at δ 4.39 (2) and 7.25 (4).

Through similar reactions, **4-methoxybenzyl bromide** [bp 94° (1 mm), lit.[19] bp 128–129° (16 mm)], which was promptly combined with isoquinoline, and **3-methoxybenzyl bromide** [bp 75° (1 mm), lit.[19] bp 127° (16 mm)] were prepared from the corresponding alcohols. The other substituted benzyl bromides utilized were commercially available. All were lachrymatory.

***N*-Benzylisoquinolinium bromides** (1) were prepared in 74–98% yields by heating solutions of a benzyl bromide and isoquinoline in benzene at reflux from 9 to 14 hr and then collecting the precipitated salt from the cooled reaction mixture. Samples for elemental analysis (Table II) were recrystallized at least twice from methanol–ethyl acetate.

***N*-(3-Trifluoromethylbenzyl)isoquinolinium chloride**, mp 215°, from the reaction of 8.3 g of isoquinoline and 12.5 g of 3-trifluoromethylbenzyl chloride in 150 ml of toluene at reflux for 24 hr, was obtained in 31% yield (6.49 g).

Reaction of *N*-(3-Methylbenzyl)isoquinclinium Bromide with Carbon Disulfide in Alkaline Aqueous Dioxane.—A 500-ml three-necked flask, containing 9.12 g (0.029 mol) of *N*-(3-methylbenzyl)isoquinolinium bromide, 30 ml of water, 30 ml of dioxane,

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Table II

N-Benzylisoquinolinium Bromides[a] 1

Benzyl substituent	Molecular formula	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Nmr data, δ, ppm
H	$C_{16}H_{14}BrN$	157–158	64.01	4.70	4.67	63.61	4.65	4.38	6.40 (s, 2), 7.0–8.5 (m, 9), 8.84 (AB, 2), 11.04 (s, 1)
3-CH_3	$C_{17}H_{16}BrN$	156–158	64.97	5.13	4.46	64.70	5.33	4.25	2.26 (s, 3), 6.50 (s, 2), 7.0–8.6 (m, 8), 8.94 (AB, 2), 11.26 (s, 1)
4-CH_3O	$C_{17}H_{16}BrNO$	235–236	61.83	4.88	4.24	62.15	4.67	4.03	
3-NO_2	$C_{16}H_{13}BrN_2O_2$	228–229	55.66	3.80	8.12	55.66	3.76	7.88	6.34 (s, 2), 7.6–9.2 (m, 10), 10.66 (s, 1)[b]
3-Br	$C_{16}H_{13}Br_2N$	210–211	50.68	3.46	3.69	50.62	3.28	3.68	6.16 (s, 2), 7.2–8.7 (m, 8), 8.84 (AB, 2), 10.56 (s, 1)[b]
4-Br	$C_{16}H_{13}Br_2N$	161–162	50.68	3.46	3.69	50.76	3.71	3.85	6.58 (s, 2), 7.2–8.5 (m, 8), 8.96 (AB, 2), 11.32 (s, 1)

[a] Other *N*-benzylisoquinolinium bromides prepared and utilized synthetically: 4-CH_3 (mp 79–81°), 3-F (155°), 4-CN (193–194°), 3-CH_3O (172–173°), 4-NO_2 (206–207°), 3-Cl (164°), and 4-Cl (100–124°). [b] In DMSO-d_6.

Table III

Analytical Data for *N*-Benzylisoquinolinium 4-Dithiocarboxylate Adducts 4

Benzyl substituent	Molecular formula	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H	$C_{17}H_{13}NS_2$	209–210	69.12	4.44	4.74	69.23	4.33	4.47
4-CH_3	$C_{18}H_{15}NS_2$	198–201	69.86	4.89	4.53	69.58	4.82	4.79
4-CH_3O	$C_{18}H_{15}NOS_2$	191–193	66.43	4.64	4.30	66.64	4.76	4.11
3-F	$C_{17}H_{12}FNS_2$	204–205	65.15	3.86	4.47	64.98	3.55	4.68
3-Cl	$C_{17}H_{12}ClNS_2$	210–213	61.90	37.6	4.25	62.04	4.09	4.38
3-Br	$C_{17}H_{12}BrNS_2$	207–208	54.55	3.23	3.74	54.32	3.22	3.82

and 20 ml of carbon disulfide was heated to 52°. Over a 3-min period, 30 ml of 11 *N* sodium hydroxide was added to the vigorously stirred mixture, which was then brought to and maintained at about 72° for 8 hr. After 2 hr at room temperature with stirring and 4 days at −20° without, the mixture was filtered. The solid collected was washed with three 30-ml portions of warm water and dried; 3.0 g of dark solid was obtained.

The filtrate was extracted with chloroform; the chloroform solution was washed twice with 0.1 *N* hydrochloric acid and once with water, dried over calcium carbonate, filtered, and concentrated, leaving a thick black oil. Chromatography of this dark oil and the 3.0 g of dark solid obtained above on 250 g of neutral Woelm II alumina with chloroform gave a sequence of 20-ml automatically collected fractions.

The early fractions contained *N*-(3-methylbenzyl)isoquinolone (**3**, X = 3′-CH_3): nmr δ 2.2 (s, 3), 5.1 (s, 2), 7 (q, 2), 7–8 (m, 7), and 8.4 (m, 1).

The middle fractions contained the 3-tolyl mesoionic adduct **2** (X = 3′-CH_3): mp 201–204° (176 mg after recrystallization from chloroform); nmr δ 2.36 (s, 3), 7–8 (m, 10).

When concentration of the oil prior to chromatography was incomplete, and dioxane remained in the residue, the isoquinolone and mesoionic adducts were separated only after a second chromatographic development on 50 g of alumina.

The sand and alumina on the top of the column were extracted with hot *N*,*N*-dimethylformamide, and the extract was concentrated to give 0.56 g of red solid, mp 191–194°. Recrystallization from DMF–acetonitrile gave 327 mg of an analytically pure $C_{18}H_{15}NS_2$ sample (**4**, X = 3′-CH_3), mp 195–197°.

Molecular formulas for this and other isoquinolinium dithiocarboxylate adducts prepared and isolated through similar procedures were secured through elemental analysis (Table III) and/or high resolution mass spectrometric determinations of *m*/*e* values for molecular ions (Table IV). These adducts had very strong infrared bands at 1040 cm^{-1} (KBr).

The dithiocarboxylate adducts were obtained in yields ranging from 16.5% for the 4-CH_3O compound to only 2.9% for the 3-CF_3 case. No adducts in this class were isolated from reaction mixtures derived from the two nitrobenzyl- and the cyanobenzylisoquinolinium salts.

Molecular formulas for the mesoionic adducts obtained in these reactions were confirmed by elemental analyses (Table V) and/or high resolution mass spectrometry (Table VI). The yields of these adducts ranged from 2.1% for the 4-CH_3O derivative to 52.2% for the 4-CN analog.

4-Bromobenzyl-α-d_2 Alcohol.—A 100-ml three-necked flask fitted with a 50-ml dropping funnel, condenser, and drying tube was flushed with nitrogen and charged with 0.50 g (11.9 mmol) of lithium aluminum deuteride (Stohler) and 25 ml of anhydrous ether. A solution of methyl 4-bromobenzoate (2.80 g, 13 mmol) in 17 ml of ether was added to the funnel. The ester was added dropwise over 15 min to the stirred reaction mixture heated to reflux. After another 1 hr at reflux, the reaction mixture was cooled, decomposed through the cautious addition of 0.5 ml of water, 0.5 ml of 15% sodium hydroxide, and an additional 1.5 ml of water, and filtered. The solid was washed several times with ether. The total filtrate was dried over magnesium sulfate, filtered, and concentrated to afford 2.29 g (93%) of light yellow solid, mp 76–78° (lit.[20] mp 76–76.5°). The nmr showed δ 2.65 (s, 1) and 7.33 (AA′BB′, 4).

Table IV

High Resolution Mass Spectrometric Molecular Ions for *N*-Benzylisoquinolinium 4-Dithiocarboxylate Adducts 4

Benzyl substituent	Molecular formula	Mp, °C	*m*/*e* Calcd	*m*/*e* Found	Error (×10^3)
H	$C_{17}H_{13}NS_2$	209–210	295.0489	295.0504	1.5
3-CH_3	$C_{18}H_{15}NS_2$	198–199	309.0646	309.0644	0.2
4-CH_3		198–201		309.0645	0.1
3-CH_3O	$C_{18}H_{15}NOS_2$	215–218	325.0595	325.0552	4.3
4-CH_3O		191–193		325.0613	1.8
3-^{35}Cl	$C_{17}H_{12}ClNS_2$	210–213	329.0100	329.0133	3.3
4-^{35}Cl		208–209		329.0116	1.6
3-CF_3	$C_{18}H_{12}F_3NS_2$	135–155	363.0363	363.0372	0.9
3-^{79}Br	$C_{17}H_{12}BrNS_2$	207–208	372.9595	372.9609[a]	1.4
4-^{79}Br		206–207		372.9709	11.4
3-^{81}Br			374.9574	374.9599[a]	2.5
4-^{81}Br				374.9633	5.9

[a] Purdue University Mass Spectrometry Center data.

4-Bromobenzyl-α-d_2 Bromide.—Treating 4-bromobenzyl-α-d_2 alcohol (1.74 g) with hydrogen bromide by the procedure detailed above gave 1.98 g (86%) of light yellow crystals, mp 50–59° (lit.[21] mp 63°). The nmr spectrum showed only the AA′BB′ pattern at δ 7.42.

***N*-(4-Bromobenzyl-α-d_2)isoquinolinium Bromide.**—A solution of 1.73 g of 4-bromobenzyl-α-d_2 bromide and 0.89 g of isoquinoline in 30 ml of benzene was heated at reflux for 7.5 hr with stirring. The reaction mixture was cooled to give 1.9 g of a colorless solid. The mother liquor, after an additional 22 hr at reflux, gave an additional 0.3 g of solid when cooled. The two crops of salt, mp 115–145°, showed no benzylic proton absorption in the nmr.

1-Cyano-2-benzoyl-1,2-dihydroisoquinoline[22] was prepared

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TABLE V

ANALYTICAL DATA FOR MESOIONIC ADDUCTS 2

Phenyl substituent	Molecular formula	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
3-F	$C_{17}H_{10}FNS_2$	213–215	65.57	3.24	4.50	65.32	3.05	4.82
4-Cl	$C_{17}H_{10}ClNS_2$	288–291	62.28	3.07	4.27	62.53	2.92	4.41
4-Br[a]	$C_{17}H_{10}BrNS_2$	299–300	54.84	2.71	3.76	55.03	2.68	3.56
3-NO_2[b]	$C_{17}H_{10}N_2O_2S_2$	279–287	60.34	2.98	8.28	60.54	2.88	8.00

[a] *Anal.* Calcd: S, 17.22; Br, 21.46. Found: S, 17.52; Br, 21.80. [b] *Anal.* Calcd: S, 18.95. Found: S, 18.74.

TABLE VI

HIGH RESOLUTION MASS SPECTROMETRIC MOLECULAR IONS FOR MESOIONIC ADDUCTS 2

Phenyl substituent	Molecular formula	Mp, °C	m/e Calcd	m/e Found	Error (×10³)
H	$C_{17}H_{11}NS_2$	223–225	293.0333	293.0303	3.0
3-CH_3	$C_{18}H_{13}NS_2$	203–206	307.0489	307.0474	2.5
4-CH_3		267–269		307.0489	
4-CN	$C_{18}H_{10}N_2S_2$	335–337	318.0285	318.0267	1.8
3-CH_3O	$C_{18}H_{13}NOS_2$	170–172	323.0405	323.0417	1.2
4-CH_3O		255–257		323.0403	0.2
3-^{35}Cl	$C_{17}H_{10}ClNS_2$	206–207	326.9943	326.9982	3.9
4-^{35}Cl		288–291		326.9959	1.6
3-NO_2	$C_{17}H_{10}N_2O_2S_2$	279–287	338.0184	338.0153	3.1
4-NO_2		300–302		338.0159	2.5
3-CF_3	$C_{18}H_{10}F_2NS_2$	218–219	361.0207	361.0194	1.3
3-^{79}Br	$C_{17}H_{10}BrNS_2$	229–230	370.9438	370.9442	0.4
4-^{79}Br		299–300		370.9463[a]	2.5

[a] Purdue University Mass Spectrometry Center data.

from 8.6 g of isoquinoline and benzoyl chloride in aqueous sodium cyanide. The crude product (8.8 g, 51%, mp 123–127°) was recrystallized from 95% ethanol to obtain 4.68 g of nearly colorless crystals, mp 125–127° (lit.[22] mp 124–126°). The nmr in $CDCl_3$ had δ 6.4 (AB, 2), 6.6 (s, 1), and 7.2–7.8 (m, 9).

1-Deuterioisoquinoline.[23]—A mixture of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline (4.3 g), tetrahydrofuran (10 ml), and deuterium oxide (10 ml) was stirred and heated at reflux for 6 hr. The cooled reaction mixture was extracted with three 20-ml portions of ether, and the ethereal solution was washed with water, dried over magnesium sulfate, filtered, concentrated, and distilled. The colorless product, bp 48° (0.3 mm), 1.57 g (73% yield), which froze readily just below room temperature, was 93% d_1 according to nmr analysis.

***N*-(4-Bromobenzyl)-1-deuterioisoquinolinium Bromide.**—A mixture of 1-deuterioisoquinoline (1.57 g, 93% d_1), a slight excess of α,4-dibromotoluene (3.15 g, Aldrich Chemical), and 60 ml of benzene was stirred at reflux for 19 hr and then cooled overnight at 5°. The colorless salt was collected and dried 7 hr over phosphorus pentoxide (0.5 mm); it had mp 126–143° and the expected nmr spectrum.

4-Deuterioisoquinoline.[24]—A solution of 4-bromoisoquinoline (2.50 g, Aldrich) in 35.2 ml of 2 *N* deuteriosulfuric acid and 1.84 g of zinc dust were stirred and heated to reflux for 2 hr. The cooled reaction mixture was filtered and the filtrate was made just basic with about 7 ml of 11 *N* sodium hydroxide. Steam distillation and the normal work-up gave 988 mg (63%) of crude product; distillation gave 817 mg of colorless 4-deuterioisoquinoline: bp 97° (13 mm); mp 25°, containing less than 3% of the starting material. The nmr spectrum of the neat product [δ 7.2–8.0 (m, 4), 8.84 (s, 1), and 9.52 (s, 1)] indicated at least 90% d_1 material and 96.4% d_1 by mass spectrometry.

***N*-(4-Bromobenzyl)-4-deuteriosoquinolinium bromide**, from 1.52 g of α-4-dibromotoluene and 790 mg of 4-deuterioisoquinoline, had mp 105–145° (2.07 g, 89%).

2-Deuteriobenzonitrile.[25]—In a 200-ml three-necked flask, 2-bromobenzonitrile (Aldrich, carcinogen), 37.2 g of zinc dust, 38.8 ml of deuterium oxide, and 17.6 g of acetic anhydride were vigorously stirred and heated to reflux for 21 hr. The cooled reaction mixture was extracted with four 20-ml portions of benzene, which were combined, washed several times with aqueous sodium bicarbonate, washed once with water, dried over magnesium sulfate, filtered, and concentrated. Distillation afforded 3.04 g (49%) of 2-deuteriobenzonitrile, bp 59° (5 mm).

2-Deuteriobenzylamine.[26]—A 200-ml three-necked flask fitted with an overhead stirrer, a reflux condenser and drying tube, and a 50-ml addition funnel was charged with 1.11 g of lithium aluminum hydride and 50 ml of anhydrous ether. To this stirred mixture heated to reflux was added a solution of 2-deuteriobenzonitrile (3.04 g) in 30 ml of ether over a 25-min period. After another hour at reflux the reaction mixture was cooled; 5.6 ml of water was added slowly to the stirred mixture, followed by 72 ml of 20% aqueous potassium sodium tartrate. The milky aqueous suspension separated; it was separated from the ether layer and was extracted twice with 25-ml portions of ether. The ethereal solutions were combined, dried over magnesium sulfate, filtered, concentrated, and distilled. The 2-deuteriobenzylamine obtained [1.41 g, 45% yield; bp 40° (2.2 mm)] had nmr absorptions (neat) at δ 1.40 (s, 2), 3.65 (s, 2), and 7.21 (broad s, 4).

Schiff's Base from 2-Deuteriobenzylamine and Glyoxal Semidiethyl Acetal.[27]—2-Deuteriobenzylamine (1.05 g) and glyoxal semidiethyl acetal[28] (1.35 g, partially polymerized according to the nmr spectrum) were combined and warmed on a steam bath 1 hr. The cooled reaction mixture was dissolved in ether, and the ethereal solution was dried, filtered, concentrated, and distilled to give 0.34 g of pale yellow product, bp 123° (5 mm).

8-Deuterioisoquinoline.[27]—To 0.5 ml of cooled, concentrated sulfuric acid was added 0.337 g of the Schiff's base derived from 2-deuteriobenzylamine and glyoxal semidiethyl acetal. The resulting tan solution was added dropwise in 5 min with stirring to 1 ml of sulfuric acid held at 160°. The reaction mixture was cooled, slowly made alkaline with 11 *N* sodium hydroxide, and steam distilled. The distillate was extracted with ether (three 6-ml portions). The ethereal material was dried, filtered, and concentrated to give 70 mg (36%) of 8-deuterioisoquinoline, 50% d_1, according to the mass spectrum (Table I).

***N*-(4-Bromobenzyl)-8-deuterioisoquinolinium Bromide.**—A solution of 70 mg of 8-deuterioisoquinoline, 50% d_1, and 227 mg of α-4-dibromotoluene in 10 ml of benzene was heated at reflux for 14.5 hr. After the usual work-up, the salt obtained (208 mg) had mp 105–143°.

***N*-(4-Bromobenzyl)isoquinolinium Bromide Exchange Reactions. A. In Alkaline Deuterium Oxide–Dioxane.**—Unlabeled isoquinolinium bromide (2.0 g) and 5.5 ml each of deuterium oxide and dioxane were heated to 72°, and 5.5 ml of approximately 11 *N* sodium deuterioxide (from 2.5 g of sodium hydroxide and deuterium oxide) was added in one portion. After 4 min at 72°, the reaction mixture was cooled in an ice bath with stirring, neutralized at temperatures below 20° with a solution of about 5 g of hydrogen bromide in 2.7 ml of deuterium oxide, and finally diluted with 75 ml each of water and chloroform. Concentration of the organic phase gave a residue from which the isoquinolinium bromide was isolated from sodium bromide and organic impurities by sequential extractions and concentrations with warm water and chloroform. The 100-MHz nmr spectrum of the recovered starting material (410 mg) was integrated and found to contain only 14% of hydrogen at the C_1 position.

(23) Compare V. Boekelheide and J. Weinstock, *J. Amer. Chem. Soc.*, **74**, 660 (1952); A. Albert and G. Catterall, *J. Chem. Soc. C*, 1533 (1967).

(24) Compare B. Bak, L. Hansen, and J. Rastrap-Andersen, *J. Chem. Phys.*, **22**, 2013 (1954); A. Murray, III, and D. L. Williams, "Organic Synthesis with Isotopes," Interscience, New York, N. Y., 1958, p 1384.

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(26) R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, **70**, 3738 (1948).

(27) E. Schlitter and J. Müller, *Helv. Chem. Acta*, **31**, 914 (1948).

(28) A. Wohl and C. Newberg, *Ber.*, **33**, 3099 (1900); E. J. Witzemann, W. L. Evans, H. Hass, and E. F. Schroeder, "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 307.

In a trial run omitting deuterated reagents, the material from the chloroform extract which failed to dissolve in warm water was thoroughly dried and shown by nmr spectroscopy to be mostly *N*-(4-bromobenzyl)isoquinolone (1.29 g, 78%).

B. 1-Deuterio Salt in Aqueous Alkaline Dioxane–Carbon Disulfide.—A stirred mixture of *N*-(4-bromobenzyl)-1-deuterioisoquinolinium bromide (93% d_1), 5.5 ml of water, 5.5 ml of dioxane, and 3.7 ml of carbon disulfide was heated to 72°, and 5.5 ml of 11 *N* sodium hydroxide was added in one portion. After 4 min, the reaction mixture was quenched in an ice bath with stirring, made just acidic at temperatures below 16° with concentrated sulfuric acid, and diluted with water (100 ml) and chloroform (50 ml). The aqueous layer was concentrated, the remaining water was removed with benzene as the azeotrope, and the dry salts obtained were extracted with chloroform. The isoquinolinium salt obtained from the chloroform extract (357 mg) had 60% hydrogen at C_1, according to nmr analysis.

Reactions of Deuterium Labeled *N*-(4-Bromobenzyl)isoquinolinium Bromides with Carbon Disulfide in Alkaline Aqueous Dioxane. A. *N*-(4-Bromobenzyl-α-d_2)isoquinolinium Bromide.—A 100-ml three-necked flask was charged with 2.00 g of this isoquinolinium salt, 5.5 ml of water, 5.5 ml of purified dioxane, and 3.7 ml of carbon disulfide. The mixture was stirred mechanically, heated, and diluted with 5.5 ml of 11 *N* sodium hydroxide; the red mixture obtained was stirred at 72° for 8 hr, cooled to room temperature with stirring, stored at −15° for 2 days, and filtered on a sintered glass funnel. The crude products were washed on the funnel with three 6-ml portions of warm water and dried in the air. The red solid obtained (1.07 g) was chromatographed in the usual way on 50 g of neutral Woelm II alumina. The yellow band was isolated and concentrated to give *N*-(4-bromo-α-d_2-benzyl)isoquinolone. No benzyl hydrogens were detected by nmr analysis. The dark material at the top of the column was extracted with hot *N*,*N*-dimethylformamide; concentration of the extract gave a dark red solid, mp 197–201°. Recrystallization of the solid from DMF–acetonitrile gave 100 mg of adduct, mp 202°, having a mass spectrum indicative of the α-d_2-benzyl moiety.

B. *N*-(4-Bromobenzyl)-1-deuterioisoquinolinium Bromide.—Following the given reaction procedure, 2.0 g of the isoquinolinium salt gave rise to 1.04 g of red solid. A slurry of the solid in chloroform was delivered to the top of a column of alumina, which was eluted with more chloroform. The residue in the sand at the top of the column was extracted with hot DMF. The red solid isolated, mp 190–260°, was extracted in a Soxhlet with chloroform for 23 hr. The residue in the thimble, 83 mg, mp 200–202°, was recrystallized to give a sample for mass spectrometric analysis, 52 mg of bright red crystals, mp 202–204°. Most, but not all, of the deuterium in the starting material had been lost (Table I).

C. *N*-(4-Bromobenzyl)-8-deuterioisoquinolinium Bromide.—The reaction of 208 mg of the isoquinolinium bromide was carried through in the normal manner. The crude product was extracted in a micro Soxhlet with 10 ml of chloroform for 16 hr. The residue from the thimble, 10.4 mg, mp 200°, was analyzed mass spectrometrically; the adduct retained the deuterium present in the starting material (Table I).

D. *N*-(4-Bromobenzyl)-4-deuterioisoquinolinium Bromide.—The crude product from 1.0 g of the isoquinolinium salt, amounting to 312 mg, was continuously extracted with chloroform for 22.5 hr. The residue was thoroughly dried; it had mp 198–205° and a mass spectrum showing no deuterium label (Table I).

Attempted Exchange in *N*-(4-Bromobenzyl)isoquinolinium 4-Dithiocarboxylate Adduct.—To 50 mg of the $C_{17}H_{12}BrNS_{12}$ adduct was added 5.5 ml each of deuterium oxide, dioxane, and 11 *N* sodium deuterioxide, and 3.7 ml of carbon disulfide. The stirred mixture was heated at 72° for 9.5 hr, cooled, and filtered to give 37 mg of starting material. Recrystallization from DMF–acetonitrile gave red crystals, mp 202–204°, having no deuterium incorporation detectable by mass spectrometric analysis.

Registry No.—1 H, 23277-04-5; 1 3-CH_3, 27415-57-2; 1 4-CH_3O, 27415-58-3; 1 3-NO_2, 27410-57-7; 1 3-Br, 27410-58-8; 1 4-Br, 27371-56-8; 2 3-F, 27371-57-9; 2 4-Cl, 27371-58-0; 2 4-Br, 27371-59-1; 2 H, 27371-60-4; 2 3-CH_3, 27371-61-5; 2 4-CH_3, 27371-62-6; 2 4-CN, 27410-59-9; 2 3-CH_3O, 27410-60-2; 2 4-CH_3O, 27410-61-3; 2 3-^{35}Cl, 27410-62-4; 2 3-NO_2, 27410-63-5; 2 4-NO_2, 27410-64-6; 2 3-CF_3, 27410-65-7; 2 3-^{79}Br, 27410-66-8; 2 4-^{79}Br, 27410-67-9; 4 3-F, 27410-68-0; 4 3-Cl, 27410-69-1; 4 3-Br, 27410-70-4; 4 H, 27371-63-7; 4 3-CH_3, 27371-64-8; 4 4-CH_3, 27410-71-5; 4 3-CH_3O, 27410-72-6; 4 4-CH_3O, 27410-73-7; 4 4-^{35}Cl, 27410-74-8; 4 3-CF_3, 27410-75-9; 4 3-^{79}Br, 27410-76-0; 4 4-^{79}Br, 27410-77-1; 4 3-^{81}Br, 27371-65-9; 4 4-^{81}Br, 27410-78-2; *N*-(4-bromobenzyl-α-d_2)isoquinolinium bromide, 27410-79-3; *N*-(4-bromobenzyl)-1-deuterioisoquinolinium bromide, 27410-80-6; *N*-(4-bromobenzyl)-4-deuterioisoquinolinium bromide, 27410-81-7; *N*-(4-bromobenzyl)-8-deuterioisoquinolinium bromide, 27410-82-8; carbon disulfide, 75-15-0.

Synthesis of Fluoroarenes by Photolysis of Aryldiazonium Salts in the Solid State[1a]

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Photolysis of crystalline aryldiazonium fluoroborates and fluorophosphates gives the corresponding fluoroarenes. In some cases yields are much better than those obtained by pyrolysis.

The photochemistry of aryldiazonium salts in the solid state seems to have been ignored except for one study[2] of gas evolution from slurries in which the organic products were not identified. As the first step in a mechanistic study of this phenomenon, the principal products formed upon irradiation of crystalline films of a number of aryldiazonium salts have been determined.

In the photolysis of diazonium tetrafluoroborates and hexafluorophosphates, the corresponding fluoroarenes were usually the only volatile product as in pyrolysis. In some cases the yields of fluoroarenes were higher than those obtained by pyrolysis of these salts (the Balz–Schiemann reaction), which remains the most generally used means of introducing a fluorine substituent into an aromatic ring.[3] The Balz–Schiemann reaction fails

(1) (a) Part of this work has been described by R. C. P. and A. D. in U. S. Patent 3,481,850 (1969); (b) Fellow of the Cancer Association of Greater New Orleans, Inc., summer 1966; (c) National Science Foundation Undergraduate Research Participant; (d) taken in part from the B.S. Thesis of J. P. Mykytka, Loyola University, New Orleans, 1968.

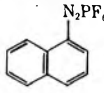
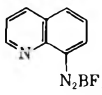
(2) G. Gavlin, "Increased Light-Sensitivity of a Diazotype Substance," Report of Armour Project No. 90-595C, Armour Research Institute, Department of Army Project, 3-99-04-052.

(3) K. O. Christe and A. E. Pavlath, *J. Org. Chem.*, **30**, 3170 (1965).

TABLE I

PHOTOLYSIS OF SOLID ARYLDIAZONIUM FLUOROBORATES AND FLUOROPHOSPHATES

$$RN_2^+BF_4^-(PF_6^-) \xrightarrow{h\nu} RF + N_2 + BF_3(PF_5)$$

Diazonium compd	Registry no.	Light source	Scale, g	Time, hr	Yield of RF, %
4-$(C_2H_5)_2NC_6H_4N_2BF_4$	347-46-6	3500 Å	1	4.5–49	53–55
			10	39	66
4-$(C_2H_5)_2NC_6H_4N_2PF_6$	733-51-7	3500 Å	1	4	72
			10	94	74
4-$(CH_3)_2NC_6H_4N_2BF_4$	24564-52-1	3500 Å	2	17	55
4-$CH_3OC_6H_4N_2BF_4$	18424-07-2	3500 Å	1	19	69[a]
4-$C_6H_5NHC_6H_4N_2BF_4$	2367-19-3	3500 Å	0.6	24	37
$C_6H_5N_2BF_4$	369-57-3	3000 Å	0.5	2	34
		Uviarc	0.5	48	25
4-$ClC_6H_4N_2BF_4$	673-41-6	Uviarc[b]	0.1	8	10[a]
3-$C_6H_5C_6H_4N_2BF_4$	323-96-6	3500 Å	0.1	2	29
	27388-25-6	3500 Å	1	12	40
	27388-19-8	3500 Å	1	54	19

[a] Product distilled as formed. [b] Quartz vessel.

completely or gives low yields occasionally. We have made a preliminary investigation of the generality and utility of the photolytic variation for small scale synthesis of fluoroarenes, the results of which are summarized in Table I. The best results by far were in making fluorobenzenes with electron-donating substituents, particularly three N-substituted fluoroanilines.

Pure 4-fluorodiphenylamine was isolated in 37% yield on the first attempt when the corresponding diazonium fluoroborate was irradiated as a solid film at 30° with 3500-Å light, although pyrolysis of this salt has been reported[4] to give only a "carbonaceous mass."

Schiemann and Winkelmüller[5] converted *p*-*N*,*N*-dimethylaminobenzenediazonium fluoroborate to 4-fluoro-*N*,*N*-dimethylaniline by heating in only 17% yield, and later workers[6] have preferred other methods for preparing the compound. By pyrolyzing a mixture of the diazonium salt with sand we improved the yield to 36%, but photolysis gave a 56% yield. Both methods also produced a small amount of the reduction product, *N*,*N*-dimethylaniline.

The synthesis of 4-fluoro-*N*,*N*-diethylaniline was studied more extensively. Pyrolysis of the corresponding diazonium fluoroborate gave a poor yield (20%) of the fluoro amine in agreement with Schiemann's report.[5] Worse, the ir spectrum of the product indicated that a significant amount of reduction product had been formed. The fluoro compound was produced by photolysis of 1 g of the fluoroborate in higher yield (55%) and, surprisingly, was uncontaminated by *N*,*N*-diethylaniline. On a 10-g scale the yield was better (66%). We have not tried any of these reactions on a scale over 10 g.

Hexafluorophosphates sometimes give better yields than tetrafluoroborates in the Balz–Schiemann reaction.[7] This is also true for the photoreaction, at least for the preparation of 4-fluoro-*N*,*N*-diethylaniline, the yields being over 70% on both a 1-g and a 10-g scale. The photolysis method is the method of choice in this case for reasons of both purity and yield.

With 4-methoxybenzenediazonium fluoroborate a new complication arose: the product is somewhat unstable to the 3500-Å light used for photolysis. The yield of 4-fluoroanisole was only 6% using the normal photolysis method. However, by vacuum distilling the product into a cold trap as it formed the yield was raised to 69%. 4-Fluorochlorobenzene was also unstable to the light used and had to be removed in the same way.

Photolysis of aryldiazonium salts substituted with electron-withdrawing groups gave much lower yields of fluoroarenes, perhaps because with the light sources available the products absorbed light about as well as the starting material and competing reactions destroyed them.

An ionic intermediate or transition state of some sort appears to be implicated in the photolysis of solid aryldiazonium fluoroborates and fluorophosphates. If aryl radicals were intermediates, they would be expected to abstract hydrogen atoms from other molecules of starting material, especially when side chains with alkyl groups are present. However, little or no reduction product was produced in the photolysis of even the dimethyl- and diethylamino compounds. In contrast, when crystalline *N*,*N*-dimethylaminobenzenediazonium *chloride* was irradiated, reduction to *N*,*N*-dimethylaniline (25%) competed strongly with conversion to 4-chloro-*N*,*N*-dimethylaniline (33%).

These observations are in accord with the results of studies of isomer distribution in the phenylation products formed when solid benzenediazonium chloride and various haloborates are pyrolyzed[8] or photolyzed[9] in the presence of substituted benzenes. The solid chlorides react as if they possessed the covalent structure ArN=NCl and lose nitrogen to give radicals, although their

(4) J. Lichtenberger and R. Thermet, *Bull. Soc. Chim. Fr.*, 318 (1951).
(5) G. Schiemann and W. Winkelmüller, *Ber.*, **66**, 727 (1933).
(6) N. J. Leonard and L. E. Sutton, *J. Amer. Chem. Soc.*, **70**, 1564 (1948).
(7) K. G. Rutherford, W. Redmond, and J. Rigamonti, *J. Org. Chem.*, **26**, 5149 (1961).
(8) G. A. Olah and W. S. Tolgyesi, *ibid.*, **26**, 2053 (1961); R. A. Abramovitch and F. F. Gadallah, *J. Chem. Soc. B*, 497 (1968).
(9) R. C. Petterson and J. P. Mykytka, unpublished work.

ir and uv spectra are very much like those of other aryldiazonium ions.

The lack of parallelism between fluoroarene yields for photolysis *vs.* pyrolysis makes it unlikely that these reactions proceed exclusively through a common intermediate. Lewis and his coworkers[10] compared photochemical with thermal reactions of diazonium salts in aqueous solution and concluded definitely that there was no single intermediate common to both.

Experimental Section

Starting Materials.—Aryldiazonium fluoroborates were generally prepared by diazotizing the corresponding amines in fluoboric acid.[11] 4-*N*,*N*-Dialkylaminobenzenediazonium fluoroborates were purchased,[12] and the 4-chloro- and 4-phenylamino compounds were made by reaction of 48% fluoboric acid with the corresponding diazonium chlorides which happened to be available from another study.

4-*N*,*N*-Diethylaminobenzenediazonium Fluorophosphate.—To 20 g of the commercial fluoroborate in water (700 ml) was added 35 ml of 65% hexafluorophosphoric acid. The yellow crystals which formed were filtered off, washed with a 1:1 methanol–ether solution, and dried *in vacuo*. The fluorophosphate (22.6 g) melted at 129.5–130.5°.

Anal. Calcd for $C_{10}H_{14}F_6N_3P$: C, 37.40; H, 4.39; F, 35.50; N, 13.09; P, 9.65. Found: C, 37.75; H, 4.11; F, 35.40; N, 13.20; P, 9.71.

8-Quinolinediazonium fluoroborate was prepared but not characterized by Roe and Hawkins.[13] It melts at 138° dec and is converted by irradiation to 8-fluoroquinoline (see Table I), the picrate of which melted at 170° (lit.[13] 170–172°).

Anal. Calcd for $C_9H_6BF_4N_3$: C, 44.71; H, 2.48. Found: C, 44.92; H, 2.70.

4-*N*,*N*-Dimethylaminobenzenediazonium chloride was prepared from 4-*N*,*N*-dimethylaminoaniline monohydrochloride (1.7 g) by reaction with isoamyl nitrite (1.4 g) in absolute ethanol (8 ml) at 0°, a variation of Knoevenagl's method.[14] After recrystallization from an ethanol–ether mixture, the melting point was 210° (slow dec above 135°): ν_{max}^{Nujol} 2152, 2240 cm^{-1}; (–N$^+$≡N) $\lambda_{max}^{H_2O}$ 375 nm (log ϵ 4.52).

Anal. Calcd for $C_8H_{10}ClN_3$: N, 22.88. Found: N, 23.01.

The zinc chloride double salt was yellow, mp 151° dec, $\lambda_{max}^{H_2O}$ 375 nm (log ϵ 4.53).

Anal. Calcd for $C_8H_{10}ClN_3 \cdot {}^1/_2ZnCl_2$: C, 38.14; H, 3.97; Cl, 28.2. Found: C, 38.33; H, 3.95; Cl, 27.85.

Methods.—Diazonium salts were irradiated as crystalline films on the inner surfaces of borosilicate glass test tubes or round-bottomed flasks of 50 ml to 3 l. capacity, except for the 4-chloro compound, which was irradiated in a quartz tube. The films were deposited by evaporation of solutions of the salts in acetonitrile or methanol at room temperature or below using a rotary evaporator. Most irradiations were done in a Rayonet photochemical chamber reactor (So. New England Ultraviolet Co.) equipped with 16 8-W F8T5/BLB lamps (3500 Å) or RPR 3000 "erythemal" lamps. In two experiments (see Table I), we used a 500-W high-pressure mercury lamp (General Electric "Uviarc") mounted in a reflector, similar to a Gates Model 420-U1.

Except for 4-fluoroanisole and 4-chlorofluorobenzene, which were produced at a pressure of 1 Torr in a tube connected to a dark trap cooled to −78°, into which they distilled as they formed, the products were isolated by conventional extractive techniques. In most cases, it was advantageous to first make the reaction mixture basic and then steam distil the fluoro compound. The products were identified by comparing their ir spectra and glc retention times with those of authentic specimens, which were either available commercially or were made by the Balz–Schiemann method.

Crystalline 4-*N*,*N*-dimethylaminobenzenediazonium chloride (0.5 g) was irradiated (3500 Å) for 7 hr in a 50-ml Pyrex test tube. Base was added and the organic products extracted with ether. Glc analysis of the concentrated extracts with an internal standard showed that the yield of 4-chloro-*N*,*N*-dimethylaniline was 33% and that of *N*-*N*-dimethylaniline was about 25%.

Registry No.—4-*N*,*N*-Dimethylaminobenzenediazonium chloride, 100-04-9, 6023-44-5 (zinc chloride salt).

Acknowledgments.—We thank the National Science Foundation (GP-11004), the Academic Grant Fund of Loyola University (New Orleans), and Photo-dek, Inc., for support, and Mr. T. G. Troendle for valuable assistance.

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(11) A. Roe, *Org. React.*, **5**, 205 (1949); E. B. Starkey, "Organic Synthesis," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 225.

(12) Fairmount Chemical Co., Inc., Newark, N. J. 07105.

(13) A. Roe and G. F. Hawkins, *J. Amer. Chem. Soc.*, **71**, 1785 (1949).

(14) E. Knoevenagl, *Ber.*, **28**, 2048 (1895).

A Reinvestigation of Some Purported 1,2,4-Oxadiazetidines

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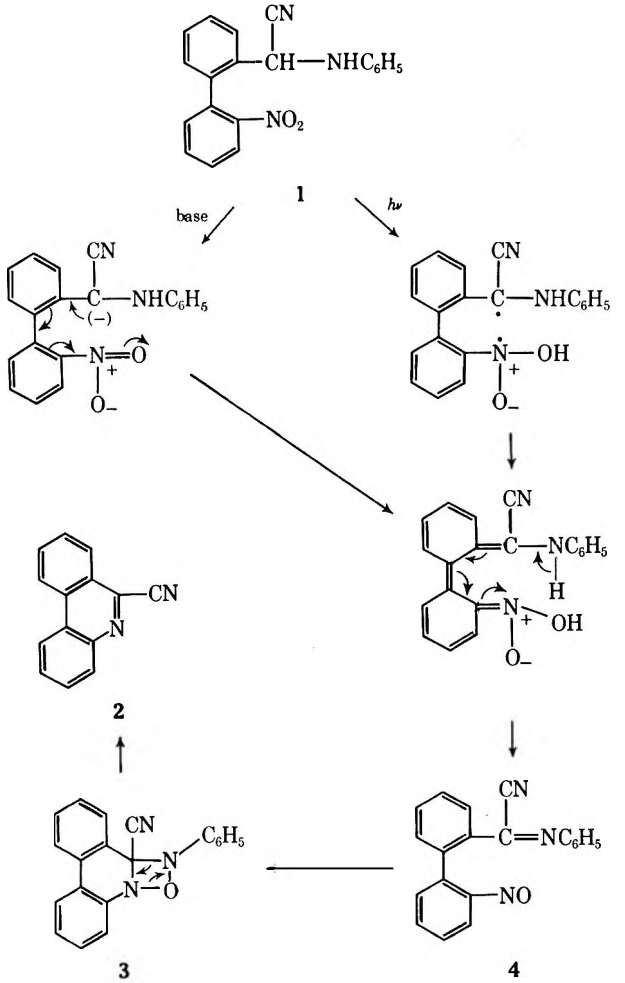
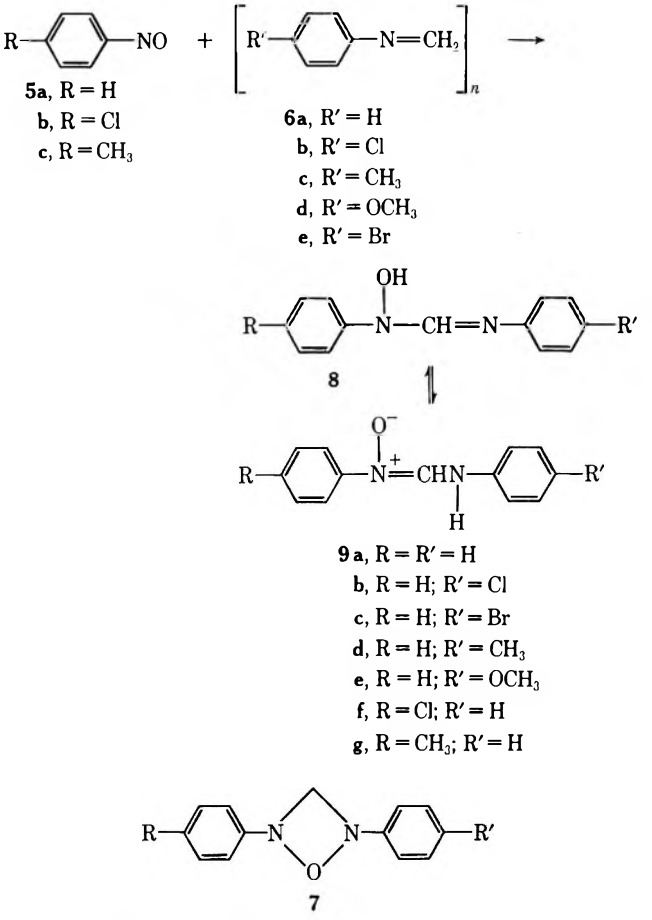
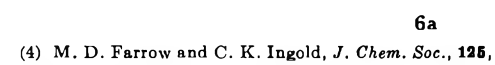
The reaction of methyleneanilines (hexahydro-1,3,5-triazines) (**6**) with aryl nitroso compounds, previously claimed to proceed *via* intermediate 1,2,4-oxadiazetidines, has been reinvestigated. It has been found that oxadiazetidines are *not* involved in the above reaction which (under the previously described conditions) yields formanilides (**10**) and azoxybenzene and, under modified conditions, yields α-arylamino-*N*-arylnitrones (**9**). Mechanisms for these reactions are discussed.

Intramolecular cyclization of 2-(2′-nitro-2-biphenylyl)-*N*-phenylglycinonitrile (**1**) to 6-cyanophenanthridine (**2**) occurs under either photolytic or basic reaction conditions.[1] The mechanism proposed for this unusual conversion involved spontaneous cyclization of an intermediate nitrosoimine **4** to a 1,2,4-oxadiazetidine (**3**), followed by collapse to **2** and nitrosobenzene (which was shown to be formed in the reaction). An apparent intermolecular precedent for the cyclization of **4** to **3** is the reported[2] formation of oxadiazetidines **7** from the reaction of aryl nitroso compounds (**5**) with "methyleneanilines" (**6**).[3] However, the products of these reactions were later claimed to be *N*-hydroxy-*N*,*N*′-diarylformamidines (**8**), α-arylamino-*N*-arylnitrones (**9**),[8] with the oxadiazetidines **7** suggested as probable reaction intermediates.[4]



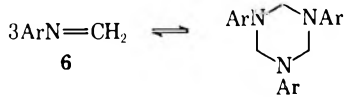




(1) E. C. Taylor, B. Furth, and M. Pfau, *J. Amer. Chem. Soc.*, **87**, 1400 (1965).

(2) C. K. Ingold, *J. Chem. Soc.*, **125**, 87 (1924).

(3) "Methyleneanilines" were earlier believed to be either monomeric (**6**) or dimeric,[2,4,5] but more recent studies have shown that they exist primarily in the trimeric hexahydro-1,3,5-triazine form (**6a**).[6,7] Evidence for partial dissociation of the trimer to the monomeric imine has been advanced;[6] we have found no peaks at *m/e* higher than those corresponding to monomer in the mass spectra of **6**, indicating dissociation of the trimer to the monomer under thermal and/or electron impact conditions.



(4) M. D. Farrow and C. K. Ingold, *J. Chem. Soc.*, **125**, 2543 (1924).

(5) C. K. Ingold and H. A. Piggott, *ibid.*, **121**, 2793 (1922); **123**, 2745 (1923).

(6) W. V. Farrar, *Rec. Chem. Progr.*, **29**, 85 (1968).

(7) E. M. Smolin and L. Rapoport, "*s*-Triazines and Derivatives," Interscience, New York, N. Y., 1959, pp 473–544.

(8) These compounds appear to be the tautomeric nitrones **9** rather than *N*-hydroxyformamidines **8**.[9] We have observed M − 16 peaks of moderate intensity in the mass spectra of all of the derivatives of **9** prepared. No M − 17 peaks were observed with the above compounds with the single exception of a very weak M − 17 peak for **9a** itself. Nitrones have been shown to exhibit significant M − 16 peaks,[10,11] while aryl hydroxylamines exhibit both significant M − 16 and M − 17 peaks.[12]

(9) H. G. Aurich, *Chem. Ber.*, **101**, 1761 (1968).

(10) T. H. Kinstle and J. G. Stam, *Chem. Commun.*, 185 (1968).

(11) B. Soegaard Larsen, G. Schroll, S.-O. Lawesson, J. H. Bowie, and R. G. Cooks, *Tetrahedron*, **24**, 5193 (1968).

(12) R. T. Coutts and G. Mukherjee, *Org. Mass Spectrom.*, **3**, 63 (1970).

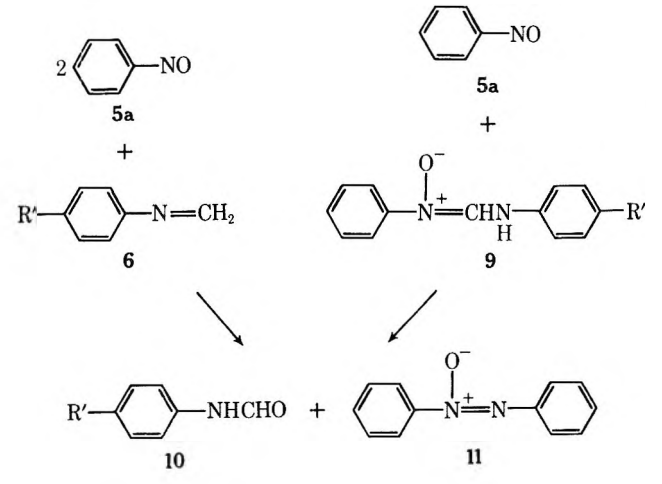
Some sort of symmetrical intermediate (*e.g.*, **7**?) was indeed implied by the earlier work because, *e.g.*, **9d** was claimed to be the product of the reaction of **5a** and **6c**, as well as the product of **5c** and **6a**.[4] However, no reason was advanced for unilateral ring opening of the suggested symmetrical intermediate **7** to give only one of the two possible isomeric nitrones **9**.

The intermediacy of oxadiazetidines such as **7** in these condensation reactions was challenged[13] on the basis of conflicting analytical results for degradation products of **9**. No further experimental work has appeared, however; the existence of **7** as a reaction intermediate has recently received further support in reviews on cycloaddition reactions[14] and imines.[15]

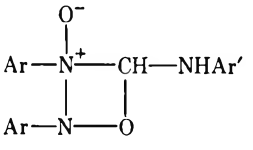
This ambiguous situation, coupled with refutations[16] of earlier claims of other four-membered systems,[17] led us to a reinvestigation of this phase of "oxadiazetidine chemistry."

Contrary to the original work,[4] we found that *different* nitrones **9** were formed from the reaction of permuted pairs of aryl nitroso compounds (**5**) and "methyleneanilines" (**6**). Thus, reaction of **5a** with **6b** gave **9b**, and reaction of **5b** with **6a** gave **9f**. The nonidentity of the products of these reactions was established beyond question by comparison of ir, uv, nmr, tlc, and mass spectral data. Furthermore, many of the nitrones **9** were synthesized independently from aryl hydroxylamines and imidate esters, according to the method of Farrow and Ingold.[4] Our results are thus incompatible with a symmetrical intermediate such as **7**. We note, however, that this refutation of an intermolecular precedent for the intermediate **3** does not necessitate rejection of the previously proposed mechanism[1] for the formation of 6-cyanophenanthridine (**2**) from the biphenyl **1**, since steric proximity of the ortho,ortho′ substituents in biphenyls leads to many unique cyclization reactions which have no intermolecular precedent.[18]

We have found that the reaction of equimolar amounts of an aryl nitroso compound (**5**) and a "methyleneaniline" (**6**), or reaction of an excess of **6** with **5**, is required for the formation of the nitrones **9**. Use of the previously prescribed ratio of reactants (a 2:1 molar excess of **5**)[2,4] led to the formation of formanilides (**10**) and azoxybenzene (**11**). That these products arose by condensation of the initially formed nitrone **9** with excess **5** was demonstrated by the independent observation that preformed **9** reacted with an equimolar amount of **5** to give both **10** and **11**.[19]



We suggest that the reaction of aryl nitroso compounds (**5**) with "methyleneanilines" (**6**) proceeds by nucleophilic attack by the nitrogen lone pair of **5** on the monomeric imine form of **6**[3] to give **9** directly. However, the reaction of **5** with the nitrones **9** to give formanilides (**10**) and azoxybenzene (**11**) may well involve a discrete 1,2,3-oxadiazetidine intermediate (**13**).



13

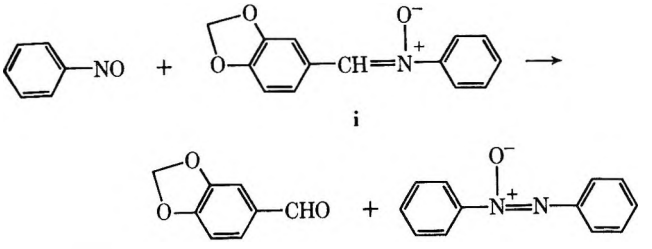
Experimental Section[21]

Preparation of Intermediates.—"Methyleneanilines" (**6**) were prepared from the appropriate aniline and aqueous formaldehyde as previously described.[2] Aryl hydroxylamines were prepared by standard methods.[22] Nitrosobenzene (**5a**) (Aldrich Chemical Co.) was purified by sublimation before use. Other aryl nitroso compounds were prepared by dehydrogenation of aryl hydroxylamines with diethyl azodicarboxylate.[23] Formimidates were prepared from the corresponding anilines and ethyl orthoformate as described.[24] The nitrones **9** were prepared by a modification of the published procedure.[2]

α-Anilino-*N*-*p*-chlorophenylnitrone (**9f**).—A solution of 2.10 g (0.02 mol) of *p*-chloronitrosobenzene and 1.41 g (0.01 mol) of "methyleneaniline" (**6a**) in 150 ml of chloroform was allowed to stand in the dark at room temperature for 2 days. Evaporation of the solvent gave a solid which was recrystallized from benzene to give 0.70 g (28%) of almost colorless crystals, mp 148.5–149.5°.

Anal. Calcd for $C_{13}H_{11}N_2OCl$: C, 63.27; H, 4.50; N, 11.36; Cl, 14.38. Found: C, 63.41; H, 4.43; N, 11.08; Cl, 14.45.

α-*p*-Anisidino-*N*-phenylnitrone (**9e**).—In a similar manner, 2.02 g (0.015 mol) of nitrosobenzene and 1.61 g (0.015 mol) of "methyleneanisidine" (**6d**) gave 1.96 g (40%) of almost colorless crystals, mp 149–150°.



(13) G. N. Burkhardt, A. Lapworth, and E. B. Robinson, *J. Chem. Soc.*, **127**, 2234 (1925).

(14) L. L. Muller and J. Hamer, "1,2-Cycloaddition Reactions," Interscience, New York, N. Y., 1967, pp 301–304.

(15) R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).

(16) (a) G. N. Burkhardt and A. Lapworth, *J. Chem. Soc.*, **127**, 1742 (1925); (b) G. N. Burkhardt, A. Lapworth, and J. Walkden, *ibid.*, **127**, 2458 (1925); (c) N. F. Hepfinger and C. E. Griffin, *Tetrahedron Lett.*, 1361 (1963); (d) C. E. Griffin, N. F. Hepfinger, and B. L. Shapiro, *Tetrahedron*, **21**, 2735 (1965); (e) J. Hamer and A. Macaluso, *Tetrahedron Lett.*, 381 (1963); (f) E. Fahr and H. Lind, *Angew. Chem., Int. Ed. Engl.*, **5**, 372 (1966); (g) reference 14, pp 257–261.

(17) (a) C. K. Ingold and S. D. Weaver, *J. Chem. Soc.*, **125**, 1456 (1924); (b) C. K. Ingold and S. D. Weaver, *ibid.*, **127**, 378 (1925).

(18) R. E. Buntrock and E. C. Taylor, *Chem. Rev.*, **68**, 209 (1968).

(19) A precedent for this condensation of nitrosobenzene with the nitrone **9** to give a formanilide and azoxybenzene is found in the reported reaction of nitrosobenzene with the nitrone i to give piperonal and azoxybenzene.[20]

(20) L. Alessandri, *Gazz. Chim. Ital.*, **54**, 426 (1924).

(21) All melting points are uncorrected. Mass spectra were determined on an AEI MS-9 instrument.

(22) (a) G. E. Utzinger and F. A. Regenass, *Helv. Chim. Acta*, **37**, 1895 (1954); (b) G. E. Utzinger, *Justus Liebigs Ann. Chem.*, **556**, 50 (1944); (c) A. A. Staklis, Ph.D. Thesis, University of Nebraska, Lincoln, 1965; *Diss. Abstr.*, **26**, 1354 (1965).

(23) E. C. Taylor and F. Yoneda, *Chem. Commun.*, 199 (1967).

(24) R. M. Roberts and D. J. Vogt in "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, p 464.

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.26; H, 5.74; N, 11.59.

All other nitrones were prepared similarly; the results are summarized in Table I.

TABLE I
PREPARATION OF NITRONES (9)

Reactants	Product	Mp, °C	Lit. mp, °C	Yield, %
5a + 6a[d]	9a	119–122	126–127[a]	29
5a + 6b[d]	9b	158–158.5	162[b]	32
5a + 6c[d]	9c	166–168	171[b]	35
5a + 6d[d]	9d	148.5–149	150[b]	54
5c + 6a[e]	9g	148.5–150	151–152[c]	39

[a] Beilstein's "Handbuch der Organischen Chemie," 4th ed, Vol. 15, Springer Verlag, Berlin, 1932, p 8. [b] Reference 2. [c] Reference 4. [d] 2:1 molar excess of 6. [e] Equimolar amounts of reactants employed.

In addition, these nitrones were prepared independently by condensation of aryl hydroxylamines with imidate esters as previously described.[4]

p-**Bromoformanilide (10, R′ = Br). Method A.**—A solution of 4.28 g (0.04 mol) of nitrosobenzene and 3.66 g (0.02 mol) of "methylene-*p*-bromoaniline" (6e) in 150 ml of chloroform was allowed to stand in the dark at room temperature. After 1 day, tlc examination of the reaction mixture revealed the presence of the nitrone 9c. After 4 days, the reaction mixture was evaporated to dryness and the residue recrystallized from benzene to give 2.05 g (52%) of tan crystals of 10 (R = Br), identical with an authentic sample prepared independently.[25] The presence of azoxybenzene in the reaction mixture was confirmed by vpc.

Method B.—A mixture of 1.46 g (0.005 mol) of the nitrone 9c, 0.54 g (0.005 mol) of nitrosobenzene, and 50 ml of chloroform was allowed to stand at room temperature in the dark for 5 days. Evaporation of the reaction mixture and recrystallization of the residue from benzene gave 0.28 g (28%) of tan crystals of *p*-bromoformanilide, identical with the material prepared by method A above. Again, azoxybenzene was present in the crude reaction mixture, as determined by vpc.

Other substituted formanilides (10) were prepared analogously; the results are summarized in Table II.

TABLE II
PREPARATION OF PARA-SUBSTITUTED FORMANILIDES (10)

Reactants	Product	Yield, %
2 5a + 6a	10, R = H	*a*
2 5a + 6b	10, R = Cl	49
5a + 9b	10, R = Cl	38
2 5a + 6c	10, R = CH_3	*a*
5a + 9d	10, R = CH_3	*a*
5a + 9e	10, R = OCH_3	*a*

[a] Product identified by vpc but not isolated.

Registry No.—9e, 27396-35-6; 9f, 27396-36-7.

(25) L. F. Fieser and J. F. Jones in "Organic Syntheses," Collect. Vol. III, E. C. Horning, Ed., Wiley, New York, N. Y., 1955, p 590.

Study of the Michael and Mannich Reactions with Benzothiazole-2-thiol[1a]

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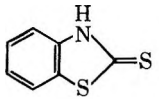
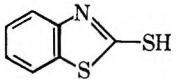
Received May 7, 1970

The reaction of the anion of benzothiazole-2-thiol (MBT) with activated olefins in the presence of sodium hydride with Michael reaction acceptors produced 3-substituted benzothiazoline-2-thiones. Similarly, the Mannich reaction of MBT anion with formaldehyde and primary or secondary amines produced the N- (or 3-) substituted benzothiazoline-2-thiones. Possible mechanisms and supporting nmr, ir, and uv data are discussed. The N substitution of MBT anion is discussed within the framework of the oxibase scale which can predict the condition for formation of N products or S products from this ambident anion.

The object of the present investigation was to study the Michael and Mannich reactions of the ambident anion of benzothiazoline-2-thione (I), the so-called 2-mercaptobenzothiazole or MBT of the rubber industry, with various activated vinyl compounds as well as with formaldehyde and various amines. Harman,[1b,2]



I



IA

studying the reaction of organic mercaptans such as I with acrylonitrile, formulated the MBT addition product as an S-substituted benzothiazole-2-thiol derivative. We have now found that the correct structure is the N derivative. Likewise we have shown that the Michael reaction products with activated carbon–carbon double bonds such as methyl vinyl ketone, phenyl vinyl ketone, 2-vinylpyridine, 4-vinylpyridine, divinyl sulfone (which produces a diadduct), and 2-nitro-1-butene, are all N-substituted benzothiazoline-2-thione derivatives.

The fact that benzothiazoline-2-thione (I) also enters into a variety of Mannich reactions with formaldehyde and various aliphatic and aromatic amines or phenols to give N-substituted 3-alkylbenzothiazoline-2-thiones is not well known. This paper constitutes a correction for a number of such products incorrectly postulated as S-substituted compounds[3–9] reported in the older literature. The structural assignments of the few N-substituted products were made by Morton and Stubbs[10] based on the absorption at 320–325 mμ indicative of the (–N–(S=)C–S dithio carbamate) structure. These results were confirmed later by Koch[11] and Moore

(1) (a) Presented in part before the Organic Chemistry Division of the American Chemical Society, Atlantic City, N. J., Sept 17, 1965; (b) M. W. Harman, *Ind. Eng. Chem.*, **29**, 205 (1937).

(2) M. W. Harman, U. S. Patents 1,951,052 (1934); 2,010,000 (1935); and 2,049,229 (1935).

(3) M. H. Zimmerman, U. S. Patent 1,960,197 (1934).

(4) W. J. S. Naunton, W. Baird, and H. M. Bunbury, *J. Soc. Chem. Ind. London Trans.*, **53**, 127 (1934); *Rubber Chem. Technol.*, **7**, 417 (1934).

(5) D. F. Twiss and F. A. Jones, *J. Soc. Chem. Ind. London Trans.*, **54**, 13 (1935).

(6) J. L. Kurychek, U. S. Patent 2,358,402 (1944).

(7) M. Bogemann and E. Zauker, German Patent 575,114 (1933).

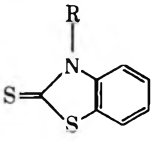
(8) C. Cokman, U. S. Patent 1,901,582 (Sept 13 1933).

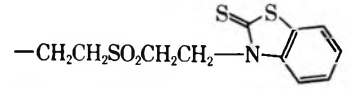
(9) R. Robinson, H. Bunbury, J. Davies, and W. J. S. Naunton, British Patent 377,253 (1944).

(10) R. A. Morton and A. L. Stubbs, *J. Chem. Soc.*, 1321 (1939).

(11) H. P. Koch, *ibid.*, 401 (1949).

TABLE I
MICHAEL REACTION PRODUCTS[c]



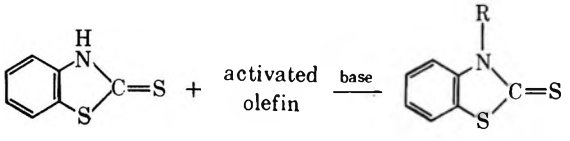
Products[c]	R	Solvent	Mp, °C	Yield, %	Ir data, μ	Uv data, mμ	Nmr (ppm)[a] AB type splitting (Figure 2) 4,5,6,7 aromatic protons
II	$-CH_2CH_2COCH_3$	THF	140–141	70–75	5.95, 9.20, 6.90	228, 240, 262, 320	7.0
III	$-CH_2CH_2COPh$	THF	144.5–145	95.0	5.86, 6.20, 9.30	..., 242, 260, 320	7.20
IV[b]	2-Pyridylethyl	THF	(1) 94–95 (2) 123–124	80.0	6.10, 9.30, 13.20	236, 258, 321	7.20
V[b]	4-Pyridylethyl	THF	(1) 141–142 (2) 159–160	80	6.10, 9.30, 13.20	235, 258, 321	7.21
VI	$-CH_2CH_2CH(NO_2)CH_3$	EtOH	89–90	85	6.45, 7.30, 9.10, 13.50	240, 255, 321	7.30
VII	$-CH_2CH_2CN$	EtOH	165–166	90	4.50, 6.20, 9.30	240, 154, 320	7.20
VIII		THF	215–216	50	6.70, 9.30, 8.30	240, 270, 320	7.40

[a] The AB type splitting, accompanied by some secondary splitting, we describe as the one envelope type (AB) as compared to the two envelope (A_2B_2). [b] Two crystalline modifications of each of the pyridyl compounds were observed. In each case, the low-melting modification was formed from the reaction mixture, and after melting and resolidification, then crystallized in the more stable, high melting modification. In each case, the low- and high-melting forms showed identical elementary analysis, which, coupled with identical uv, ir, and nmr spectra, indicated the absence of organic structural isomers. [c] Satisfactory analytical data were reported (±0.35%) for C, H, N, and S, Ed.

and Wright.[12] Stavroskaya and Kolosova[13] offered additional chemical evidence.

Discussion of Results

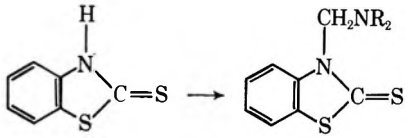
The reaction of benzothiazoline-2-thione (I) with compounds containing activated carbon–carbon double bonds proceeded readily at ambient temperature in tetrahydrofuran as a solvent using catalytic amounts of sodium hydride.



II–VIII

The products were isolated as white crystalline solids and characterized as indicated in Table I. The adducts from the 2- and 4-vinylpyridines gave two different solids for each starting material, identified as two crystal modifications of the same product in each case.

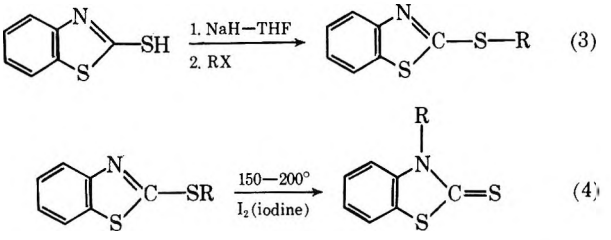
Similarly, the reactions of benzothiazoline-2-thione (I) with primary and secondary amines in anhydrous ether produced the amine salts of compound I in quantitative yield. When these salts were dissolved in water and allowed to react with formaldehyde at ambient temperatures, the corresponding Mannich reaction products were formed in high yields (eq 2).



(2)

The Michael as well as the Mannich reaction products (Tables I and II) all showed among other absorptions a distinct band at 320–325 mμ in the ultraviolet. This intense band was assigned to the $\pi \rightarrow \pi^*$ transition of the nonbonding ($3p^2$) electron pair of the sulfur atom and the other π electron of the heterocyclic ring. The infrared absorption at 1074 cm^{-1} (medium) was assigned to the thione (C=S) vibrational frequency.

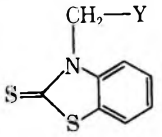
The 3-alkylbenzothiazoline-2-thiones (see eq 4) were prepared from the corresponding 2-alkylthiobenzothiazoles, which in turn were prepared by modification of the procedures of Moore[14] and Sexton;[15] see Table III. The 2-alkylthiobenzothiazoles were prepared by nucleophilic displacement on the corresponding alkyl halides using sodium hydride in tetrahydrofuran (eq 3). These were rearranged thermally to the 3-alkylbenzothiazoline-2-thione in accordance with eq 4.



Examination of the nmr spectra of all the described products, II–XXIV resulted in the discovery of characteristic differences in the nature of the aromatic protons

(12) C. G. Moore and E. S. Wright, *J. Chem. Soc.*, 4237 (1952).
(13) V. I. Stavroskaya and M. O. Kolosova, *Zh. Obshch. Khim.*, **30**, 711 (1960).
(14) C. G. Moore, *J. Chem. Soc.*, 4237 (1952).
(15) W. A. Sexton *ibid.*, 470 (1939).

TABLE II
MANNICH REACTION PRODUCTS[c]



Products[c]	Y	Solvent	Mp, °C	Yield, %	Ir data, μ	Uv data, mμ	Nmr data AB type splitting (Figure 2) 4,5,6,7 aromatic protons
IX	Piperidino[a]	Water	159–161	73.4	6.20, 9.30, 13.40, 14.20	244, 258, 320	7.0[b]
X	Pyrrolidino	Water	122–125	80.3	6.20, 9.28, 13.40, 14.20	245, 252, 320	7.10
XI	Benzylamino	Water	128–130	75.6	6.20, 9.36, 13.40, 14.20	230, 258, 325	7.40
XII	*N,N*-Diethylamino[a]	Water	88–89	80.5	6.35, 9.38, 13.80, 14.50	240, 260, 322	7.80
XIII	Cyclohexylamino[a]	Water	157–158	88.0	6.40, 9.40, 13.70, 14.59	245, 265, 325	7.60
XIV	Morpholino[a]	Water	149–150	79.0	6.32, 9.42, 13.69, 14.60	240, 260, 320	7.50

[a] These compounds were reported in the literature, see ref 13. [b] The AB type of splitting, accompanied by some secondary splitting, we describe as the one envelope type (AB) as compared to the two envelope (A_2B_2). [c] Satisfactory analytical data were reported (±0.35%) for C, H, N, and S, Ed.

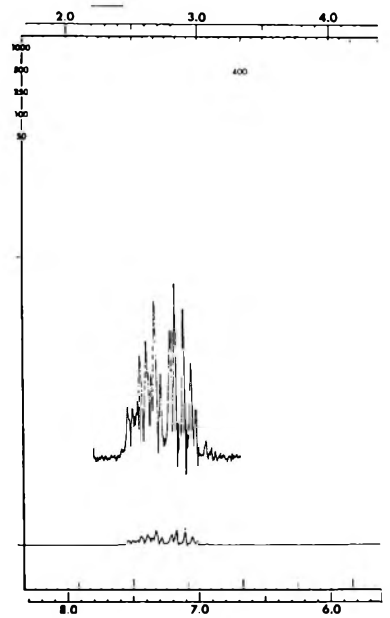


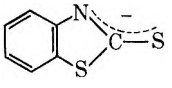
Figure 1.

on the benzene rings for the two classes of the derivatives of various benzothiazoles and similar aromatic heterocyclic compounds. In the S-alkyl esters of benzothiazole-2-thiol (XV–XX), the heterocyclic ring is aromatic and in conjugation with the benzene ring. The ring current in the heterocyclic ring causes a change in the electronic environment, different for the 5 and 6 protons. Hence, the resonance peaks from the four aromatic protons are split into two distinct envelopes of several lines, each representing two protons close together or sometimes overlapping, resembling a somewhat off-symmetrical A_2B_2 type splitting, Figure 1.

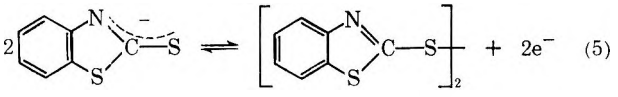
Thus, the 4,7 protons of compounds XV–XX, which are highly deshielded by the heterocyclic ring current, form the downfield envelope. The degree of deshielding in the benzothiazole system depends on the density of the circulating current from the heterocyclic ring. Since the sulfur and nitrogen atoms of the heterocyclic thiazole ring cannot produce identical environments for the adjacent protons on the benzene ring, it is highly improbable for the two envelopes to be perfectly symmetrical. Still, elements of symmetry can be seen. Analogy is made with the nmr spectra of aromatic protons of α,α'- and β,β'-substituted naphthalene derivatives[16] where for similar reasons, two perfectly symmetrical envelopes are formed.

On the other hand, the N- or 3-substituted derivatives of benzothiazoline-2-thione, II–XIV and XXI–XXIV including the 3-alkyl esters as well as the Michael and Mannich reaction products, even including compound I, all showed a single envelope for the four aromatic protons, resembling an AB type splitting in which the chemical shift, δ, of the 4,7 protons *vs.* that of the 5,6 protons, is much smaller than the J values (splitting constants), Figure 2.

Application of the Oxibase Scale to Rationalize the Production of N-Substituted Products.—The anion of MBT can be formulated as follows



in which two nucleophilic sites, either nitrogen or sulfur, can be easily identified. The sulfur atom is the most easily oxidized site as treatment of MBT^- with mild oxidants produce the disulfide in a half-cell reaction



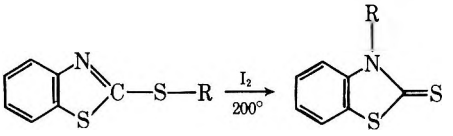
(5)

$$E = \epsilon^\circ + 2.60\ \text{V} = 2.23\ \text{V}$$

(16) See J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p 147.

TABLE III

2-ALKYLTHIOBENZOTHIAZOLES AND 3-ALKYLBENZOTHIAZOLINE-2-THIONES



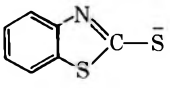
Products	R	Mp or bp (mm), C°	Solvent	Yield, %	Ir data, μ	Uv data, mμ	Nmr data A_2B_2 type (Figure 1) 4,7 protons, ppm	5,6 protons, ppm	AB type of splitting (Figure 2) 4,5,6,7 protons, ppm
			2-Substituted Thiobenzothiazoles[a,c]						
XV	CH_3–[a]	48–49 133–135 (0.5)	THF	93	6.20, 13.30, 14.20	244, 275, 289, 298	7.80	7.50	
XVI	$CH_3CH_2CH_2$–[a]	168–175 (15)	THF	81	6.23, 13.34, 14.20	246, 278, 289, 298	7.69	7.50	
XVII	$(CH_3)_2CH$–[a]	110–115 (0.5)	THF	79	6.10, 13.30, 14.24	245, 277, 286, 298	7.70	7.50	
XVIII	$CH_3(CH_2)_3$–[a]	145–146 (1)	THF	80	6.0, 13.30, 14.24	244, 275, 287, 298	7.70	7.50	
XIX	$(CH_3)_2CHCH_2CH_2$–	125–128 (0.5)	THF	73	6.10, 13.30, 14.24	242, 280, 285, 301	7.80	7.50	
XX	$CH_3CH_2CHCH_2$– CH_3	139–140 (0.5)	THF	70	6.20, 13.30, 14.24	240, 279, 284, 298	7.80	7.50	
			3-Substitituted Benzothiazoline-2-thiones[b,c]						
XXI	CH_3–[b]	90–91	None	71.5	6.20, 9.30, 14.20	225, 281, 298, 320			7.0
XXII	$CH_3CH_2CH_2$–[b]	74–75	None	65.0	6.10, 9.30, 14.30	298, 281, 290, 321			7.10
XXIII	$(CH_3)_2C$–[b] R	66–67	None	53.0	6.20, 9.30, 14.30	245, 278, 298, 320			7.40
XXIV	$CH_3(CH_2)_3$–		None	45.0	6.05, 9.41, 14.30	245, 278, 300, 320			6.9

[a] Some of the compounds were reported in literature ref 15. [b] Some of the compounds were reported in literature ref 15. [c] Satisfactory analytical data were reported (±0.35%) for C, H, N, and S, Ed.

The oxidation potential of this oxidative dimerization potential has been estimated to be −0.37 V (American convention) in water at 25° by O'Connor.[17] Relative to water, the oxibase scale E value is 2.23 V. The high E value of MBT^- can be explained within molecular orbital theory by noting that the highest filled molecular orbital on the sulfur is quite large (large coefficient of the atomic orbital) and that its energy is high.

Thus the electrons are easily removed by an oxidant. Secondly, the charge density on the sulfur atom in the MBT^- is quite low, on the basis of Hückel π electron theory.

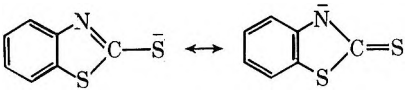
In terms of the oxibase scale[18–21] the result is that the E value of the S^- is high and the H value, defined as $H = pK_a + 1.74$, is small.



E_{S^-} high

H_{S^-} small

The nitrogen anion, on the other hand, has a larger charge density than the sulfur anion, thus indicating



(6)

that the nitrogen is a stronger base toward a proton. The H_{N^-} is therefore larger than H_{S^-}, a fact well attested by the observation that MBT exists in the thion form (eq 6).[22–24]

The orbital on nitrogen which would serve as the source of the nucleophilic electrons is smaller and of lower energy. Thus E_{N^-} is low compared to E_{S^-}.

Attack of a H.—The proton in solution[25] has an α of 0.00 and a β of 1.00; therefore one observes an N–H attack.

$$\log K_{S^-}/K_{N^-} = 1.00[H_{S^-} - H_{N^-}]$$

$$\log K_{S^-}/K_{N^-} < 0 \text{ since } H_{N^-} > H_{S^-}$$

Attack on CH_3I.—Methyl iodide is an α reagent (α = 2.95 while β = −0.003). To a good approximation the methylation is controlled by the E term and S methylation results.

$$\log K_S/K_{N^-} = 2.96[E_S - E_{N^-}] + 0.003[H_{S^-} - H_{N^-}]$$

$$\log K_S/K_N > 0 \text{ because } E_{S^-} > E_{N^-} \text{ and } H_{N^-} > H_{S^-}$$

(17) J. O'Connor, Ph.D. Thesis, Purdue University, June 1969.

(18) R. E. Davis in "Survey of Progress in Chemistry," A. Scott, Ed., Academic Press, New York, N. Y., 1964, pp 189–238.

(19) R. E. Davis, R. Nehring, W. J. Blume, and C. R. Chuang, *J. Amer. Chem. Soc.*, **91**, 91 (1969).

(20) R. E. Davis, S. P. Molnar, and R. Nehring, *ibid.*, **91**, 97 (1969).

(21) R. E. Davis, H. Nakshbendi, and A. Ohno, *J. Org. Chem.*, **31**, 2702 (1966).

(22) B. Stanovnik and M. Tisler, *Vestn. Sloven. Kem. Drust.*, **10**, 1 (1963).

(23) B. Ellis and P. J. F. Griffiths, *Spectrochim. Acta*, **22**, 2005 (1966).

(24) R. A. Morton and A. L. Stubbs, *J. Chem. Soc.*, 1321 (1939).

(25) J. O. Edwards, *J. Amer. Chem. Soc.*, **76**, 1540 (1954).

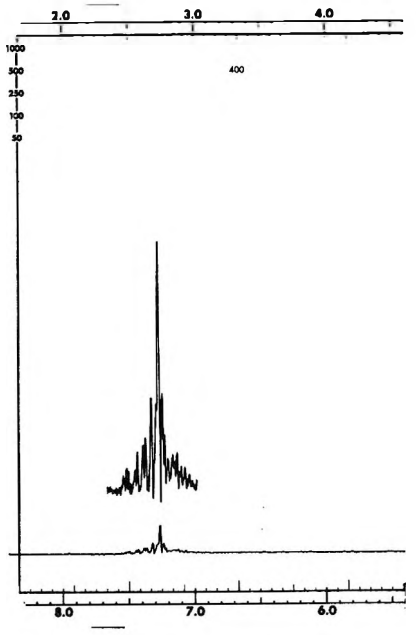


Figure 2.

The oxibase scale also predicts that the amount of N methylation would increase relative to S methylation with the series CH_3I, CH_3Br, CH_3Cl, and CH_3OTs.

Attack on Benzoyl Chloride.—Benzoyl chloride[26] is an α reagent ($\alpha = 3.5$ and $\beta = 0.01$). The α value is large because the lowest unfilled acceptor orbital is of low energy while the β value is low because of the reduced amount of positive charge on the carbonyl carbon caused by the electronic effects of the benzene ring.

$$\log K_{S^-}/K_{N^-} = 3.5[E_{S^-} - E_{N^-}] + 0.01[H_{S^-} - H_{N^-}]$$
$$\cong 3.5[E_{S^-} - E_{N^-}] \gg 0$$

Thus, the result is -S-(O=)C-Ph.

Attack on Acetyl Compounds.—Data are available[27] from which α and β values can be computed on $CH_3C(=O)O^-$ as an acetylating agent: $\alpha = 0.70$; $\beta = 0.46$. The value of β is the dominate term (β range up to 1.0 for H^+) and the acetylation is controlled by the βH term.

$$\log K_{S^-}/K_{N^-} = 0.70[E_{S^-} - E_{N^-}] + 0.46[H_{S^-} - H_{N^-}]$$

The first term is small and the second term is negative; therefore the result is $N(O=)CCH_3$.

The foregoing discussions should show the power of the oxibase scale to predict ambident anion reactivities.

As predicted by the oxibase scale, our experiments showed that the reaction of MBT with benzoyl chloride gave the S-substituted thio ester S(O=)CPh, whereas the reaction with acetyl chloride gave the N-substituted amide, $N(O=)CCH_3$. The physical data obtained by ir, nmr, and uv supported the structural assignments. The thio ester, S(O=)CPh, showed a strong absorption at 5.92 μ in the ir spectrum characteristic of thio esters, whereas the amide, $N(O=)CCH_3$, showed a strong absorption band at 6.20 μ indicative of amide absorption. The nmr spectrum of the benzoyl derivative of MBT gave the usual pattern of the A_2B_2 type absorption showing the double envelope pattern, indicative of S substitution. However, the acetyl derivative showed the usual AB type pattern at 7.30 ppm, indicative of N substitution. Similarly the $CH_3(O=)CN$ methyl group appeared at 2.70 ppm, at lower field than the $CH_3(O=)CS$ methyl group which appeared at 2.40 ppm downfield from TMS.

Thus the experimental facts indeed support the predictions based on the oxibase scale, that benzoylation proceeds on the sulfur to give the S-substituted benzothiazole while the acetylation gives the N-substituted benzothiazoline-2-thione.

Let us now consider the addition of a nucleophile to an unsaturated ketone, such as methyl vinyl ketone, or to an aldehyde, such as formaldehyde, in the Mannich and Michael reactions.

Methyl vinyl ketone	C=C—C(=O)—C	α	low
Formaldehyde	H—C(=O)—H	β	high

The structural analogies between these compounds and acetylation agents for the introduction of the acetyl group are at once obvious, and in contrast to the case of the introduction of the benzoyl group. That is, whereas the presence of the benzene ring reduces the amount of the positive charge on the carbonyl carbon (high α) of the benzoyl, the methyl and ethylenic groups and protons exert an opposite influence on the carbon in formaldehyde and methyl vinyl ketone. Hence, these aliphatic carbonyl substrates have low α values, and, correspondingly, relatively high β values. Examination of the literature shows that Mannich and Michael additives are fast with strong bases (*e.g.*, toward protons with the highest α values) and slow with poor bases (*e.g.*, toward I^-), in spite of the fact that the attacking species are "good" nucleophiles in the sense that they have high E values toward carbon.

In the present case, the attacking ambident MBT anion offers two choices, S^- with high E_S and low H_S as against N^- with low E_{N^-} and high H_{N^-}. As with the acetylating reagents, the substrate species exhibit a low α and high β. Hence, in the equation derived from oxibase scale considerations

$$\log K_{S^-}/K_{N^-} = \alpha[E_{S^-} - E_{N^-}] + \beta[H_{S^-} - H_{N^-}]$$

the high value of H_{N^-} makes the second term negative, while a low E_{N^-} makes the first term small; therefore K_{N^-} is larger than K_{S^-}, the N^- anion wins out in the competition, and the N-substituted benzothiazoline-2-thiones are the products observed.

Attempts were made to isolate the S-substituted Michael addition products by interrupting the reaction at various times before completion; however, only N-substituted products were prepared and no S-substituted products could be isolated at any time during the reaction.

Experimental Section

General Procedure for the Michael Reaction Products.—The Michael reaction adducts generally were prepared by adding the freshly distilled activated olefinic compounds to a cooled solution of benzothiazole-2-thiol in tetrahydrofuran containing a catalytic amount of sodium hydride. The resulting solution was then heated for 48 hr at 40–45°. The products isolated from solution were solids which were purified by recrystallization from suitable

(26) R. E. Davis, "Organosulfur Chemistry," M. J. Janssen, Ed., Interscience, New York, N. Y., 1967, pp 311–328. (Data taken from Table 18.1 except for b.)

(27) W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, **82**, 1778 (1960).

solvents. Specific examples are detailed below including some special cases where the activated olefinic compounds were prepared *in situ*. See Tables I–III.

3-(3-Oxobutyl)benzothiazoline-2-thione (II).—A solution of benzothiazole-2-thiol (I) (17.0 g, 0.101 mol) in 200 ml of anhydrous tetrahydrofuran and 50 mg of sodium hydride contained in a 58.1% oil dispersion was cooled to 5° and methyl vinyl ketone (8.0 g, 0.114 mol) was added over a period of 15 min. The reaction mixture was stirred for 48 hr at 40–45°. Concentrating the solvent to half its volume by evaporation under reduced pressure followed by cooling to −78° resulted in 17.5 g, 70–72% yield, of crude crystalline product, II, mp 138–140°. Two recrystallizations from isopropyl ether gave analytically pure II: mp 140.0–140.5°; λ_{max}^{Nujol} 5.85 (C=O), 6.30 (C=C), and 9.30 μ (C=S).

Anal. Calcd for $C_{11}H_{11}NOS_2$: C, 55.76; H, 4.67; N, 5.90. Found: C, 55.50; H, 4.83; N, 5.86.

The oxime of compound II was prepared in the usual manner.[28] A 90% yield of the product was obtained after recrystallization from absolute ethanol, mp 149–150°.

Anal. Calcd for $C_{11}H_{12}N_2OS_2$: C, 52.35; H, 4.79; N, 11.10; S, 25.41. Found: C, 51.85; H, 4.84; N, 11.08; S, 25.44.

3-(2-Benzoylethyl)benzothiazoline-2-thione (III).—Into a 500-ml round bottom flask were placed 95% ethanol (200 ml), compound I (16.70 g, 0.10 mol), and sodium hydride (4.10 g, 0.10 mol, contained in a commercial 58.1% dispersion in oil). To this cooled solution was added dropwise 50 ml of an ethanol solution of β-chloropropiophenone (16.8 g, 0.10 mol). The reaction mixture was heated to 40–45° for 48 hr. After filtration of the sodium chloride, the reaction mixture was cooled to −78° and filtered, resulting in 27.10 g, 90% yield, of white, crystalline product, III, mp 140–145°. Recrystallization from ethanol produced analytically pure material: mp 144.5–145°; λ_{max}^{Nujol} 5.85 (C=O), 6.20 (C=C), and 9.30 μ (C=S).

Anal. Calcd for $C_{16}H_{13}NOS_2$: C, 64.21; H, 4.35; N, 4.68; S, 21.40. Found: C, 64.22; H, 4.39; N, 4.70; S, 21.59.

Bis[2-(2-benzothiazolinethion-3-yl)ethyl] Sulfone (VIII).—To a solution of compound I (16.70 g, 0.10 mol) in 200 ml of anhydrous tetrahydrofuran was added 50 mg of sodium hydride contained in a 58.1% dispersion in oil. After cooling to 5°, freshly distilled divinyl sulfone (11.8 g, 0.10 mol) was added slowly with stirring. The reaction mixture was heated to 40–45°, with stirring for 48 hr. Cooling to −78° and filtration resulted in 22.0 g (50% yield) of crude compound VIII, mp 214–216°. Recrystallization from isopropyl ether produced analytically pure material: mp 215–216°; λ_{max}^{Nujol} 6.20 (C=C), 9.30 (C=S), and 8.30 μ (SO_2).

Anal. Calcd for $C_{18}H_{16}N_2O_2S_5$: C, 47.76; H, 3.56; N, 6.19; S, 35.42. Found: C, 47.63; H, 3.56; N, 5.97; S, 35.62.

3-(2-Nitrobutyl)benzothiazoline-2-thione (VI).—To compound I (16.70 g, 0.10 mol) dissolved in 100 ml of ethanol were added sodium hydride (4.10 g, 0.10 mol, contained in 58.1% oil dispersion) and then, dropwise, freshly distilled 2-nitro-*n*-butyl acetate[29] (16.10 g, 0.10 mol). The reaction mixture was heated with stirring 48 hr at 40–45°. Acidification with 10% hydrochloric acid and cooling to −78° and filtration produced 20.99 g, 83% yield, of white, crystalline, crude VI, mp 88–90°. Recrystallization from isopropyl ether resulted in analytically pure material: mp 89.5–90°; λ_{max}^{Nujol} 6.45 and 7.30 (NO_2), 9.10 (thione), 13.50, and 14.20 μ (aromatic).

Anal. Calcd for $C_{11}H_{12}N_2O_2S_2$: C, 49.23; H, 4.51; N, 10.44; S, 23.89. Found: C, 48.80; H, 4.72; N, 9.95; S, 23.66.

Procedure for the Synthesis of the 2-Alkylthiobenzothiazoles.—The 2-alkylthiobenzothiazoles were prepared by addition of the appropriate alkyl halide, with stirring, to a solution of the sodium salt of benzothiazole-2-thiol prepared from compound I and sodium hydride in tetrahydrofuran under reflux. The reaction was usually completed in 2–3 hr. After completion, the reaction mixture was filtered, the filtrate was distilled to remove the solvent, and the products were isolated as liquids by vacuum distillation. This is similar to the previous method[15] except that a cleaner reaction was obtained by the use of sodium hydride in tetrahydrofuran solvent.

2-*n*-Butylthiobenzothiazole (XVIII).—To a solution of compound I (50.1 g, 0.30 mol) in anhydrous tetrahydrofuran was added sodium hydride (7.20 g, 0.30 mol) with constant stirring. While heating to a gentle reflux, *n*-butyl bromide (48 g, 0.35 mol) was added dropwise. The reaction was then cooled to room temperature and filtered. The solvent was removed by distillation and the resulting oil was washed with distilled water and dried. Distillation under reduced pressure gave a clear liquid, yield 80%, bp 145–146° (1 mm).

Anal. Calcd for $C_{11}H_{13}NS_2$: C, 59.13; H, 5.86; S, 28.71. Found: C, 58.98; H, 5.76; S, 29.12.

Procedure for the Synthesis of 3-Alkylbenzothiazoline-2-thiones.—The 3-alkylbenzothiazoline-2-thiones were prepared by rearrangement of the 2-alkylthiobenzothiazoles in the presence of catalytic amounts of iodine[15] without solvent at 200–250°. Yields of the 3-alkylbenzothiazoline-2-thiones decreased with the length of the alkyl group, and alkyl groups above isopropyl produced liquids which were purified by distillation *in vacuo*.

3-Methylbenzothiazoline-2-thione (XXI).—Into a 50-ml round bottom flask equipped with thermometer and condenser were placed 2-methylthiobenzothiazole (9.0 g, 0.05 mol) and 0.50 g of iodine. The mixture was heated to 200–250° and the temperature was maintained for 6–8 hr. Cooling and washing with 10% hydrochloric acid produced 6.47 g, 71.5% yield, of yellowish solid, mp 85–90°. Recrystallization from ethanol gave mp 90.0–90.5° (lit.[15] mp 90–91°).

Procedure for the Preparation of Mannich Reaction Products.—The Mannich reaction products were prepared from the corresponding substituted ammonium salts of compound I and formaldehyde at room temperature in aqueous solution. The ammonium salts were prepared by adding the desired amine to a solution of compound I in ether. The crystalline salt was filtered, washed with ether, dried, and dissolved in water. Aqueous formaldehyde (40%) was added in excess to form the Mannich reaction products of compound I in excellent yields.

3-Pyrrolidinomethyl-2-benzothiazoline-2-thione (X).—To a solution of compound I (16.7 g, 0.10 mol) in 800 ml of anhydrous ether was added pyrrolidine (7.10 g, 0.1 mol). The salt precipitated immediately and was filtered, washed with ether, and dried. The salt was formed in quantitative yield. (A solution was prepared by dissolving 23.6 g (0.10 mol) of this salt in 200 ml of distilled water). To this solution was added with stirring 30 ml of 40% formaldehyde. A white solid formed immediately, which was collected and dried, 20.0 g, 80% yield, mp 122–125°. Recrystallization from acetone gave analytically pure material, mp 124–125°.

Anal. Calcd for $C_{12}H_{14}N_2S_2$: C, 57.54; H, 5.42; N, 11.19; S, 25.62. Found: C, 57.40; H, 5.63; N, 11.09; S, 26.08.

Registry No.—IA, 149-30-4; II, 27410-83-9; oxime of II, 27410-84-0; III, 27410-85-1; IV, 5525-04-2; V, 27410-87-3; VI, 27410-88-4; VII, 27410-89-5; VIII, 20752-60-7; IX, 6957-11-5; X, 23124-36-9; XI, 27410-38-4; XII, 22075-92-9; XIII, 27410-40-8; XIV, 27410-41-9; XV, 615-22-5; XVI, 27410-43-1; XVII, 27410-44-2; XVIII, 2314-17-2; XIX, 27410-46-4; XX, 27371-67-1; XXI, 2254-94-6; XXII, 27410-48-6; XXIII, 27410-49-7; XXIV, 21261-91-6.

(28) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, Wiley, New York, N. Y., 1964, p 254.

(29) H. Feuer and R. Miller, *J. Org. Chem.*, **26**, 1348 (1961).

Studies on 4-Quinazolinones. II.[1] Self-Condensation of Anthranilamide

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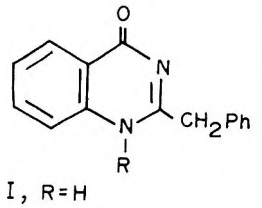
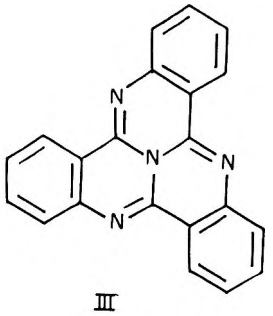
Condensation of phenylacetic acid with anthranilamide in xylene in the presence of phosphorus pentoxide furnished 2-benzyl-4-quinazolinone (I), *o*-aminobenzonitrile, tricycloquinazoline (III), 2-(*o*-aminophenyl)-4-quinazolinone (IV), 6,12-diaminophenohomazine (VI), and a compound, $C_{29}H_{21}N_5O$, mp 281°, for which the most probable structure VII has been advanced. The mass spectral fragmentation of III, IV, and VII are discussed.

In connection with some oxidation and reduction studies, we required glycosminine (I), one of the minor alkaloids[2,3] from *Glycosmis arborea* (Roxb) DC (*Rutaceae*), in quantities. Though a single-step synthesis[4] of arborine (II) from N^1-methylanthranilamide has been recorded in the literature, the condensation of anthranilamide with phenylacetic acid in boiling xylene in the presence of phosphorus pentoxide[5] afforded I in only *ca.* 10% yield. Among a number of side products (tlc), compounds A–E could be definitely characterized. Since the first four were obtained when anthranilamide alone was similarly treated, only compound E involved phenylacetic acid also. Thus, the modified general method of synthesis of 4-quinazolinones reported[1] from this laboratory appears to be the method of choice for the preparation of I.

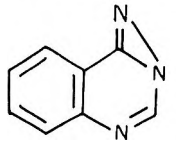
Compound A was *o*-aminobenzonitrile. Compound B was a trimer; the tricycloquinazoline structure III[6-10]



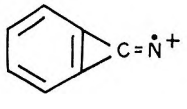
I, R = H
II, R = CH_3



III



a



b

was confirmed by its preparation from 2-(*o*-aminophenyl)-4-quinazolinone (IV). The infrared spectrum of the compound (Nujol) deserves comment in view of the varied observations[11] on the position of C=N stretching vibration particularly in conjugation in a cyclic system. The sharp and intense bands at 1618 and 1592 cm^{-1} appear to be those for C=N stretching frequency, considerably lowered by conjugation with aromatic rings. Similarly, VI exhibits the corresponding bands at 1613 and 1567 cm^{-1}.

The mass spectrum of the compound is characterized by strong peaks for both M + 1 and M − 1. It, however, shows only a few major fragmentations and no metastable peak. The peaks at *m/e* 293 (M − 27) and at *m/e* 230 (M − 90) clearly result from the expulsion of a molecule of HCN and C_6H_4N radical, respectively, supported by a prominent peak at *m/e* 90 in the latter case. Loss of a CN radical and HCN from *m/e* 230 would lead to the respective ions 204^+ and 203^+. Either further loss of HCN from *m/e* 204 or expulsion of a neutral $C_8H_5N_3$ fragment assigned to structure a directly from the M^+ appears to be the genesis of peak at *m/e* 177. Species b would account for *m/e* 102.

Compound C, $C_{14}H_{11}N_3O$, gave a crystalline acetyl derivative and is assigned the structure of 2-(*o*-aminophenyl-4-quinazolinone) (IV), which has been suggested[12,13] as the precursor of III. Further condensation of IV with anthranilic acid gave III, ruling out the other possible isomer V. The mass spectrum of IV showed a base peak at M + 1, compatible with a free amino group.

The first fragmentation step appears to follow that of the other 4-quinazolinones,[3] *viz.*, loss of atoms 2 and 3 with substituent, except hydrogen transfer has to be envisaged in this case. The ion peak at *m/e* 121 and a more intense one at *m/e* 120 could be assigned to species c and d or e, respectively. The observed metastable peaks at *m/e* 61.75 (calcd for $238^+ \rightarrow 121^+$, 61.52; $237^+ \rightarrow 121^+$, 61.79) and *m/e* 60.75 (calcd for $238^+ \rightarrow 120^+$, 60.50; $237^+ \rightarrow 120^+$, 60.77) favor the transition from M^+ rather than M + 1 ion. Species e may either lose a molecule of HCN to afford ion peak at *m/e* 93, corroborated by the metastable peak at *m/e* 72.0 (calcd for $120^+ \rightarrow 93^+$, 72.1), or species d may expel CO to lead to *m/e* 92.

Compound D, mp 94°, retained a molecule of solvent of crystallization, but analysis of the base and the

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(2) S. C. Pakrashi and J. Bhattacharyya, *Ann. Biochem. Exp. Med.*, **23**, 123 (1963).
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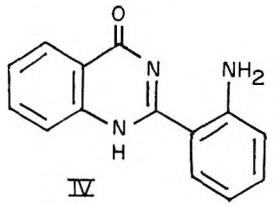
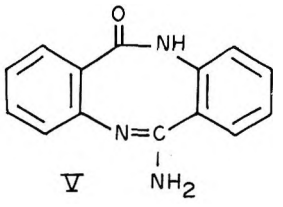
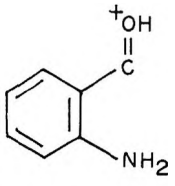
dihydrochloride were in agreement with the molecular formula, $C_{14}H_{12}N_4$. The physical constants are in accord with 6,12-diaminophenohomazine (VI) prepared by Cooper and Partridge[10] though, however, the slight discrepancy in the uv data reported by them cannot readily be explained.



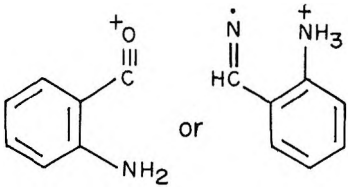
IV



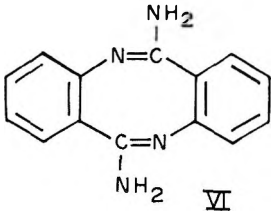
V



c, m/e 121



d or e, m/e 120



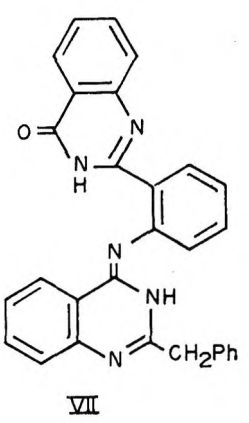
VI

The formula $C_{29}H_{21}N_5O$ was indicated by analysis of compound E, mp 280–281°. The M^+ and M^{2+} ion peaks respectively at *m/e* 455 and 227.5 in the mass spectrum confirmed the molecular formula. To gain insight into the mode of combination of 3 mol of anthranilamide with 1 mol of phenylacetic acid, 2-(*o*-aminophenyl)-4-quinazolinone (IV) was condensed first with 2-benzyl-4-quinazolinone (I) and then separately with N^4-phenylacetylanthranilamide, the intermediate in the synthesis of I, in presence of phosphorus pentoxide. The desired compound was only obtained in the latter case along with I which was also recovered unchanged from the former reaction. Among a number of possible structures, VII and VIII (or their tautomers) appeared to be the most likely representation of compound E.

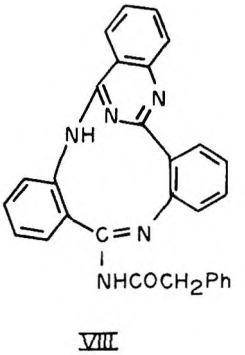
The infrared band at 3030 cm^{-1} indicated the presence of a bonded NH, and a number of typical bands between 1681 and 1417 cm^{-1} supported[3] the presence of an intact 4-quinazolinone rather than a phenyl acetamide moiety. The structure VII appears also to explain the mass spectral fragmentation pattern better.

The intense M − 1 ion peak and the corresponding peaks at *m/e* 91 and at *m/e* 364 (M − 91) are characteristic of a free benzyl substituent in the molecule in this series.[3] The two equally strong peaks at *m/e* 336 and *m/e* 335 must be due to the expulsion of species f from the 4-quinazolinone moiety of M^+ and M − 1 ions, respectively. The ion peak at *m/e* 119 and its protonated species at *m/e* 120 as well as the metastable peak at *m/e* 248.5 (calcd for $455^+ \rightarrow 336^+$, 248.1) corroborate the above transition.

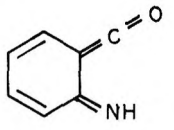
Primary loss of OH from the M − 1 peak (m* observed 420.5 − 0.5; calcd for $454^+ \rightarrow 437^+$, 420.6) followed by expulsion of 116 mass units assignable to radical g appears to be the genesis of the peak at *m/e* 321. The more important and intense peak at *m/e* 310 may result directly from the M^+ as evidenced by the presence of metastable peak at *m/e* 211 (calcd for $455^+ \rightarrow 310^+$, 211.2). Expulsion of the 4-quinazolinone moiety as such (loss of 145 mass units) would lead to a highly stabilized ion species h. Further loss of benzyl group would lead to ion at *m/e* 219 and subsequent expulsion of HCN to *m/e* 192.



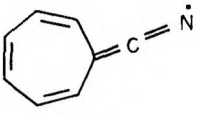
VII



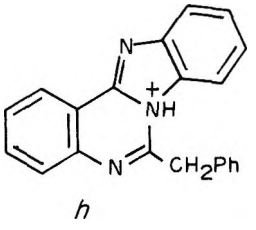
VIII



f



g



h

When, however, N^1-methylanthranilamide was condensed with phenylacetic acid in the presence of phosphorus pentoxide under similar condition, arborine (II) was indeed[4] obtained as the major product. The only recognizable side product was *o*-(N-methylamino)-benzonitrile.

The above result was not unexpected in view of our observed[1] difference in the rate of dehydrocyclization between N^1-acylated anthranilamides and their N^1-methyl derivatives. The N^1-methylation has also been found to have remarkable influence on the oxidation[14] and reduction[15,16] of 4-quinazolinones.

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(15) S. C. Pakrashi and J. Bhattacharyya, Abstracts, 3rd IUPAC Symposium on the Chemistry of Natural Products, Kyoto, Japan, April 12–18, 1964, p 74.

(16) S. C. Pakrashi, *J. Indian Chem. Soc.*, **44**, 887 (1967).

Experimental Section[17]

Condensation of Anthranilamide with Phenylacetic Acid.—Anthranilamide (2 g) and phenylacetic acid (2 g) were dissolved in dry xylene (100 ml) and refluxed with excess phosphorus pentoxide for 1 hr under anhydrous conditions. After cooling, the reaction mixture was poured over crushed ice. The xylene layer was separated, extracted once with 2 *N* hydrochloric acid (50 ml), then washed, dried (Na_2SO_4), and evaporated to obtain the neutral fraction A (1.5 g). The pooled aqueous acid part was basified (Na_2CO_3) and filtered. The filtrate was thoroughly extracted with chloroform which yielded fraction B (1.43 g) as a viscous mass. The residue (0.15 g) was crystallized (five times) from chloroform–ethanol to afford compound E in granules: mp 280–281° dec; R_f 0.42 (light brown); uv max (0.1 *N* HCl–EtOH) 201, 240, and 310 mμ (log ε 4.45, 4.43, and 4.20); ir (Nujol) 3030, 1681, 1631, 1608, 1570, 1538, 1490 (m), 1417, 1412, 1359, 1311, 1267, 950, 882, 760, 748, 722 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 455 (M^+, 100), 454 (59.5), 437 (2.2), 364 (6), 336 (5.5), 335 (6), 322 (6), 321 (9), 310 (21), 309 (6), 308 (6), 234 (5.5), 227.5 (M^{2+}, 7.1), 219 (9), 218 (8.5), 192 (6), 120 (8.5), 119 (12), 102 (8.8), 92 (12), 91 (36). 90 (10.5).

Anal. Calcd for $C_{29}H_{21}N_5O$: C, 76.46; H, 4.65; N, 15.38. Found: C, 75.98; H, 4.64; N, 15.82.

Fraction B was subjected to column (1.5 × 12 cm) chromatography over alumina. After separation of phenylacetic acid (0.43 g), mp 77–78°, R_f 0.53 (light pink, iodine chamber), benzene (1.5 l.) eluted fraction C (0.27 g), mp 210–215° (frothing), containing a mixture of components. Benzene–chloroform (4:1, 450 ml) separated a solid (0.1 g) which crystallized from ethanol in long white needles of glycosminine, mp 249°. Further increase in the polarity of solvents up to chloroform–methanol (98:2) eluted fraction D as a brownish yellow, viscous oil (0.5 g) responding positively to alkaloidal test.

Fraction C was resolved by preparative tlc into glycosminine (0.23 g) and two minor components, one of which could only be obtained crystalline, mp 240–241°.

Fraction D was converted to the picrate (0.23 g) in benzene solution, fractionally crystallized from methanol–benzene, and separately regenerated through ion-exchange resin (IRA-400). The bases liberated from the first two crops (0.12 g, yellow, mp 200–215°) were identified as unconverted anthranilamide (0.03 g), mp 107–109° (benzene), R_f 0.27 (yellowish brown, iodine chamber). The regenerated bases from the third crop (0.1 g, brown, mp 225–230°) and the mother liquor of the above picrates on chromatography and crystallization from petroleum ether gave white long rods (0.25 g), mp 50–51°, identified as *o*-aminobenzonitrile through their alkaline hydrolysis to anthranilamide: R_f 0.67 (orange); ir (Nujol) 2203 cm^{-1}.

Anal. Calcd for $C_7H_6N_2$: C, 71.25; H, 5.13; N, 23.74. Found: C, 70.67; H, 5.31; N, 23.92.

Fraction A (xylene layer) was chromatographed through an alumina column (1.2 × 15 cm). After the initial separation of an oil, petroleum ether eluates (total 550 ml) furnished a crude material (0.03 g) crystallizing (0.02 g) out of benzene–chloroform to give III in long yellow needles: mp 315–316°; R_f 0.74 (light green); uv (dioxane) max 252, 284, 296, and 310 mμ (log ε 4.51, 4.26, 4.38, and 4.33); ir (Nujol) 1618, 1592, 1565 (m), 1475, 1333 (m), 1295 (w), 1280 (w), 1136, 768, 762, 755, 695 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 321 (M + 1, 25.5), 320 (M^+, 100), 319 (M − 1, 7.7), 293 (1.1), 292 (0.8), 291 (0.5), 230 (0.5), 218 (0.6), 217 (0.65), 204 (1.3), 203 (0.9), 191 (0.5), 186 (0.5), 177 (1.1), 176 (0.6), 165 (0.5), 164 (0.7), 160.5 (M^{2+}, 5), 160 (19.4), 159.5 (1.9), 129 (0.6), 106.6 (M^{3+}, 0.8), 102 (6.2), 90 (1.3), 76 (5), 74 (4).

Anal. Calcd for $C_{21}H_{12}N_4$: C, 78.82; H, 3.78; N, 17.51. Found: C, 78.83; H, 3.75; N, 17.22.

Petroleum ether–benzene (3:1, 600 ml) eluted *o*-aminobenzonitrile, mp 50–51°, and benzene (650 ml) gave phenylacetic acid, mp 77–78°.

In one experiment, the xylene layer, after being extracted with acid and left overnight, deposited a substance (0.1 g) which recrystallized from benzene–chloroform in colorless needles: mp 187–188°; ir (Nujol) 1690, 1668, 1600, 1580, 1525, 1405 (m), 1261 cm^{-1} (vs). In an attempted chromatography through neutral alumina, chloroform–methanol (98:2) eluted a compound (7 mg), mp 249°, while traces of the mother substance could only be separated from the benzene–acetic acid (5%) eluate. As such, it could not be further characterized.

Self-Condensation of Anthranilamide.—Anthranilamide (5 g) was dissolved in dry xylene (400 ml) and refluxed for 3 hr with an excess of phosphorus pentoxide under anhydrous conditions. Processed as before, the acid and xylene layers, respectively, furnished 3.67 and 1.15 g of viscous residues.

The basic fraction was chromatographed over alumina (1.5 × 22 cm). Petroleum ether–benzene (3:1, 150 ml) eluted *o*-aminobenzonitrile (0.85 g). The fractions eluted with benzene and chloroform, and their mixtures in various proportions (1.5 l.) gave an oil embedded with solid (2.4 g) which on crystallization several times from benzene–chloroform afforded light yellow needles (0.25 g), mp 240–241°, of 2-(*o*-aminophenyl)-4-quinazolinone. Another 0.35 g of the material was obtained from the filtrate: R_f 0.5 (violetish brown); uv (EtOH) max 208, 242, and 286 mμ (log ε 4.25, 4.25, and 4.02); ir (Nujol) 3425 (sh), 3330, (3171, 3125 sh), 1670, 1613, 1577 (m), 1550, 1504 (w), 1480, 1337 (m), 1266, 950, 772, 764, 740, 692 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 238 (M + 1, 100), 237 (M^+, 6), 121 (20.5), 120 (64), 119.5 (M^{2+} + 1, 11), 119 (6.5), 103 (2), 93 (16), 92 (8), 91 (5), 77 (1.5).

Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.90; H, 4.70; N, 17.70. Found: C, 70.57; H, 4.94; N, 17.50.

It formed an acetate, mp 273–274° (lit.[12] mp 274–275°), with acetic anhydride and pyridine.

The acid extract was made ammoniacal, the base taken up in chloroform, and the residue (1.7 g) chromatographed. Benzene–chloroform (6:4, 1.5 l.) eluted anthranilamide (1.03 g), mp 109°; an increase in polarity up to chloroform yielded fraction E as an oil (0.45 g), while chloroform–methanol (98:2) separated an oil (0.32 g) containing a number (tlc) of unisolated alkaloidal components.

Fraction E was converted to the picrate, mp 230° (frothing) after repeated crystallizations from methanol. The regenerated base (0.4 g) was chromatographed (silica gel, column, 1 × 8 cm). Benzene and its mixture with chloroform (3:1) eluted a material (0.38 g) which on several crystallizations from benzene yielded Dragendorff-positive light yellow prisms (0.3 g) of 6,12-diaminophenohomazine: mp 93–94°; R_f 0.48 (reddish brown); uv (EtOH) max 207, 250, 262 (sh), and 298 mμ [log ε 4.3, 4.3, 4.21, and 3.96 (calcd with 1 mol of C_6H_6 of crystallization), 4.17, 4.17, 4.08, and 3.8 (without)]; ir (Nujol) 3413, 3279, 3125, 1634, 1613, 1567, 1538 (m), 1497, 1480, 1359, 1307 (w), 1277 (w), 1244 (m), 1157 (m), 767, 748, 690 cm^{-1} (vs).

Anal. Calcd for $C_{14}H_{12}N_4 \cdot C_6H_6$: C, 76.42; H, 5.78; N, 17.82. Found: C, 76.25; H, 5.70; N, 17.83.

It formed a hydrochloride which was crystallized from ethanol in yellow needles, mp 288° dec.

Anal. Calcd for $C_{14}H_{12}N_4 \cdot 2HCl$: C, 54.38; H, 4.57, N, 18.13. Found: C, 54.18; H, 4.41; N, 18.40.

The neutral part (xylene layer) on recrystallization from chloroform–benzene furnished yellow needles (0.14 g) of tricycloquinazoline, mp 315–316° dec; 15 mg more of the compound could be recovered from the mother liquor.

Petroleum ether–benzene (3:1, 500 ml) separated *o*-aminobenzonitrile (0.33 g).

Condensation of *N*-Methylanthranilamide with Phenylacetic Acid.—*N*-Methylanthranilamide (2 g) and phenylacetic acid (2 g) in dry xylene (150 ml) were refluxed over phosphorus pentoxide for 1 hr and worked up as described earlier.

The basic fraction (1.4 g) was chromatographed through a column (1.5 × 19 cm) of alumina. Benzene (150 ml) separated phenylacetic acid (0.2 g), mp 77°. With increasing proportions of chloroform and finally chloroform itself arborine was eluted (0.9 g), mp 156–157° (benzene).

The neutral part (2.5 g) was subjected to column (1.5 × 25 cm) chromatography. The only definite product (0.9 g) obtained was *o*-(*N*-methylamino)benzonitrile eluted by petroleum ether–benzene (9:1, 1.25 l.). It solidified on standing overnight

(17) All melting points are uncorrected. Column chromatography was carried out over acid-washed alumina (E. Merck), thin layer chromatography was run with benzene–ethyl acetate (6:4) for identification and ethyl acetate–methylene chloride–formic acid (5:4:1) for preparative purposes using silica gel G, iodine was used as spot developer, and Dragendorff's reagent was used as spraying agent. Identity with known compounds was established by direct comparison (tlc, mixture melting point, and ir) where possible. The mass spectra were recorded on a CEC 21-110 B mass spectrometer; samples were introduced through direct inlet system at 150, 140, and 230°, respectively, for the samples III, IV, and VII. The ionizing current used was 50 μA.

and crystallized from petroleum ether in colorless flakes: mp 72–73°; R_f 0.68 (light orange); ir (Nujol) 2212 cm^{-1}.

Anal. Calcd for $C_8H_8N_2$: C, 72.79; H, 6.1; N, 21.2. Found: C, 72.55; H, 5.90; N, 21.5.

Condensation of Anthranilamide with Anthranilic Acid.—Thionyl chloride (3 ml) was added to a pyridine (3 ml) solution of anthranilamide (1 g) and anthranilic acid (1 g) and kept for 24 hr (i) at room temperature and (ii) at 0° in separate experiments. Crushed ice was then added; the reaction mixture was left for 2 hr and extracted with chloroform. The aqueous layer was filtered, an insoluble residue (0.4 g), not yet characterized, was kept aside, and the filtrate was mixed with the 2 *N* hydrochloric acid extract of the chloroform layer. The latter yielded a mixture of solid substances (1 g).

The combined acid aqueous solution was basified and extracted with chloroform, and the crude product (0.26 g) was chromatographed. Benzene–chloroform (9:1) eluted first an uncharacterized yellow crystalline compound (0.04 g), mp 208–212°, giving a positive test for alkaloid, and then 2-(*o*-aminophenyl)-4-quinazolinone (0.04 g), mp 240–241°. Further increase in the chloroform percentage (20%) eluted uncoverted anthranilamide (0.15 g) along with VI, mp 94°.

The reaction at 0° afforded the insoluble residue (0.8 g), solid substance (0.6 g) from the original chloroform layer, and a mixture of bases liberated from the acid aqueous part. The base on chromatography resolved into IV (0.09 g), mp 241°, anthranilamide (0.26 g), an uncharacterized compound (0.07 g), mp 210–212°, and trace amount of VI.

Tricycloquinazoline (III) from IV.—A mixture of 2-(*o*-aminophenyl)-4-quinazolinone (0.06 g) and an equal amount of anthranilic acid dissolved in xylene (25 ml) was refluxed in the presence of phosphorus pentoxide for 3 hr. The insoluble residue (0.01 g) left after being treated with crushed ice was filtered and chromatographed over acid-washed alumina. The benzene eluate (30 ml) afforded tricycloquinazoline, mp 316° (benzene–chloroform).

Preparation of VII from IV.—2-(*o*-Aminophenyl)-4-quinazolinone (25 mg) and N^4-phenylacetylanthranilamide (50 mg) in xylene were refluxed in the presence of phosphorus pentoxide for 3 hr. The acid layer, after usual work-up and chromatography with benzene–chloroform (8:2) as eluents, yielded VII (3 mg), mp 280–281°, identical in all repects with compound E, besides IV (8 mg) and I (6 mg).

On the other hand, equal proportions (40 mg) of IV and 2-benzyl-4-quinazolinone (I) on similar treatment led only to the recovery of the starting materials and not even a trace of VII could be detected.

Registry No.—*o*-Aminobenzonitrile (compound A), 1885-29-6; III (compound B), 195-84-6; IV (compound C), 27259-73-0; VI (compound D), 27259-74-1; VI 2HCl, 27259-75-2; VII (compound E), 27259-76-3; anthranilamide, 88-68-6; *o*-(*N*-methylamino)benzonitrile, 17583-40-3.

Acknowledgments.—The author is indebted to Mr. P. P. Ghosh-Dastidar, Senior Laboratory Assistant, for expert technical assistance, to Dr. K. G. Das for the mass spectra, and to Dr. A. Bernhardt, W. Germany, and Dr. K. W. Zimmermann, C.S.I.R.O., Melbourne, Australia, for microanalyses.

Reaction of 1-Acetyl-3-piperidinoindole with Acetylenic Esters

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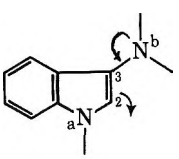
Received July 23, 1970

The reaction of 1-acetyl-3-piperidinoindole (2) with dimethyl acetylenedicarboxylate and methyl propiolate gave the benzazepine derivatives **3a** and **3b**, respectively. These products were subjected to a degradation sequence (**3** → **5** → **7** → **8**), each step of which was supported by spectral evidence; in the case of **8b**, direct correlation with authentic material was made. An alternative structure (**9**) for the product of the transformations **7** → **8** was ruled out by synthesis. Compound **11** was obtained and shown to be an intermediate for the formation of **3b**. Compounds **3a** and **3b** as well as a number of their degradation products exhibited geometrical isomerism due to restricted rotation about the *N*-acetyl function. In the case of **3b**, temperature-variable 100-Mc nmr spectra have been recorded and discussed.

Even a cursory reading of the literature of indole compounds reveals that the chemistry of simple 2- and 3-aminoindole derivatives has received scant attention.[1] The lack of activity in this area is undoubtedly related to the absence of versatile methods for the preparation of these compounds[2] and to their pronounced inherent instability.[1,3] Recent work dealing with new aspects of aminoindole chemistry[4,5] further emphasizes the latter point. The above survey gave impetus to devise new synthetic routes to ammoindoles[6] and to investigate some of their reactions. In particular, our intention was to put to experimental test the hypothesis that the system **1** may behave



1

to some extent like an enamine (arrows). This proposal had potentially important synthetic implications since enamine behavior of the N^b-enamine system would allow acylation and alkylation reactions to occur at

(1) A. Albert, "Heterocyclic Chemistry," 2nd ed, Oxford University Press, New York, N. Y., 1968, pp 205–206, and references to reviews therein.

(2) There are recent scattered investigations which may have a bearing on any new developments in aminoindole syntheses: (a) M. Colonna, P. Bruni, and G. Guerra, *Gazz. Chim. Ital.*, **99**, 3 (1969); (b) A. S. Bailey, M. C. Chum, and J. J. Wedgwood, *Tetrahedron Lett.*, 5953 (1968); (c) T. Hino, M. Nakagawa, and S. Akoboshi, *Chem. Commun.*, 656 (1967); (d) F. Yoneda, T. Miyamae, and Y. Nitta, *Chem. Pharm. Bull.*, **16**, 8 (1967); (e) D. Raileanu, V. Daniel, E. Mosanu, and C. D. Nenitzescu, *Rev. Roum. Chim.*, **12**, 1367 (1967). For an obvious but apparently unexplored approach, see E. Coxworth, *Alkaloids*, **8**, 40 (1965).

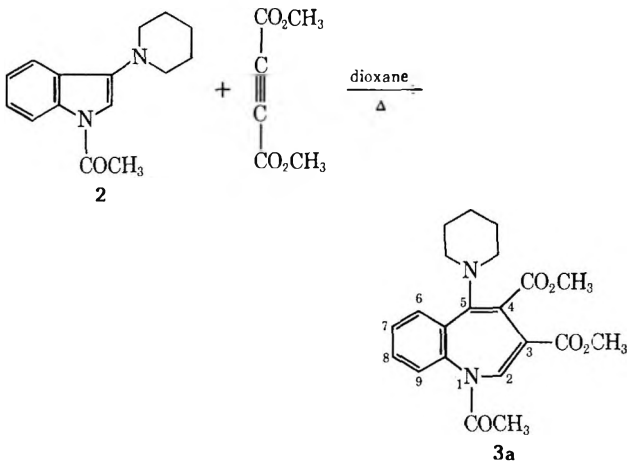
(3) J. Kebrle and K. Hoffmann, *Helv. Chim. Acta*, **39**, 116 (1956).

(4) J. Schmitt, M. Langlois, G. Callet, and C. Perrin, *Bull. Soc. Chim. Fr.*, 2008 (1969), and previous papers in this series.

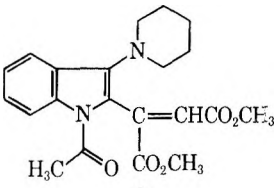
(5) M. Colonna and L. Greci, *Gazz. Chim. Ital.*, **99**, 1264 (1969), and references cited therein.

(6) For an unsuccessful attempt, see V. Snieckus and M.-S. Lin, *J. Org. Chem.*, **35**, 3994 (1970).

the indole 2 position.[7] Our investigations with the reasonably accessible 1-acetyl-3-piperidinoindole (2)[2e] have failed to uncover this desired enamine behavior notwithstanding the fact that the presence of the *N*-acetyl function may have been predicted to impart favorable effect on such reactions.[2e,11] On the other hand, in agreement with a generalized reaction in enamine chemistry,[12] we have found that **2** undergoes smooth cycloaddition–ring expansion with dimethyl acetylenedicarboxylate and methyl propiolate to yield the benzazepine derivatives **3a** and **3b**, respectively. Although the reactions of indole with acetylenic esters have been extensively studied,[13] our results constitute only the second example of this type of ring expansion reaction in the indole series.[14] When a mixture of **2** and dimethyl acetylenedicarboxylate was refluxed in dioxane solution for 1 day, a 96% yield of a 1:1 crystalline adduct was obtained. The ir spectrum of the adduct **3a** showed absorptions at 1725 and 1665 cm^{-1} while the 60-Mc nmr spectrum exhibited the following peaks: τ 2.0–2.38 and 2.40–2.76 (m, 4, aromatic), 2.97 (br s, 1, vinyl H), 6.28 (s, 6, $2CO_2CH_3$), 6.82 (br s, 4, α-CH_2 of piperidine ring), 7.77 (br d, 3, $COCH_3$), 8.25 (br s, 6, β- and γ-CH_2 of piperidine ring). It was suspected that the broad doublet at τ 7.77 was caused by hindered rotation about the acetyl function. This observation foreshadowed the more well-defined result of the same phenomenon obtained with compound **3b** (*vide infra*). The uv spectrum is tabulated in Table I. The spectral evidence was in agreement with two formulations **3a** and **4** as reasonable structures for the adduct.



In order to distinguish between structures **3a** and **4**, the chemical degradation outlined in Scheme I (series **a**) was undertaken. When the adduct from the reaction

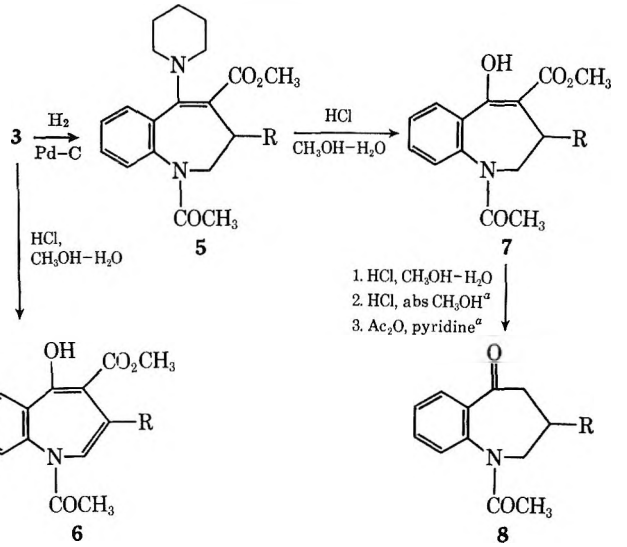


4

of **2** with dimethyl acetylenedicarboxylate was carefully hydrogenated over palladium on carbon, a dihydro derivative was obtained whose spectral properties [ir absorption at 1725 (saturated ester C=O), 1700 (unsaturated ester C=O), and 1665 (amide C=O) cm^{-1}; uv, see Table I; nmr absorption at τ 2.51–3.08 (m, 4, aromatic), 4.94–5.38 (m, 1), 6.02 (m, 1), 6.32 (s, 3, unsaturated CO_2CH_3), 6.40 (m, 1), 6.82 (s, 3, saturated CO_2CH_3), 7.03 (m, 4, α-CH_2 of piperidine ring), 8.19 (s, 3, $COCH_3$), 8.32 (br s, 6, β- and γ-CH_2 of piperidine ring)] were clearly consistent with structure **5a** and eliminated the alternate dihydro compound (**4**, reduced side-chain double bond). The nmr spectral evidence also ruled out any of the other possible dihydro tautomers corresponding to **5a**. Parenthetically, the readily accessible enol **6a** did not prove useful in attempts to develop an alternate degradation plan for compound **3a**.

Further evidence for structure **5a** was obtained by hydrolysis to **7a** which was then converted to **8a** according to Scheme I. At this point, however, literature

SCHEME I



[a] Only in the case of **7a**.

precedent[15] led us to seriously consider the alternate structure **9** for the product of the above three-step sequence (**7a** → **8a**). Clearly, ir and uv data could not

(7) There are only two known methods by which such substitution can be safely introduced: (a) *via* the 2-lithio derivative, the formation of which requires prior N^a alkylation[8] which decreases the overall synthetic utility of the method; and (b) *via* a 3-substituted indole in which intermolecular alkylation usually leads mainly to 2-substituted product.[9] There are many examples of intramolecular 2 substitution which lead to 2,3-bridged systems.[10]

(8) J. Kebrle, A. Rossi, and K. Hoffmann, *Helv. Chim. Acta*, **42**, 907 (1959); F. E. Ziegler and E. B. Spitzner, *J. Amer. Chem. Soc.*, **92**, 3492 (1970).

(9) See G. Casnati, M. Francioni, A. Guareschi, and A. Pochini, *Tetrahedron Lett.*, 2485 (1969); M. Wakselman, G. Decodts, and M. Vilkas, *C. R. Acad. Sci., Ser. C.*, **266**, 1089 (1969).

(10) See, for example, F. E. Ziegler, J. A. Kloek, and P. A. Zoretic, *J. Amer. Chem. Soc.*, **91**, 2342 (1969).

(11) Recent work shows that 2-carbethoxy-3-hydroxyindole undergoes facile alkylation at the 2 position: H. Plieninger and H. Herzog, *Monatsh. Chem.*, **98**, 807 (1967). In this case, the ester function obviously enhances the observed reactivity.

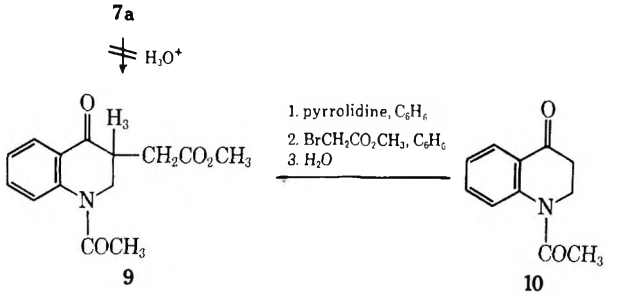
(12) For reviews, see (a) A. G. Cook, "Enamines," A. G. Cook, Ed., Marcel Dekker, New York, N. Y., 1969, pp 230–232; (b) R. Fuks and H. G. Viehe, "Chemistry of Acetylenes," H. G. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, pp 435–439.

(13) R. M. Acheson, *Advan. Heterocycl. Chem.*, **1**, 138 (1963).

(14) H. Plieninger and D. Wild, *Chem. Ber.*, **99**, 3070 (1966).

(15) J. A. Moore and E. Mitchell, *Heterocycl. Compounds*, **9**, 271, 284, (1967). See also E. D. Hannah, W. C. Pearson, and G. R. Proctor, *J. Chem. Soc. C*, 1280 (1968), and A. H. Rees and K. Simon, *Can. J. Chem.*, **47**, 1227 (1969).

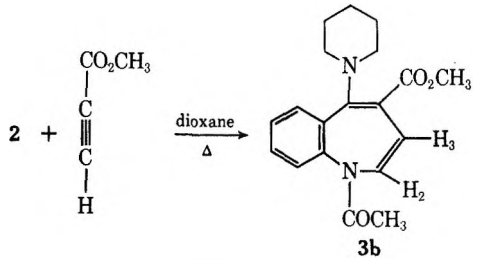
distinguish between **8a** and **9** and the complicated nmr spectrum of the product added a final element of uncertainty. Independent synthesis of **9** from the known 1-acetyl-1,2,3,4-tetrahydro-4-quinolone (**10**)[16] ruled out the potential rearrangement and supported the structural assignment **8a**.



9 **10**

Our original plan was to convert **8a** into the known 1-acetyl-1*H*-2,3,4,5-tetrahydrobenzazepin-5-one (**8b**).[17] However, several attempts to achieve this goal proved unsuccessful and we turned to the reaction between **2** and methyl propiolate in the expectation[12] that the adduct **3b** would be formed, thus allowing for an unambiguous proof of ring structure by a similar degradative sequence to that carried out for adduct **3a**.

Indeed the reaction between **2** and methyl propiolate in refluxing dioxane gave 1-acetyl-4-carbomethoxy-5-piperidino-1(1*H*)-benzazepine (**3b**) in 68% yield. The structure was fully supported by spectral and chemical data. The ir spectrum again showed unsaturated ester (1700 cm^{-1}) and *N*-acetyl (1665 cm^{-1}) carbonyl absorptions while the uv spectrum was similar to that of compound **3a**. The 60-Mc nmr spectrum showed, in addition to absorptions due to the protons of the piperidine ring (7.07, br s, 4, α protons and 8.39, br s, 6, β and γ protons), peaks at τ 8.01 and 7.85 (2 s, 3, $COCH_3$), 6.26 (s, 3), 3.82 (m, 2) and 2.07–3.11 (m, 4). The multiplet at τ 3.82 assignable to the vinyl protons H_2 and H_3 in **3b** was in good agreement with observed vinyl proton chemical shifts in a similar 4,5-disubstituted benzazepine system.[18] Moreover, on the basis of the nmr data, the alternate 3-carbomethoxybenzazepine structure arising from the less likely opposite mode of cycloaddition[12a] could be dismissed from further consideration.

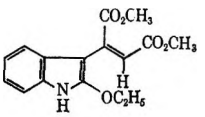


3b

Monitoring the formation of compound **3b** by thin layer chromatography led to the isolation of an intermediate in the reaction which was assigned structure **11** on the basis of the following spectral and chemical data. The uv spectrum showed lack of extensive conjugation and similarity to that of acetanilide (see Table I) while the salient features of the nmr spectrum

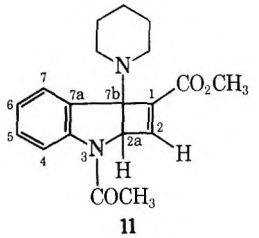
(16) R. F. Collins, *J. Chem. Soc.*, 2053 (1960).
(17) W. H. Bell, E. D. Hannah, and G. R. Proctor, *ibid.*, 4926 (1964).
(18) A. Cromarty and G. R. Proctor, *Chem. Commun.*, 842 (1968).

TABLE I
ULTRAVIOLET SPECTRA OF BENZAZEPINE DERIVATIVES AND RELATED MODEL SYSTEMS

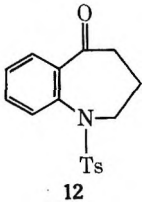
Compd	λ_{max}^{MeOH}, mμ (ε)[a]
2[b]	222 (22,000), 248 (sh, 9900), 307 (8730)
3a	234 (18,000), 350 (8400)
 **i**[c]	225 (36,300), 267 (12,000), 356 (18,600)
6a	236 (19,200), 295 (9500)
5a	255 (12,000), 351 (8200)
$PhNHCOCH_3$[d]	242 (12,000)
7a	232.5 (15,600), 257 (7500), 306 (3600)
8a	227 (11,600), 250 (sh, 6750), 298 (1600)
9	237 (23,400), 261 (10,800), 322 (3000)
10	237 (22,600), 261 (10,600) 321 (3150)
3b	234 (19,600), 267 (6900), 350 (6900)
11	248.5 (12,700), 255 (11,700), 280 (3700)
6b	233 (19,300), 255 (sh, 10,200), 321 (6500)
5b	254 (15,000), 348 (9400)
7b	220 (sh, 18,800), 290 (15,700)
8b	226 (13,300), 250 (sh, 6750), 295 (1600)

[a] sh = shoulder. [b] Reference 2e; determined in ethanol. [c] Reference 14. [d] A. I. Scott, "Interpretation of the Ultra-violet Spectra of Natural Products," Pergamon Press Ltd., Oxford, 1964, p 130.

were two slightly broadened one-proton singlets at τ 5.00 and 3.52 which may be assigned to the H_{2a} and H_2 protons, respectively, in **11**.[19] Chemical confirmation of this structure was obtained by its conversion into the benzazepine derivative **3b** using longer reaction times.



11



12

Final structure proof of the ring expansion product **3b** and, by implication, that of the analogous compound **3a**, was obtained by the degradation sequence outlined in Scheme I (series **b**). Mild acid hydrolysis of the adduct **3b** gave compound **6b** which was not amenable to further degradation due to the same reason as already mentioned for compound **6a**. Like **3a**, however, adduct **3b** was transformed to the analogous saturated keto ester **7b** by successive hydrogenation and hydrolysis reactions. The latter compound was easily converted to the known 1-acetyl-1(1*H*)-2,3,4,5-tetrahydrobenz-

(19) For assignments in analogous adducts, see (a) D. C. Neckers, J. H. Dopper, and H. Wynberg, *Tetrahedron Lett.*, 2913 (1969); (b) K. C. Brannock, R. D. Burpitt, V. W. Goodett, and J. G. Thweatt, *J. Org. Chem.*, **29**, 818 (1964).

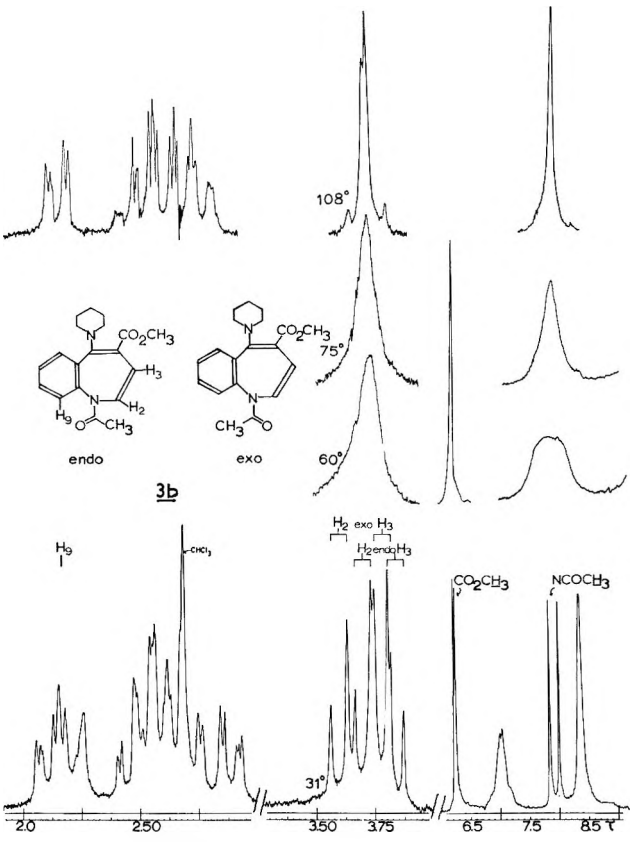


Figure 1.—Variable-temperature 100-Mc nmr spectrum of 1-acetyl-4-carbomethoxy-5-piperidino-1(1*H*)-benzazepine (**3b**). Determined at 250-Hz sweep width except for τ 6.0–9.0 portion at 31° which was run at 500 Hz.

azepin-5-one (**8b**).[17] An authentic sample of **8b** was prepared from the corresponding 1-tosyl derivative **12** according to the published procedure[17] and identity of the two substances was established.[20]

The mechanism of cycloaddition and ring opening of the resulting adducts has been previously discussed.[19b,21]

Temperature-Variable Nmr Spectra of 3b.—The well-known phenomenon[22] of restricted rotation about formal single bonds in amides has received substantial attention recently in connection with studies of heterocyclic systems.[23] Among the large number of benzazepine systems at various levels of oxidation in the heterocyclic ring which have been studied,[15,17,18] only Plieninger has briefly referred to observing such an effect.[14] The temperature-variable nmr spectrum of **3b** (Figure 1) at 31° shows approximately equal intensity spikes at τ 7.85 and 8.01 separated by 8 Hz which may be assigned to the *N*-acetyl methyl function in the exo and endo isomers, respectively, on the basis of the expected deshielding effect by the aromatic ring on the methyl group of the exo isomer. Analogous effect has been observed in the *N*-acetyl-1,2,3,4-tetrahydroquinoline and *N*-acetylindoline series.[23b,e] The multiplet centered at τ 2.14 (1 H) is attributed to overlapping signals of C_9 H for both exo and endo isomers.[24] At 108° this multiplet collapses to four lines as a result of rapid interconversion of the two conformers. This pattern now appears to be a deceptively simple X portion of an ABX system which cannot be further analyzed owing to the inability to extract the AB part from the other complex aromatic multiplet.[25] The vinyl proton region displays two overlapping AB quartets at τ 3.59 and 3.79 (J = 7 Hz) and at 3.69 and 3.84 (J = 7 Hz), the former pair corresponding to H_2 and H_3 of the exo isomer and the latter to H_2 and H_3 of the endo isomer.

At 60° the *N*-acetyl signals coalesce ($\Delta G^{\ddagger} \approx 14$ kcal) indicating an averaging of signals from the separate conformers. As the temperature is raised further, this peak begins to sharpen (75°) and becomes a singlet at 108°. Likewise, the two overlapping AB quartets due to H_2 and H_3 collapse to a broad peak at 60°, and then this in turn resolves into a quartet (J = 7 Hz) at 108°. The averaging effect is probably due to a combination of two rapid processes: (a) that of exo–endo rotational interconversion and (b) that due to conformational inversion of the seven-membered ring.[26] Finally, it is noted that at 31° the methyl ester resonance at τ 6.26 appears as two lines separated by 1.5 Hz and that these signals collapse to a single peak at 60°. We attribute this observation to the presence of two conformational isomers which result from restricted rotation about the carbomethoxy group.

Experimental Section

Microanalyses were performed by A. B. Gygli Toronto, and Microtech Laboratories, Skokie, Ill. Melting points were measured on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were determined with Beckman IR-5A and -10 instruments in chloroform solution unless otherwise indicated; in recording the spectra, abbreviations used are w = weak and sh = shoulder. Ultraviolet spectra were recorded on a Hitachi EPS-3T spectrophotometer in methanol solution. Nuclear magnetic resonance spectra were obtained with JEOL C-60, Varian T-60, A-60, and HA-100 spectrometers in deuteriochloroform solution using tetramethylsilane as internal standard and are tabulated in the order: chemical shift (τ value), multiplicity (s = singlet, d = doublet, q = quartet, m = multiplet, br = broad), number, coupling constant in hertz, and assignment of protons. Column, thin layer, and thick layer chromatography was carried out with silica gel obtained from Brinkmann (Canada) Ltd. Solvents were reagent grade and distilled before use.

The Preparation of 1-Acetyl-3,4-dicarbomethoxy-5-piperidino-1(1*H*)-benzazepine (3a).—A mixture of 1.21 g (5 mmol) of 1-acetyl-3-piperidinoindole (**2**) and 1.14 g (8 mmol) of dimethyl acetylenedicarboxylate in 10 ml of dioxane was refluxed for 24 hr. Evaporation of solvent and trituration of the residue with ether gave 1.86 g (96%) of yellow crystals, mp 171–172°. Three recrystallizations from methanol–ether gave an analytical sample, mp 171–174°; see text for spectral data.

Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.60; H, 6.25; N, 7.29. Found: C, 65.64; H, 6.32; N, 7.40.

(20) We are indebted to Professor Proctor for a sample of **12** and for helpful correspondence.

(21) G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, **28**, 1459 (1963); L. A. Paquette and R. W. Begland, *J. Amer. Chem. Soc.*, **88**, 4685 (1966); A. Risaliti, E. Valentin, and M. Forchiassin, *Chem. Commun.*, 233 (1969); T. W. Doyle, *Can. J. Chem.*, **48**, 1629, 1633 (1970).

(22) G. Binsch, *Topics Stereochem.*, **3**, 97 (1968).

(23) Systems investigated include (a) pyrroles: T. Matsuo and H. Shosenji, *Chem. Commun.*, 501 (1969); (b) indolines: H. Wyler and J. Chiovini, *Helv. Chim. Acta*, **51**, 1476 (1968); (c) isoindolines: K. Fang and J. T. Gerig, *J. Amer. Chem. Soc.*, **91**, 3045 (1969); (d) 1,2,3,4-tetrahydroisoquinolines: D. R. Dalton, K. C. Ramey, H. J. Gisler, Jr., L. J. Lendvay, and A. Abraham, *ibid.*, **91**, 6367 (1969); (e) 1,2,3,4-tetrahydroquinolines: A. M. Monro and M. J. Sewell, *Tetrahedron Lett.*, 595 (1969).

(24) This may be contrasted to the situation in the tetrahydroquinoline and indoline series in which only the similarly disposed peri proton in the endo isomers is shifted substantially downfield from the rest of the aromatic resonances.[23b,e]

(25) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, p 105 ff.

(26) For an analysis of this effect in dibenzoazepine derivatives, see M. Nogradi, W. D. Ollis, and I. O. Sutherland, *Chem. Commun.*, 158 (1970).

1-Acetyl-3,4-dicarbomethoxy-5-hydroxy-1(1*H*)-benzazepine (6a).—A mixture of 100 mg (0.26 mmol) of **3a** in 5 ml of methanol containing 2 drops of concentrated hydrochloric acid was heated to boiling and then treated with 1 ml of water. After a reflux period of 10 min, the solution was concentrated to a small volume and the resulting crystalline material was collected and dried yielding 74 mg (88%) of colorless crystals, mp 160–162°. Three recrystallizations from methanol furnished the analytical sample: mp 163–165°; ir 3400–3100 (OH), 1720 (ester C=O), 1655 (enolic C=C and amide C=O) cm^{-1}; nmr τ −2.35 (s, 1, OH, exchanged with D_2O), 2.07–2.30 and 2.46–3.09 (m, 4, aromatic), 6.27 (s, 3, CO_2CH_3), 6.33 (s, 3, CO_2CH_3), 7.9 (br s, 3, $COCH_3$).

Anal. Calcd for $C_{16}H_{15}NO_6$: C, 60.57; H, 4.77; N, 4.41. Found: C, 60.42; H, 4.65; N, 4.56.

1-Acetyl-3,4-dicarbomethoxy-5-piperidino-1(1*H*)-2,3-dihydrobenzazepine (5a).—A solution of 1.54 g (4 mmol) of **3a** in 25 ml of alcohol was hydrogenated over 0.5 g of 10% palladium on charcoal and the reaction was stopped after 1 equiv of hydrogen (100 ml) was consumed. Normal isolation procedure and trituration with ether gave 1.06 g of crystals, mp 145°. Consecutive recrystallizations from ether and acetone–ether gave an analytical sample, mp 150–152°; see text for spectral data.

Anal. Calcd for $C_{21}H_{26}N_2O_5$: C, 65.27; H, 6.78; N, 7.25. Found: C, 65.50; H, 7.04; N, 7.25.

1-Acetyl-3,4-dicarbomethoxy-1(1*H*)-2,3,4,5-tetrahydrobenzazepin-5-one (7a).—The procedure described for the preparation of **6a** was followed except that the reflux time was extended to 1 hr. The mixture was concentrated, diluted with water, and extracted with chloroform. From 664 mg (1.71 mmol) of **5a** there was obtained 540 mg (98%) of crude **7a**. Four recrystallizations from acetone–ether gave an analytical sample: mp 116–119°; ir 3400–3050 (OH), 1740 (ester C=O), 1670 (br, enolic C=C, ketone and amide C=O) cm^{-1}; nmr τ 2.02 and 2.35–2.87 (m, 4, aromatic), 5.68 and 6.12–6.77 (m, 4, aliphatic), 6.25 (d, 6, $2CO_2CH_3$), 7.87 (s, 3, $COCH_3$). The spectrum was strongly concentration and solvent dependent.

Anal. Calcd for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found: C, 60.40; H, 5.40; N, 4.32.

1-Acetyl-3-carbomethoxy-1(1*H*)-2,3,4,5-tetrahydrobenzazepin-5-one (8a).—A suspension of 540 mg (1.7 mmol) of **7a** in 5 ml of 4 *N* hydrochloric acid was refluxed for 2 hr. The mixture was evaporated to dryness *in vacuo* and the residue was dissolved in 10 ml of absolute methanol. This solution was saturated with gaseous hydrochloric acid and refluxed for 14 hr. The reaction mixture was evaporated to dryness and the residue was treated with aqueous sodium bicarbonate solution. Extraction of the basic solution with methylene chloride followed by evaporation to dryness of the organic extract yielded 380 mg of solid which, upon acetylation with acetic anhydride and pyridine gave 430 mg (94%) of **8a**. Three recrystallizations from methanol–ether gave an analytical sample: mp 96–97°; ir 1735 (ester C=O), 1685 (C=O), 1665 (amide C=O) cm^{-1}; nmr τ 2.06 and 2.28–2.79 (m, 4, aromatic), 5.74 (br s, 1, C_3H), 6.40–6.79 (m, 4, C_2 and C_4 H), 6.33 (s, 3, CO_2CH_3), 8.0 (s, 3, $COCH_3$).

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.40; H, 5.76; N, 5.36.

The Preparation of 1-Acetyl-3-carbomethoxymethyl-1,2,3,4-tetrahydro-4-quinolone (9).—In an adaption of the conventional Stork procedure,[27] a solution of 386 mg (2 mmol) of 1-acetyl-1,2,3,4-tetrahydro-4-quinolone (**10**), 2 ml of pyrrolidine, and a trace of *p*-toluenesulfonic acid in 50 ml of dry benzene was refluxed under a Dean–Stark trap for 18 hr. An additional 2 ml of pyrrolidine was added and reflux was continued for 72 hr. The pale yellow solution was evaporated to dryness *in vacuo*, treated with 25 ml of benzene, and again evaporated to dryness. This process was repeated. The residue was dissolved in 25 ml of benzene; the resulting solution was flushed with dry nitrogen and then treated with 1.22 g (8 mmol) of methyl bromoacetate. The mixture was refluxed for 21.5 hr and treated with 15 ml of water. Following a further reflux period of 1.5 hr, the solution was cooled, diluted with 5 ml of water, and extracted with ether. The ether extracts were dried (Na_2SO_4), filtered, and taken to dryness *in vacuo*. The resulting mobile oil was chromatographed (25 g). Elution with ether–benzene (1:3) gave 422 mg of an oil from which 247 mg of starting material could be recovered by crystallization from ether. The filtrate was subjected to preparative tlc (ether) to yield 50 mg (25% based on recovered starting material) of a pale yellow oil which crystallized on standing. Recrystallization from petroleum ether (bp 30–60°)–ether yielded an analytical sample: mp 100–101.5°; ir (CCl_4) 1735 (ester C=O), 1680 (amide and ketone C=O) cm^{-1}; nmr τ 2.15 and 2.47–3.30 (m, 4, aromatic), 5.60 (m, 1, H_3), 6.38 (s, 3, CO_2CH_3), 6.20–6.49 and 7.08–7.64 (m, 4, CH_2N– and CH_2CO_2-CH_3), 7.78 (s, 3, $COCH_3$).

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.20; H, 5.92; N, 5.16.

1-Acetyl-4-carbomethoxy-5-piperidino-1(1*H*)-benzazepine (3b).—A mixture of 2.8 g (11.5 mmol) of **2** and 1.7 g (20 mmol) of methyl propiolate[28] in 25 ml of dioxane was refluxed for 11 days. Evaporation of solvent *in vacuo* and trituration of the residue with ether gave 2.5 g (68%) of yellow crystals, mp 149–151°. Three recrystallizations from acetone–ether gave an analytical sample, mp 150–151°; see text for spectral data.

Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 70.16; H, 7.03; N, 8.48.

3-Acetyl-2a,7b-dihydro-7b-piperidino-3*H*-cyclobut[*b*]indole-1-carboxylic Acid Methyl Ester (11).—When a mixture of 484 mg (2 mmol) of **2** and 336 mg (4 mmol) of methyl propiolate in 10 ml of dioxane was refluxed for 2 days and the crude reaction product treated as above, there was obtained 168 mg (26%) of **11**, mp 172–174°. Two recrystallizations from acetone–ether furnished an analytical sample: mp 172–174°; ir 1725 (C=O), 1665 (amide C=O) cm^{-1}; nmr τ 1.82 and 2.34–3.21 (m, 4, aromatic), 3.52 (s, 1, H_2), 5.00 (s, 1, H_{2a}), 6.28 (s, 3, CO_2CH_3), 7.57 (br s, 4, α-piperidine protons), 7.67 (s, 3, $COCH_3$), 8.44 (br s, 6, β- and γ-piperidine protons).

Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.82; H, 6.89; N, 8.51.

When **11** was refluxed in dioxane solution for 44 hr, it rearranged completely to **3b** as shown by tlc, ir, and uv comparison with an authentic sample.

1-Acetyl-4-carbomethoxy-5-hydroxy-1(1*H*)-benzazepine (6b).—The procedure was essentially that used for the preparation of **6a** except that the reflux time was extended to 2 hr. From 417 mg of **3b** there was obtained 145 mg (43%) of yellow crystals of **6b**, mp 133–135°. Two recrystallizations from methanol–ether and then one from ether gave an analytical sample: mp 137–139°; ir 3200 (br, OH), 1735 (w sh, $>CHCO_2CH_3$), 1655 (br, C=C, $C=CCO_2CH_3$, and amide C=O) cm^{-1}; nmr τ −3.36 (s, 1, OH, exchanged with D_2O), 2.02 and 2.38–3.14 (m, 4, aromatic), 3.67 (m, 2, H_2, H_3), 6.10 (s, 3, CO_2CH_3), 7.78 and 8.00 (2 s, 3, $COCH_3$, conformational isomers in ratio 1:2).

Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 65.04; H, 5.13; N, 5.45.

1-Acetyl-4-carbomethoxy-5-piperidino-1(1*H*)-2,3-dihydrobenzazepine (5b).—Following the procedure described for the preparation of **5a**, 1.06 g of **3b** was hydrogenated to yield 1.0 g (95%) of yellow crystals of **5b**. Three recrystallizations from methanol–ether gave an analytical sample: mp 165–166°; ir 1680 (C=O), 1655 (amide C=O) cm^{-1}; nmr τ 1.85–2.61 (m, 4, aromatic), 4.78–5.42 (m, 1, C_2 or C_3 H), 6.1 (s, 3, CO_2CH_3), 6.36–7.34 (m, 7, remaining C_2 and C_3 H and α-piperidine protons), 8.15 (s, 3, $COCH_3$), 8.29 (br s, 6, β- and γ-piperidine protons).

Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.33; H, 7.27; N, 8.56.

1-Acetyl-4-carbomethoxy-1(1*H*)-2,3,4,5-tetrahydrobenzazepin-5-one (7b).—Compound **7b** was obtained from **5b** (1.57 g, 98% yield) according to the procedure used for the preparation of **7a**. Three recrystallizations from acetone–ether gave an analytical sample: mp 93–97°; ir 3200 (br, OH), 1745 ($>CHCO_2CH_3$), 1650 (br, C=C, $C=CCO_2CH_3$, and ketone C=O) cm^{-1}; nmr τ −2.53 (s, 0.67, OH, exchanged with D_2O), 1.94–2.92 (m, 4, aromatic), 4.91–5.48 (m, 0.33, C_4 H of keto form), 5.7 (d, 0.67, J = 4, C_2 or C_3 H of enol form), 6.16 and 6.23 (2 s, 3, CO_2CH_3 of enol and keto forms, respectively), 6.32–6.77 and 6.93–7.82 (m, 3, remaining C_2 and C_3 H), 8.00 and 8.21 (2 s, 3, $COCH_3$, conformational isomers in ratio 1:2).

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.31; H, 5.88; N, 5.54.

1-Acetyl-1(1*H*)-2,3,4,5-tetrahydrobenzazepin-5-one (8b).—A suspension of 480 mg (1.8 mmol) of **7a** in 4 ml of 4 *N* hydrochloric acid was heated until carbon dioxide evolution ceased (45 min). Water was added and the solution was extracted with methylene chloride. Evaporation to dryness of the organic extract yielded

(27) L. H. Hellberg, R. J. Milligan, and R. N. Wilke, *J. Chem. Soc. C*, 35 (1970).

(28) H. O. House, W. L. Roelofs, and B. M. Trost, *J. Org. Chem.*, **31**, 646 (1966).

350 mg (94%) of crude product. Trituration with ether gave crystals of **8b** which were recrystallized consecutively from acetone–ether, methanol–ether, and petroleum ether (bp 60–80°)–acetone to yield colorless crystals: mp 115–117° (lit.[17] 122°); ir 1680 (w, C=O), 1655 (amide C=O) cm^{-1}; nmr τ 1.97–3.0 (m, 4, aromatic), 5.97, 7.33, and 7.7–8.42 (m, 6, aliphatic), 8.08 (s, 3, $COCH_3$). This sample was characterized by identical ir, uv, and nmr spectra, melting point, and mixture melting point with those of authentic material prepared from the corresponding 1-*p*-toluenesulfonyl derivative **12** according to the method of Proctor.[17]

Registry No.—**2**, 19501-93-0; **3a**, 27150-46-5; **3b**, 27150-47-6; **5a**, 27150-48-7; **5b**, 27150-49-8; **6a**, 27150-50-1; **6b**, 27150-51-2; **7a**, 27150-52-3; **7b**, 27150-53-4; **8a**, 27150-54-5; **9**, 27150-55-6; **11**, 27150-56-7; dimethyl acetylenedicarboxylate, 762-42-5; methyl propiolate, 922-67-8.

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Novel Cyclizations and Ring-Opening Reactions of 3-Phenylindene Derivatives

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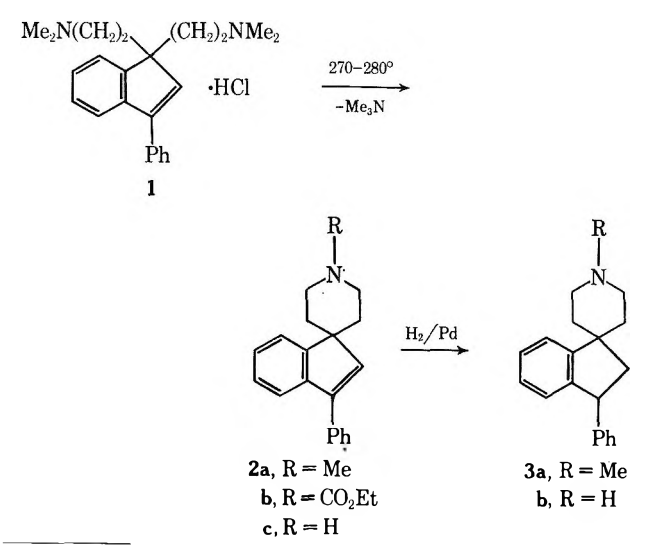
A spiroindenopiperidine **2a** is obtained by pyrolysis of the 1,1-dialkylated 3-phenylindene **1**. However, similar treatment of the 1,3-substituted isomer **4** yields a fused indenopyrrole **5**. Attempted N-demethylation of **5** with ethyl chloroformate causes ring opening to **10**. On refluxing **10** with alcoholic potassium hydroxide, competing intramolecular cyclization to **5** and bimolecular displacement of halogen by ethoxide ion to **12** occurs. Mechanisms of these transformations are discussed.

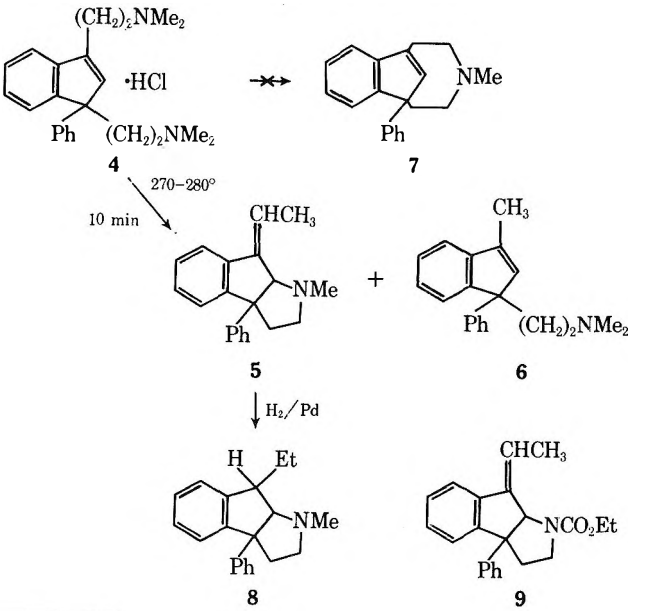
Our interest in alkylamino-3-phenylindene derivatives as CNS agents[1] led us to investigate the synthesis of some phenylindeno- and phenylindano heterocycles. Publications by Dykstra, *et al.*,[1] and by Ganellin, Loynes, and Ansell,[2] established the structure of the products of alkylation of 3-phenylindene with sodium amide and 2-dimethylaminoethyl chloride. They identified three monoalkylated materials as well as the 1,1- and 1,3-dialkylated materials. The present paper discusses some interesting transformations of these dialkylated compounds **1** and **4**.

The dialkylated indenes were obtained by a modification of the previously used method.[2] On pyrolysis of the diamine **1** monohydrochloride, according to the method of Blicke, *et al.*,[3] compound **2a** was isolated in high yield along with trimethylamine.

Treatment of the indene derivative **2a** with ethyl chloroformate[4] yielded the carbamate **2b**, which hydrolyzed to the secondary amine **2c** with ethanolic potassium hydroxide. The spiroindenes **2a** and **2c** were converted to the corresponding indans by hydrogenation over a palladium-on-carbon catalyst.

Pyrolysis of the 1,3-substituted compound **4**, however, did not give the bridged indene **7** but yielded a mixture of products from which **5** (42%) and **6** (9.5%) were separated by column chromatography.





(1) S. J. Dykstra, J. M. Berdahl, K. N. Campbell, C. M. Combs, and D. G. Lankin, *J. Med. Chem.*, **10**, 418 (1967).

(2) G. Ganellin, J. Loynes, and M. Ansell, *Chem. Ind. (London)*, 1256 (1965).

(3) F. F. Blicke, J. A. Faust, J. Krapcho, and E. Tsao, *J. Amer. Chem. Soc.*, **74**, 1844 (1952).

(4) J. D. Hobson and J. G. McCluskey, *J. Chem. Soc. C*, 2015 (1967), and references therein.

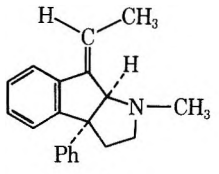
The structure of **5** was established by analysis, and nmr and mass spectra. The nmr spectrum showed **5** to be a 70:30 mixture of isomers (Table I) from which a pure sample of the major isomer was separated by repeated crystallizations of its picrate salt.

Table I
Nmr Spectrum of 5 in CCl_4

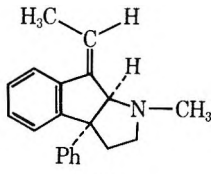
Position, δ, ppm				Multiplicity and coupling constant
Major isomer	Minor isomer	Type or proton	No. of protons	(J in Hz)
7.0–7.9	7.0–7.9	Aromatic	9	m
6.15	5.65	=CH	1	q,[a] 7 Hz
3.73	3.17	>CH	1	s[a]
2.45–2.95	2.45–2.95	$-CH_2CH_2-$	4	m
2.37	2.30	$>NCH_3$	3	s
1.90	2.07	$=CCH_3$	3	d, 7 Hz

[a] Fine splitting ($J \sim 1$ Hz) was also observed.

Four enantiomeric pairs of isomers of **5** are possible owing to geometrical isomerism at the olefinic bond and the possibility of cis or trans fusion of the five-membered rings. Rigorous stereochemical assignments could not be made on the basis of the nmr spectrum. However, since the compounds with cis ring fusion are probably much more stable[5] than the trans-fused isomers, the products **5** are likely to be cis fused as in structures **5a** and **5b**.



5a



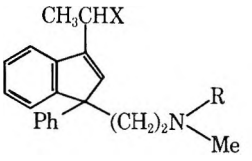
5b

The conversion of a 95:5 mixture of the isomers of **5** to a 65:35 mixture by ultraviolet irradiation provides additional evidence for isomerization at the olefinic bond rather than at the ring junction.

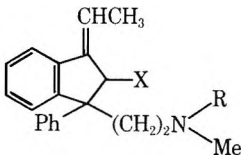
On the basis of the chemical shifts of the olefinic hydrogen atoms, structure **5a** is favored for the major isomer and **5b** for the minor isomer. The chemical shifts in **5a** and **5b** were calculated[6] to be δ 5.86 and 5.57, respectively, which agree well with the values δ 6.15 and 5.65 found for the major and minor isomers (Table I).

The structure of **5** was further confirmed by hydrogenation of its hydrochloride salt over a palladium-on-carbon catalyst to yield **8** HCl. The two doublets due to the *N*-methyl group in the nmr spectrum of **8** HCl showed it to be a 50:50 mixture of two isomers. The same isomer distribution was obtained on hydrogenation of either the pure major isomer of **5** or a mixture of the isomers, in agreement with the expected products from hydrogenation of **5a** and **5b**.

Reaction of **5** with ethyl chloroformate failed to give the expected product **9**. Instead, a product was obtained in quantitative yield which was identified as **10** by its analysis, and nmr and infrared spectra. Structure **10**, rather than **11**, was assigned to the product because the nmr signals for the vinylic and tertiary hydrogen atoms appear as a sharp singlet at δ 6.55 and a quartet at δ 5.15, respectively. Structure **11** would require the quartet, in this case for the vinyl hydrogen atom, to be downfield from the singlet due to the tertiary hydrogen atom.



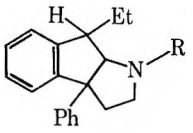
10, R = CO_2Et; X = Cl
12, R = H; X = OEt



11, R = CO_2Et; X = Cl
13, R = H; X = OEt

On refluxing the ethoxycarbonyl compound **10** with ethanolic potassium hydroxide, two products were formed, one of which was identical with **5** (65:35 mixture of isomers) and the other was identified as the ether **12** by its analysis, and nmr and infrared spectra. Structure **13** was ruled out, since the nmr signals due to the vinylic and tertiary hydrogen atoms appeared as a singlet at δ 6.36 and a quartet at δ 4.58, respectively.

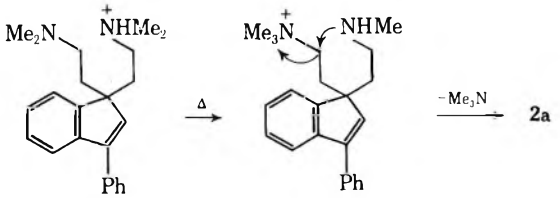
N-Demethylation of compound **8** with ethyl chloroformate occurred normally to yield the ethoxycarbonyl compound **14**, which hydrolyzed with ethanolic potassium hydroxide to the secondary amine **15**.



14, R = CO_2Et
15, R = H

Discussion and Mechanisms

Formation of Compounds 2a and 5.—The formation of the spiro compound **2a** from **1** presumably occurs by an initial intramolecular disproportionation involving migration of a methyl group, followed by nucleophilic displacement of trimethylamine.



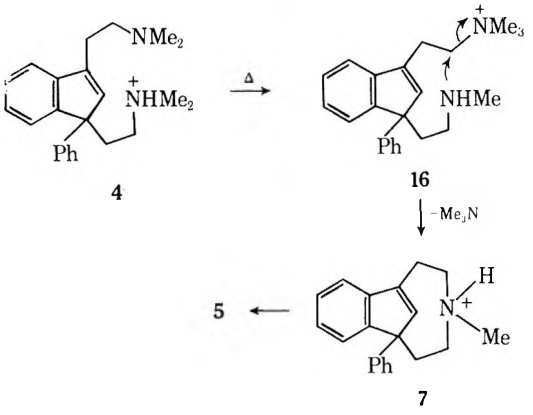
1

A similar mechanism was proposed by Snyder, *et al.*,[7] to account for the formation of dibenzylmethylamine and trimethylamine by heating benzyldimethylamine with an acid catalyst or with a catalytic amount of its methiodide salt.

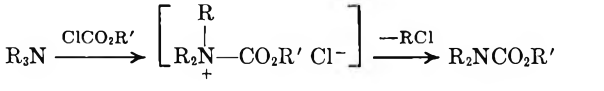
The formation of **5** rather than **7** from **4** may be accounted for by a similar process. In this case, cyclization gives the strained eight-membered ring system **7**, formed *via* **16** by nucleophilic displacement of trimethylamine by the secondary amine function. Due to the close proximity of the *N*-methyl group and the olefinic bond in the eight-membered ring, this species may then

(5) H. Booth, F. E. King, K. G. Mason, J. Parrick, and R. L. St. D. Whitehead, *J. Chem. Soc.*, 1050 (1959).
(6) C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966).
(7) H. R. Snyder, R. E. Carnahan, and E. R. Lovejoy, *J. Amer. Chem. Soc.*, **76**, 1301 (1954).

undergo transannular rearrangement to yield the observed product **5**. Similar transformations are known to occur during alkaloid degradations.[8]

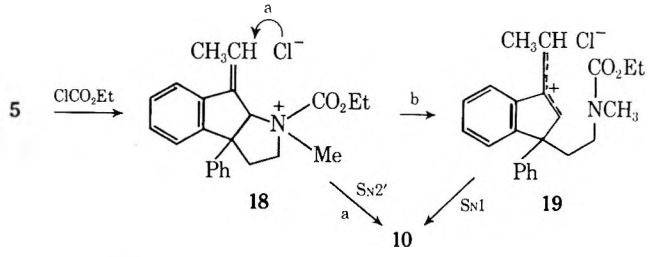


Reaction of 5 with Ethyl Chloroformate.—Chloroformates[4] are well known for their ability to cleave tertiary aliphatic and alicyclic amines to the corresponding dialkyl carbamates *via* the intermediate **17**. The alkyl group that forms the most stable carbonium ion is cleaved.[9]

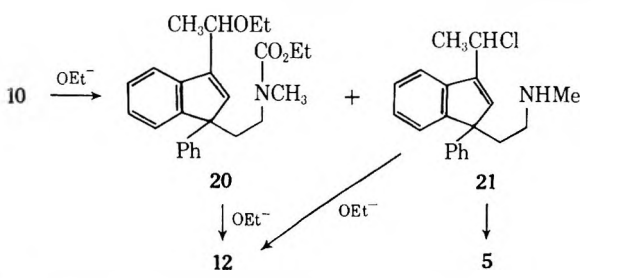


17

In the reaction of **5** with ethyl chloroformate, the chloride ion attacks the allylic carbon atom rather than the *N*-methyl carbon atom. This ring-opening reaction may occur by an S_N2' process (route a), by synchronous displacement of the amino function to give **10**. Alternatively, C–N bond breaking may occur first (S_N1, route b) to afford a resonance-stabilized allylic carbonium ion **19**, which then adds chloride ion.



Hydrolysis of 10.—On refluxing an ethanolic potassium hydroxide solution of **10**, two competing reactions occur. Direct bimolecular displacement of halogen by ethoxide ion yields the intermediate **20**, which hydrolyzes further to **12**. Hydrolysis of the carbamate function before displacement of halogen, however, affords **21**, which then either undergoes intramolecular cyclization to **5** or forms **12** by reaction with ethoxide ion.



(8) K. W. Bentley, "Isoquinoline Alkaloids," 1st ed, Pergamon Press, London, 1965, p 173.

(9) W. B. Wirght, Jr., and H. J. Brabander, *J. Org. Chem.*, **26**, 4057 (1961).

Experimental Section[10]

1,1- and 1,3-Bis(2-dimethylaminoethyl)-3-phenylindene (1 and 4).—A solution of 3-phenylindene[11] (64 g, 0.33 mol) in dry benzene (250 ml) was stirred and refluxed with sodium amide (15.6 g, 0.4 mol) for 1 hr. A solution of 2-dimethylaminoethyl chloride (43 g, 0.4 mol) in dry benzene (100 ml) was added dropwise, and the mixture was stirred and refluxed for 1.5 hr. The cooled mixture, after further treatment with sodium amide (0.4 mol) and 2-dimethylaminoethyl chloride (0.4 mol) as described above, was stirred overnight at 25°. Water was added dropwise to the stirred mixture and the benzene layer was separated, washed with water, and extracted several times with 3 *N* HCl. The combined acid extracts were washed with benzene and made basic with NaOH. The precipitated oil was extracted with ether, washed with water, and dried (anhydrous K_2CO_3) to give a yellow oil (93 g), showing three spots on tlc on silica gel/DMF–ethanol–hexane (3:1:1) at R_f values 0.15, 0.40, and 0.75. The products were separated by the method of Ganellin, Loynes, and Ansell,[2] to afford pure 1-(2-dimethylaminoethyl)-1-phenylindene hydrochloride (21%), **1** dihydrochloride (11%), and **4** dihydrochloride (32%).

Pyrolysis of 1,1-Bis(2-dimethylaminoethyl)-3-phenylindene Hydrochloride (1 HCl).—A solution of **1** (5.0 g, 0.0148 mol) and its dihydrochloride salt (6.0 g, 0.0148 mol) in methanol was evaporated, and the residual oil was heated under reduced pressure (water pump) at 270–280° for 10 min. The evolved gas was collected in a Dry Ice trap and converted to its hydrochloride salt to yield trimethylamine hydrochloride (1.55 g, 54%). The pyrolyzed product was dissolved in chloroform and shaken with 10% NaOH solution. The chloroform layer was separated, washed with water, and dried (anhydrous K_2CO_3). The oil obtained by evaporation of the solvent was identified as ***N*-methyl-3-phenylspiro[indene-1,4′-piperidine] (2a)**: R_f 0.4 on silica gel/MeOH–DMF (9:1); nmr ($CDCl_3$) δ 7.2–7.8 (m, 9 H, aromatic), 6.90 (s, 1 H, =CH), 2.8–3.2 (m, 2 H, ring CH), 2.0–2.8 (m, 3 H, ring CH), 2.43 (s, 3 H, NCH_3), 0.7–1.9 (m, 3 H, ring CH). **2a** was converted to its hydrochloride salt (83%), mp 292–294° dec, which crystallized from isopropyl alcohol–isopropyl ether.

Anal. Calcd for $C_{20}H_{22}ClN$: C, 77.02; H, 7.11; Cl, 11.37. Found: C, 77.15; H, 6.98; Cl, 11.21.

Ethyl 3-Phenylspiro[indene-1,4′-piperidine]-1-carboxylate (2b).—A solution of **2a** (17.6 g, 0.064 mol) in benzene (30 ml) was added dropwise with stirring to a hot solution of ethyl chloroformate (21.7 g, 0.2 mol) in benzene (20 ml). A precipitate formed immediately and the reaction mixture became almost solid. After refluxing the mixture for 6 hr, water and ether were added until all the precipitate dissolved. The layers were separated and the organic phase was extracted with 3 *N* HCl, from which a precipitate of **2a** HCl (1.7 g, 8.5%) separated. The organic layer was dried and evaporated to yield 15.4 g (72%) of crude product, which, on crystallization from absolute ethanol, gave 13.6 g (63.5%) of the ethoxycarbonyl derivative **2b**: mp 116–118°; ir absorption (Nujol) 1695 cm^{-1} [NC(=O)OEt]; nmr ($CDCl_3$) δ 7.2–7.8 (m, 9 H, aromatic), 6.85 (s, 1 H, =CH), 4.2 (q, 2 H, OCH_2, J = 7 Hz), 4.0–4.5 (m, 2 H, ring CH), 1.1–3.5 (m, 6 H, ring CH), 1.30 (t, 3 H, CCH_3, J = 7 Hz).

Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; O, 9.60. Found: C, 79.55; H, 6.55; O, 9.90.

3-Phenylspiro[indene-1,4′-piperidine] Hydrochloride Monohydrate (2c HCl).—A solution of the ethoxycarbonyl derivative **2b** (12.5 g, 0.038 mol) in 95% ethanol (80 ml) containing KOH (50 g) was refluxed under nitrogen for 10 hr. The mixture was diluted with water, concentrated under reduced pressure to remove ethanol, and extracted with ether. On shaking the ethereal extract with 2 *N* HCl, a precipitate formed. This solid (10.3 g), mp 220–223°, was filtered off and crystallized from 95% ethanol to yield 9.2 g (76%) of **2c** HCl monohydrate.

(10) Nmr spectra were recorded on a Varian A-60 spectrometer with tetramethylsilane as the internal standard. Ir spectra were obtained on a Beckman IR-9 spectrometer. Mass spectra were recorded at 70 eV using a direct inlet system on a Consolidated Electrodynamics CEC Model 21104 instrument. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected.

(11) K. N. Campbell, U. S. Patent 2,884,456 (1959); *Chem. Abstr.*, **53**, 18931C (1959).

Anal. Calcd for $C_{19}H_{22}ClNO$: C, 72.25; H, 7.02; Cl, 11.23; H_2O, 5.71. Found: C, 72.52; H, 7.30; Cl, 10.98; H_2O, 6.1.

2c (free base): ir absorption (Nujol) 3275 cm^{-1} (NH); nmr ($CDCl_3$) δ 7.1–7.8 (m, 9 H, aromatic), 6.95 (s, 1 H, =CH), 2.7–3.3 (m, 4 H, ring CH), 1.7–2.4 (m, 3 H, NH and ring CH), 1.2–1.6 (m, 2 H, ring CH).

1-Methyl-3-phenylspiro[indan-1,4'-piperidine] (3a).—A solution of the indene **2a** (7.1 g, 0.0257 mol) in absolute ethanol (70 ml) was hydrogenated in a Parr apparatus at 60 psi over a 10% palladium-on-carbon catalyst for 1.5 hr. After removal of the catalyst and solvent, the residue (5.8 g) crystallized from heptane to give 3.7 g (52%) of the indan **3a**: mp 105–108°; nmr ($CDCl_3$) δ 6.8–7.5 (m, 9 H, aromatic), 4.36 (t, 1 H, >CH, J = 9 Hz), 2.33 (s, 3 H, NCH_3), 1.4–3.0 (m, 10 H, ring CH).

Anal. Calcd for $C_{20}H_{23}N$: C, 86.59; H, 8.36; N, 5.05. Found: C, 86.33; H, 8.32; N, 4.74.

3-Phenylspiro[indan-1,4'-piperidine] Hydrochloride (3b).—A solution of the indene **2c** (31.3 g, 0.12 mol) in 95% ethanol (100 ml) was hydrogenated in a Parr apparatus at 60 psi over a 10% palladium-on-carbon catalyst for 30 hr. After removal of the catalyst and solvent, the solid residue was dissolved in ether and extracted with 3 *N* HCl (100 ml). The white precipitate that formed in the aqueous layer was collected and crystallized from 95% ethanol to yield 32 g (81%) of the indan **3b** HCl: mp 238–239.5°.

Anal. Calcd for $C_{19}H_{22}ClN$: C, 76.10; H, 7.40; Cl, 11.83. Found: C, 76.17; H, 7.51; Cl, 11.88.

3b (free base): ir absorption (film) at 3340 cm^{-1} (broad, NH); nmr ($CDCl_3$) δ 6.9–7.5 (m, 9 H, aromatic), 4.45 (t, 1 H, >CH, J = 8 Hz), 1.4–3.3 (m, 11 H, NH and ring CH).

Pyrolysis of 1,3-Bis(2-dimethylaminoethyl)-3-phenylindene Hydrochloride (4 HCl).—A solution of **4** (16.7 g, 0.05 mol) and its dihydrochloride salt (20.3 g, 0.05 mol) in methanol was concentrated to an oil, which was heated under reduced pressure (water pump) at 270–280° for 10 min. Volatile material, that collected in a Dry Ice trap, was identified as trimethylamine by converting it to its hydrochloride salt (3.2 g, 38%). The nonvolatile residue, dissolved in 3 *N* HCl, was converted to the free base with NaOH and extracted with ether to yield a yellow oil (23 g). Tlc of the oil on silica gel/methanol–DMF (9:1) showed at least four spots at R_f 0.8, 0.6, 0.5, and close to the origin. The oil was chromatographed on silica gel (600 ml).

Elution with ether–petroleum ether (1:3) gave a single product (9.5 g), R_f 0.8, identified by nmr (Table I) as a 70:30 mixture of isomers of **8-ethylidene-1,2,3,3a,8,8a-hexahydro-1-methyl-3a-phenylindeno[2,1-*b*]pyrrole (5)**. The mass spectrum showed a molecular ion at *m/e* 275, a M + 1^+ peak at 276, and abundant peaks at *m/e* 246, 232, 219, 218 (base peak), 217, 216, 215, 203, 202, and 44. The free base, in boiling methanol, formed a mucate monohydrate salt, mp 162–164°, which crystallized from methanol–isopropyl ether as a 85:15 mixture of isomers.

Anal. Calcd for $C_{23}H_{28}NO_5$: C, 70.52; H, 6.86; N, 3.78. Found: C, 70.50; H, 6.85; N, 3.53.

Repeated recrystallizations of **5** picrate from ethanol afforded the pure major isomer, mp 198–200°, which was converted to **5** hydrochloride monohydrate, mp 149.5–159°.

Elution with ether–petroleum ether (1:1) gave a yellow oil (3.1 g), R_f 0.6 and 0.5, which was converted to its hydrochloride salt and crystallized several times from acetone to yield 1.8 g (9.5%) of 1-(2-dimethylaminoethyl)-3-methyl-1-phenylindene hydrochloride[12] (6 HCl): R_f 0.5; mp and mmp 197–199°. The other components of the mixture were not identified.

Hydrogenation of 5 HCl. A.—A solution of **5** hydrochloride 3.15 g, 0.02 mol) in ethanol was hydrogenated in a Parr apparatus at 50 psi over a 10% palladium-on-carbon catalyst. After removal of the catalyst and solvent, the residue crystallized from acetone–isopropyl ether to yield 2.6 g (84%) of **8-ethyl-1,2,3,3a,8,8a-hexahydro-1-methyl-3a-phenylindeno[2,1-*b*]pyrrole hydrochloride (8 HCl)**: mp 154–160°; nmr ($CDCl_3$) δ 3.0 (d, J = 4 Hz) and 2.6 (d, J = 4 Hz) due to *N*-methyl protons indicates a 50:50 mixture of isomers. **8** (free base): bp 143–146° (0.1 mm); nmr (CCl_4) δ 7.0–7.4 (m, 9 H, aromatic), 2.4–3.2 (m, 6 H, >CH, NCH<, NCH_2), 2.35 (s, 3 H, NCH_3), 0.7–1.7 (m, 5 H, CH_2CH_3). The mass spectrum showed a molecular ion at *m/e* 277, a M + 1^+ peak at 278, and abundant peaks at *m/e* 220, 205, 192, 191, 172, 159, 158, 144, 91, 58, 57, 44 (base peak), and 42.

(12) H. Ueberwasser, U. S. Patent 2,798,888 (1957); *Chem. Abstr.*, **52**, 1261 (1958).

Anal. Calcd for $C_{20}H_{23}N$: C, 86.60; H, 8.35; N, 5.05. Found: C, 86.55; H, 8.24; N, 4.99.

B.—The same 50:50 mixture of isomers was obtained by hydrogenation of the pure major isomer of **5** as described above.

Photolysis of 5 HCl.—A solution of **5** hydrochloride (0.2 g, 95:5 isomer mixture) in isopropyl alcohol (25 ml) was irradiated with a short-wave uv lamp UVS-11 for 60 hr. After evaporation of the solvent, the residue was converted to the free base with NaOH. Nmr showed the product to be a 65:35 mixture of the isomers.

Reaction of 5 with Ethyl Chloroformate.—A solution of **5** (5.5 g, 0.02 mol) (85:15 mixture of isomers), in dry benzene (25 ml), was added slowly to a boiling solution of ethyl chloroformate (6.5 g, 0.06 mol) in benzene (15 ml). The solution, after being refluxed for 18 hr, was cooled and washed with 3 *N* HCl and water. The dried ($MgSO_4$) solution was concentrated to a pale yellow oil (7.5 g), identified as **3-(1-chloroethyl)-1-(2-ethoxycarbonylmethylamino)-1-phenylindene (10)**: R_f 0.4 by tlc on silica gel/chloroform; ir absorption (film) at 1695 cm^{-1} [C(=O)]; nmr (CCl_4) δ 7.0–7.6 (m, 9 H, aromatic), 6.55 (s, 1 H, =CH), 5.15 (q, 1 H, *tert*-CH, J = 7 Hz), 4.1 (q, 2 H, OCH_2, J = 7 Hz), 2.1–3.5 (m, 4 H, CH_2), 2.75 (s, 3 H, NCH_3), 1.95 (d, 3 H, $=CCH_3$, J = 7 Hz), 1.2 (t, 3 H, CCH_3, J = 7 Hz).

Anal. Calcd for $C_{23}H_{26}ClNO_2$: C, 71.97; H, 6.83; Cl, 9.23; N, 3.65. Found: C, 72.19; H, 6.74; Cl, 9.33; N, 3.65.

Hydrolysis of 10.—A solution of the carbamate (5.2 g, 0.0136 mol) and KOH (11.2 g, 0.2 mol) in 95% ethanol (30 ml) was refluxed under nitrogen for 36 hr. The cooled solution was diluted with water and extracted with ether. Basic material was extracted from the ether with 3 *N* HCl. Product was isolated by basifying the acid solution with 10% NaOH, followed by extraction of the precipitated oil with ether. The ether solution was washed with water, dried (anhydrous K_2CO_3), and concentrated to a yellow oil (3.9 g), which showed spots at R_f 0.8 and 0.35 by tlc on silica gel/methanol–DMF (9:1). The products were separated by column chromatography on silica gel.

Elution with ether–petroleum ether (1:2) gave 1.60 g (43%) of a colorless oil: R_f 0.8; ir and nmr spectra identical with **5**. The nmr spectrum indicated a 65:35 mixture of isomers.

Elution with ether and ether–methanol yielded 2.2 g (50.5%) of **3-(1-ethoxyethyl)-1-(2-methylaminoethyl)-1-phenylindene (12)** as a colorless oil: ir absorption (film) at 3300 (broad, NH), 1100 and 1170 cm^{-1} (COC); nmr ($CDCl_3$) δ 7.1–7.7 (m, 9 H, aromatic), 6.40 (s, 1 H, =CH), 4.60 (q, 1 H, OCH, J = 7 Hz), 3.52 (q, 2 H, OCH_2, J = 7 Hz), 2.3–2.8 (m, 4 H, CH_2CH_2N), 2.30 (s, 3 H, NCH_3), 2.03 (s, 1 H, NH), 1.55 (d, 3 H, $=CCH_3$, J = 7 Hz), 1.22 (t, 3 H, CCH_3, J = 7 Hz). **12** oxalate crystallized readily from isopropyl alcohol, mp 183–184°.

Anal. Calcd for $C_{24}H_{29}NO_6$: C, 70.05; H, 7.10; N, 3.40. Found: C, 70.07; H, 7.02; N, 3.34.

12 hydrochloride, mp 164–166°, crystallized slowly from acetone–isopropyl ether.

N-Demethylation of 8 with Ethyl Chloroformate.—A solution of **8** (2.89 g, 0.01 mol) in dry benzene (20 ml) was added dropwise with stirring to a hot solution of ethyl chloroformate (3.3 g, 0.03 mol) in benzene (5 ml). After refluxing the mixture for 24 hr, solvent and excess ethyl chloroformate were removed under reduced pressure. A solution of the residual oil in ether was washed with 3 *N* HCl and water. The dried ($MgSO_4$) ether solution was concentrated under vacuum to a pale yellow oil (3.2 g): ir absorption (film) at 1700 cm^{-1} [NC(=O)OEt]; nmr ($CDCl_3$) δ 6.9–7.5 (m, 9 H, aromatic), 4.20 (q, 2 H, OCH_2, J = 7 Hz), 2.0–3.7 (m, 6 H, >CH, NCH< and ring CH), 1.1–1.7 (m, 5 H, $OCCH_3$, CH_2), 0.90 (t, 3 H, CCH_3, J = 7 Hz).

A solution of the oil in 95% ethanol (25 ml), containing KOH (9 g, 0.15 mol), was refluxed under nitrogen for 48 hr. The mixture was cooled, diluted with water, and extracted with ether. Basic material was isolated by extraction of the ether solution with 3 *N* HCl, basification of the acid extract with 10% NaOH, and extraction of the precipitated oil with ether. Concentration of the dried (anhydrous K_2CO_3) ether solution gave a colorless oil (2.3 g) identified as **8-ethyl-1,2,3,3a,8,8a-hexahydro-3a-phenylindeno[2.1-*b*]pyrrole (15)**: ir absorption (film) at 3300 cm^{-1} (broad, NH); nmr ($CDCl_3$ δ 7.0–7.6 (m, 9 H, aromatic), 3.73 (broad, 1 H, NCH<), 2.0–3.4 (m, 6 H, ring CH and NH), 1.1–1.8 (m, 2 H, CH_2C), 0.97 (t, 3 H, CCH_3, J = 7 Hz). Compound **15** formed a hydrochloride salt, mp 200–203°, which crystallized from acetone–isopropyl ether.

Anal. Calcd for $C_{19}H_{22}ClN$: C, 76.08; H, 7.30; N, 4.67. Found: C, 76.08; H, 7.33; N, 4.81.

Registry No.—2a, 27415-49-2; 2a HCl, 27415-50-5; 2b, 27371-44-4; 2c, 27415-51-6; 2c HCl, 27415-52-7; 3a, 27371-45-5; 3b, 27415-53-8; 3b HCl, 27415-54-9; 5a, 27390-80-3; 5a $^1/_2$-mucate, 27425-33-8; 5a HCl, 27390-81-4; 5b, 27390-82-5; 5b $^1/_2$-mucate, 27494-97-9; *cis,cis*-8, 27390-83-6; *cis,cis*-8 HCl, 27390-84-7; *cis,trans*-8, 27390-85-8; *cis,trans*-8 HCl, 27390-86-9; 10, 27371-46-6; 12, 27371-47-7; 12 oxalate, 27371-48-8; 12 HCl, 27371-49-9; 15, 27415-55-0; 15 HCl, 27415-56-1.

High Pressure Studies. VI. Polar Effects in Decomposition of Substituted *tert*-Butyl Phenylperacetates in Solution[1,2]

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The pressure dependences of the rates of thermal decomposition of the *m*-Cl-, *p*-Cl-, H-, *p*-CH_3-, and *p*-CH_3O-substituted *tert*-butyl phenylperacetates in cumene have been determined. The observed decomposition activation volumes are lower than expected for two-bond homolytic scission reactions and are also pressure dependent. The values of ΔV^*_{obsd} are concluded to be a composite of contributions from bond stretching and solvation of a polar transition state. The data indicate that the polarity of the transition states varies with substituent and also that the pressure dependence of the values of ΔV^*_{obsd} probably resides in the pressure dependence of solvent compressibility.

Activation volumes[3] for homolytic scission reactions in which the primary radical pair cannot return to starting material reflect the pressure dependence of the bond breaking process.[1a,3b,4] Examples of general systems which would be expected to fit this category are azo compounds and peresters, which decompose *via* simultaneous two-bond scission (eq 1 and 2). Activation

$$RN{=}NR \longrightarrow \overline{R\cdot\ N_2\ \cdot R} \qquad (1)$$

$$RCO_2OR' \longrightarrow \overline{R\cdot\ CO_2\ \cdot OR'} \qquad (2)$$

volumes for representative cases (Table I) seem to fall

TABLE I

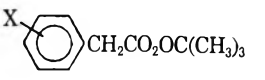
SOME ACTIVATION VOLUMES FOR HOMOLYTIC SCISSION[a]

Compd	T, °C	ΔV^*, cc/mol	Ref
$C_6H_{11}CO_3C(CH_3)_3$	79.6	+3.9	3b, 5a
$(CH_3)_3CON{=}NOC(CH_3)_3$	55.0	+4.3	1a
$C_6H_5C(CH_3)_2N{=}NC(CH_3)_2C_6H_5$	55.0	+4.9	*b*
$NCC(CH_3)_2N{=}NC(CH_3)_2CN$	70.0[c]	+4.0	6

[a] Cumene solvent. [b] R. Neuman and M. Amrich, unpublished results. [c] Toluene solvent.

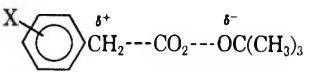
within the range of +4 to +5 cc/mol, and they are relatively constant over a range of several thousand atmospheres.[1a,3b,5,6]

The ring-substituted *tert*-butyl phenylperacetates (**1**) are also thought to decompose by two-bond scission[7,8]



1

and would be expected to show similar behavior in pressure studies. However, we have previously reported that the low pressure activation volume for *tert*-butyl phenylperacetate (**1**, X = H) while positive is significantly lower (+0.5 cc/mol) than those for the compounds in Table I and is pressure dependent.[3b] We have suggested[3b,5] that this is due to the polar character of the homolytic scission transition state **2**.[7b] Formation of such a transition state should lead to an increase in solvent organization over that for the reactant. Such a process would be facilitated by pressure ($\Delta V^*_{solv} < 0$) and might be expected to partially compensate for the positive activation volume associated with bond stretching.[9]



2

We now report the effect of ring substitution on the pressure dependence of the decomposition rates of *tert*-butyl phenylperacetate. The data are in agreement with the general conclusions previously outlined for the unsubstituted perester.[3b] Additionally they suggest that transition state polarity **2** varies with substituent, and they also provide a basis for explaining the pressure dependence of the observed activation volumes.

(1) (a) Part V: R. C. Neuman, Jr., and R. J. Bussey, *J. Amer. Chem. Soc.*, **92**, 2440 (1970). (b) Support by the National Science Foundation (GP-4287, 7349, and 8670) is gratefully acknowledged.

(2) Taken from the Ph.D Dissertation of J. V. Behar, University of California, Riverside, 1969.

(3) (a) Activation volumes are related to the pressure dependence of reaction rate constants according to the equation $\partial \ln k/\partial P = -\Delta V^*/RT$. A detailed list of reviews has been presented.[3b] (b) See R. C. Neuman, Jr., and J. V. Behar, *J. Amer. Chem. Soc.*, **91**, 6024 (1969).

(4) For the general scheme for homolytic scission reactions, the observed

$$\text{initiator} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{geminate radicals} \xrightarrow{k_d} \text{free radicals}$$

decomposition rate constant is given by the equation $k_{obsd} = k_1/(1 + k_{-1}/k_d)$. The quantity $k_{obsd} = k_1$ (and $\Delta V^*_{obsd} = \Delta V^*_1$) only when the geminate radicals cannot recombine to regenerate initiator ($k_{-1} = 0$).[1a,3b]

(5) (a) R. C. Neuman, Jr., and J. V. Behar, *Tetrahedron Lett.*, 3281 (1968); (b) *J. Amer. Chem. Soc.*, **89**, 4549 (1967).

(6) A. H. Ewald, *Discuss. Faraday Soc.*, **22**, 138 (1956).

(7) (a) On the basis of kinetic and product data for these[7b] and other peresters,[7c] Bartlett concluded that the peresters **1** decompose by simultaneous two-bond scission (eq 2). (b) P. D. Bartlett and C. Rüchardt, *J. Amer. Chem. Soc.*, **82**, 1756 (1960). (c) P. D. Bartlett and R. R. Hiatt, *ibid.*, **80**, 1398 (1958).

(8) For leading references to Bartlett's studies of peresters, see J. P. Lorand and P. D. Bartlett, *ibid.*, **88**, 3294 (1966).

(9) (a) Activation volumes expected for solvation or solvent electrostriction are reviewed by W. J. LeNoble, *Progr. Phys. Org. Chem.*, **5**, 207 (1967); (b) see also M. G. Evans and M. Polanyi, *Trans. Faraday Soc.*, **31**, 375 (1935).

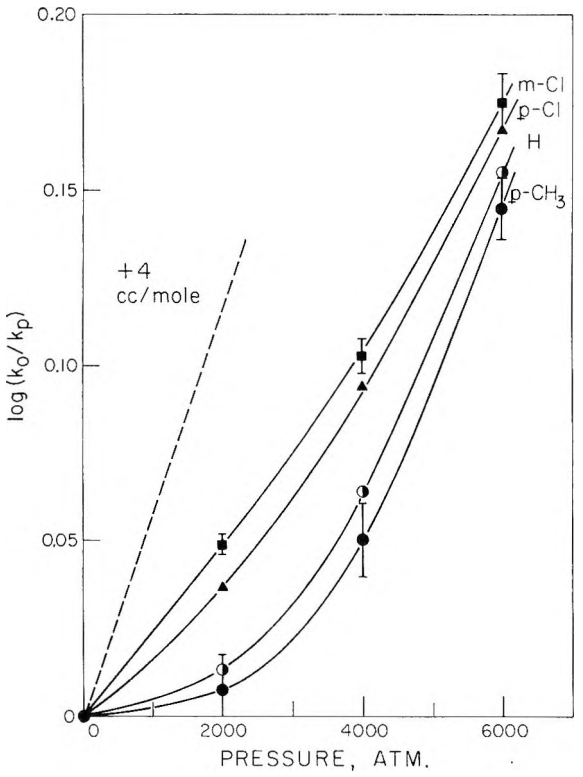


Figure 1.—Pressure dependence of the decomposition rate constants for the *m*-Cl- (■), *p*-Cl- (▲), H- (◐), and *p*-CH_3- (●) substituted *tert*-butyl phenylperacetates (cumene, 79.6°).

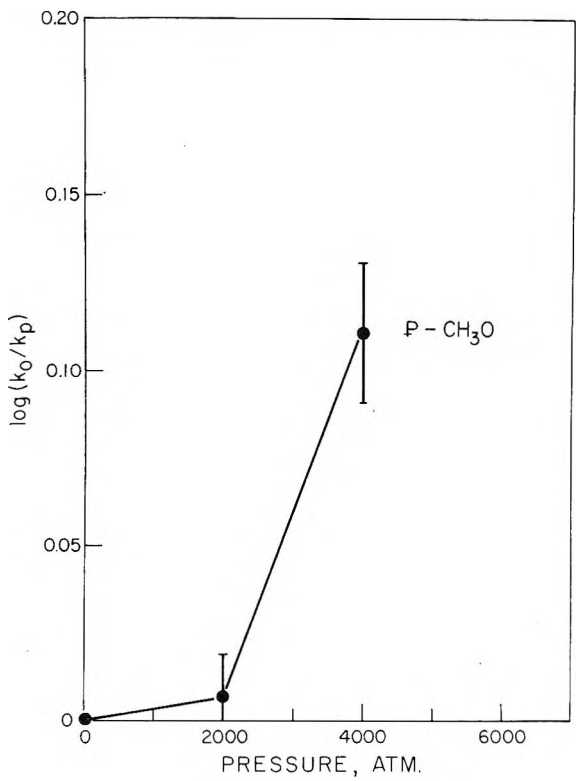


Figure 2.—Pressure dependence of the decomposition rate constant for *tert*-butyl *p*-methoxyphenylperacetate (cumene, 60.0°).

Results and Discussion

The rate constants for decomposition of 0.1 *M* cumene solutions of the *m*-Cl- (**1a**), *p*-Cl- (**1b**), H- (**1c**), *p*-CH_3- (**1d**), and *p*-MeO- (**1e**) substituted *tert*-butyl phenylperacetates at several pressures are given in Table II. Each high-pressure rate constant was determined using at least five sets of duplicate kinetic points and the errors shown are standard deviations arising from a least-squares analysis of all of the data for a perester at a given pressure. Each *kinetic point* for a high-pressure rate constant represents a separate experiment (see Experimental Section). The rates were determined by monitoring the decrease of the perester carbonyl band (1783 cm^{-1}) in the infrared. Most of the data were gathered at 79.6°; however, the rapid decomposition rate precluded high pressure studies of **1e** at this temperature and these data were obtained at 60.0°.[10]

The pressure dependences of log *k* for each of the peresters (Figures 1 and 2) are somewhat different from each other, and all give low-pressure activation volumes significantly less than +4 cc/mol (see Table II). Error bars are shown in Figure 1 for the top curve (*m*-Cl) and for the bottom curve (*p*-CH_3). While these are rather large, it is clear that the pressure dependence plots of the decomposition rate constants for the *m*-Cl- and *p*-CH_3-substituted peresters are different; the former is relatively linear while the latter shows distinct curvature. These two substituents possess the extreme val-

TABLE II

RATE CONSTANTS FOR DECOMPOSITION OF SUBSTITUTED *tert*-BUTYL PHENYLPERACETATES AS A FUNCTION OF PRESSURE (CUMENE, 79.6°)

Perester[a]	σ^{+}[b]	Pressure, atm	$k \times 10^4$, sec^{-1}	ΔV^{*},[c] cc/mol
1a, *m*-Cl	+0.399	1	0.298 ± 0.001	
		2000	0.266 ± 0.001	1.6
		4000	0.235 ± 0.002	1.8
		6000	0.199 ± 0.003	2.4
1b, *p*-Cl	+0.114	1	0.654 ± 0.010	
		2000	0.601 ± 0.006	1.2
		4000	0.527 ± 0.008	1.9
		6000	0.445 ± 0.007	2.5
1c, H	0.0	1	0.677 ± 0.004	
		2000	0.657 ± 0.002	0.4
		4000	0.584 ± 0.006	1.7
		6000	0.474 ± 0.004	3.0
1d, *p*-CH_3	−0.311	1	1.649 ± 0.022	
		2000	1.622 ± 0.019	0.2
		4000	1.469 ± 0.015	1.4
		6000	1.180 ± 0.008	3.2
1e, *p*-OMe	−0.778	1	5.942 ± 0.039	
		1	0.685 ± 0.010[d]	
		2000	0.675 ± 0.007[d]	0.2
		4000	0.531 ± 0.017[d]	3.5

[a] 0.1 *M* in cumene. [b] σ^{+} substituent constants for the ring substituents; see J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 204. [c] Obtained from the slope of the line connecting the data points at pressures *P* and *P* + 2000. [d] 60.0°.

(10) (a) It is unlikely that these rate constants contain contributions from induced decomposition. While Bartlett noted that a small amount of induced decomposition may have been present in studies of the peresters **1** at relatively high concentration in chlorobenzene, the use of cumene[10b] and the lower concentration used in these studies should have precluded such problems. Decomposition rates for **1c** are higher in chlorobenzene than in cumene; however, the apparent decomposition activation volumes are very similar.[3b,5b] A previous pressure study in which induced decomposition was proposed showed a dramatic rate increase at high pressures, a result quite contrary to those found here.[10c] (b) See P. D. Bartlett and J. M. McBride, *J. Amer. Chem. Soc.*, **87**, 1727 (1965). (c) C. Walling, H. N. Moulden, J. H. Waters, and R. C. Neuman, Jr., *ibid.*, **87**, 518 (1965).

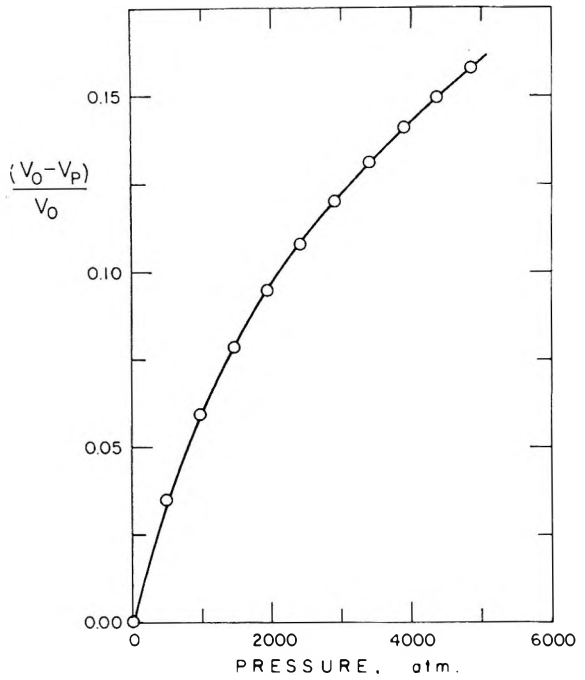


Figure 3.—Effect of pressure on the volume of cumene at "room temperature" (see text).

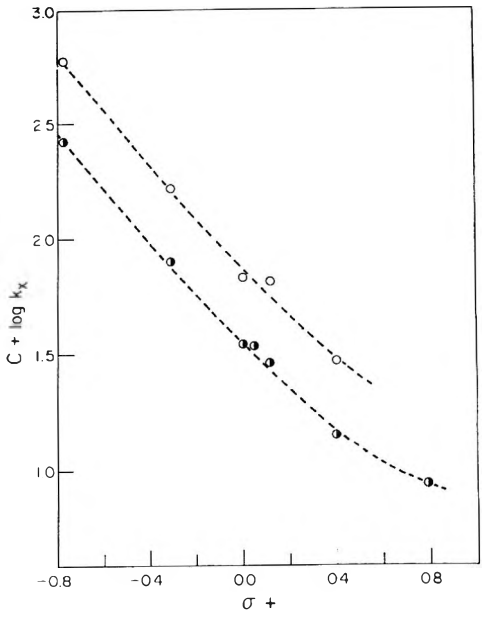


Figure 4.—Plot of log k_x at atmospheric pressure *vs.* σ^+ for the variously substituted *tert*-butyl phenylperacetates in cumene at 79.6° ($C = 5$) (○) and chlorobenzene (Bartlett, see text) at 90.7° ($C = 5$) (◑).

ues of σ^+ (Table II) *among those represented in Figure 1*, and the evident trends in these plots are an increase in curvature and a decrease in initial slope as σ^+ decreases.

The observed decomposition activation volumes can be thought of as the resultant of separate contributions for bond stretching (ΔV^*_{bond}) and solvation changes (ΔV^*_{solv}) (eq 3).[9b] If it is assumed that ΔV^*_{bond}

$$\Delta V^*_{obsd} = \Delta V^*_{bond} + \Delta V^*_{solv} \quad (3)$$

can be approximated by the observed decomposition activation volumes in Table I, *e.g.*, +4 cc/mol, the low pressure values for ΔV^*_{solv} (units of cc/mol) would be −2.4 (*m*-Cl), −2.8 (*p*-Cl), −3.6 (H), and −3.8 (*p*-CH_3).[11,12] The negative signs of these numbers support a transition state 2 more polar than the reactant, and their magnitudes increase as the electron-donating ability (as measured by σ^+) of the substituent group increases.[13] This trend suggests that the amount of polar character in the transition state increases as the substituents become better able to stabilize electron deficiency on the benzylic carbon (see 2).

The activation volumes for those systems in Table I used as models for ΔV^*_{bond} are pressure independent.[1a,3b,5,6] The increasing slopes of the log *k vs. P* plots (*i.e.*, increasing values of ΔV^*_{obsd}) for the *tert*-butyl phenylperacetates (Figures 1 and 2) thus suggest that the magnitudes of the quantities ΔV^*_{solv} decrease with increasing pressure. The solvation activation volumes (ΔV^*_{solv}) reflect the solvent's response to a change in polarity between the reactant and transition state. This response should depend on the solvent's compressibility (χ_T) (eq 4),[14] and it seems reasonable

$$\chi_T = (-1/V_o)(\partial V/\partial P)_T \quad (4)$$

that a decrease in χ_T would lead to a smaller value of ΔV^*_{solv}. The compressibility of cumene at "room temperature" is given by the slope of the plot in Figure 3.[15] Its decrease with pressure thus provides a rationale for the observed decreases in the magnitudes of ΔV^*_{solv} with pressure.

The variation in ΔV^*_{solv} with pressure should be most noticeable in those systems with the greatest transition state polarity. In agreement, the pressure dependence of ΔV^*_{obsd} is greatest for *tert*-butyl *p*-methoxyphenylperacetate (**1e**) (Figure 2).[16] However, the low pressure value of ΔV^*_{obsd} for this system rather than being lower is about the same as that for *tert*-butyl *p*-methylphenylperacetate (**1d**) (Table II). This discrepancy may be due to the 20° temperature differential between the decomposition temperatures for **1d** and **1e**. Compressibility decreases as temperature is decreased and the values of χ_T at each pressure for cumene at 60° would be lower than at 79.6°. These differences in compressibility are in the correct direction to explain the larger values of ΔV^*_{obsd} (smaller values of ΔV^*_{solv}) for **1e** than expected.

Plots of the decomposition rates at atmospheric pressure *vs.* σ^+ are shown in Figure 4. The data using chlorobenzene (90.7°) are those of Bartlett[7b] and those using cumene (79.6°) are taken from Table II. In calculating an apparent ρ value of *ca.* −1.1, Bartlett excluded the data point for the *p*-nitro-substituted perester, and our data also give essentially the same apparent ρ value.

(11) The assumption that ΔV^*_{bond} can be approximated by the values in Table I is based on the presumed absence of transition state polarity for those compounds and the similarity of their values of ΔV^*_{obsd} in spite of their structual differences.

(12) The "low pressure" values of ΔV^*_{solv} were obtained using the equation $\Delta V^*_{solv} = \Delta V^*_{0,2000} - \Delta V^*_{bond}$ (see Table II).

(13) Negative activation volumes indicate a contraction of the system on proceeding from reactants to the transition state.

(14) See W. A. Steele and W. Webb, "High Pressure Physics and Chemistry," Vol. 1, R. S. Bradley, Ed., Academic Press, New York, N. Y., Chapter 4i.

(15) P. W. Bridgman, "Collected Experimental Papers," Vol. VI, Harvard University Press, Cambridge, Mass., 1964, pp 3915–3931.

(16) A determination of the decomposition rate for **1e** at 6000 atm (60°) was in progress when the high pressure apparatus failed. The apparatus had to be dismantled and overhauled precluding further studies on these systems by Dr. Behar.

However, in view of the proposals made to explain the variable pressure results (*vide supra*), the Hammett relationship should not rigorously apply to any of these data. If this constraint is removed, the *p*-nitro point need not be interpreted as an abnormally fast rate for this substituted perester.[7b] Rather, the upward curvature in the plot of Bartlett's data *including the latter point* can be interpreted as a reflection of both the increasing polar character and solvation of the transition state with an increase in electron-donating ability of the substituent (*vide supra*).

Based on our limited high pressure data at 79.6° (cumene solvent) for the *p*-CH_3, H, *p*-Cl, and *m*-Cl peresters, the *apparent* ρ value is pressure insensitive (*ca.* −1.1). This is not surprising in view of the small variation in the rate constants with pressure and the narrow range of σ^+ covered by these substituents. However, this result does indicate that no *major* mechanism variations occurred at high pressure.[17]

A small inverse viscosity dependence of the decomposition rate for **1c** at atmospheric pressure had led to the suggestion that its decomposition mechanism involves both one-bond (O–O) and concerted two-bond (C–C and O–O, eq 2) scission processes.[18] The rates of decomposition of **1d** and **1e** were viscosity invariant.[18] However, observed activation volumes of +7 to +10 cc/mol for authentic one-bond scission peresters[19] indicate that those of the peresters **1** are too small to be consistent with such a mechanism.[3b] Additionally, the similarity in the plots for **1c** and **1d** (Figure 1) precludes the gross mechanistic variation implied by the comparative viscosity results. All other observations support the two-bond scission mechanisms.[20]

(17) (a) The reaction products from decomposition of the substituted peresters are analogous to those formed from *tert*-butyl phenylperacetate,[3b] and their relative yields show the expected dependence on pressure.[17b] (b) R. C. Neuman, Jr., and J. V. Behar, *J. Org. Chem.*, **36**, 657 (1971), accompanying paper.

(18) (a) W. A. Pryor and K. Smith, *Intra-Sci. Chem. Rep.*, **3**, 255 (1969); (b) *J. Amer. Chem. Soc.*, **92**, 5403 (1970).

(19) (a) These data were obtained from a study of *tert*-butyl perbenzoate in cumene[3b] and from a study of the cis and trans isomers of *tert*-butyl 2-propyl-2-peroxypentenoate in cumene.[19b] (b) R. C. Neuman, Jr., and G. D. Holmes, unpublished results.

(20) (a) T. Koenig and R. Wolf, *J. Amer. Chem. Soc.*, **91**, 2574 (1969); (b) T. Koenig, J. Huntington, and R. Cruthoff, *ibid.*, **92**, 5413 (1970).

Experimental Section

Perester Syntheses.—The substituted *tert*-butyl phenylperacetates were synthesized from the corresponding phenylacetyl chlorides and *tert*-butyl hydroperoxide.[3b,7b] The acid chlorides and *tert*-butyl hydroperoxide were distilled prior to their use. All peresters showed a carbonyl absorption in the infrared at 1783 cm^{-1}.

Attempts at iodometric titration of the peresters gave widely varying results on portions of the same sample. Samples were rechromatographed until their infrared spectra were free of extraneous carbonyl bands as well as any OH absorption. In addition, infrared spectra of completely decomposed samples (infinite time samples) in cumene exhibited only solvent absorption bands in the carbonyl stretching frequency region, indicating the absence of any contaminating carbonyl containing species among the decomposition products. The peresters were crystalline solids and decomposition rate constants did not vary for different samples of the same perester. All peresters were stored at low temperature.

High Pressure Apparatus and Kinetic Studies.—A complete description of the apparatus and experimental techniques has been presented.[3b] Kinetic runs and the data analysis were carried out following the procedures reported for unsubstituted *tert*-butyl phenylperacetate.[3b] Each kinetic point represented a separate pressure experiment.[3b]

Registry No.—**1a**, 27396-17-4; **1b**, 27396-18-5; **1c**, 3377-89-7; **1d**, 27396-20-9; **1e**, 27396-21-0.

High Pressure Studies. VII. The Pressure Dependence of Cage Effects. Products from Substituted *tert*-Butyl Phenylperacetates[1,2]

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Thermal decompositions of ring-substituted *tert*-butyl phenylperacetates in cumene (79.6°) give the corresponding *tert*-butyl benzyl ethers, toluenes, bibenzyls, benzylcumyls, bicumyl, and *tert*-butyl alcohol as reaction products. The pressure dependences of the ether/*tert*-butyl alcohol ratios give the pressure dependence of the cage effect (combination *vs.* diffusion) for the initially generated geminate benzyl and *tert*-butoxy radicals. The cage effects increase with pressure but not so rapidly as might be expected. An analysis of the trends involving the potential role of the intervening carbon dioxide molecule is outlined. The remaining products reflect the distribution of diffused benzyl radicals, and the pressure dependences of yields indicate that a major source of the toluenes involves hydrogen abstraction by the benzyl radicals from the solvent cumene.

We have been investigating the effects of pressure on the rates of free-radical reactions in solution. Studies of homolytic scission reactions have shown that care must be used in interpreting the significance of the observed activation volume (ΔV^*_{obsd}) for decomposition of radical initiators.[1a,3] If the initially formed geminate radicals (eq 1) can return to starting material

$$A\text{–}B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \overline{A\cdot B\cdot} \xrightarrow{k} \qquad (1)$$

(k_{-1}), ΔV^*_{obsd} is not simply related to the activation volume for homolytic scission (ΔV^*_1) but depends as well on the competition between recombination (k_{-1}) and other processes (k) available to the caged pair (eq 2).

$$\Delta V^*_{obsd} = \Delta V^*_1 + RT\partial \ln (1 + k_{-1}/k)/\partial P \qquad (2)$$

(1) (a) Part VI: R. C. Neuman, Jr., and J. V. Behar, *J. Org. Chem.*, **36**, 654 (1971), accompanying paper. (b) Support by the National Science Foundation through Grants GP-4287, 7349, and 8670 is gratefully acknowledged.

(2) Taken from the Ph.D. Dissertation of J. V. Behar, University of California, Riverside, 1969.

(3) R. C. Neuman, Jr., and J. V. Behar, *J. Amer. Chem. Soc.*, **91**, 6024 (1969).

TABLE I

PRODUCT RATIOS FOR SUBSTITUTED *tert*-BUTYL PHENYLPERACETATES (1) IN CUMENE (79.6°)[a]

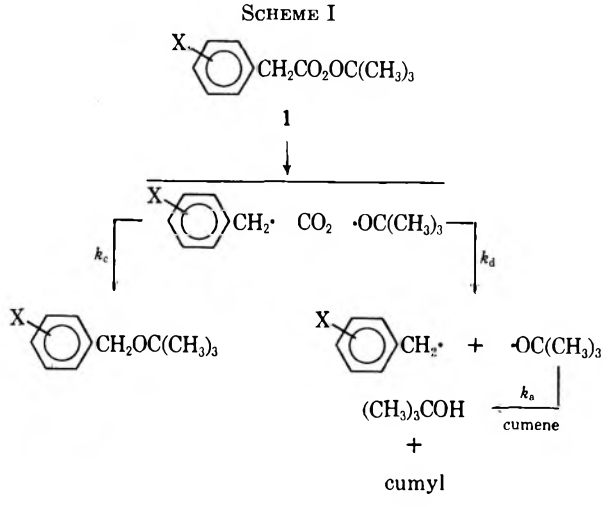
X	P (atm)	% ND[b]	Ether[c]	Toluene	Bibenzyl	Benzylcumyl[d]	Bicumyl
m-Cl	1		0.26	0.19	0.15	(0.28)	0.21
	2000		0.57	0.29	0.14	(0.31)	0.16
	4000	5	0.82 (0.86)	0.32	0.22	(0.30)	0.16
	6000	13	1.04 (1.24)	0.43	0.20	(0.22)	
p-Cl	1		0.26	0.15	(0.4)[e]		
	2000	4	0.69 (0.72)	0.30	(0.4)[e]		
	4000	5	0.79 (0.83)	0.31	(0.3)[e]		
	6000	12	1.15 (1.38)	0.39	(0.3)[e]		
H	1		0.37	0.17	0.19	(0.29)	0.27
	2000		0.78	0.30	0.15	(0.25)	0.30
	4000	4	1.01 (1.05)	0.41	0.11	(0.27)	0.25
	6000	13	1.26 (1.49)	0.49	0.09	(0.37)	0.16
p-CH_3	1		0.33	0.11	(0.5)[e]		0.26
	2000	7	0.64 (0.67)	0.22	(0.3)[e]		0.20
	4000	19	0.84 (1.02)	0.26	(0.3)[e]		0.17
	6000	37	1.18 (2.50)	0.29	(0.4)[e]		0.21
p-OMe	1		0.33[g]	0.04	0.18	(0.24)	0.16
	1[f]		0.38[g]	0.04	0.16	(0.26)	0.15
	2000[f]	11	0.98[g]	0.12	0.13	(0.17)	0.12
	4000[f]	28	1.29[g]	0.18	0.17	(0.31)	0.27
	6000[f]		1.25[g]	0.20	0.13	(0.21)	0.17

[a] Determined by glpc; moles of product divided by moles of *tert*-butyl alcohol. [b] Per cent decomposition under nonequilibrium conditions (see text). [c] Numbers in parentheses are corrected for decomposition during nonequilibrium conditions (see text). [d] Authentic samples were not available; the correction factor used for relative thermal conductivity comparison was the average of those for the bibenzyl and bicumyl; see Experimental Section. [e] Only peak for bibenzyl detected; peak for benzylcumyl assumed to overlap; see Experimental Section. [f] 60.0°. [g] Authentic sample not available; thermal conductivity correction used was average of those for other ethers in this table.

In the simplest case described by eq 1, the rate constant k is that for separative diffusion (k_d). Information about the pressure dependence of such combination–diffusion competitions would thus be helpful in interpretations of values of ΔV^*_{obsd} for systems described by eq 1.

We recently completed a study of the pressure dependence of the decomposition rates and products from ring-substituted *tert*-butyl phenylperacetates (1). These compounds decompose as shown in Scheme I.[4]

SCHEME I



The rate data have been reported and demonstrate variations in ΔV^*_1 when polar effects are important in free-radical reactions.[1a] The product data provide information about the pressure dependence of combination–diffusion competitions as well as about the pathways leading to the formation of the various reaction products subsequent to separative diffusion of the initial geminate radicals.

Results and Discussion

Cumene solutions (*ca.* 0.1 *M*) of the unsubstituted, and *m*-Cl-, *p*-Cl-, *p*-CH_3-, and *p*-OCH_3-substituted *tert*-butyl phenylperacetates (1) were completely decomposed at a thermostated bath temperature of 79.6° at various pressures. The products were analyzed by glpc and the mole ratios of each product relative to *tert*-butyl alcohol are reported in Table I. In these systems, *tert*-butyl alcohol is formed by reaction of diffused *tert*-butoxy radicals with cumene, and the virtual absence of acetone indicates that the reaction is quantitative. Thus, the ether/*tert*-butyl alcohol ratio is a direct measure of the cage effect (Scheme I) and the other ratios (except that for bicumyl) represent the partitioning of the diffused benzyl radicals among the various reaction products.[5]

During the initial phase of each high-pressure decomposition reaction, the sample was subjected to nonequilibrium pressure and temperature conditions. During pressurization of samples, heat is generated in the hydraulic fluid surrounding the reaction vessel due to com-

(4) P. D. Bartlett and C. Rüchardt, *J. Amer. Chem. Soc.*, **82**, 1756 (1960).

(5) Absolute yields were not determined in these studies; however, they appeared to be essentially quantitative in a previous study of unsubstituted *tert*-butyl phenylperacetate.[3] No extraneous peaks were observed in the glpc traces.

pression of the fluid. Temperature equilibration is usually achieved within about 12 min after a run has been started by dissipation of the heat into the walls of the high pressure bomb. This annoying problem can be eliminated in kinetic studies by the choice of an appropriate zero time after equilibration and careful reproduction of the procedures used during pressurization for each subsequent sample.[3] However, it could not be avoided in the product analyses, since products were analyzed by glpc and samples containing unreacted perester could not be accurately analyzed. Thus, the product ratios are composite quantities including the product distributions during both the equilibrium and nonequilibrium portions of each decomposition.

The amount of decomposition of the samples during the nonequilibrium period was estimated by comparing the intensities of the perester carbonyl infrared absorbtions in the master solutions with those of samples withdrawn from the high pressure apparatus after 15 min from initial insertion. The available data are included in Table I and indicate that the product ratios for all systems at 6000 atm, those at 4000 atm for the p-CH_3 and p-CH_3O perester, and those at 2000 atm for the p-CH_3O system may contain significant contributions from nonequilibrium decomposition.

Cage Effect.—The ether/*tert*-butyl alcohol ratios, which represent the competition between combination and separative diffusion of the initial geminate radical pair (Scheme I), increase for each perester with increasing pressure. During the nonequilibrium portion of each run, the mean pressure was lower than that at equilibrium and the temperature was higher (*vide supra*). Since cage effects generally decrease with increasing temperature[6] (compare the data for the p-CH_3O perester at 60 and 79.6°), both features of the nonequilibrium period would tend to lower the cage effect. We have estimated a maximum correction by assuming that the decomposition during the nonequilibrium period of the pressure runs was characterized by an ether/*tert*-butyl alcohol ratio equal to that for the corresponding perester at 1 atm. This leads to the corrected values of ether/*tert*-butyl alcohol shown in Table I.

The values of log (ether/*tert*-butyl alcohol) are plotted as a function of pressure in Figure 1. Both the observed and corrected values at each pressure are included and they are connected by the bars. If the ether/*tert*-butyl alcohol ratios are equal to k_c/k_d (Scheme I), the slopes of the various curves for each perester are directly related to the difference in the activation volumes for diffusion and combination ($\Delta V^*_d - \Delta V^*_c$).[3,7] These differences appear to be pressure dependent and the approximate values are given in Table II.

We have previously reported the effect of pressure on the competition between coupling and diffusion of two geminate *tert*-butoxy radicals generated from di-*tert*-butyl hyponitrite in *n*-octane (45°) (Scheme II).[7] The pressure dependence of the rate constant ratio k_c/k_d (2 × di-*tert*-butyl peroxide/*tert*-butyl alcohol) is qualitatively similar to the perester data, and the values of $\Delta V^*_d - \Delta V^*_c$ decrease with increasing pressure (Table III). The low pressure values of $\Delta V^*_d - \Delta V^*_c$ are

(6) S. F. Nelsen and P. D. Bartlett, *J. Amer. Chem. Soc.*, **88**, 143 (1966).
(7) R. C. Neuman, Jr., and R. J. Bussey, *ibid.*, **92**, 2440 (1970).

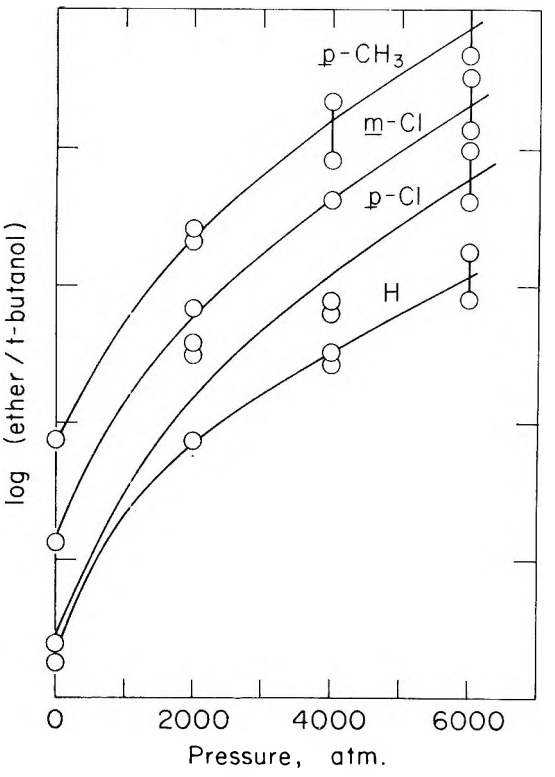


Figure 1.—Pressure dependence of the ether/*tert*-butyl alcohol product ratios. Each division on the vertical axis corresponds to 0.2 log units and the placement of the curves was arbitrary (see Table I).

TABLE II
PRESSURE DEPENDENCE OF VALUES OF $\Delta V^*_d - \Delta V^*_c$ FOR DECOMPOSITION OF *tert*-BUTYL PHENYLPERACETATES IN CUMENE (79.6°)

Pressure range, atm × 10^{-3}	$\Delta V^*_d - \Delta V^*_c$, cc/mol[a]			
	m-Cl	*p*-Cl	H	*p*-CH_3
0–1	+14	+14	+14	+12
1–2	+8	+9	+7	+8
2–3	+6	+7	+5	+6
3–4	+5	+6	+4	+5
4–5	+5	+5	+4	+5
5–6	+4	+5	+4	+4

[a] Calculated from the slopes of chords connecting points on the plots (Figure 1) at the extremes of the pressure ranges indicated in the first column.

SCHEME II

$$(CH_3)_3CON{=}NOC(CH_3)_3 \longrightarrow \overline{(CH_3)_3CO\cdot\ N_2\ \cdot OC(CH_3)_3}$$

$$\overline{(CH_3)_3CO\cdot\ N_2\ \cdot OC(CH_3)_3} \xrightarrow{k_c} (CH_3)_3COOC(CH_3)_3$$

$$\overline{(CH_3)_3CO\cdot\ N_2\ \cdot OC(CH_3)_3} \xrightarrow{k_d} 2(CH_3)_3CO\cdot + N_2$$

significantly larger in the di-*tert*-butyl hyponitrite system; however, it is interesting to note that the low-pressure cage effect is simultaneously much smaller than for the perester systems. When the cage effect for *tert*-butoxy radical combination becomes approximately equal to those at atmospheric pressure for the peresters, the values of $\Delta V^*_d - \Delta V^*_c$ are rather comparable for the two systems (see Table III).

TABLE III
COMPARISON OF THE PRESSURE DEPENDENCES OF THE CAGE EFFECTS AND VALUES OF $\Delta V^*_d - \Delta V^*_c$ FOR DI-*tert*-BUTYL HYPONITRITE AND *tert*-BUTYL *m*-CHLOROPHENYLPERACETATE

	Hyponitrite[a]		Perester[b]	
P,[c] atm	k_c/k_d	$\Delta V^*_d - \Delta V^*_c$, cc/mol	k_c/k_d	$\Delta V^*_d - \Delta V^*_c$, cc/mol
1	0.10		0.26	
1000	0.27	+26	(0.42)[d]	+14
2000	0.46	+15	0.57	+8
3000	(0.71)[d]	+11	(0.68)[d]	+6
4000	0.88	+8	0.82	+5

[a] Taken from the data given in ref 7; *n*-octane, 45°. [b] From Tables I and II; cumene, 79.6°. [c] Values of k_c/k_d are those observed, or calculated from the plots, at each pressure; values of $\Delta V^*_d - \Delta V^*_c$ for each pressure P were calculated from the slopes of chords connecting points on the plots at P and $P + 1000$ atm. [d] Calculated from the plots; see *c*.

Limited data indicate that values of ΔV^*_d are positive;[8] diffusion processes are retarded by increasing pressure. It is well documented that pressure increases the viscosity of most liquids[9] and diffusion constants decrease with increasing viscosity at atmospheric pressure.[10] Since homolytic scission reactions are pressure retarded,[1a,3,7] one would anticipate that their reverse, radical combination during an encounter, would be pressure accelerated;[11] values of ΔV^*_c should be negative. *A priori* the observed values of $\Delta V^*_d - \Delta V^*_c$ (Tables II and III) do not disagree with these predictions; however, it should be noted that these activation volume differences become rather small in the perester systems above 3000 atm. For a value of $\Delta V^*_d - \Delta V^*_c$ equal to +5 cc/mol, approximate extreme cases conforming to the predictions above would be ΔV^*_d and ΔV^*_c equal to +4 and −1 cc/mol, respectively, or equal to +1 and −4 cc/mol, respectively. We have previously estimated a value of −5 cc/mol for *tert*-butoxy radical combination, and this might suggest that the latter case was applicable. However, the requisite value of ΔV^*_d seems small.[12]

In our previous discussions of ΔV^*_c we have ignored the possible presence of an inert molecule (nitrogen or carbon dioxide) between the geminate radicals in the primary cage.[13] While recombination of two nearest neighbor radicals would seem in most cases to require a negative activation volume, it seems equally true that radicals in the primary cage could not recombine without first becoming nearest neighbors. Such a reorganization could be formally represented as shown in eq 3

$$\overline{\text{A}\cdot\ \text{X}\ \cdot\text{B}} \xrightarrow{k_r} \overline{\text{A}\cdot\ \text{B}\cdot\ \text{X}} \xrightarrow{k_c} \text{AB} + \text{X} \qquad (3)$$

(k_r), and since it should be akin to diffusion it seems quite possible that its rate would decrease with increasing pressure ($\Delta V^*_r > 0$). This could lead to the small positive values observed for $\Delta V^*_d - \Delta V^*_c$ since the *apparent* activation volume for combination might be actually positive at all pressures or become so as pressure increased. There seems to be ample precedent for assuming that the rate of the reorganization process is comparable to those for combination and separative diffusion.[14]

This analysis indicates that the pressure dependence of cage effects for systems initially containing an inert molecule interposed between the radical pair may not be good models for the pressure dependence of the quantity k_{-1}/k (eq 2) even when k is simply equal to k_d. It seems probable that this ratio might increase more rapidly with pressure in the absence of an intervening inert molecule and perhaps be characterized by a slope with a significantly smaller pressure dependence.

Pressure Dependence of Products Formed Subsequent to Diffusion.—The net result of separative diffusion is the formation of equivalent amounts of solvent-separated benzyl and cumyl radicals (Scheme I). We have previously indicated[3] that eq 4–9 represent the reactions available to these radicals and the more extensive product data now available (Table I) do not disagree with this. However, contrary to our previous suggestion,[3] these data indicate that reaction 5 (hydrogen abstraction from cumene) must be a major source of the toluenes.

$$\text{benzyl} + \text{benzyl} \xrightarrow{k_{B,B}} \text{bibenzyl} \qquad (4)$$

$$\text{benzyl} + \text{cumene} \xrightarrow{k_{B,CH}} \text{toluene} + \text{cumyl} \qquad (5)$$

$$\text{benzyl} + \text{cumyl} \xrightarrow{k_{B,C}} \text{toluene} + \alpha\text{-Ms} \qquad (6)$$

$$\xrightarrow{k'_{B,C}} \text{benzylcumyl} \qquad (7)$$

$$\text{cumyl} + \text{cumyl} \xrightarrow{k_{c,c}} \text{cumene} + \alpha\text{-Ms} \qquad (8)$$

$$\xrightarrow{k'_{c,c}} \text{bicumyl} \qquad (9)$$

Toluenes can be formed from benzyl radicals by hydrogen abstraction either from cumene (eq 5) or cumyl radicals (eq 6). The latter bimolecular reaction must be competitive with coupling to yield the benzylcumyls (eq 7). Data obtained in a study of the pressure dependence for competition between coupling and disproportionation of a cyclohexyl radical–*tert*-butoxy radical pair suggest that these two processes have very similar activation volumes.[3] Since the yields of the benzylcumyls remain relatively constant as pressure is increased (see data for H-, *m*-Cl-, and *p*-MeO-substituted peresters) while those for the toluenes increase significantly, the major source of the toluenes must not be *via* reaction 6. Reaction 5 is the only one among the competitive group of reactions 4–9 which is monomolecular in radicals. Since the efficiency of radical production decreases with pressure, all of those processes which involve bimolecular radical interactions should become decreasingly competitive with reaction 5, and this is borne out in the product data.

Scatter in the product data and overlap of the peaks for the bibenzyl and benzylcumyl products from the *p*-

(8) (a) D. W. McCall, D. C. Douglass, and E. W. Anderson, *J. Chem. Phys.*, **31**, 1555 (1959); (b) W. A. Steele and W. Webb in "High Pressure Physics and Chemistry," Vol. 1, R. S. Bradley, Ed., Academic Press, New York, N. Y., 1963, pp 163–176.

(9) See, for example, P. W. Bridgeman, "Collected Experimental Papers," Vol. IV, Harvard University Press, Cambridge, Mass., 1964, p 2043.

(10) See, for example, G. Houghton, *J. Chem. Phys.*, **40**, 1628 (1964).

(11) Previous attempts to determine combination activation volumes have required rather severe approximations and the results are ambiguous. See ref 20 and 21 in our previous report.[7]

(12) There is some indication that values of ΔV^*_d decrease with increasing pressure.[8a] However, it is hard to imagine that they would become almost zero.

(13) We wish to thank Professor T. Koenig for helpful comments which prompted us to begin worrying about this feature of certain primary cages.

(14) (a) H. Kiefer and T. Traylor, *J. Amer. Chem. Soc.*, **89**, 6667 (1967); (b) T. Koenig, *ibid.*, **91**, 2558 (1969); (c) F. D. Greene, M. A. Berwick, and J. C. Stowell, *ibid.*, **92**, 867 (1970); (d) K. R. Kopecky and T. Gillan, *Can. J. Chem.*, **47**, 2371 (1969).

Cl- and p-CH_3-substituted peresters preclude a detailed analysis of substituent effects on the product yields. However, it should be noted that, with the exception of the data for the unsubstituted perester, the toluene yields appear to follow a reactivity trend with σ^+ which parallels the expected stability of the benzyl radicals (Figure 2).

Experimental Section

Peresters.—The synthetic origins have been outlined.[1a,3,4]

Benzyl *tert*-Butyl Ethers.—The ethers were prepared by the dropwise addition of the corresponding benzyl bromide or benzyl chloride to a refluxing solution prepared by the addition of *tert*-butyl alcohol to a suspension of sodium hydride in dry tetrahydrofuran.[15] The reaction mixtures were refluxed for several hours, washed with water, dried over anhydrous magnesium sulfate, and distilled under reduced pressure.

The nmr spectrum of each ether is consistent with structure (*vide infra*) and the glpc retention time of each ether corresponded to that of the product identified as ether in each reaction mixture. The ether retention times varied with structure in a manner analogous to those of the substituted toluenes and bibenzyls (see Table IV). (a) **Unsubstituted:** bp 84–87° (12 mm) [lit.[15] 98° (20 mm)]; nmr three singlets at 71, 259, and 430 Hz in the ratio 9:2:5, respectively. (b) ***m*-Chloro:** bp 56–59° (0.5 mm); nmr singlets at 74 and 264 Hz, multiplet at 436 Hz, in the ratio 9:2:4, respectively. (c) ***p*-Chloro:** mp 33.5–34.5°; nmr three singlets at 73, 260, and 431 Hz in the ratio 9:2:4, respectively. (d) ***p*-Methyl:** bp 49–50° (0.1 mm); nmr three singlets at 72, 136, and 267 Hz, multiplet at 432.5 Hz, in the ratio 9:3:2:4, respectively. (e) ***p*-Methoxy:** attempts to prepare the benzyl halide precursor were unsuccessful; this compound was not synthesized.

TABLE IV

GLPC RETENTION TIMES FOR TOLUENES, ETHERS, AND BIBENZYLS[a,b]

	Time, min		
Substituent	Toluene	Ether	Bibenzyl
H	5.4	15.7	21.1
p-CH_3	8.3	16.6	23.0
m-Cl	10.1	17.4	23.9
p-Cl	10.5	18.2	25.1
p-OCH_3	13.0	(18.7)[c]	24.5

[a] Samples in cumene solution. [b] Analyzed using conditions outlined in the section describing product analyses. [c] Authentic sample not available; retention time of supposed ether peak in glpc traces of reaction mixtures.

Substituted Toluenes.—All of the variously substituted toluenes were reagent grade chemicals obtained from Matheson Coleman and Bell.

Substituted Bibenzyls.—Bibenzyl was furnished to us by Dr. Kenji Kawoka. The **3,3′-dichloro-**, **4,4′-dichloro-**, and **4,4′-dimethylbibenzyl** were prepared from the corresponding benzyl bromides using the procedure of Boekelheide, *et al.*[16] The **4,4′-dimethoxybibenzyl** was prepared by reaction of p-methylanisole with *tert*-butyl peroxide. The physical properties of all of the bibenzyls corresponded to those previously available in the literature,[16-18] and the nmr spectra were consistent with structure.

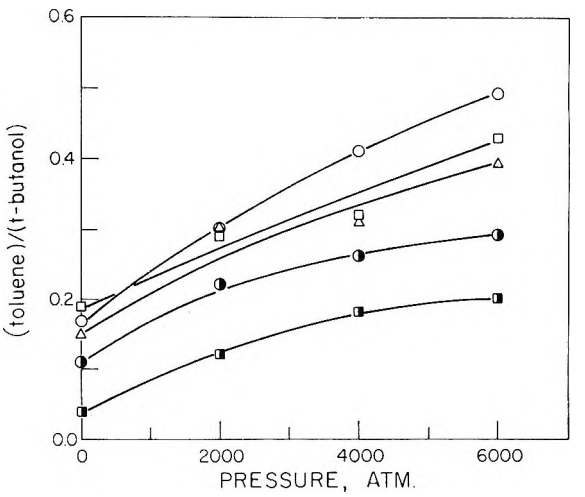


Figure 2.—Pressure dependence of the toluene/*tert*-butyl alcohol product ratio from decomposition of the m-Cl- (□), p-Cl- (△), H- (○), p-CH_3- (◑), and p-MeO- (◨) substituted *tert*-butyl phenylperacetates.

High Pressure Apparatus.—A complete description of the apparatus and experimental techniques has been presented.[3]

Product Analyses.—The products were determined by glpc analyses of completely reacted samples of the peresters in cumene using an F & M Model 700 gas chromatography instrument with WX filaments equipped with an F & M Model 240 power proportioning temperature programmer. The instrument contained a matched pair of 6 ft × 1/8 in. columns packed with 10% SE-30 on 80–100 AWDMCS-700; helium was the carrier gas. For all analyses the columns were held at 65° for 4 min after sample injection and then programmed to 220° at a rate of 10°/min.

Products (Table I) were identified by comparison with authentic samples and quantitatively determined by comparison with standard solutions containing authentic samples, with the exception of the benzylcumyls and p-methoxybenzyl *tert*-butyl ether.

A sample containing unsubstituted benzylcumyl along with bibenzyl and bicumyl was prepared by decomposition of *tert*-butyl peroxide in a mixture of toluene and cumene. This permitted assignment of the benzylcumyl retention time for studies of *tert*-butyl phenylperacetate but precluded quantitative yield measurements. The quantitative data presented for benzylcumyl were calculated using an average of the area ratio–molar ratio proportionality factors for bibenzyl and bicumyl. The latter procedure was also used for the substituted benzylcumyls, and their assignments were based on an elimination process. Separate peaks for the benzylcumyls in the p-Cl and p-CH_3 systems were not observed. They are assumed to overlap the corresponding bibenzyl peaks because of the large apparent areas for the latter (see Table I).

Registry No.—**1** (X = m-Cl), 27396-17-4; **1** (X = p-Cl, 27396-18-5; **1** (X = H), 3377-89-7; **1** (X = p-CH_3), 27396-20-9; **1** (X = p-OMe), 27396-21-0.

(15) H. Normant and T. Cuvigny, *Bull. Soc. Chim. Fr.*, **6**, 1866 (1965).

(16) W. S. Lindsay, P. Stoker, L. G. Humber, and V. Boekelheide, *J. Amer. Chem. Soc.*, **83**, 947 (1961).

(17) W. Baker, J. F. W. McOmie, and J. M. Norman, *J. Chem. Soc.*, 1114 (1951).

(18) K. M. Johnston and G. H. Williams, *ibid.*, 1168 (1960).

Orientation in Base-Catalyzed β Elimination from 2-Butyl Halides. A Dichotomy between Alcoholic and Dipolar Aprotic Solvents

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Olefinic products from reactions of 2-butyl halides with a variety of bases in alcoholic, dipolar aprotic, and mixed solvents are reported. Comparison of these results with those from the literature for other base–solvent systems reveals a striking dichotomy between orientation in base-catalyzed β elimination in alcoholic and in dipolar aprotic solvents. In alcoholic solvents, an inverse dependence of the *trans*-:*cis*-2-butene ratio and the per cent of 1-butene exists. However, in dipolar aprotic solvents, high *trans*-:*cis*-2-butene ratios of 3.0–4.0, which are independent of the per cent of 1-butene, are observed. Novel linear free-energy relationships between log (% *trans*-2-butene/% 1-butene) and log (% *cis*-2-butene/% 1-butene) for 52 base–solvent–leaving group combinations are discussed.

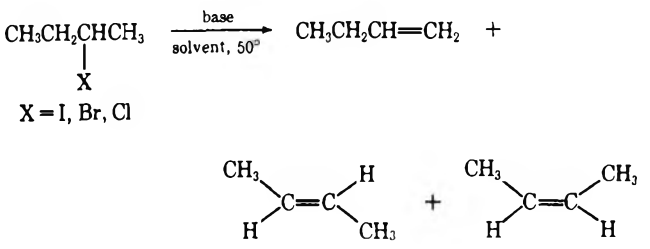
During the last decade, a number of investigations of the factors affecting positional and geometrical orientation[2] in base-catalyzed β eliminations from 2-alkyl halides have appeared.[3] The effects of the nature of the leaving group, the base, the solvent, and the 2-alkyl group have been examined.

The base–solvent systems employed in these studies have usually been alkoxide ions in the corresponding alcohols or in dipolar aprotic solvents. When compared to alcoholic solvents, unusually high *trans*-:*cis*-2-alkene ratios have been noted in eliminations from 2-alkyl halides (excluding 2-alkyl fluorides) induced by alkoxide ions in dipolar aprotic solvents.[3b,e] Recently the variety of base–solvent combinations was expanded by report of halide ion promoted dehydrohalogenation of 2-butyl halides in DMF and DMSO.[3a] In this investigation, unusual orientation was again observed: *trans*-:*cis*-2-butene ratios were uncommonly high and were essentially invariant with change in the per cent 1-butene. Thus it appeared that high *trans*-:*cis*-2-alkene ratios might be characteristic of base-catalyzed eliminations from 2-alkyl halides in dipolar aprotic solvents. In order to investigate this possibility, a study of eliminations from 2-butyl halides induced by several previously unexamined bases in dipolar aprotic solvents was undertaken. In addition, eliminations promoted by a number of alkoxide and phenoxide ions in alcohols and alkoxide ions in mixed solvent systems were examined to further delineate the differences between the effects of alcoholic and dipolar aprotic solvents.

Results

Using gas–liquid partition chromatography (glpc), the relative proportions of the three isomeric olefins formed in reactions of 2-butyl iodide, bromide, and chloride with a variety of base–solvent combinations have been determined (Scheme I). The reactions were all conducted at 50° for comparison with reported values from other systems.

SCHEME I



Reactions of 2-Butyl Iodide with Unusual Bases in DMF.—The relative amounts of isomeric olefins resulting from reactions of cyanide, acetate, benzoate, and phenoxide ions with 2-butyl iodide in DMF are presented in Table I (systems 1–5). In all cases, the 2-butenes, Saytzeff olefins, strongly predominate and high *trans*-:*cis*-2-butene ratios (3.3–3.8) obtain. Comparison of systems 1 and 2 indicates an insensitivity of orientation to the identity of the metal counterion. In previously reported fluoride ion promoted eliminations (Table I, systems 12, 13, 14, and 15; Table III, systems 34, 35, 36, and 37; Table IV, systems 52, 53, 54, and 55), an apparent dependence of orientation upon the cation has been attributed to small amounts of water in the solvent for reactions of the tetraalkylammonium fluoride hydrates.[3a]

Under the reaction there is a negligible contribution from E1 processes.[3a] Sodium nitrite, nitrate, and thiocyanate were of insufficient strength to produce clean E2 reactions. No attempt was made to measure the low butene yields.

Reactions of 2-Butyl Halides with Phenoxide and Alkoxides in Alcohols.—The relative proportions of isomeric butenes resulting from a number of previously unreported phenoxide and alkoxide ion induced eliminations from 2-butyl halides in alcoholic solvents are presented in Table II (systems 16, 17, 18, 19, and 21), Table III (systems 26, 27, 28), and Table IV (systems 46 and 47).

Control experiments demonstrated the absence of a significant unimolecular elimination pathway under the reactions conditions. That phenoxide ion is the effective base in the phenoxide–alcohol systems was demonstrated by the constancy of olefinic proportions in eliminations from 2-butyl bromide promoted by varying concentrations of phenoxide in ethanol containing an excess of phenol (see Experimental Section).

The effects upon butene composition of variation of the alcoholic solvent for a common base are shown in re-

(1) National Science Foundation Undergraduate Research Participant.

(2) Positional orientation refers to the relative proportions of 1- and 2-alkenes formed, whereas geometrical orientation compares the relative amounts of *trans*- and *cis*-2-alkene produced.

(3) (a) R. A. Bartsch, *J. Org. Chem.*, **35**, 1023 (1970); (b) *ibid.*, **35**, 1334 (1970); (c) R. A. Bartsch and J. F. Bunnett, *J. Amer. Chem. Soc.*, **90**, 408 (1968); (d) *ibid.*, **91**, 1376 (1969); (e) *ibid.*, **91**, 1382 (1969); (f) H. C. Brown and R. L. Klimisch, *ibid.*, **88**, 1425 (1966); (g) D. H. Froemsdorf, M. E. McCain, and W. W. Wilkison, *ibid.*, **87**, 3984 (1965); (h) D. L. Griffith, D. L. Meges, and H. C. Brown, *Chem. Commun.*, 90 (1968); (i) W. H. Saunders, Jr., S. R. Fahrenholtz, E. A. Caress, J. P. Lowe, and M. Schreiber, *J. Amer. Chem. Soc.*, **87**, 3401 (1965); (j) W. H. Saunders, Jr., S. R. Fahrenholtz, and J. P. Lowe, *Tetrahedron Lett.*, 1 (1960).

Table I

Olefinic Products from Reactions of 2-Iodobutane with Various Bases in Dipolar Aprotic Solvents at 50°

System no.	Base	Solvent	Total butenes, % 1-Butene	*trans*-2-Butene	*cis*-2-Butene	*trans*-2-Butene: *cis*-2-butene
1	KCN[a,b]	DMF	3.3 ± 0.1[c]	74.4 ± 0.5	22.3 ± 0.5	3.34 ± 0.11
2	NaCN[a,b]	DMF	3.7 ± 0.2	73.8 ± 0.6	22.6 ± 0.7	3.27 ± 0.09
3	NaOAc[a,b]	DMF	6.7 ± 0.2	73.7 ± 0.3	19.6 ± 0.3	3.76 ± 0.06
4	NaOCOPh[a,b]	DMF	7.4 ± 0.1	72.8 ± 0.6	19.8 ± 0.6	3.68 ± 0.14
5	PhOK[b,d]	DMF	11.5 ± 0.1	69.5 ± 0.4	19.0 ± 0.5	3.66 ± 0.11
6	LiI[e]	DMF	1.5	76.8	21.6	3.55
7	LiI[e]	DMSO	2.2	75.2	22.6	3.33
8	LiBr[e]	DMF	2.1	77.6	20.3	3.83
9	LiBr[e]	DMSO	3.3	74.4	22.3	3.33
10	LiCl[e]	DMF	2.4	78.0	19.6	3.95
11	LiCl[e]	DMSO	2.6	75.8	21.7	3.50
12	LiF[e]	DMF	18.9	63.1	18.0	3.51
13	LiF[e]	DMSO	19.4	61.5	19.1	3.23
14	Me_4NF[e]	DMF	9.5	71.1	19.4	3.66
15	n-Bu_4NF[e]	DMF	10.6	69.6	19.7	3.53

[a] Saturated solution. [b] [2-BuI] = 0.4 *M*. [c] Standard deviation. [d] [PhOK] = 0.4 *M*. [e] Reference 3a.

Table II

Olefinic Products from Reactions of 2-Iodobutane with Various Bases in Alcohols and Toluene at 50°

System no.	Base	Solvent	Total butenes, % 1-Butene	*trans*-2-Butene	*cis*-2-Butene	*trans*-2-Butene: *cis*-2-butene
16	EtOK[a]	EtOH	11.7 ± 0.3[b]	67.6 ± 0.2	20.8 ± 0.2	3.25 ± 0.02
17	PhOK[c]	EtOH	7.9 ± 0.4	72.2 ± 0.2	19.9 ± 0.5	3.62 ± 0.11
18	*sec*-BuOK[a]	*sec*-BuOH	17.1 ± 0.3	61.0 ± 0.3	21.8 ± 0.2	2.79 ± 0.03
19	PhOK[c]	*sec*-BuOH	8.9 ± 0.4	70.8 ± 0.5	20.3 ± 0.4	3.48 ± 0.08
20	*tert*-BuOK[d]	*tert*-BuOH	33.5	44.5	22.0	2.02
21	PhOK[c]	*tert*-BuOH	10.6 ± 0.4	67.8 ± 0.6	21.5 ± 0.3	3.16 ± 0.06
22	Et_3COK[d]	Et_3COH	49.3	30	20	1.50
23	*tert*-BuOK[d]	Toluene	36.1	40	23	1.70
24	Et_3COK[d]	Toluene	46.8	34	19	1.75

[a] [2-BuI] and [base] = 0.1–0.2 *M*. [b] Standard deviation. [c] [2-BuI] = 0.15 *M*, [PhOK] = 0.1 *M*, [PhOH] = 1.0 *M*. [d] Reference 3h.

Table III

Olefinic Products from Reactions of 2-Bromobutane with Various Base–Solvent Systems at 50°

System no.	Base	Solvent	Total butenes, % 1-Butene	*trans*-2-Butene	*cis*-2-Butene	*trans*-2-Butene: *cis*-2-butene
25	MeONa[a]	MeOH	14.6	65.8	19.6	3.36
26	EtOK[b]	EtOH	17.9 ± 0.2[c]	62.3 ± 0.2	19.8 ± 0.2	3.14 ± 0.03
27	PhOK[d]	EtOH	11.8 ± 0.1	67.8 ± 0.3	20.4 ± 0.4	3.32 ± 0.08
28	*sec*-BuOK[b]	*sec*-BuOH	26.3 ± 0.2	53.7 ± 0.2	20.0 ± 0.2	2.68 ± 0.04
29	*tert*-BuOK[e]	*tert*-BuOH	53.5	27.7	18.8	1.47
30	Et_3COK[e]	Et_3COH	71.3	16	13	1.26
31	*tert*-BuOK[e]	Toluene	52.2	28	20	1.38
32	Et_3COK[e]	Toluene	65.8	20	14	1.37
33	LiCl[f]	DMF	9.8	70.1	20.1	3.48
34	LiF[f]	DMF	29.3	55.0	15.7	3.50
35	LiF[f]	DMSO	29.5	54.2	16.3	3.32
36	Me_4NF[f]	DMF	15.5	66.5	18.0	3.68
37	n-Bu_4NF[f]	DMF	16.7	64.5	18.7	3.45
38	EtOK[g,h]	DMSO	27	57	16	3.35
39	*tert*-BuOK[a]	DMF	30.5	55.1	14.4	3.82
40	*tert*-BuOK[i,j]	DMAC	26.7 ± 0.1	57.0 ± 0.1	16.3 ± 0.2	3.50 ± 0.04
41	*tert*-BuOK[j,k]	Sulfolane	27.7 ± 0.3	54.1 ± 0.1	18.2 ± 0.2	2.97 ± 0.03
42	*tert*-BuOK[a]	DMSO	30.4	53.8	15.8	3.40
43	*tert*-BuOK[j]	50% *tert*-BuOH–50% DMSO	29.4 ± 0.2	53.1 ± 0.2	17.5 ± 0.2	3.03 ± 0.04
44	*tert*-BuOK[j]	75% *tert*-BuOH–25% DMSO	29.1 ± 0.2	52.4 ± 0.3	18.5 ± 0.2	2.84 ± 0.04
45	*tert*-BuOK[j]	90% *tert*-BuOH–10% DMSO	32.9 ± 0.1	48.7 ± 0.1	18.4 ± 0.1	2.65 ± 0.01

[a] Reference 3b. [b] [2-BuBr] = 0.1–0.6 *M*, [base] = 0.1–0.2 *M*. [c] Standard deviation. [d] [2-BuBr] = 0.17 *M*, [PhOK] = 0.1 *M*, [PhOH] = 1.0 *M*. [e] Reference 3h. [f] Reference 3a. [g] At 55°. [h] Reference 3g. [i] *N*,*N*-Dimethylacetamide. [j] [2-BuBr] = 0.2 *M*, [*tert*-BuOK] = 0.5 *M*. [k] Tetramethylene sulfone.

TABLE IV

OLEFINIC PRODUCTS FROM REACTIONS OF 2-CHLOROBUTANE WITH VARIOUS BASE–SOLVENT SYSTEMS AT 50°

System no.	Base	Solvent	Total butenes, % 1-Butene	*trans*-2-Butene	*cis*-2-Butene	*trans*-2-Butene: *cis*-2-butene
46	EtOK[a]	EtOH	22.3 ± 0.2[b]	58.9 ± 0.2	18.8 ± 0.3	3.13 ± 0.05
47	*sec*-BuOK[c]	*sec*-BuOH	33.7 ± 0.3	47.2 ± 0.3	19.1 ± 0.6	2.46 ± 0.09
48	*tert*-BuOK[d]	*tert*-BuOH	67	18.5	14.5	1.28
49	Et_3COK[d]	Et_3COH	80.1	11	9	1.14
50	*tert*-BuOK[d]	Toluene	66.8	17	16	1.03
51	Et_3COK[d]	Toluene	77.0	13	10	1.29
52	LiF[e]	DMF	39.8	47.6	12.6	3.79
53	LiF[e]	DMSO	40.8	45.6	13.6	3.36
54	Me_4NF[e]	DMF	22.1	61.3	16.6	3.72
55	*n*-Bu_4NF[e]	DMF	22.5	61.1	16.4	3.76

[a] [RCl] = 0.4 *M*, [EtOK] = 0.1 *M*. [b] Standard deviation. [c] [RCl] = 0.15 *M*, [*sec*-BuOK] = 0.2 *M*. [d] Reference 3h. [e] Reference 3a.

actions of 2-butyl iodide with potassium phenoxide in ethanol, *sec*-butyl alcohol, and *tert*-butyl alcohol (Table II, systems 17, 19 and 21). The relatively small changes in butene proportions indicate that the much larger effects noted for variation of alkoxides in the respective alcohols (Table II systems 16, 18, and 20) are attributable primarily to differing base strengths and not to a solvent effect.

Reactions of 2-Butyl Bromide with Potassium *tert*-Butoxide in Dipolar Aprotic Solvents and in *tert*-Butyl Alcohol–DMSO Mixtures.—Previous investigations of base-catalyzed eliminations from 2-alkyl halides in dipolar aprotic solvents have been confined to DMF and DMSO. Orientation in elimination from 2-butyl bromide promoted by potassium *tert*-butoxide in *N*,*N*-dimethylacetamide and tetramethylene sulfone are reported in Table III (systems 40 and 41). The *trans*-:*cis*-2-butene ratios are high, in agreement with earlier studies in DMF and DMSO.[3a,b]

The results from a study of olefinic proportions from reactions of 2-butyl bromide with potassium *tert*-butoxide in the mixed solvent system of *tert*-butyl alcohol–DMSO are presented in Table III (systems 43, 44, and 45). As the proportion (by volume) of DMSO is increased from 0 to 10%, a pronounced effect upon both positional and geometrical orientation is observed (compare systems 29 and 45). Further increases in the proportion of DMSO to 25 and then 50% (systems 44 and 43, respectively) exhibit much smaller effects. Dramatic enhancement of the rate of elimination from 2-arylethyl bromides promoted by potassium *tert*-butoxide in *tert*-butyl alcohol upon addition of small amounts of DMSO has been reported by Saunders and coworkers.[4]

Discussion

In addition to the results of the present study, reported olefinic proportions from dehydrohalogenation of 2-butyl halides with other base–solvents systems at 50°[3a,b,f–h] are collected in Tables I–IV. In all, 55 base–solvent–leaving group combinations are included.

Reactions of 2-Butyl Halides with Bases in Dipolar Aprotic Solvents.—Orientation in eliminations from 2-butyl iodide, bromide, and chloride induced by a wide variety of bases in DMF and DMSO at 50° has now been observed (Table I; Table III, systems 33–39, 42; Table IV, systems 52–55). The first atoms of these bases range from oxygen (alkoxide, phenoxide, carboxylate ions) to carbon (cyanide ion) to halogen (halide ions). With this variety of bases, the proportion of 1-butene varies from 2 to 40%. However, the *trans*-:*cis*-2-butene ratios remain high and essentially constant in the range 3.3–4.0. It is apparent that the concomitant changes observed in the per cent of 1-butene and the *trans*-:*cis*-2-butene ratios for reactions of 2-alkyl halides with alkoxide ions in alcohols[3b–d,f–j] are not found when DMF and DMSO are the reaction solvents.

The geometrical orientation noted for eliminations induced by potassium *tert*-butoxide in *N*,*N*-dimethylacetamide and tetramethylene sulfone (Table III, systems 40 and 41) suggests that high *trans*-:*cis*-2-butene ratios are a general feature of base-catalyzed eliminations from 2-butyl halides in dipolar aprotic solvents.

In eliminations from 2-substituted alkanes, *trans*-:*cis*-2-alkene ratios have been interpreted as indicating the extent of double bond formation in the internal olefin transition states.[3b,d,g,i] The greater the degree of double bond character, the greater is the eclipsing of cis-destined alkyl groups, resulting in a higher *trans*-:*cis*-2-alkene ratio. According to this criterion, a high degree of double bond character exists in the internal olefin transition states for all base-catalyzed eliminations from 2-butyl halides in dipolar aprotic solvents.[5] The reason for this divergence of orientation for eliminations in dipolar aprotic solvents from that observed in alcoholic solvents is not evident at this time.

Effect of Base and Solvent upon Orientation in Elimination from 2-Butyl Halides.—The availability of data on such a large number of base–solvent–leaving group combinations encourages a search for novel relationships. In Figure 1, log (% *cis*-2-butene/% 1-butene) (*i.e.*, the relative rates of formation of *cis*-2-butene and 1-butene) is plotted against log (% *trans*-2-butene/% 1-butene) for eliminations in dipolar aprotic solvents. Figure 2 is a similar plot for reactions in which the solvents were alcohols and toluene. Both plots exhibit excellent linearity when the number of sources of data is considered. These linear free-energy relationships attest to regularities in the effects of base, solvent, and leaving group upon product compositions in base-catalyzed β eliminations from 2-butyl halides.

The plot for eliminations in dipolar aprotic solvents (Figure 1) has a slope of 1.00. Thus, the aforementioned insensitivity of the relative rates of formation of

(4) A. F. Cockerill, S. Rottschaefer, and W. H. Saunders, Jr., *J. Amer. Chem. Soc.*, **89**, 901 (1967).

(5) A high degree of double bond character exists in internal olefin transition states for reactions of 2-bromoalkanes with potassium *tert*-butoxide in DMSO.[3b]

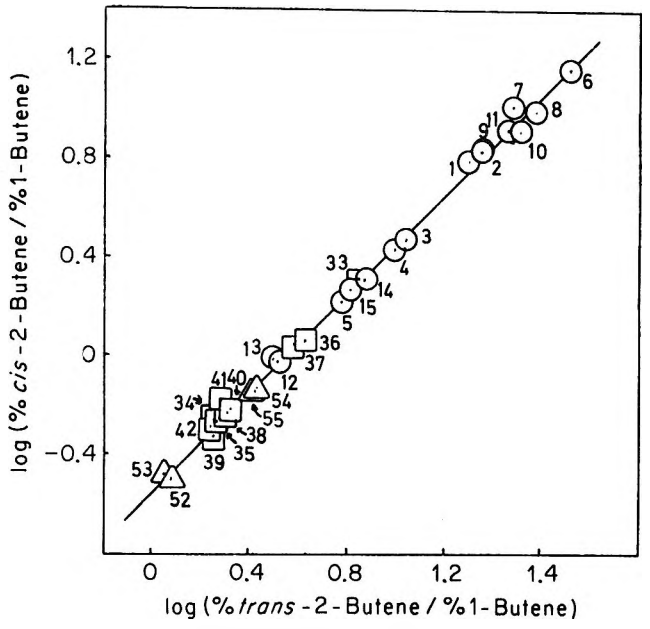


Figure 1.—Plot of log (% *cis*-2-butene/% 1-butene) *vs.* log (% *trans*-2-butene/% 1-butene) for base-catalyzed elimination from 2-butyl halides in dipolar aprotic solvents at 50°: ⊙ = 2-butyl iodide; ⊡ = 2-butyl bromide; △ = 2-butyl chloride.

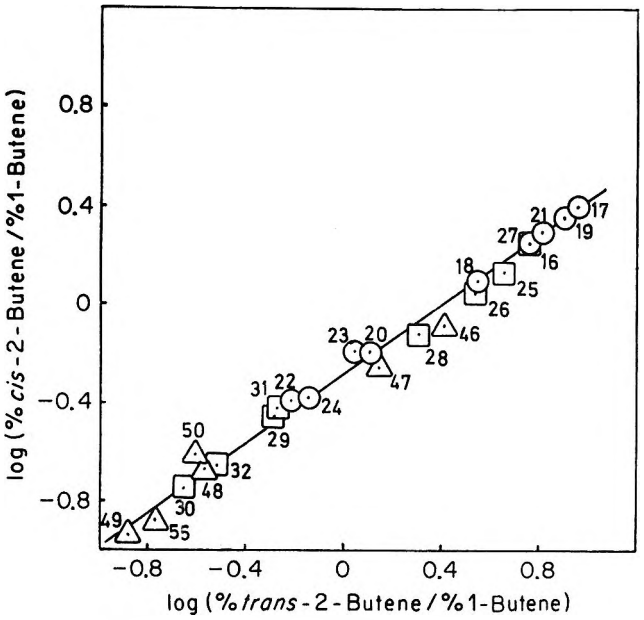


Figure 2.—Plot of log (% *cis*-2-butene/% 1-butene) *vs.* log (% *trans*-2-butene/% 1-butene) for base-catalyzed elimination from 2-butyl halides in alcohols and toluene at 50°: ⊙ = 2-butyl iodide; ⊡ = 2-butyl bromide; △ = 2-butyl chloride.

trans- and *cis*-2-butene (*i.e.*, the *trans*-:*cis*-2-butene ratio) to that for 1-butene is clearly demonstrated.

The slope in Figure 2 for the alcoholic solvents is 0.70. This means that as the per cent of 1-butene increases, the per cent of *trans*-2-butene suffers a proportionately greater decrease than the per cent of *cis*-2-butene. Thus, in alcoholic media, *trans*-:*cis*-2-butene ratios of 3.2–3.6 are observed when the per cent of 1-butene has a low value of 8–15% (systems 16, 17, 19, 21, 25, and 27). However, much lower *trans*-:*cis*-2-butene ratios of 1.1–1.5 are noted when the relative proportions of 1-butene is 49–80% (systems 22, 29, 30, 48, and 49). Rationalizations of this inverse relationship between the *trans*-:*cis*-2-alkene ratio and the per cent of 1-alkene have been offered.[3c,d,g] It is indeed interesting that the products of eliminations induced by alkoxide ions in toluene (systems 23, 24, 31, 32, 50, and 51) correlate with products from eliminations employing alkoxide ions in alcohols (Figure 2).

The linear free-energy relationships presented in Figures 1 and 2 allow certain inferences concerning base-catalyzed β eliminations from 2-butyl halides to be made. First, the linearity strongly suggests that the stereochemistry of elimination in dipolar aprotic solvents and in alcoholic media is invariant. A change from anti- to syn-elimination stereochemistry should produce significant irregularities in the relative rates of formation of *trans*- and *cis*-2-alkene because of the strong destabilization of the syn elimination *cis*-2-alkene transition state by eclipsing effects.[3e,6] An anti-elimination stereochemistry has been demonstrated in eliminations from *erythro*-3-deuterio-2-bromobutane in a variety of dipolar aprotic and alcoholic solvents.[7] It therefore appears that anti elimination occurs for the entire series of base–solvent–leaving group combinations.

Although the steric requirements of the base are varied widely, Figures 1 and 2 exhibit no discontinuities in the relative rates of formation of the internal olefins. A sudden onset of steric interactions with bulky bases,[8] such as potassium *tert*-butoxide, would be expected to strongly influence the relative rates of formation of *trans*- and *cis*-2-butene because of the different steric interactions in the two transition states. Similar conclusions concerning the unimportance of the steric proportions of the base upon orientation have been reached previously.[3b]

Orientation in eliminations from 2-butyl *p*-toluenesulfonate induced by 13 base–solvent combinations at 55° has been reported by Froemsdorf.[9] When points for these reactions were entered onto the plots for the 2-butyl halides, no correlation was found. This observation further reveals the significant differences between halide and *p*-toluenesulfonate leaving groups,[3c] which probably result from the asymmetry of the latter.

Experimental Section

Reagents.—Anhydrous dimethylformamide and dimethyl sulfoxide (Baker, reagent) were stored over molecular sieves. *N*,*N*-Dimethylacetamide and tetramethylene sulfone (Aldrich, reagent) and anhydrous ethanol were used directly. *sec*-Butyl and *tert*-butyl alcohol were distilled from calcium hydride. 2-Butyl halides were obtained as before.[3b] Potassium *tert*-butoxide (MSA) was used directly.

Base–Solvent Solutions.—Potassium *tert*-butoxide in *tert*-butyl alcohol was prepared as before.[3d] Potassium ethoxide in ethanol and *sec*-butoxide in *sec*-butyl alcohol were prepared in similar fashion. Solutions of 0.1 *N* potassium phenoxide and 1.0 *N* phenol in alcohols resulted from addition of 2.5 ml of 0.2 *N* potassium alkoxide in alcohol to 0.52 g of phenol in a 5-ml volumetric flask, addition of the 2-butyl halide, and dilution to 5 ml with the appropriate alcohol. Potassium *tert*-butoxide in *tert*-butyl alcohol–DMSO mixtures were prepared from potassium

(6) D. S. Bailey and W. H. Saunders, Jr., *Chem. Commun.*, 1598 (1968).

(7) R. A. Bartsch, *Tetrahedron Lett.*, 297 (1970); R. A. Bartsch, unpublished results.

(8) Evidence that orientation in elimination from 2-alkyl halides by alkoxide ions of moderate proportions is not controlled by steric factors has recently been obtained: R. A. Bartsch, C. F. Kelly, and G. M. Pruss, *Tetrahedron Lett.*, 3795 (1970).

(9) D. H. Froemsdorf and M. D. Robbins, *J. Amer. Chem. Soc.*, **89**, 1737 (1967).

tert-butoxide and appropriate amounts (by volume) of *tert*-butyl alcohol and DMSO.

Reaction Procedure.—Reactions of 2-butyl halides with potassium phenoxide and alkoxides in alcohols,[3b] and with bases in dipolar aprotic solvents and *tert*-butyl alcohol–DMSO mixtures,[3a] were conducted and elimination products were analyzed as before.

Control Experiments.—Negligible amounts of butenes (determined by glpc) were formed in the reaction of 2-butyl iodide (starting material most prone to E1 reaction) with an equivalent amount of 2,6-lutidine (sterically hindered base, present to inhibit acid-catalyzed reaction) in *tert*-butyl alcohol at 50° for 24 hr.

Reaction of 2-butyl iodide with varying concentrations of potassium phenoxide in ethanol in the presence of excess phenol gave the following olefinic proportions ([PhOK], [PhOH], % 1-butene, % *trans*-2-butene % *cis*-2-butene): 0.05 *M*, 1.05 *M*, 7.8 ± 0.2, 72.3 ± 0.2, 19.9 ± 0.1; 0.10 *M*, 1.00 *M*, 7.9 ± 0.3, 72.1 ± 0.6, 20.0 ± 0.3; 0.15 *M*, 0.95 *M*, 8.0 ± 0.2, 71.6 ± 0.2, 20.4 ± 0.4. Within experimental error, the relative amounts of butenes are invariant, indicating the absence of significant ethoxide ion promoted elimination. Based upon the pK_a's of ethanol and phenol in ethanol,[10] less than 1% of ethoxide is calculated to be present in an ethanolic solution of 0.1 *M* phenoxide and 1.0 *M* phenol.

Registry No.—2-Iodobutane, 513-48-4; 2-bromobutane, 78-76-2; 2-chlorobutane, 78-86-4.

(10) B. D. England and D. A. House, *J. Chem. Soc.*, 4421 (1962).

A Discussion of Inductive, Conjugative, and Steric Strain Effects on Polarographic Reduction Potentials of a Series of Biphenyl- and Phenanthrene-Related Compounds[1]

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In this study are reported the polarographic half-wave reduction potentials in dimethylformamide of a series of alkyl-substituted phenanthrenes and biphenyls. The shifts in the half-wave potential *vis-à-vis* the unsubstituted parent compounds are discussed in terms of hyperconjugative, inductive, and steric strain effects. Using the inductive model for alkyl substitution and making suitable correction for the hyperconjugative effect, correlation of half-wave potential shifts with HMO coefficients is attempted. Deviations from the expected correlation are explained in terms of steric interactions, and a semiquantitative estimate of these interactions is presented.

There has been rather sustained interest in recent years in the effects that substituent alkyl groups have on the physical and chemical properties of fused and bridged aromatic hydrocarbons. Changes in electronic spectra,[3-7] polarographic half-wave potentials ($E_{1/2}$),[6-11] and ionization potentials[7,12] have been discussed. In certain cases, such as that of biphenyl, the steric requirements of substitution can result in a change in the planarity of one part of the conjugated system relative to the rest of the molecule. Such perturbations of the conjugative resonance interaction have been shown to result in shifts of the so-called ultraviolet conjugation band (~250 nm)[3-5,11,13] and in shifts of polarographic $E_{1/2}$ values.[10,11]

Where rigid conjugated systems, such as fluorenes and phenanthrenes, are involved, changes in planarity on substitution are not so significant. However, Streitwieser and Schwager[9] showed that, besides the normal inductive effect, hyperconjugative interaction of the added alkyl group with the π system of the aromatic parent compound constitutes an appreciable portion of the shift in $E_{1/2}$ when substitution is made at a site with a fairly large Hückel molecular orbital (HMO) coefficient (c). When a correction is made for the conjugative interaction, fairly successful correlation of $E_{1/2}$ shifts (with respect to the unsubstituted parent) with the HMO coefficients was obtained.[9] If the hyperconjugative interaction is neglected, the results are not so satisfactory.[8,9] Valenzuela and Bard have also shown hyperconjugation to be an important consideration.[14]

When the alkyl substituent takes the form of a bridge between two parts of a conjugated system (such as in fluorene and 9,10-dihydrophenanthrene) $\Delta E_{1/2}$ values are even more difficult to correlate with inductive effects alone.[8] Steric effects may be important in the $E_{1/2}$ shifts of these compounds, but in earlier studies they have either not been a major factor or they have not been considered where inconclusive results were obtained.[8]

In this investigation the reduction $E_{1/2}$ values of a series of biphenyl- and phenanthrene-related compounds (where the added substituent is an alkyl group) were obtained in dimethylformamide (DMF) media. All of the factors enumerated above have been considered, with particular attention paid to molecules possessing steric strain, and to those species where the alkyl substituent is a bridging group. For many molecules it was found that correlation of $E_{1/2}$ shifts (corrected for conjugation effects) with the inductive effect of the added alkyl group is far from successful. These deviations from the "normal" correlation behavior are equated to steric strain, and this strain is estimated semiquantitatively.

(1) This work was supported in part by the National Science Foundation, Grant No. GP-9307, and in part by the American Chemical Society, Petroleum Research Fund, Grant No. 2880-A3,5.

(2) Chemistry Department, The University of Cincinnati, Cincinnati, Ohio 45221.

(3) G. H. Beaven, D. M. Hall, M. S. Lesslie, and E. E. Turner, *J. Chem. Soc.*, 854 (1952).

(4) G. H. Beaven, and G. R. Bird, *ibid.*, 131 (1954).

(5) E. A. Braude and W. F. Forbes, *ibid.*, 3776 (1955).

(6) A. Zweig, J. E. Lancaster, M. T. Neglia, and W. H. Jura, *J. Amer. Chem. Soc.*, **86**, 4130 (1964).

(7) E. S. Pysh and N. C. Yang, *ibid.*, **85**, 2124 (1963).

(8) R. Gerdil, and E. A. C. Lucken, *ibid.*, **88**, 733 (1966).

(9) A. Streitwieser, Jr., and I. Schwager, *J. Phys. Chem.*, **66**, 2316 (1962).

(10) A. J. Bard, K. S. V. Santhanam, J. T. Maloy, J. Phelps, and L. O. Wheeler, *Discuss. Faraday Soc.*, 167 (1968).

(11) R. Dietz and M. E. Peover, *ibid.*, 154 (1968).

(12) A. Streitwieser, Jr., *J. Phys. Chem.*, **66**, 368 (1962).

(13) H. Suzuki, *Bull. Chem. Soc. Jap.*, **32**, 1340, 1350, 1357 (1959).

(14) J. A. Valenzuela and A. J. Bard, *J. Phys. Chem.*, **73**, 779 (1969).

Experimental Section

Instrumentation.—Polarograms were obtained using a three-electrode system based on the operational amplifier circuits of DeFord[15] and were recorded on an Electro Instruments Model 500 X-Y recorder without damping. The reference electrode employed for all measurements was an anodized silver wire immersed in a 0.01 *M* $AgClO_4$–0.1 *M* tetra-*n*-butylammonium perchlorate (TBAP) solution in DMF. The stability of this system has been discussed earlier.[16] Details of the construction of the reference and salt-bridge compartments have been given elsewhere.[17] Measured $E_{1/2}$ values are accurate to at least ±10 mV except for those above −3.2 V, as background breakdown begins to be significant in this region making determination of accurate values difficult. Procedures for deaeration of the solution have been elaborated in an earlier report.[18]

Chemicals and Solutions.—The DMF solvent was Matheson Coleman and Bell Spectroquality grade. Purification was effected by passing dried solvent (Linde Type 4A Molecular Sieves) through an approximately 4-ft column of Woelm alumina at a rate of about 15 drops per minute.[19] This method of purification resulted in a product as free of reducible impurities as that obtained by an earlier reported distillation procedure,[18] and it had the advantage of being a much easier and faster method.

Phenanthrene (purchased from Matheson Coleman and Bell), 4,5-methylenephenanthrene (4,5-MeP) (from Aldrich Chemical Company), fluorene (Baker photosensitizer grade), and 2-methylbiphenyl (K and K Laboratories) were used as received. Biphenyl was recrystallized by standard methods. The 4,5-methylene-9,10-dihydrophenanthrene (4,5-Me-9,10-DHP) was recrystallized from methanol and melted at 140–141°. The 9,10-dihydrophenanthrene (9,10-DHP), from K and K Laboratories, was recrystallized from ethanol at acetone–Dry Ice temperatures, filtered, and washed with cold ethanol. The solid, melting near room temperature, was stored over silica gel in a refrigerator. Pure samples of 2,7-dimethylphenanthrene (2,7-DMeP), 4,5-dimethylphenanthrene (4,5-DMeP), 2,4,5,7-tetramethylphenanthrene (2,4,5,7-TMeP), 3,4,5,6-tetramethylphenanthrene (3,4,5,6-TMeP), and 1,8-dimethylfluorene (1,8-DMeF) were obtained from Professor M. S. Newman (Department of Chemistry, Ohio State University, Columbus, Ohio).

Hydrocarbon solutions in DMF were 0.1 *M* in TBAP and millimolar in sample.

Results and Discussion

As is the usual practice, it is assumed that the electron added in the reduction process occupies the lowest unoccupied molecular orbital of the hydrocarbons. According to Streitwieser and Schwager,[9] a substituent alkyl group can be considered as making the carbon atom to which it is attached less electronegative by its electron-donating (inductive) ability. The altered coulomb integral can be defined as

$$\alpha_r = \alpha_0 + h_r\beta_0 \tag{1}$$

where h_r is negative. The change in the energy, ϵ_{m+1}, of the lowest vacant molecular orbital is given by

$$\delta\epsilon_{m+1} = c^2_{m+1,\,r}\,\delta\alpha_r \tag{2}$$

where $c_{m+1,\,r}$ is the coefficient of the rth atomic orbital in the $(m + 1)$st molecular orbital, the lowest vacant orbital. However as

$$\delta\alpha_r = \alpha_r - \alpha_0 = h_r\beta_0 \tag{3}$$

$$\delta\epsilon_{m+1} = c^2_{m+1,\,r}\,h_r\beta_0 \tag{4}$$

The result is that the inductive effect raises the energy of the vacant orbital and shifts $E_{1/2}$ to more negative potentials. It is also expected that inductive effects are additive so that if more than one alkyl group is involved then

$$\delta\epsilon_{m+1,\,r} = \sum_r c^2_{m+1,\,r}\,h_r\beta_0 \tag{5}$$

Therefore a linear correlation of shifts of half-wave reduction potentials from those of the unsubstituted compound with $\Sigma_r c^2_{m+1,\,r}$ should be obtained in this case. It is assumed that the c_{m+1} values do not change on methyl substitution.

As mentioned earlier, Streitwieser and Schwager have shown that hyperconjugative interaction of the added alkyl group also may be an important factor in changes in $E_{1/2}$.[9] Correction for this effect is easily made, however, based on the assumption that the ultraviolet conjugation band, which is related to transitions of an electron from the highest occupied to the lowest vacant π-molecular orbital, is affected solely by conjugative and not by inductive effects.[9] Likewise, as the spatial geometry is assumed not to change during an electronic transition (Franck–Condon principle), shifts in the conjugation band ought not to reflect strain effects except as they give rise to changes in resonance interaction.[13] Therefore the bathochromic shift in the frequency of the conjugation band (ν parent–ν substituted) can be converted to volts (1 eV = 8066 cm^{-1}) and added to the measured $E_{1/2}$ values. This correction has been applied to all compounds in this study. Where significant deviation from the expected correlation behavior (where only hyperconjugative and inductive effects are present) is found, the cause is attributed to steric effects, as discussed below. Apparently steric strain is more extensive in the excited state than in the ground state, and the LVMO is raised in energy more than the HFMO.

Phenanthrene Related Compounds.—Polarographic and ultraviolet spectral data for phenanthrene and related compounds is given in Table I. Analysis of the polarograms showed them to be reversible, one-electron waves.[16,18] The $E_{1/2}$ of 4,5-MeP was corrected for the small anodic shift (about 20 mV) resulting from the self-protonation (ECE) sequence. This correction was estimated from the results of Janata and Mark.[16,20] Also given in Table I are the $c^2_{m+1,\,r}$ values for phenanthrene.

All of the compounds in this series are considered to be essentially planar, although some twist of the phenanthrene ring system occurs with substitution in the 4 and 5 positions.[21a] Even phenanthrene itself is somewhat strained because of proton–proton interaction at the 4 and 5 positions,[22] although some of the strain is relieved by a slight twist away from coplanarity.[21a]

In Figure 1 is shown the correlation of $E_{1/2}$ (corrected for conjugation effects) *vs.* $\Sigma_r c^2_{m+1,\,r}$ obtained by Streit-

(15) (a) D. D. DeFord, Analytical Division, 133rd National Meeting of the American Chemical Society, San Francisco, Calif., 1958; (b) W. M. Schwartz and I. Shain, *Anal. Chem.*, **35**, 1770 (1963).

(16) J. Janata and H. B. Mark, Jr., *J. Phys. Chem.*, **72**, 3616 (1968).

(17) J. R. Jezorek and H. B. Mark, Jr., *ibid.*, **74**, 1627 (1970).

(18) J. Janata, J. Gendell, R. C. Lawton, and H. B. Mark, Jr., *J. Amer. Chem. Soc.*, **90**, 5225 (1968).

(19) N. S. Moe, *Acta Chem. Scand.*, **21**, 1389 (1967).

(20) Estimates of the pK_a of this and other compounds in this study containing the methylene bridge range from 20 [C. D. Ritchie and R. E. Ushold, *J. Amer. Chem. Soc.*, **89**, 1721 (1967)] to 25 (A. Streitwieser, "Molecular Orbital Theory," Wiley, New York, N. Y., 1962, pp 414–415). A radical anion of the hydrocarbon is able to abstract a proton from another molecule of hydrocarbon at the electrode giving an anodic shift to $E^1/_2$.

(21) (a) H. Suzuki, "Electronic Absorption Spectra and Geometry of Organic Molecules," Academic Press, New York, N. Y., 1967, pp 380–383; (b) p 287.

(22) A. Streitwieser, "Molecular Orbital Theory," Wiley, New York, N. Y., 1962, p 344.

TABLE I

POLAROGRAPHIC AND ULTRAVIOLET SPECTRAL DATA FOR PHENANTHRENES IN DMF

Compd	$E_{1/2}$, measured[a]	λ (nm)	ν (cm^{-1})	—From phenanthrene— Δλ	Δν	Correction, mV	$E_{1/2}$, corrected	$\Delta E_{1/2}$, corrected	$\Sigma c^2_{m+1,r}/r$	Spectral ref
Phenanthrene	−2.904	292.1	34,235							*b*, *c*
2,7-DMeP	−2.946	295	33,898	+2.9	−337	42	−2.988	84	0.004	*b*
4,5-DMeP	−2.814	312.5	32,020	+20.4	−2215	275	−3.089	185	0.108	*b*
4,5-MeP	−2.881	299	33,445	+7	−801	99	−3.000	96	0.054	*c*
	+20 mV								0.108	
	(ECE) = −2.901									
2,4,5,7-TMeP	−2.853	315.9	31,598	+23.8	−2637	327	−3.180	276	0.112	*d*
3,4,5,6-TMeP	−2.948	316.8	31,565	+24.7	−2670	332	−3.280	376	0.306	*d*

[a] Reference electrode is Ag/AgClO$_4$ (0.01 *M*) in DMF. [b] P. Nounou, *J. Chim. Phys. Physicochim. Biol.*, 64, 276 (1967). [c] C. Karr, Jr., *Appl. Spectrosc.*, **13**, 15 (1959). [d] This work, in CH_3CN, Cary 14 spectrometer.

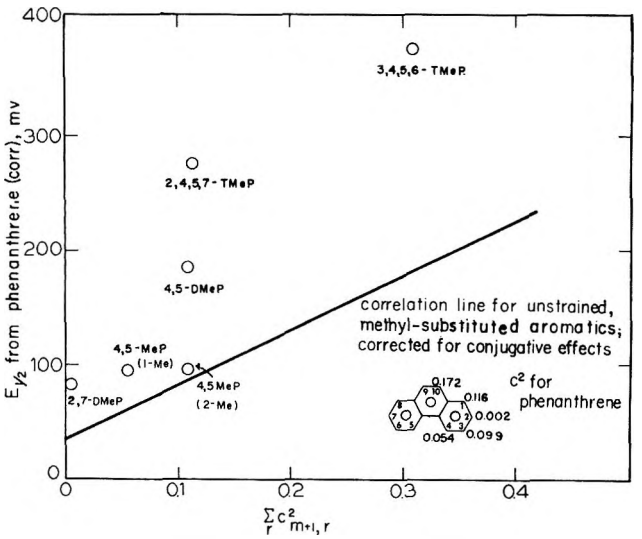

Figure 1.—Attempted correlation of polarographic half-wave potentials, corrected for conjugation, with the effect of alkyl substituents in phenanthrene using the inductive model. The solid line was obtained by Streitwieser for unstrained, methyl-substituted, alternant aromatic hydrocarbons.

wieser and Schwager for alkyl-substituted, unstrained, alternant aromatic hydrocarbons.[9] That this line does not go through the origin seems strange. Streitwieser and Schwager do not discuss this problem, and while Neikam and Desmond[23] also note the situation, they do not offer any explanation. However, the effect seems real, and the experimental correlation will be used. Results of the present study are then compared with this correlation line. Satisfactory fit is obtained for 2,7-DMeP and 4,5-MeP. The deviation of 4,5-DMeP from the purely inductive correlation line is about 100 mV. This is equivalent to about 2.3 kcal/mol of steric energy (1 eV = 23 kcal/mol) over and above that which is present in phenanthrene itself. When further substitution is made alongside the 4- and 5-methyl groups to give 3,4,5,6-TMeP, an even greater deviation is observed, equivalent to about 4.4 kcal/mol. The additional 2.1 kcal/mol results from methyl–methyl crowding in the 3,4 and 5,6 positions, as well as increased overlap of the 4- and 5-methyl groups, the so-called "buttressing effect" noted by Newman, *et al.*[24] The steric overlap of the 4- and 5-methyl groups is evident for 2,4 5,7-TMeP as well, but it seems as if other effects are present beyond this, as the deviation from the correlation is greater than the sum of those of 2,7-MeP and 4,5-MeP. A form of "buttressing" interaction is possible in the 2,3,4 and 5,6,7 positions, *i.e.*, methyl–proton–methyl crowding. Interactions of this type have been discussed by Braude and Forbes for meta substitution in biphenyl.[5]

Biphenyl and Related Compounds.—In Table II are given the polarographic and spectral data for biphenyl and substituted biphenyl compounds. Of these species biphenyl and 9,10-DHP deviate from planarity.[25] In order to relieve steric overlap in the ortho position, biphenyl is twisted about the bridging bond, while twisting in 9,10-DHP occurs in order that the sp^3 angles of the ethylene bridge be more closely accommodated.[3,5,13] A twist of up to 20° in both compounds has been shown to cause very little reduction in the π–π interaction of the aromatic rings compared to the hypothetical planar molecule.[26] Indeed the slight loss of resonance interaction is balanced by the decrease in steric overlap of the ortho protons.[5] For those compounds containing bridging methylene groups, the assumption is made that the $E_{1/2}$ shift of the self-ECE process is the same as that of 4,5-MeP, and a 20-mV correction is applied, as estimated from Janata and Mark.[16] In Figure 2 is shown the shift in $E_{1/2}$ (corrected for conjugation) *vis-à-vis* biphenyl, of the compounds under study, the experimentally determined correlation line of Streitwieser and Schwager,[9] and the c^2 values for biphenyl. Because some doubt exists as to whether a bridging methylene or ethylene group is equivalent to one or two substituent methyl groups, all possibilities have been considered. As mentioned above, the 2,2′-proton interaction of biphenyl is minimized with the twist about the bridging bond.[5,13] When the bridging methylene group is introduced between the 2 and 2′ positions to give fluorene, however, the ortho protons remaining are now forced into a strained, eclipsed conformation. The minimum deviation from the correlation line, using the rather doubtful assumption that the methylene group is considered to have the same effect as two methyl groups,[8] is equivalent to about 4.8 kcal/mol of steric strain compared to biphenyl itself.

That 4,5-DMeP seems to have less strain energy than fluorene, which has only two protons sterically interacting instead of two larger methyl groups, is understandable when it is remembered that this method of estimat-

(23) W. C. Neikam and M. M. Desmond, *J. Amer. Chem. Soc.*, **86**, 4811 (1964).

(24) H. A. Karnes, B. D. Kybett, M. H. Wilson, J. L. Margrave, and M. S. Newman, *ibid.*, **87**, 5554 (1965).

(25) Braude and Forbes (ref 5) contend that 9,10-DHP, while twisted in the ground state, is nearly coplanar in the excited state. This contention is disputed by Suzuki (ref 13) who assumes no geometric rearrangement during an electronic transition according to the Franck–Condon principle.

(26) K. Ishizu, *Bull. Chem. Soc. Jap.*, **37**, 1093 (1964).

TABLE II
POLAROGRAPHIC AND ULTRAVIOLET SPECTRAL DATA FOR BIPHENYL AND SUBSTITUTED BIPHENYLS IN DMF

Compd	$E_{1/2}$, measured[a]	λ (nm)	ν (cm⁻¹)	From biphenyl: Δλ	From biphenyl: Δν	Correction, mV	$E_{1/2}$, corrected	$\Delta E_{1/2}$, corrected	$\Sigma c^2_{m+1,r}$	Spectral ref
Biphenyl	−3.034	249.5	40,080							*b*
Fluorene	−3.123	261.5	38,241	+12	−1839	+228	−3.371	−337	0.089	*b*
	+20 mV (ECE)								0.178	
	= −3.143									
9,10-DHP	−3.043	263.5	37,951	+14	−2129	+264	−3.307	−273	0.089	*b, c*
									0.178	
4,5-Me-9,10-DHP	-3.24_0	272	36,765	+22	−3315	+412	−3.652	−638	0.178	*d*
	+20 mV (ECE)								0.267	
	$= -3.26_0$								0.356	
1,8-DMeF	−3.004	255.4	39,154	+5.9	−926	+115	−3.139	−105	0.127	*e*
	+20 mV (ECE)								0.216	
	= −3.024									
2-Me-biphenyl	-3.20_2	235	42,548	−14.5	+2468	+52[f]	−3.254	−220	0.089	*b*
4-Me-biphenyl		253	39,525	+3.5	−555					*b*

[a] Reference electrode is Ag/$AgClO_4$ (0.01 *M*) in DMF. [b] Reference 13. [c] Reference 3. [d] R. N. Jones, *J. Amer. Chem. Soc.*, **63**, 1658 (1941). [e] This study, in CH_3CN, Cary 14 spectrometer. [f] Correction calculated from shift of 4-Me-biphenyl.

ing strain energies does not give "absolute" energies, but only yields a value with respect to the parent compound. In 4,5-DMeP two overlapping methyl groups are substituted for the two overlapping 4- and 5-position protons of phenanthrene. In fluorene two protons are brought into geometric interaction, whereas in biphenyl they are able to avoid each other *via* the twist of the molecule. In addition there is probably a certain amount of internal strain in the fluorene molecule as it is forced into a planar or near planar configuration.[3,13,21b] It may be that this "internal" ring strain is of the "hybridization effect" type discussed by Streitwieser,[27] whereby the ring juncture carbon atoms rehybridize to accommodate the small bond angles of the strained portion of the molecule. This situation results in an anodic shift to $E_{1/2}$, as discussed by Rieke, *et al.*, for some naphthalene base compounds[28] or the internal strain could be of a type which introduces a further cathodic shift to $E_{1/2}$ beyond that of spatial overlap of the ortho protons. It is also noticed that the bathochromic shift produced by hyperconjugation of the methylene bridge is considerably larger than one would expect even for two methyl groups. This large effect probably results from the possibility of stabilization of the hyperconjugated conformation by both phenyl rings, the liklihood of some $\pi-\pi$ interaction of the phenyl rings through the methylene bridge,[5] and also from the planar structure which allows better conjugation across the bridging bond.[3,13,21b] The $E_{1/2}$ value of fluorene has been corrected for all these increases in conjugative interaction, *via* the uv shift, in order to yield the steric strain energy.

If an ethylene bridge is introduced across the ortho positions of biphenyl, yielding 9,10-DHP, the molecule is still allowed a measure of twist,[5] so that the remaining ortho protons are essentially staggered. However, the protons of the ethylene bridge may still be subject to some overlap as the ethylene carbon atoms may not be able to attain the full tetrahedral angle. The estimated strain energy of about 3.8 kcal/mol then seems reasonable for partial overlap of the remaining ortho protons and those of the ethylene bridge.

If the ortho protons of 9,10-DHP are replaced with a methylene bridge to give 4,5-Me-9,10-DHP, the molecule is forced to assume a planar configuration.[13] It is noted that the deviation from the correlation line for this compound is the most marked of any studied. The strain energy equivalent is about 9.8 kcal/mol. This energy can probably be traced in part to the interaction of the four ethylene protons which are now "locked" into an eclipsed configuration. The energy barrier for rotation of ethane from the staggered to the eclipsed conformation is about 3 kcal/mol.[29] Also probably contributing to the total is the fairly significant "internal" strain in the molecule as a whole, as the ethylene carbon atoms are not able to attain tetrahedral geometry because of the forced coplanar structure. The comments concerning the effect of this "internal" strain on $E_{1/2}$ which were made about fluorene are also applicable here. The very large "strain energy" found

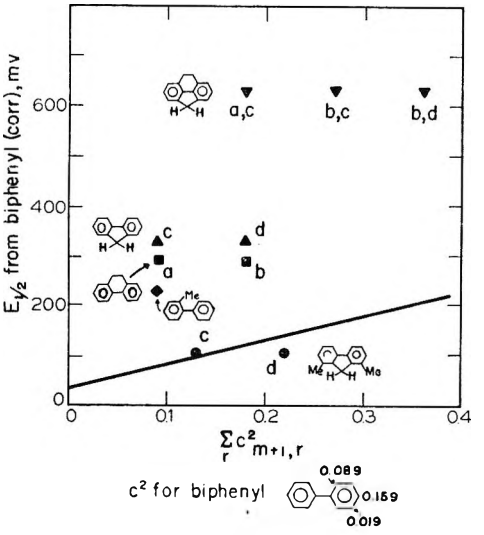

Figure 2.—Attempted correlation of polarographic half-wave potentials, corrected for conjugation, with the effect of alkyl substituents in biphenyl using the inductive model: (a) ethylene equivalent to one methyl group; (b) ethylene equivalent to two methyl groups; (c) methylene equivalent to one methyl group; (d) methylene equivalent to two methyl groups. The solid line is that obtained by Streitwieser for unstrained, methyl-substituted, alternant aromatic hydrocarbons.

(27) A. Streitwieser, Jr., G. R. Ziegler, P. C. Mowery, A. Lewis, and R. G. Lawler, *J. Amer. Chem. Soc.*, **90**, 1357 (1968).

(28) R. D. Rieke, W. E. Rich, and T. H. Ridgway, *Tetrahedron Lett.*, 4381 (1969).

(29) C. R. Noller, "Chemistry of Organic Compounds," W. B. Saunders, Philadelphia, Pa., 1965, p 64.

would seem to indicate that a cathodic shift of $E_{1/2}$ is the result, not the anodic shifts observed by Rieke, *et al.*[28] The reason for a cathodic shift is not apparent at this time.

That 1,8-DMeF falls very close to the correlation line is perhaps surprising. However, this good correlation is actually indicative of the breakdown of the hyperconjugative correction procedure for this nonalternant hydrocarbon. In all other cases discussed so far, alkyl substitution has been seen to produce a shift of the ultraviolet conjugation band to lower energies, while substitution in the 1 and 8 positions of fluorene has the opposite effect. Sandorfy has stated that, for nonalternant hydrocarbons, methyl substitution can cause either bathochromic or hypsochromic shifts, depending on the position of substitution.[30] Despite the fact that, in this case, methyl substitution would be expected to yield a cathodic shift in addition to that resulting from the inductive effect, the actual measured $E_{1/2}$ is more anodic than that of fluorene itself. It appears then that the usual relationships between ultraviolet spectral and polarographic data do not hold for the nonalternant hydrocarbon fluorene.

The polarographic reduction potential for 2-methylbiphenyl has also been determined. However, the usual hyperconjugative correction is not possible because the shift of the conjugation band is composed of two components acting in opposite directions.[13] Conjugation of the methyl group with the biphenyl π system causes the typical bathochromic shift, while steric overlap of the ortho methyl with the ortho proton, resulting in increased twist about the bridging bond (58°),[13] causes a hypsochromic shift because of reduced π–π interaction. (The decrease in resonance interaction across the bridging bond has been estimated by Braude and Forbes[5] to be 7 kcal/mol, but their interpretation has been strongly disputed by Suzuki.[13]) Therefore the hyperconjugative shift for 4-methylbiphenyl, multiplied by the ratio of the HMO coefficients for the 2 and 4 positions, has been applied as a correction to 2-methylbiphenyl. When this is done, $E_{1/2}$ falls about 145 mV above the correlation line, equivalent to a strain effect of about 3.3 kcal/mol. This energy results from methyl–proton interaction at the ortho position, as well as decreased π–π interaction across the bridging bond with respect to biphenyl.

It is seen then that using the inductive model of alkyl substitution in alternant aromatic hydrocarbons, and applying an appropriate correction for hyperconjugative effects, a rough estimate of steric interaction can be obtained polarographically. It appears, however, as if this procedure is not valid for substituted nonalternant aromatic hydrocarbons such as fluorene.

Registry No.—Phenanthrene, 85-01-8; 2,7-DMeP 1576-69-8; 4,5-DMeP, 3674-69-9; 4,5-MeP, 203-64-5; 2,4,5,7-TMeP, 7396-38-5; 3,4,5,6-TMeP, 7343-06-8; biphenyl, 92-52-4; fluorene, 86-73-7; 9,10-DHP, 776-35-2; 4,5-Me-9,10-DHP, 27410-55-5; 1,8-DMeF, 1207-11-0; 2-methylbiphenyl, 643-58-3; 4-methylbiphenyl, 644-08-6.

Acknowledgments.—The authors wish to sincerely thank Professor M. S. Newman for the methyl-substituted phenanthrenes which he so kindly supplied, and Professor R. C. Lawton for helpful discussions.

(30) C. Sandorfy, "Electronic Spectra and Quantum Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1964, p 344.

The Acetylation of Cyclooctene, 1,3-Cyclooctadiene, and 1,5-Cyclooctadiene

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The acetylation of the three title olefins in the presence of aluminum chloride and of stannic chloride, employing a variety of conditions, has been surveyed. Acetylation of cyclooctene using pure acetyl chloride and aluminum chloride gives mainly ring-contraction products reported earlier, whereas use of stannic chloride leads mainly to 1-acetyl-4-chlorocyclooctane and 4-acetylcyclooctene. Acetylation with acetic anhydride in several solvents gives mixtures of acetylchlorocyclooctane, acetoxycyclooctyl acetate, and acetylcyclooctenes. From the acetylation of 1,3-cyclooctadiene in the presence of stannic chloride, there was isolated 1-acetyl-4-chlorocyclooctene and a mixture of 1- and 2-acetyl-1,3-cyclooctadiene; aluminum chloride gives only tars. Acetylation of 1,5-cyclooctadiene using either catalyst produces 50–60% of 2-acetyl-6-chlorobicyclo[3.3.0]-octane, which was degraded to bicyclo[3.3.0]octane-2,6-dione.

The Friedel–Crafts acylation of eight-membered cyclic olefins is of interest both as part of the chemistry of medium-ring compounds, a class noted for multitudinous rearrangements and transannular reactions,[2] and as a synthetic entry into substituted eight-carbon mono- and bicyclic systems. In an early investigation the reaction of acetyl chloride–stannic chloride with cyclooctene, followed by distillation of the product from base, was employed in the preparation of 1-acetylcyclooctene.[3] More recently, Jones, Taylor, and Rudd stated that aluminum chloride catalyzed acetylation of cyclooctene, followed by treatment with base, gave the same product.[4] This result was subsequently shown to be incorrect by two groups. We reported in preliminary fashion the finding that aluminum chloride catalyzed acetylation of cyclooctene gave 4-chloro-4-ethyl-1-acetylcyclohexane (40%) and 4-methyl-1-ace-

(1) (a) Author to whom correspondence should be addressed; (b) National Defense Education Act Fellow, 1965–1968.

(2) See, for example, V. Prelog and J. G. Traynham in "Molecular Rearrangements," Vol. I., P. DeMayo, Ed., Wiley, New York, N. Y., 1963, Chapter 9.

(3) L. Ruzicka and H. A. Boekenhoogen, *Helv. Chim. Acta*, **14**, 1319 (1931).

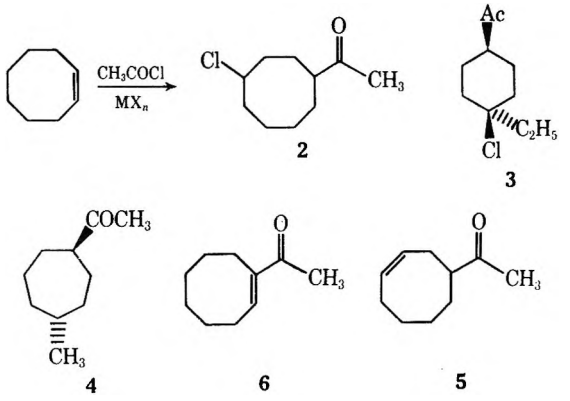
(4) N. Jones, H. T. Taylor, and E. J. Rudd, *J. Chem. Soc.*, 1342 (1961).

TABLE I

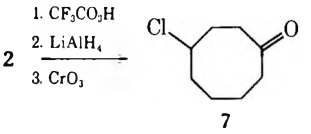
Substrate	Catalyst	Acylating agent	Solvent	Temp, °C	Products (yields, %)
	$SnCl_4$	AcCl	CH_2Cl_2	−10	**2** (67), **5** + **6** (20)
	$AlCl_3$	AcCl	CH_2Cl_2	−10	**3** (45), **4** (12), **2** (9)
cis-Cyclooctene	$SnCl_4$	AcCl	CS_2	−10	**2** (54), **5** + **6** (28)
	$SnCl_4$	Ac_2O		−27	**2** (~4), **5** + **6** (19, 1:1), **9** (~9)
	$SnCl_4$	Ac_2O	CH_2Cl_2	−5	**2** (60), **6** (11), **9** (6)
	CF_3COOH	$(CF_3CO)_2O$		−27	**6** (73)
	$SnCl_4$	AcCl	CS_2	25	**2** (32) + **5** and **6** (40)
1,3-Cyclcoctadiene	$AlCl_3$	AcCl	CH_2Cl_2	−55	Polymer
	$SnCl_4$	AcCl	CH_2Cl_2	−55	**10** (40), **11** (~8), **12** (12)

tylcycloheptane (10%), in addition to minor amounts of an acetylchlorocyclooctane.[5] Very recently Jones and Groves have published their results of a reinvestigation of the acetylation reaction, in which they find the nature of the products to be dependent on the state of the aluminum chloride used.[6] Freshly sublimed aluminum chloride gave the ring-contracted products mentioned above, whereas commercial material from a bottle opened several days before gave almost exclusively 1-acetyl-4-chlorocyclooctane. We now report the results of an exhaustive investigation conducted in our laboratories of the acetylation of the three eight-membered ring olefins, cyclooctene, 1,3-cyclooctadiene, and 1,5-cyclooctadiene, employing a variety of Lewis acid catalysts, solvents, and reaction temperatures.

Cyclooctene.—The results of our study of the acylation of cyclooctene are summarized in Table I. As was reported earlier by one of us, the use of highly pure aluminum chloride leads to the ring contraction products 4-chloro-4-ethyl-1-acetylcyclohexane (**3**, 40–45%) and 1-acetyl-4-methylcycloheptane (**4**, 10–12%); under the best conditions, less than 5% of 1-acetyl-4-chlorocyclooctane (**2**) is produced. However, when aged aluminum chloride is employed, high yields of **2** are obtained, in agreement with the findings of Jones and Groves.[6]



When stannic chloride is employed as catalyst, again in methylene chloride at −10°, 1-acetyl-4-chlorocyloctane (**2**) is obtained in 60–70% yield, accompanied by 18% of a mixture of 4-acetyl- and 1-acetylcyclooctene (**5** and **6**). Compound **2** was initially identified by means of analytical and spectral data (see Experimental Section); its structure was confirmed by chemical degradation as shown below. Thus, Baeyer–Villiger oxidation of **2** gave the corresponding chloro acetate which was reduced with lithium aluminum hydride to the carbinol. Subsequent oxidation with Jones reagent 4-chlorocyclooctanone (**7**), identical in every respect with an authentic sample.[7]



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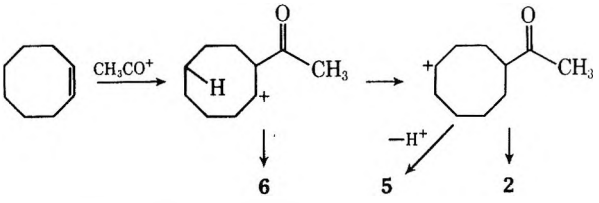
The structure of compound **5** was inferred from spectral data; particularly helpful was the infrared carbonyl stretching band at 1710 cm^{-1}, whose location is indicative of a saturated ketone. Catalytic hydrogenation of **5** gave 1-acetylcyclooctane, whose semicarbazone showed no melting point depression on admixture with that of an authentic sample.[6]

The formation of **2** and of **5** can be accounted for by the occurrence of 1,5- or 1,3-hydride transfers in the initially formed 2-acetylcyclooctyl cation. Such hydride shifts are a common phenomenon in medium-ring compounds.[2]

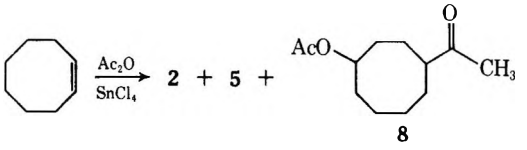


Olefin acylations performed in carbon disulfide have been reported to give improved yields of unsaturated ketones.[8] Jones and Groves reported that acetylation of cyclooctene with stannic chloride in carbon disulfide at room temperature gave 1-acetylcyclooctene (**6**, 38%) and **2** (25%). Groves[6,8c] ascribes the increased yields of the conjugated ketone **6** in carbon disulfide to a medium effect, whereby in the solvent of lower polarity hydride transfer is less efficient and more of the β-chloro ketone which gives rise to **6** is produced. However, we believe that the critical factor is the temperature employed, rather than the medium. Conducting the acetylation of cyclooctene with stannic chloride in carbon disulfide at −10° gave a reaction mixture whose composition was essentially identical with that obtained using methylene chloride as solvent. Several years ago Cantrell and Shechter had obtained 1-acetylcyclooctene as a major product of the stannic chloride

(5) T. S. Cantrell, *J. Org. Chem.*, **32**, 1667 (1967).
(6) J. K. Groves and N. Jones, *J. Chem. Soc. C*, 1718 (1969).
(7) J. G. Traynham and T. Couvillon, *J. Amer. Chem. Soc.*, **89**, 3205 (1967); we are grateful to Professor Traynham for furnishing us with a sample of this material.
(8) R. E. Christ and R. C. Fuson, *ibid.*, **59**, 893 (1937); (b) W. Taub and J. Szmuszkovicz, *ibid.*, **74**, 2117 (1952); (c) J. K. Groves, private communication.

catalyzed acetylation of cyclooctene in carbon disulfide, in contrast to our present experiences.[9] The earlier result may have been the consequence of impurities in the solvent or catalyst employed, or of longer reaction times. Certainly Jones and Groves[6] and we have found cases of profound changes in product distribution caused by seemingly minor changes in reaction conditions, *e.g.*, reagent purity, in the acylation of olefins. Finally, we have observed that, when 2 is stirred with stannic chloride in carbon disulfide at 25°, there is formed 1-acetylcyclooctene (**6**, 25%) and 4-acetylcyclooctene (**5**, 15%). Treatment of 2 with stannic chloride at −15° for a similar period produced far less rearrangement. Thus, the temperature at which the olefin acylations are conducted seems to be of considerable importance in determining product ratios. The work of Lansbury[10] has given indication that transannular hydride transfers may sometimes have a large activation energy and the rates of various such processes should therefore by strongly temperature dependent.

Acetylation of olefins using acetic anhydride has been reported to give cleaner reaction mixtures with less residual chlorine in the dehydrohalogenated products.[11] Acetylation of cyclooctene using stannic chloride–acetic anhydride without solvent gave a mixture of products in low yield, with the unsaturated ketones **5** and **6** predominating. When the reaction was conducted in methylene chloride, greatly improved yields were obtained, the chloro ketone 2 now predominating. Appreciable quantities of an acetoxyacetylcyclooctane (**8**) are obtained when acetic anhydride is employed. The location of the acetoxy group has been established by conversion of 2 to **8** on treatment with silver acetate. Even in the presence of excess acetic anhydride the chloro ketone is the major product, rather than the acetoxy ketone, **8**.



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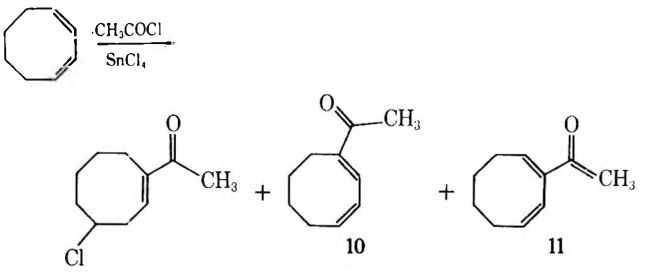
1,3-Cyclooctadiene.—Acylation of 1,3-cyclooctadiene with acetyl chloride–aluminum chloride in methylene chloride at −60° afforded a mixture of products which decomposed before they could be purified or characterized. However, acetylation of 1,3-cyclooctadiene using stannic chloride as catalyst did afford tractable products. Under the above conditions there was produced a mixture from which could be isolated 1-acetyl-4-chlorocyclooctene (**9**) and 1-acetyl-1,3-cyclooctadiene (**10**) (in yields of 12 and 40%, respectively), together with 2-acetyl-1,3-cyclooctadiene (**11**, *ca.* 8%) which appears to be an artifact produced by isomerization of **10**. When the reaction was quenched at low temperatures, the crude product showed infrared absorption for only a nonconjugated carbonyl group; it seems likely that the actual primary product of the acylation is 3-acetyl-8-chlorocyclooctene, which undergoes facile isomerization to **9** and elimination to give **10**.



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The structure of compound **9** was suggested by analytical and spectral data. The infrared and ultraviolet spectra were as expected for an unsaturated ketone. The nmr spectrum, which displays a one-hydrogen triplet at τ 3.35 (J = 8 H_z), a complex multiplet at τ 5.8 (hydrogen on C-4), a one-hydrogen doublet at τ 7.19 (J = 8 Hz, H_A on C-3), a one-hydrogen pair of doublets at τ 7.28 (J = 8, J' = 2 Hz, H_B on C-3), a two-hydrogen multiplet at τ 7.5 (H on C-8), a methyl singlet at τ 7.72, and a six-hydrogen complex pattern at τ 8.1–8.6, is in fair accord with structure **9**. Irradiation of the signals at τ 7.2–7.3 caused partial collapse of the multiplet at 5.8, showing that the two hydrogens responsible for the 7.2 signals are coupled to the hydrogen on the chlorine-bearing carbon. Structure **9**, in which the C-3 methylenes would be expected to couple to the hydrogen α to chlorine, is in best accord with this result.

Attempted dehydrohalogenation of chloro ketone **9** by distillation from sodium carbonate gave no reaction. However, distillation from 1,5-diazabicyclo[4.3.0]nonene-5 (DBN) was successful, an 85:15 mixture of dienones **10** and **11** being produced. Analysis of a sample of pure **10** which had been stored for several weeks at 5° showed that it had undergone isomerization to an identical mixture of **10** and **11**. Thus **11** seems likely to be a secondary product derived from **10**.

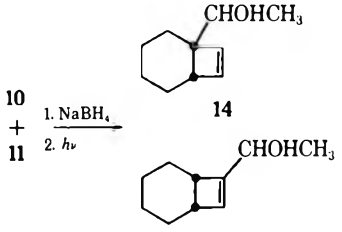
Compound **10**, purified by regeneration from the semicarbazone, was initially identified by its spectral properties, including infrared bands at 1662 and 1610 cm^{-1}, indicative of an α,β-unsaturated ketone, its ultraviolet spectrum [λ_{max} 276 nm (ϵ 10,000)], which corresponds closely to that calculated for **10** using Woodward's rules[12] (λ_{max} 273 nm), and the nmr spectrum, which exhibits, *inter alia*, a one-hydrogen apparent triplet at τ 3.06 (J = 2.0 Hz) whose chemical shift is indicative of a vinyl hydrogen β to a carbonyl group. The signal of the vinyl hydrogen β to carbonyl in structure **11** (H-8) might also appear as a triplet. However, in the nmr spectra of known 1,3-cyclooctadienes,[13] the coupling constant between vinyl and adjacent allylic hydrogens (H-1 and H-8 of **11**) is observed to be 7–8 Hz, in contrast to our observed coupling of 2 Hz. This small splitting is consistent with that reported for $J_{2,3}$ of 1,3-cyclooctadienes and other twisted dienes. In compound **10**, $J_{2,4}$ should be of the same magnitude, thus producing the observed apparent triplet for the hydrogen at C-2. This assign-

(9) T. S. Cantrell and H. Shechter, *J. Amer. Chem. Soc.*, **89**, 5867 (1967).
(10) P. T. Lansbury and F. D. Saeva, *ibid.*, **89**, 1890 (1967).
(11) For pertinent references, see C. D. Nenitzescu and A. T. Balaban in "Friedel–Crafts and Related Reactions," G. Olah, Ed., Interscience, New York, N. Y., 1964, Chapter 37.
(12) See L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 15 ff.
(13) (a) J. G. Atkinson, D. W. Ayer, G. Büchi, and E. W. Robb, *J. Amer. Chem. Soc.*, **85**, 2257 (1963); (b) L. A. Paquette and R. W. Begland, *J. Org. Chem.*, **34**, 2896 (1969).

ment was confirmed by a double resonance experiment. Irradiation of the vinyl signal at τ 4.2 while simultaneously sweeping the low field signal at 3.06 caused the low field signal to collapse to a singlet, as expected for structure **10**. In the cross-conjugated dienone **11** this would not occur, since the coupling of H-1 would be to the allylic hydrogens at C-8.

On standing in the refrigerator for several weeks, compound **10** underwent partial isomerization to **11**. This dienone was never obtained completely pure due to the great similarity of the retention times of **10** and **11**; a sample had been enriched in **11** by gc exhibited a one-hydrogen vinyl signal as an apparent triplet at τ 3.26 (J = 7 Hz) and an acetyl methyl singlet at τ 7.78. Gas chromatographic analysis indicates that *ca.* 8% of **11** was present in the original reaction mixture.

In an attempt to secure additional proof of structure for **10**, this dienone (as an 85:15 mixture with **11**) was reduced with sodium borohydride to the corresponding carbinol **12** (contaminated with **13**). The carbinol mixture was irradiated in ether solution in order to effect electrocyclic closure to bicyclo[4.2.0]-oct-7-enes.[14] The linear dienone **10** would afford compound **14** which possesses two vinyl hydrogens, whereas the bicyclic carbinol **15** derived from the cross-conjugated dienone 11 would possess only one vinyl hydrogen. Irradiation through Vycor of an ether solu-

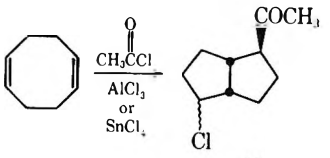


tion of the dienol mixture gave, even after extended periods of time, only a 70% conversion to two new compounds, with ~30% of **12** and **13** still being present. The nmr spectrum of this mixture exhibited quartets at τ 5.85 and 6.35. The lower field position of the first quartet suggests a methine hydrogen which is both allylic and α to hydroxyl; we assign this signal to compound **15**. The proton at τ 6.35 is evidently a methine which is no longer allylic but is α to hydroxyl and is still split by an adjacent methyl. The nmr spectrum exhibits overlapping quartets near τ 5.8 due to the unreacted dienols **12** and **13**. Unfortunately, the precise ratio of vinyl hydrogens could not be determined from the complexity of the mixture and overlapping signals; however, it is evident that the predominant product is that exhibiting the quartet at τ 6.35, *viz.*, **14**, and that the major dienone has structure **10**.

Thus, the intermediate allylic cation formed in the acylation of 1,3-cyclooctadiene does not undergo transannular hydride transfer, but rather the simple chloride capture or proton loss characteristic of cations produced from simpler enes and dienes. This would be expected, since hydride transfers to produce less stable cations from more stable ones are not favored.

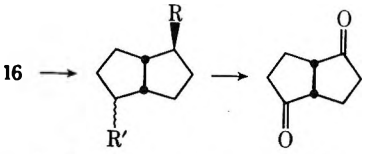
(14) For pertinent examples, see R. O. Kan, "Organic Photochemistry," McGraw-Hill, New York, N. Y., 1966, pp 32 ff.

1,5-Cyclooctadiene.—We previously reported the isolation of 2-acetyl-6-chlorobicyclo[3.3.0]octane (**16**) from the aluminum chloride catalyzed acetylation of 1,5-cyclooctadiene.[5] Ketone **16** appears to be a mixture of the *endo*- and *exo*-chloro compounds, as shown by capillary gc. Use of stannic chloride as catalyst also gave **16**, albeit contaminated with a small amount of an isomer which exhibited vinyl hydrogen nmr signals, probably 5-acetyl-6-chlorocyclooctene. The location of the chlorine atom in ketone **16** had not

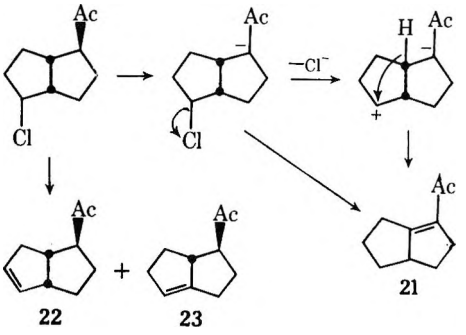


16

been securely established in our earlier work but only inferred from spectral data. Its presence at C-6 has now been confirmed by the chemical degradation outlined below. The accessibility of **16** and the reasonable yields in the degradative scheme offer a practical synthetic route to 2,6-disubstituted bicyclo[3.3.0]octane



derivatives. The identity of the dione **20** was established by comparison with an authentic sample.[15] The first step in the sequence could also be accomplished with potassium acetate in refluxing acetic acid; however, this method also led to considerable amounts of the elimination products **21**, **22**, and **23**. The



structure of the major component of the mixture (**21**) followed from the presence of an infrared absorption band characteristic of an unsaturated ketone function (1681 cm^{-1}) and the absence of any vinyl hydrogen signal in its nmr spectrum. Hydrogenation gave *endo*-2-acetylbicyclo[3.3.0]octane, identical with an authentic sample. The two minor components of the elimination product mixture were not separated; the structures are inferred from the nmr data (see Experimental Section). The formation of **21** seems to require a 1,4- or 1,3-hydride shift. This seems quite reasonable for the *exo*-chloro isomer of **16**. Here abstraction of a

(15) V. R. Ben, Ph.D. Thesis, University of Washington, Seattle, Wash., 1953; see *Chem. Abstr.*, **52**, 16309 (1958).

proton at C-2 could be followed by (or concerted with) ionization of the chlorine and 1,3-hydride transfer from C-1 to C-6, the ionization being assisted by the enolate ion moiety.

Experimental Section

General.—The aluminum chloride used was from a freshly opened bottle of Baker and Adamson sublimed reagent grade material, unless stated otherwise. Stannic chloride was Baker and Adamson reagent grade. The methylene chloride and carbon disulfide were reagent grade materials, used without further purification. Magnesium sulfate was used for all drying operations. The infrared spectra were obtained on a Beckman IR-8 instrument and the nmr spectra on a Varian A-56/60-A instrument operating at 46°. Gas chromatographic work was performed on a Varian Aerograph Model 202-1 instrument (thermal conductivity detector) utilizing the following columns: column A, 5 ft × 0.25 in., 20% SE-30 on Chromosorb P; column B, 6 ft × 0.25 in., 10% QF-1 fluorosilicone on Chromosorb W; column C, 5 ft × 0.25 in., 15% Carbowax 20 M on Chromosorb P; and column D, 5 ft × 0.25 in., 20% diethylene glycol succinate on Chromosorb W. Elemental analyses were performed by Elek Laboratories, Torrance, Calif.

Acetylation of *cis*-Cyclooctene in the Presence of Aluminum Chloride.—This reaction has been described earlier;[5] repetition of the reaction using identical conditions gave, in addition to the acetylcyclohexane and cycloheptane derivatives **3** and **4**, 9% of the saturated chloro ketone previously mentioned; this material proved to be identical with 1-acetyl-4-chlorocyclooctane (**2**), obtained as described below.

Acetylation of *cis*-Cyclooctene Using Stannic Chloride as Catalyst.—To a solution of stannic chloride (26 g, 0.10 mol) in 50 ml of methylene chloride at −10° was added dropwise a solution of acetyl chloride (7.8 g, 0.10 mol) and cyclooctene (11.0 g, 0.10 mol) in 50 ml of methylene chloride over 40 min. The reaction mixture was stirred at −10° for 1 hr, allowed to warm to 0°, and then poured onto a slurry of ice and dilute hydrochloric acid. The aqueous layer was washed once with methylene chloride and the washings were combined with the original organic layer. The organic extracts were washed with water until neutral, dried, and concentrated under reduced pressure to give a yellow oil (15.6 g). Analysis on column B at 160° indicated the presence of 77% (68% yield) of **2** and 23% (22% yield) of three products of shorter retention times. The oil was fractionally distilled to afford two fractions: A, bp 35–60° (0.5 mm), was a mixture of **5** and **6**; B, bp 95–100° (0.5 mm), was ~90% 1-acetyl-4-chlorocyclooctane (**2**). Further fractional distillation led to considerable losses through decomposition; a more efficient method of purification was by cleavage of the semicarbazone of **2**. This derivative, obtained from the distilled material by a standard procedure, crystallized from aqueous ethanol as white flakes, mp 152–153° (lit.[6] mp 157–158°). *Anal.* Calcd for $C_{11}H_{20}N_3OCl$: C, 53.76; H, 8.14. Found: C, 54.01; H, 8.49. Pure **2**, from cleavage of the semicarbazone, exhibited the following spectral parameters: ir (film) 1710 cm^{-1}; nmr (CCl_4) τ 5.85 (1 H, pentet, $J \sim 5$ Hz, -CHCl-), 7.55 (1 H, m, -CHCO), 7.93 (3 H, s, CH_3CO), and 8.3–8.6 (12 H, m, methylenes).

Fraction A showed the presence of two major and one minor products on column B; the infrared spectrum of the mixture displayed both conjugated and nonconjugated carbonyl stretching bands (1660 and 1710 cm^{-1}). Conversion of the mixture to the semicarbazones was performed in the usual manner; fractional crystallization gave the semicarbazone of 4-acetylcyclooctene as white prisms, mp 176–177° (lit.[6] mp 177–178°). The less soluble semicarbazone, mp 202–203°, was identical with that of an authentic sample of 1-acetylcyclooctene semicarbazone. The ratio of **5** to **6** was ~30:70.

Cleavage of the semicarbazone of **5** by steam distillation from phtahalic anhydride afforded pure **5**: bp 52–56° (0.4 mm); nmr (CCl_4) τ 4.3 (2 H, m, C=CH), 7.7 (5 H, m, CHCO and CH_2-C=C), 7.91 (3 H, S, $COCH_3$), and 8.2–8.5 (6 H, m).

Degradation of 1-Acetyl-4-chlorocyclooctane to 4-Chlorocyclooctanone (7).—A solution of trifluoroperacetic acid was prepared by dropwise addition of trifluoroacetic anhydride (3.8 ml) to 90% hydrogen peroxide (0.74 ml) in 20 ml of cold (0°) methylene chloride. The solution thus obtained was added dropwise to a vigorously stirred solution of ketone **2** (5.0 g) whose infrared spectrum indicated it to be the desired ester contaminated with *ca.* 20% of unchanged ketone **2**. The ketone was removed by treatment with Girard's reagent. A solution of the crude ester (5.2 g) and 4.7 g of Girard's reagent T and 5 ml of acetic acid was refluxed in ethanol (50 ml) for 1 hr. The reaction mixture was cooled, poured into water, and extracted with ether. The ether extracts were washed with 10% sodium carbonate, with saturated brine, and with water, and then dried and concentrated under reduced pressure. Distillation gave the chloro ester as a colorless liquid (2.9 g): bp 92–98° (0.5 mm); ir (film) 1733 and 1240 cm^{-1}.

A solution of the chloro ester as obtained above (2.9 g) in ether (25 ml) was added dropwise to lithium aluminum hydride (0.5 g) in ether (25 ml) over 0.5 hr. The reaction mixture was refluxed for an additional hour, after which the excess hydride was destroyed by addition of water (0.5 ml). The solution was poured into ice and aqueous ammonium chloride. The ether layer was separated, washed with water, dried, and concentrated to give 4-chlorocyclooctanol as a colorless cloudy oil: ir (film) 3460 and 1045 cm^{-1}; no carbonyl absorption was present.

A solution of the crude 4-chlorocyclooctanol obtained above (0.47 g) in reagent grade acetone (15 ml) was treated dropwise at 20–30° with Jones reagent until the color persisted for at least 0.5 hr (*ca.* 0.4 ml). The acetone was evaporated and the residue was stirred with ice water (10 ml) and extracted four times with ether (20 ml each); the combined extracts were dried and evaporated. The residue was ~85% 4-chlorocyclooctanone, as shown by comparison on columns B and C with an authentic sample.[7] The 2,4-dinitrophenylhydrazone was prepared in the usual manner and recrystallized from ethyl acetate–ethanol to give orange needles, mp 151–152°, undepressed on admixture with the 2,4-dinitrophenylhydrazone of authentic **7**.

Acetylation of *cis*-Cyclooctene Using Stannic Chloride in Carbon Disulfide.—To a solution of stannic chloride (26 g, 0.10 mol) in carbon disulfide (50 ml) at −10° was added over 0.5 hr a solution of acetyl chloride (7.8 g, 0.10 mol) and cyclooctene (11 g, 0.10 mol) in carbon disulfide (40 ml). The solution was stirred for 15 min at −10°, let warm to 0°, and worked up as before. Evaporation of the solvents gave a yellow oil (18 g) whose composition, as shown by gas chromatography on columns B and D was essentially identical with that of the mixture obtained when the acetylation was run in methylene chloride. The infrared spectra of the two mixtures were identical.

When the acetylation in carbon disulfide was performed at 25–30°, the crude mixture obtained exhibited a gc pattern different from that of the reaction run at −10° in that the shorter retention time peaks composed considerably more of the mixture. Collection of the material of retention time 2–3 min at 160° gave material which was shown to be **5** and **6** by preparation of the semicarbazones and fractional crystallization. The **5**:**6** ratio was ~1:2 by analysis on column D, on which partial resolution was obtained.

Treatment of 1-Acetyl-4-chlorocyclooctane (2) with Stannic Chloride.—A solution of ketone **2** (0.2 g) and excess stannic chloride (2 g) in carbon disulfide (50 ml) was stirred at room temperature for 6 hr. The black solution was poured onto ice and worked up in the usual manner to give an orange oil (0.12 g). Analysis of this material on columns B and D showed it to be composed of *ca.* 45% **6**, 20% conjugated ketone **5**, and 35% unchanged **2**.

Acetylation of Cyclooctene Using Stannic Chloride–Acetic Anhydride in Methylene Chloride.—The reaction was performed exactly as in the previously described cases with the exception that acetic anhydride (10 g, 0.10 mol) was employed as the acylating agent. There was obtained 16 g of an orange oil, which analysis on column A at 180° indicated to be composed of 15% **6**, 75% **2**, and 8% of 4-acetoxy-1-acetylcyclooctane (**8**). Fractional distillation of this material on a 24-in. spinning-band column gave a fairly pure sample of **6**, bp 60–63° (0.5 mm), identified by comparison of its semicarbazone with that of material previously obtained and by comparison of spectral properties; a second fraction, bp 110–112° (1.2 mm), was almost pure chloro ketone **2**. The third fraction, bp 135–137° (1.2 mm) (1.4 g total) appeared on the basis of spectral data [ir (film) 1720 (ester C=O), 1706 (ketonic C=O), and 1250 cm^{-1}; (CO) nmr (CCl_4) τ 5.1 (1 H, m, -CHOAc-), 7.3 (1 H, br, -CHAc) 7.91 and 8.04 (3 H each, singlets, CH_3CO), and 8.1–8.7 (12 H)] to be the acetoxyacetylcyclooctane **8**. The positions of the acetate and acetyl groups were established by treatment of **2** (1.0 g) in acetic acid (20 ml) with silver acetate (0.8 g) overnight at room tem-

perature. Distillation of the reaction mixture gave a sample of **8** (~95% pure), identical with that obtained as described above.

When the acetylation using acetic anhydride was performed without additional solvent at 25°, there was obtained as crude product a red oil (7.1 g) which was shown by gc to be mainly (60%) the acetylcyclooctenes **5** and **6**, with *ca.* 10% of **2** and 20% of **9**.

Acetylation of 1,3-Cyclooctadiene with Acetyl Chloride–Stannic Chloride.—A solution of 1,3-cyclooctadiene (21.6 g, 0.20 mol) in methylene chloride (80 ml) was added dropwise to a solution of stannic chloride (52 g, 0.20 mol) and acetyl chloride (15.6 g, 0.20 mol) in methylene chloride (200 ml) over 0.5 hr at −50 to −60°. The reaction mixture was stirred at this temperature for an additional 0.5 hr, warmed to 0°, and then poured onto ice–dilute hydrochloric acid slurry. The layers were separated; the water layer was washed once with methylene chloride. The combined organic phases were washed with water until neutral (four times) and with brine, and then dried and concentrated under reduced pressure to afford a yellow oil (16.9 g). This material showed five peaks on column B at 155°, of retention times 2.2 (1% of area), 2.8 (28%), 3.5 (7%), 6 (2%), and 8 min (62%). Rapid distillation, without fractionation, gave 14.5 g of pale yellow liquid, bp 32–80° (0.2 mm). Redistillation on a 24-in. spinning-band column gave the following fractions.

A, bp 46–49° (0.4 mm), was essentially pure 1-acetyl-1,3-cyclooctadiene (**10**, 9.9 g, 41%), containing a small amount of **11** as shown by analysis on column B: ir (film) 3015, 1661, 1613, and 695 cm^{-1}; nmr (CCl_4) τ 3.06 (1 H, t, J = 2 Hz, H-2), 4.17 (2 H, m, H-3 and H-4), 7.5–7.7 (4 H, m, allylic CH_2), 7.72 (3 H, s, CH_3CO), and 8.4–8.6 (4 H, m); uv (EtOH) max 276 nm (ϵ 10,000). A semicarbazone was prepared by the usual procedure and recrystallized from aqueous ethanol to give white leaflets, mp 204–205°. *Anal.* Calcd for $C_{11}H_{17}ON_3$: C, 63.77; H, 8.21. Found: C, 63.79; H, 8.24.

On standing at room temperature for several days, **10** was converted to a mixture of 80–85% **10** and 15–20% **11**, as shown by the appearance of a second peak on column B at 155° (retention time 2.1 min, as compared to 1.9 min for **10**) and the new triplet at τ 3.3 in the nmr spectrum of the sample.

B, bp 50–73° (0.4 mm), 1.4 g, was a mixture of four components; the two major ones were **10** and **11**; one of the minor components was a nonconjugated ketone, as shown by infrared absorption at 1714 cm^{-1}.

Fraction C, bp 75–77° (0.4 mm) (1.9 g), a pale yellow oil which darkened rapidly on standing, was fairly pure 1-acetyl-4-chlorocyclooctene, **9**. This material exhibited the following spectral properties: ir (film) 3010, 1668, and 1639 cm^{-1}; nmr (CCl_4) τ 3.35 (1 H, t, J = 8 Hz, H-2), 5.82 (1 H, m, CHCl–), 7.19 (1 H, d, J = 8 Hz, H_A on C-3), 7.28 (1 H, 2 d, J = 8, J' = 2 Hz, H_B on C-3), 7.50 (2 H, m, H on C-8), 7.72 (3 H, s, CH_3CO), and 8.1–8.6 (6 H, m); uv (EtOH) max 240 nm (ϵ 11,100). The semicarbazone, prepared in the usual manner, was recrystallized from ethanol to give white prisms, mp 210–211° dec. *Anal.* Calcd for $C_{11}H_{18}N_3OCl$: C, 54.33; H, 7.39. Found: C, 54.58; H, 7.74.

Distillation of compound **12** from sodium carbonate gave only starting material. However, distillation of a mixture of 1.0 g of **9** and 1.0 g of 1,5-diazabicyclo[4.3.0]nonene at 1 mm gave a distillate (0.4 g) which was a mixture of **10** and **11** in a ratio of 85:15; this material had an infrared spectrum identical with that of a sample obtained by redistillation of dienone **10** which had stood at room temperature for 2 weeks.

When the reaction mixture from acylation of 1,3-cyclooctadiene as described above was not allowed to warm to 0° but was poured while still cold into an ice–dilute hydrochloric acid slurry, there was obtained as crude product a yellow oil whose infrared spectrum showed only one carbonyl band, at 1712 cm^{-1}, indicative of a nonconjugated ketone. The nmr spectrum of this material exhibited, *inter alia*, a multiplet at τ 4.3 (vinyls) and two acetyl singlets at 7.82 and 7.87. Distillation of the material so obtained was accompanied by evolution of hydrogen chloride and the only products in the distillate were **9**, **10**, and **11**.

Conversion of Dienones 10 and 11 to Bicyclic Alcohols 14 and 15.—A solution of an 80:20 mixture of **10** and **11** (1.9 g) in methanol (40 ml) was added at 0° to a solution of sodium borohydride (1.0 g) in methanol (20 ml). The mixture was stirred for 1 hr in the ice bath after addition was complete and was then concentrated under reduced pressure. The residue was treated with ice water and then extracted with three portions (30 ml) of ether. The combined extracts were washed with saturated sodium chloride, dried, and evaporated to give a colorless oil (1.8 g, 95%) which on column A at 165° showed one major peak (retention time 7.8 min) and an incompletely resolved minor peak (retention time 7.5) in a ratio of 88:12, assigned to compounds **12** and **13**. This material exhibited infrared absorption at 3600, 3410, 1650, and 695 cm^{-1}; no carbonyl absorption was present. The nmr spectrum (CCl_4) displayed signals at τ 4.15 (1 H, m, vinyl), 4.32 (2 H, m, vinyls), 5.84 (1 H, quartet, J = 7 Hz, $CHOHCH_3$), 7.09 (1 H, br, OH), 7.8 (4 H, *m*, $CH_2{=}C{=}C$), and 8.75 (3 H, d, J = 7 Hz, CH_3).

The 80:20 mixture of dienols obtained above (0.7 g) was dissolved in dry ether (100 ml) and irradiated through a Vycor filter, using a Hanovia 450-W medium-pressure mercury arc, for 13 hr. Evaporation of the ether and distillation of the residue in a short-path apparatus gave 0.26 g of a pale yellow oil, bp 98–115° (bath) (0.3 mm). Analysis on column A at 145° showed the presence of four components, the two minor ones of retention times identical with those of the starting dienols. The two major components could be isolated by preparative gc on column A at 150°. Silica gel tlc of the collected material showed two spots; preparative scale tlc gave no separation. The nmr spectrum (CCl_4) of the product mixture displayed signals at (*inter alia*) τ 4.1–4.5 (complex vinyl absorption), 5.85 (q, J = 7 Hz, C=C-$CHOHCH_3$), 6.4 (q, J = 8 Hz, $-CHOHCH_3$), 6.8 (broad singlet, OH), and 8.85 and 8.80 two doublets, J = 7 and J = 8 Hz, respectively, $CHOHCH_3$). The number of vinyl hydrogens could not be accurately determined; however, the quartet at τ 6.4 was of much greater intensity than that at 5.85, allowing the assignment of structure **14** to the major component. *Anal.* Calcd for $C_{10}H_{16}O$: C, 80.03; H, 9.30. Found: C, 79.75; H, 9.51.

Acetylation of 1,5-Cyclooctadiene with Acetyl Chloride and Aluminum Chloride.—The acetylation was carried out as described previously,[5] on a 0.2-mol scale; a temperature of −15 ± 3° was maintained. The crude product was distilled rapidly at 0.5 mm to give 27 g of faintly yellow oil. Fractional distillation of this material at 0.3 mm gave, first, a fraction, bp 32–50° (0.3 mm), which consisted of chlorocyclooctenes and chlorocyclootadienes, and then the product, *exo*-2-acetyl-6-chlorobicyclo[3.3.0]octane (**16**), bp 88–90° (0.3 mm) (identified by comparison of its spectra with those of a sample prepared earlier.[5]) Analysis on a 20-ft column of silicone rubber showed two partially resolved peaks in a ratio of ~70:30, the *exo*- and *endo*-chloro compounds, respectively.

When stannic chloride was added slowly to a equimolar mixture of acetyl chloride and 1,5-cylooctadiene at −50°, there was obtained on work-up a fraction which was mainly ketone **16**, corresponding to a yield of *ca.* 45%. However, the sample obtained in this manner appeared to be less pure than that obtained using aluminum chloride, as shown by the presence of vinyl hydrogen signals at τ 4.2 in its nmr spectrum. The intensity suggests a content of ~5% of an unsaturated chloro ketone.

Conversion of Chloro Ketone 16 to Dione 20.—To a solution of chloro ketone **16** (92 g, 0.50 mol) in acetic acid (400 ml) was added silver acetate (100 g, 0.60 mol) and the resulting suspension was heated at 100 ± 5° for 12 hr. The bulk of the acetic acid was removed by evaporation under reduced pressure; ether (300 ml) was added; and the suspension was filtered through Celite. The solvents were evaporated from the filtrate and the residue was distilled. After a small forerun of unsaturated ketones, bp 45–50° (0.2 mm) (4 g), the mixture of 2-acetyl-6-acetoxybicyclo[3.3.0]octane epimers, **17**, bp 90–96° (0.2 mm), ir (film) 1705 and 1727 cm^{-1}, was collected (59 g, 56%). Analysis on columns A and B showed three components; however, the resolution was poor. When potassium acetate in refluxing acetic acid was employed instead of silver acetate as described above, there was obtained on distillation two fractions. The higher boiling fraction, bp ~95° (0.2 mm) (45 g, 43%), was a mixture of stereoisomers of structure **17**, contaminated with ~2% of unchanged **16**. The lower boiling fraction, bp 40–46° (0.3 mm) (17 g, 22%), consisted of three components in the ratio 16:26:58 (10 ft × 0.25 in. QF-1). The major component **21** was obtained pure by collection from column A, or in larger amounts, by purification and cleavage of the semicarbazone. A sample thus obtained exhibited the following spectral properties: ir (film) 1681 cm^{-1}; nmr (CCl_4) complex absorption at τ 6.9–8.6; uv (CH_3OH) max 244 nm. Hydrogenation at 10 psi, over palladium/charcoal in ethyl acetate solution, gave a quantitative yield of *endo*-2-acetylbicyclo[3.3.0]octane, identical with an authentic sample. The semicarbazone of **21** crystallized from ethanol as shiny white

leaflets, mp 208.5–209.5°. *Anal.* Calcd for $C_{11}H_{17}N_3O$: C, 63.77; H, 8.21. Found: C, 63.40; H, 8.33.

The isomeric olefins **22** and **23** were identified by the spectral properties of the mixture [ir (film) 1712 and 3070 cm^{-1}; nmr (CCl_4) τ 4.5 (1.3 H, m)].

A solution of the 2-acetyl-6-acetoxybicyclo[3.3.0]octane isomers (**17**, 36 g) in chloroform (200 ml) was treated with *m*-chloroperbenzoic acid (85%, 45 g) and was refluxed gently for 16 hr. Hexane was added to the warm solution and the mixture was chilled in the refrigerator. The crystalline mass of *m*-chlorobenzoic acid was filtered and washed twice with 9:1 hexane–chloroform. The combined filtrates were evaporated to give a colorless, faintly cloudy oil whose infrared spectrum [ν_{max} (film) 1729 cm^{-1}] indicated it to be the desired diacetate, **18**. Distillation gave a colorless oil, bp 84–88° (0.2 mm). The diacetate thus obtained (32 g) was hydrolyzed by stirring overnight at 5–15° with 100 ml of 10% aqueous sodium hydroxide. The reaction mixture was extracted continuously with ether for 30 hr; the ether extracts were washed with saturated sodium chloride solution and concentrated under reduced pressure. The residue was distilled to give a mixture of stereoisomers of bicyclo-[3.3.0]octane-2,6-diol (**19**) as a colorless, extremely viscous syrup: bp 90–96° (0.3 mm) (11.4 g, 81% from **17**); ir (film) 3500 (broad) and 1050–1100 cm^{-1}. Analysis on a 20 ft × $^1/_8$ in. SE-30 column showed two components in a ratio 63:37, of respective retention times 10.8 and 11.6 min at 215°. Treatment of a sample with phenyl isocyanate at 80–100° without solvent for 0.5 hr and fractional crystallization of the reaction mixture from ethyl acetate–benzene gave two bis(phenylurethanes). The major, less soluble, isomer had mp 190–192°, whereas the minor isomer melted at 136–137°.

The diol mixture was oxidized by treatment of a solution in reagent grade acetone (10 g in 100 ml) with Jones reagent[16] (20 ml, 8 *N* in oxygen) and stirring at 20–30° for 6 hr. Most of the acetone was removed by evaporation under reduced pressure and the residue was treated with water (100 ml). The resulting mixture was extracted continuously with ether overnight; the ether extract was washed with saturated sodium chloride solution, dried, and concentrated under reduced pressure. The oil thus obtained (6.4 g) showed two peaks on column B at 200°, in a ratio of 80:20. The major component, collected from a 5 ft × $^3/_8$ in. Carbowax column, was identical (infrared spectrum and mixture melting point) with an authentic sample of bicyclo-[3.3.0]octane-2,6-dione. The minor component appeared to be a mixture of the epimers of 6-hydroxybicyclo[3.3.0]octan-2-one.

Registry No.—*cis*-Cyclooctene, 931-87-3; 1,3-cyclooctadiene, 1700-10-3; 1,5-cyclooctadiene, 111-78-4; **9**, 26908-76-9; **9** semicarbazone, 26908-77-0; **10**, 26908-78-1; **10** semicarbazone, 26963-84-8; **14**, 26908-79-2; **21**, 26908-80-5; **21** semicarbazone, 26908-81-6.

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(16) See L. F. Fieser and M. Fieser, "Reagents in Organic Synthesis," Wiley, New York, N. Y., 1967, pp 142–144.

The Isomerization and Chlorination of Decachlorobi-2,4-cyclopentadien-1-yl

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Decachlorobi-2,4-cyclopentadien-1-yl, $C_{10}Cl_{10}$, mp 125° (**1**), yielded on heating above its melting point or on contacting with aluminum chloride a mixture of isomeric chlorocarbons with extended conjugation (linear and cross). Structural assignments are given to the three major constituents of the equilibrium mixture, which is obtainable also from each of the pure isomers. A new structure is offered for the major photochlorination product of **1**, $C_{10}Cl_{12}$, mp 221–223° (**7**), replacing the methanoindene structure ("Diels–Alder dimer" of C_5Cl_6) previously assigned to this derivative. Two novel $C_{10}Cl_{12}$ compounds, obtained from the chlorination of **1**, were shown to be the endo and exo isomers of the true methanoindene chlorocarbons. A new structure is assigned to the known $C_{10}Cl_{14}$ chlorocarbon, mp 169°. ^{13}C nmr, ^{35}Cl nqr, ultraviolet, infrared, and mass spectral data as well as mechanistic rationalizations are given in support of the new structures and of the chemistry involved.

In the course of a study of the thermal stability of decachlorobi-2,4-cyclopentadien-1-yl, $C_{10}Cl_{10}$, mp 125° (**1**), a commercial acaricide, it was observed that the heating of **1** above its melting point, but below 240°, brought about complete isomerization.[1] When the isomerization was carried out to the point where the infrared spectrum of the mixture remained constant, none of the characteristic bands of **1** was detectable.

By elution chromatography over alumina or by suitable crystallization from acetic acid, the reaction mixture was separated into two pale-yellow (nearly colorless) $C_{10}Cl_{10}$ isomers of melting point 111° (**3**) and 82° (**4**) and one bright yellow isomer of melting point 114° (**5**). By heating each of these isomers under the original isomerization conditions, a mixture of all three was produced.

The ease of equilibration suggested that the three isomers differed from **1** only in regard to the position of the double bonds. That **3**, **4**, and **5** have the same carbon skeleton as the starting material **1** was confirmed by their catalytic hydrogenation to bicyclopentyl, $C_{10}H_{18}$, and by their photochemical chlorination to the known chlorocarbon $C_{10}Cl_{14}$, mp 169° (**6**), which also has been shown to yield bicyclopentyl on catalytic hydrogenation.[2]

Eight double bond position isomers of the $C_{10}Cl_{10}$ chlorocarbons with the bicyclopentyl skeleton are possible (excluding strained cumulene structures). Of these structures A was assigned[2] to the isomer with mp 125° (**1**) and confirmed by its ready dechlorination to perchlorofulvalene under mild reaction conditions.[3–5]

In the selection of structures for **3**, **4**, and **5** from the remaining seven alternatives (B to H), two with the

(1) E. D. Weil, U. S. Patent 3,219,710 (1965); *Chem. Abstr.*, **64**, 3377c (1965).

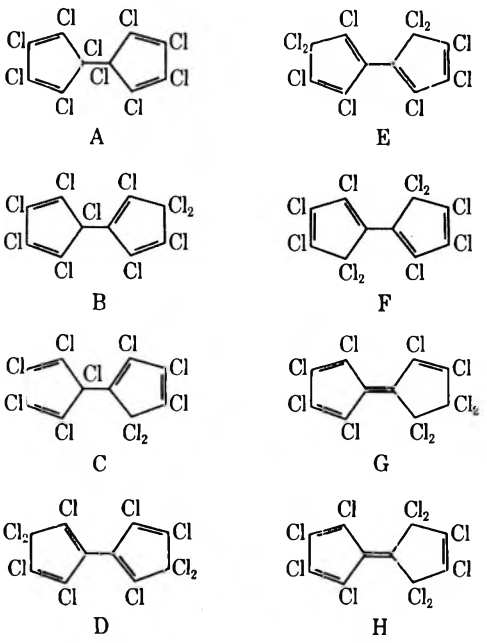
(2) E. T. McBee, J. D. Idol, and C. W. Roberts, *J. Amer. Chem. Soc.*, **77**, 4375 (1955).

(3) V. Mark, *Tetrahedron Lett.*, 333 (1961); *Org. Syn.*, **46**, 93 (1966).

(4) (a) None of the new $C_{10}Cl_{10}$ isomers, **3**–**5**, yield perchlorofulvalene under the conditions reported. Instead they undergo an alkylation reaction, similar to that described for polyhalocyclopentadienes[4b] which will be the subject of a separate publication. (b) V. Mark, *Tetrahedron Lett.*, 296 (1961).

(5) D. C. F. Law, Ph.D. Thesis, The University of Wisconsin, 1966.

fulvenoid features (G and H) can be excluded on the basis of the absence of intense absorption in the visible region.[6]



On the basis of converging evidence to be discussed below, structures D, E, and F are suggested for **3**, **4**, and **5**, respectively.

Ultraviolet Spectra.—These were as follows (λ_{max} isooctane, ϵ in parentheses): **3**, 207 mμ (16,500), 274 (5800), and 327 (2400); **4**, 205 (12,600), 228 (shoulder), and 319 (4200); **5**, 204 (18,100), 233 (6900), and 352 (4650). The long wavelength maximum of **5**, which tails into the visible region accounting for its yellow color, represents a marked bathochromic shift relative to analogs with two conjugated bonds[8] and suggests a more extended conjugation, thus excluding structures B and C for **5**.[9]

(6) (a) Perchlorofulvalene has maxima at 277 mμ (ε 9850), 288 (16,100), 298 (22,300), 309 (21,600), 322 (11,500), and 444 (320) in cyclohexane[12] (at 450 mμ in benzene[7]), and perchlorofulvalene has maxima at 386 mμ (ε 36,000) and 590 (500) in isooctane.[3-5] (b) Very recently the preparation of H [λ_{max} 512 mμ (ε 230), 302 (18,600), and 227 (sh)] and of C [324 mμ (ε 3720) and 228 (sh)] by the chlorination of perchlorofulvalene under mild conditions was reported.[6a] (c) R. West and R. M. Smith, *J. Org. Chem.*, **35**, 2681 (1970).

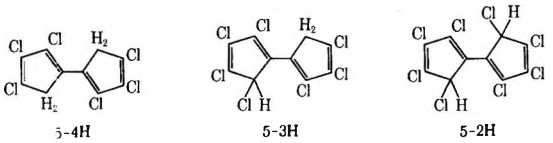
(7) A. Roedig, *Justus Liebigs Ann. Chem.*, **569**, 161 (1950).

(8) Under identical analytical conditions **1** has maxima at 280 mμ (ε 2060) and 330 (2800), and hexachlorocyclopentadiene (**2**), at 324 mμ (ε 1670).

(9) No appropriate chlorocarbon model could be located for the ultraviolet spectra of cross-conjugated systems (D and E). It is probable that no definite conclusion could be obtained from the ultraviolet parameters of hydrocarbon models even if they were available, since steric interactions due to the presence of chlorine may drastically affect the planarity and hence the electronic spectrum of the system.[10,11]

(10) The X-ray analysis of perchlorofulvalene shows, for instance, that the cyclopentadiene rings are twisted through an angle of 41° due presumably to nonbonding chlorine–chlorine repulsion: P. J. Wheatley, *J. Chem. Soc.*, 4936 (1961).

(11) Steric repulsion and resultant enhanced deviation from coplanarity are probably the cause of the hypsochromic shift in **5** (for which structure F is assigned; *vide infra*) relative to its orange-colored hexa-, hepta- and octachloro analogs, which have the longest wavelength maxima at 370–380 mμ and for which structures **5**-4H, **5**-3H, and **5**-2H, respectively, have been proposed.[5]



Infrared Spectra.—The infrared maxima of **3**, **4**, and **5** are abstracted in Table I. Inspection and analysis

TABLE I
INFRARED PARAMETERS OF CHLOROCARBONS 3–5[a]

3	4	5
1640 m	1650 m	
1610 s		
1600 s	1600 vs	
1580 m	1585 s	1590 vs
	1550 m	1540 s
1306 m	1299 m	1282 w
	1235 vs	1230 vs
1209 s		
1190 m	1193 s	
1180 s	1177 s	1173 m
1140 s	1144 s	1153 s
	1125 m	
1035 m		
	1009 w	
		992 w
	970 m	962 m
896 s	900 s	903 s
808 vs	812 vs	807 vs
755 s		
	737 m	
729 s		728 w
		699 m
676 s	668 s	665 s
	553 m	
550 w	547 m	550 s
537 s	533 m	533 w

[a] Absorption peaks, cm^{-1}; vs, very strong; s, strong; m, medium; w, weak.

of the data yield the following interpretation. (a) All three isomers contain very strong maxima in the 807–812 cm^{-1} region. A maximum in this region is characteristic of the CCl_2 group between two double bonds in chlorinated five-membered cyclic systems and may be ascribed to the asymmetric C–Cl stretch.[12] The somewhat weaker absorptions in the 665–710 cm^{-1} regions might be the symmetric stretching of the CCl_2 group and the C–Cl bending modes.[12] Compound **1**, which lacks this feature, has no comparable strong absorption at 807–812 cm^{-1} but shows three maxima between 645 and 705 cm^{-1}, ascribable to C–Cl bending and to the tertiary C–Cl stretching modes. (b) A second region of very strong absorption common in all three isomers is between 1209 and 1235 cm^{-1}; the corresponding maxima in hexachlorocyclopentadiene (**2**) and **1** are at 1230 and 1250 cm^{-1} and are assigned as ring-breathing vibrations.[13] (c) The third area of high maxima is due to the C=C stretching vibrations. Hexachlorocyclopentadiene (**2**) and compounds **1** and **5** have only one very strong and one medium intensity peaks,

(12) V. Mark, unpublished correlations. As representative examples, the following compounds can be cited: hexachlorocyclopentadiene 804 (vs), 680 (s); octachloro-4-methylene-1-cyclopentene (mp 183°) 806 (vs), 665 (s); octachloroindene 805 (s), 650 cm^{-1} (s); chlorocyclopentadienes with no CCl_2 function (*e.g.*, 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene, perchlorofulvalene) have no strong absorption in the 800–815 cm^{-1} region. When the dichloromethylene group becomes adjacent to one double bond only in the polychlorocycloolefin ring strong maxima occur in the 750–785 cm^{-1} region (*e.g.*, tetrachlorocyclopropene 750, hexachlorocyclobutene 783, octachlorocyclopentene 755, octachloro-1,2-dimethylenecyclobutane 780, decachloroindan 752 cm^{-1}).

(13) (a) H. Gerding, H. J. Prins, and H. van Brederode, *Recl. Trav. Chim. Pays-Bas*, **65**, 168 (1946); (b) J. C. Wood, R. M. Elofson, and D. M. Saunders, *Anal. Chem.*, **30**, 1341 (1958).

whereas **3** and **4** have four peaks each in this region (1540–1650 cm^{-1}).

An interesting feature emerges from the comparison of the infrared spectra of these isomers: most of the bands present in the spectrum of **4** are either a reproduction of the maxima present in both **3** and **5**, or they are single bands at an intermediate position. This observation, in conjunction with the conclusion derived from the ultraviolet spectra, suggests the assignment of the symmetrical structures D and F to the isomers with the simpler spectra, **3** and **5**, respectively, and the assignment of the unsymmetrical structure E to the isomer **4** with the hybrid spectrum.

Best support for the structures of compounds **3**–**5** is provided by their ^{13}C nmr (cmr) spectra. These, together with the spectra of **1** and **2**, are abstracted in Table II. As is the case in the nonchlorinated hydro-

TABLE II

^{13}C NMR PARAMETERS OF CHLOROCARBONS **1**–**6**, **9**, **10**, **12**[a]

Compd	sp^2 carbons	sp^3 carbons
1	60.8, 61.8	119.7
2	59.2, 63.8	110.6
3	51.8, 61.1, 64.3, 67.0	110.5
4	49.6, 54.9, 55.9, 59.4, 61.9, 62.9, 64.5, 66.5	109.7, 110.4
5	54.3, 54.5, 60.4, 64.7	109.4
9	51.5, 54.1, 57.4, 60.9	94.9, 99.5, 104.0, 106.1, 109.0, 109.5
10	57.8, 59.3, 61.4, 63.7	88.2, 98.4, 104.6, 106.3, 107.9, 109.5
6	48.3, 61.8	91.6, 99.7, 100.7
12	57.6	93.4, 99.9

[a] δ, ppm, upfield from CS_2 (0.0 ppm).

carbon analogs, there is a clear and wide spread separation in the resonances of the sp^2 and sp^3 carbons, the latter occurring at higher field.[14] It is evident that the various structures (A–H) considered above require the following numbers of nonequivalent carbons: A, 3; B and C, 8 each; D and F, 5 each; H, 6; E and G, 10 each. Since compounds **3**, **4**, and **5** have 5, 10, and 5 resonance peaks of equal intensities, respectively, and thus the same numbers of magnetically different carbons, it is apparent that on the basis of the cmr spectra alone all structures except those of D–G can be excluded from further consideration. Since the electronic spectrum already eliminated G as a possible structure, the presence of ten different carbons in the cmr spectrum identifies **4** definitely with structure E. With further help from uv (*vide supra*) of the two remaining structures, F is assigned to **5** and D to **3**. The good match of the ten chemical shifts of the hybrid structure **4** with those of the two pure constituent compounds, **3** and **5**, possessing five resonance peaks each is noteworthy. As expected, compounds **3**, **4**, and **5** had peaks of about equal intensities, whereas **1** and **2** showed the correct 2:2:1 ratios for the sp^2:sp^2:sp^3 carbons.

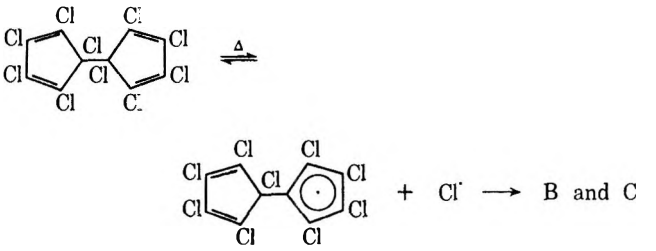
On the basis of these data and interpretation, we propose structures D, E, and F for the bicyclic $C_{10}Cl_{10}$ chlorocarbons **3**, **4**, and **5**, respectively.[15]

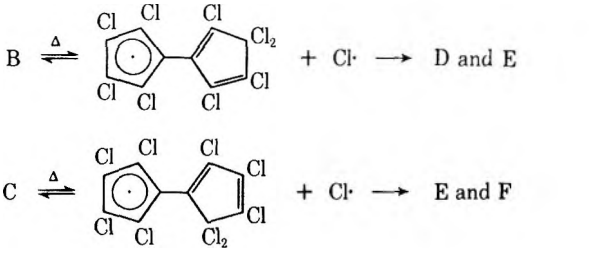
(14) J. B. Stothers, *Quart. Rev., Chem. Soc.*, **19**, 144 (1965).

(15) The assigned structures are also consistent with the relative chromatographic elution rates (**1** > **3** > **4** > **5**) over alumina. The low melting point of **4** is again more compatible with the hybrid structure E than with those having elements of symmetry and thus, very likely, better packing in the crystal lattice.

The only previous reference in the literature to an isomer of **1** is found in a paper by Rabovskaya and Kogan, who obtained a $C_{10}Cl_{10}$ compound, mp 110.1–110.3°, from the γ-ray irradiation of **2** and to which they have assigned structure B or C.[16] On the basis of the data presented above, we propose the reassignment of the structure for their chlorocarbon, mp 110.1–110.3° (whose published infrared spectrum is identical with that of our compound **3**), to D.

The probable mechanism of the thermal isomerization of **1** to **3**, **4**, and **5** involves a homolytic C–Cl bond rupture on the doubly allylic sp^3 carbon.[17] Recombination of Cl with the organic radical would yield A, B, or C. Since the tertiary sp^3 carbon in B and C is triply allylic, an even more facile cleavage of the carbon–chlorine bond to the corresponding stabilized radicals is expected.[6b,c] These, on recombination with Cl would yield D, E, and F.[18]





The fact that pure **1**, **3**, **4**, and **5** on thermolysis yield exactly identical reaction mixtures indicates a thermodynamic control and the relative abundance of D (**3**) and E (**4**) over F (**5**) suggests that steric influences outweigh conjugation effects.

The isomerization of **1** was also effected under mild conditions by aluminum chloride yielding essentially the same equilibrium mixture that results from the thermal reaction.[20] A mechanism similar to that outlined above is proposed, except that Cl· is replaced by

(16) N. S. Rabovskaya and L. M. Kogan, *Proc. Acad. Sci. USSR*, **165**, 1094 (1965). *Dokl. Akad. Nauk SSSR*, **165**, 337 (1965); *Chem. Abstr.*, **64**, 4899 (1966).

(17) The equally feasible homolytic rupture of the C–C bond connecting the two rings probably also takes place. Recombination of the two pentachlorocyclopentadienyl radicals, however, would result in the formation of unisomerized **1** only.

(18) Present data do not indicate the detailed mode of the chlorine migration. In a study of the thermal isomerization of protio cyclopentadienes, rearrangement involving an intramolecular 1,2 hydrogen shift was proposed.[19]

(19) S. McLean and P. Haynes, *Tetrahedron*, **21**, 2329 (1965).

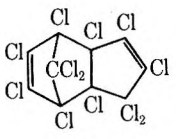
(20) We observed that the use of more than catalytic amounts of $AlCl_3$ resulted in the formation of an additional $C_{10}Cl_{10}$ isomer, mp 173–174°. The structure determination and chemistry of this novel chlorocarbon, which structurally is not directly related to **3**–**5**, are the topics of a separate publication.[21]

(21) R. M. Smith, R. West, and V. Mark, *J. Amer. Chem. Soc.*, in press.

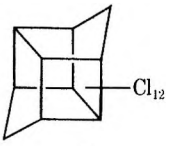
$AlCl_4^-$ and the cyclopentadienyl radicals are replaced by the corresponding cyclopentadienyl cations.[22]

The energy relationships of the proposed mechanism outlined above for the formation of **3**, **4**, and **5** from **1** also support structures D, E, and F for these isomers and militate against B and C.

In contradistinction to **1**, isomers **3**, **4**, and **5** yield on chlorination the known bicyclic chlorocarbon $C_{10}Cl_{14}$ (**6**), mp 169°, for which the bicyclopentyl skeleton basis was demonstrated.[2] The chlorination of **1**, however, was reported to yield $C_{10}Cl_{12}$, mp 221–223° (**7**), for which a structure (J) with a rearranged carbon skeleton (4,7-methanoindene) of undefined stereochemistry was proposed.[2] This earlier assignment of structure J to **7**



J

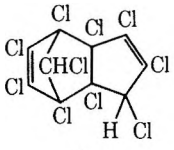


K

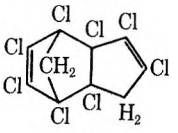
was based on the following information: elemental analyses, ir and uv spectra [λ_{max} 232 mμ (ϵ 19,500) in either hexane, cyclohexane, or ethanol], its conversion to the cage structure [K, $C_{10}Cl_{12}$, mp 485° (**8**)] by $AlCl_3$ and SbF_3–$SbCl_5$, and its thermolysis at 340° to hexachlorocyclopentadiene (**2**).[2]

On the basis of the following data we would like to suggest an alternate structure for the $C_{10}Cl_{12}$ chlorocarbon **7**, mp 221–223°.

(a) The infrared spectrum of **7** shows a very sharp and narrow band at 1600 cm^{-1}, suggesting the presence of only one kind of double bond in the molecule. Chlorocarbons with the established carbon skeleton of J, *e.g.*, L and M,[25] have two C=C stretching modes in their



L



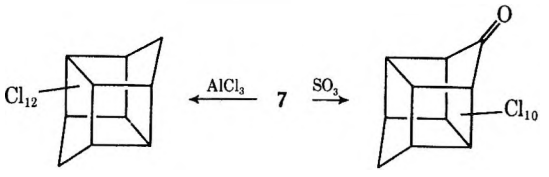
M

spectra (at 1625–1630 and at about 1605 cm^{-1}, respectively) corresponding to the two kinds of double bond in the molecule. It would be anticipated that a compound possessing structure J would also display two different double bond stretching vibrations.

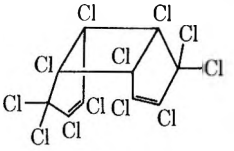
(b) When the chlorination of **1** was repeated photochemically under conditions similar to those specified, (method A) and compound **7** was separated by crystallization, infrared analysis of the mother liquor fractions revealed the presence of several additional compounds. These included small amounts of unreacted starting material **1**, the cage $C_{10}Cl_{12}$ chlorocarbon (**8**), and the bands of what were subsequently found to be two new $C_{10}Cl_{12}$ isomers, **9**, mp 186–187°, and **10**, mp 237–239°. Both **9** and **10** displayed in their infrared spectra two strong C=C stretching modes each (**9** at 1615 and 1630, and **10** at 1600 and 1630 cm^{-1}) and were assigned the exo and endo 4,7-methanoindene structures, respectively (*vide infra*).

(c) Under mild reaction conditions (room temperature), **7** was transformed by aluminum chloride quantitatively into the known isomeric cage chlorocarbon **8**.[2]

(d) Under similar mild conditions **7** yielded on contacting with sulfur trioxide in high conversion the known cage ketone, $C_{10}Cl_{10}O$ (**11**), in the form of its hydrate.[26] On the basis of these data and of the argument presented below, we propose the novel structure N (dodecachloro-1,3a,3b,4,6a,6b-hexahydro-*syn*-cyclobuta[1,2:3,4]dicyclopentane) for chlorocarbon $C_{10}Cl_{12}$, mp 221–223° (**7**), which is to replace the 4,7-methanoindene structure previously assigned to this compound.[2]



8 11



N

Analysis of structure N requires several stereochemical considerations.

(a) The first was the mode of fusion of the five-membered and four-membered rings. It is assumed that the fusion of the rings is cis. Although examples of trans-fused 5–4 bicyclic rings are known, their only known method of preparation involves the creation of the cyclopentane rings from a preformed trans-1,2-substituted cyclobutane.[27] No examples were found of trans-fused 5–4 rings from cyclization of monosubstituted cyclobutenes or cyclopentenes. It seems highly unlikely that the mild reaction conditions employed in the chlorination of **1** would allow the exclusive formation of trans-fused 5–4 rings in view of the inherent strain of this system, which is further augmented by the bulky chlorine substituents and by the double fusion.[28]

(b) The second was the syn *vs.* anti relationship of the two cis-fused cyclopentene rings. Evidence favoring the syn structure rests on the facile and essentially quantitative cyclization of **7** to **8** and to **11**, a process which requires a syn relationship of the five-membered rings. Although a multistep carbonium ion mechanism could be devised for the isomerization of an anti-fused cis,cis-5–4–5 ring system to the corresponding syn

(22) The facile formation at room temperature of pentachlorocyclopentadienyl radical and cation (a ground-state triplet) from hexachlorocyclopentadiene and Lewis acids has been reported.[23] A red 1:1 adduct of **2** and $AlCl_3$ has also been isolated and its magnetic and spectral properties accounted for on the basis of a partially ionic cyclopentadienyl cation.[24]

(23) R. Breslow., R. Hill, and E. Wasserman, *J. Amer. Chem. Soc.*, **86**, 5349 (1964).

(24) H. P. Fritz and L. Schafer, *J. Organometal. Chem.*, **1**, 318 (1964).

(25) H. E. Ungnade and E. T. McBee, *Chem. Rev.*, **58**, 249 (1958).

(26) (a) E. T. McBee, C. W. Roberts, J. D. Idol, and R. H. Earle, *J. Amer. Chem. Soc.*, **73**, 1511 (1956); (b) D. H. Zijp and H. Gerding, *Recl. Trav. Chim. Pays-Bas*, **77**, 682 (1958); (c) P. Eaton, E. Carlson, P. Lombardo, and P. Yates, *J. Org. Chem.*, **25**, 1225 (1960).

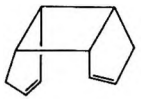
(27) (a) N. L. Allinger, M. Nakazaki, and V. Zalkow, *J. Amer. Chem. Soc.*, **81**, 4074 (1959); (b) J. Meinwald, J. Tufariello, and J. Hurst, *J. Org. Chem.*, **29**, 2914 (1964).

(28) Were only one of the five-membered rings fused trans to a cis-5–4 system, the effect of dissimilar strains would result in the presence of two different double bond stretching vibrations. It is characteristic for **7** the very sharp single band at 1600 cm^{-1} corresponding to this mode.

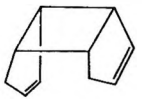
isomer, such a process seems energetically unfavorable.[29] Superimposed on the unfavorable energy relationship is the added steric influence of the bulky chlorine substituents which renders the syn,cis,cis-5–4–5 chlorocarbon even less favored in a hypothetical equilibrium reaction. Strong support for this reasoning comes from experiments in which **9** and **10** were exposed to aluminum chloride under the same mild conditions that resulted in the quantitative cyclization of **7** to **8**. The exo isomer **9** remained completely unaffected, while the endo isomer **10** underwent complete isomerization to the cage compound **8** (*vide infra*). The all-exclusive cyclization reaction of **7** to **8** is favored probably by the presence of already one cylcobutane ring in the molecule, which not only reduces the energy requirement of the overall cyclization process, but establishes a better bonding relationship (shorter distances) between the pertinent protons of the reaction intermediates. Even when both cyclobutane rings need be formed, as in **10** → **8**, no other products (*e.g.*, **9**) were detected in the reaction mixture.

These results indicate that under the mild conditions employed the ring fusions are not severed; the substrates either undergo quantitative cyclization (**7**, **10**) or they are recovered unaltered (**9**), but in both cases the original ring fusions are apparently completely preserved.

(c) The final step in the assignment of structure to chlorocarbon **7** concerns the position of the two double bonds. The cyclization experiments, resulting in the formation of **8** and **11**, and the infrared spectrum of **7** clearly indicate that the double bonds cannot be part of or attached to the cyclobutane ring, leaving structures N and O as the only alternatives. A rather unambigu-



N



O

ous choice between the two isomers can be made with the aid of appropriate molecular models, which indicate a prohibitive crowding of two of the allylic chlorines facing each other in O but do accommodate them in N.[30]

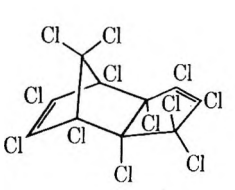
Although the low solubility of **7** at room temperature in all solvents tried precluded the determination of its cmr parameters by natural abundance ^{13}C nmr spectroscopy, additional support for the proposed structure was provided by its ^{35}Cl nuclear quadrupole resonance (nqr) spectrum. This showed the presence of three types of chlorines: two vinylic chlorines having the lowest frequency resonances (37.2 and 37.8 MHz), two geminal chlorines (38.0 and 38.3 MHz), and two bridgehead chlorines (at 39.5 and 40.0 MHz).[31] Considerably more resonance peaks were observed in the nqr spectrum of one of the methanoindene chlorocarbon isomers (*vide infra*).

Having determined the structure of the major product **7** of the light-catalyzed chlorination of **1** as being N,[32] we turned next to the analysis of the two novel chlorocarbons **9** and **10**.

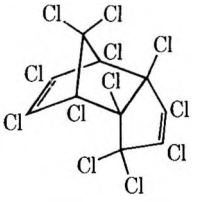
The two strong C=C stretching bands present in the infrared spectra of **9** (at 1616 and 1630 cm^{-1}) and **10** (at 1600 and 1630 cm^{-1}) suggest the presence of two different kinds of double bond in the molecule. Doublets at similar frequencies occur in the spectra of both L and M, further suggesting that the four compounds might have similar or the same carbon skeletons and that, indeed, **9** and **10** might be the exo and endo isomer pair of the chlorocarbon represented by the planar structure J. To ascertain this, both **9** and **10** were treated, under mild and identical reaction conditions, with aluminum chloride. Decomposition of the dark methylene chloride solutions by water led to the essentially quantitative recovery of **9**, whereas **10** yielded exclusively the cyclized cage isomer **8**.

The ultraviolet spectra of **9** and **10** displayed no maxima above 220 mμ thus indicating the absence of *de facto* conjugation of double bonds. While no nqr spectrum of **10** could be obtained at room and at liquid nitrogen temperature,[31c] isomer **9** showed four vinylic chlorines (between 36.91 and 37.51 MHz), four geminal chlorines (between 38.30 and 38.67 MHz), and four chlorines on tertiary carbons (between 39.13 and 39.60 MHz), thus indicating the presence of twelve distinct, nonequivalent chlorine substituents in the molecule.[31]

The analytical, spectroscopic, and isomerization data thus suggest that **9** and **10** do indeed possess the structure represented by the planar formula J and that **9** is the exo and **10** is the endo isomer.[34]



$C_{10}Cl_{12}$, mp 186–187°
9, J (*exo*)



$C_{10}Cl_{12}$, mp 237–239°
10, J (*endo*)

Convincing proof for the proposed structures was again provided by the cmr spectra of the chlorocarbons.

(29) The prevalence or the exclusive formation of the anti (trans) isomers in ring-fused or tetrasubstituted cyclobutanes is apparent from the several pertinent examples of [2 + 2] cycloaddition products illustrated in a review article by R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes," S. Patai, Ed., Interscience, New York, N. Y., 1964, pp 779–798.

(30) All efforts (*e.g.*, *via* thermolysis) to obtain the isomer of **7** corresponding to O resulted only in partial isomerization to **8** or reversion to the bicyclic ring system or in degradation and disproportionation yielding a variety of C_5, C_{10}, C_{15}, and indene chlorocarbons.

(31) (a) Nqr spectra of related pertinent chlorocarbons,[6c] including those of **2**,[31b] have been analyzed. (b) M. Hayek, D. Gill, I. Agranat, and M. Rabinovitz, *J. Chem. Phys.*, **47**, 3680 (1967), and references listed. (c) Being run on samples in solid state the nqr spectra are strongly dependent on the crystal structure(s) of the compound; for instance, merely freezing a liquid sample often results in no nqr spectrum at all.[31b]

(32) The photochemical bromination of **1** was reported to yield a dibromodecachloro analog (**7**-Br) ($C_{10}Br_2Cl_{10}$, mp 147°) of **7**, for which a structure analogous to J was proposed.[33] Based on the very close similarity between the infrared spectra of **7**-Br and **7**, we wish to suggest the N framework for **7**-Br as well, in which the two bromines occupy one of the allylic carbons each. As anticipated from its structure, **7**-Br was readily cyclized in high yield by $AlBr_3$ to a double bond-free dibromodecachloro analog of **8**.

(33) R. D. Crain, Thesis, Purdue University, 1958.

(34) A compound, $C_{10}Cl_{12}$, mp 328–329°, with the J (*exo*) structure has been reported in the literature.[35] The structure assignment was based on chlorine analysis and dipole moment. Due to the lack of additional and more meaningful structural data (*e.g.*, ultraviolet and infrared spectra, molecular weight), to the ambiguous nature and notoriously poor performance of dipole moment interpretation as a means of structural assignment,[36] to the drastic conditions (250–260°, 60 hr), and to the poor yield (5%), a reinvestigation of the structure of the above chlorocarbon seems desirable.

(35) B. A. Arbuzov and A. N. Vereshchagin, *Bull. Acad. Sci. USSR*, 586 (1965); *Chem. Abstr.*, **63**, 4142*d* (1965).

(36) A critical analysis of some of the difficulties encountered in the application of dipole moment data to structural assignments is given by J. G. Tillett, *Quart. Rep. Sulfur Chem.*, **2**, 227 (1967); for an example in a different area, see A. T. Blomquist and A. G. Cook, *Chem. Ind. (London)*, 873 (1960).

TABLE III

MASS SPECTRAL PARAMETERS OF THE $C_{10}Cl_{12}$ ISOMERS 7, 9, AND 10

	Relative intensities of the higher fragments[a]													
m/e	540	505	470	435	400	388	365	353	330	318	306	295	283	270
Compd	$C_{10}Cl_{12}^+$	$C_{10}Cl_{11}^+$	$C_{10}Cl_{10}^+$	$C_{10}Cl_9^+$	$C_{10}Cl_8^+$	$C_9Cl_8^+$	$C_{10}Cl_7^+$	$C_9Cl_7^+$	$C_{10}Cl_6^+$	$C_9Cl_6^+$	$C_8Cl_6^+$	$C_{10}Cl_5^+$	$C_9Cl_5^+$	$C_5Cl_6^+$
7	0.1	0.4	8.7	1.7	100	2.1	12.4	2.2	99.7	0.5	5.3	6.8	2.1	28.1
9	0.07	0.5	4.8	37.0	100	0.09	5.2	11.3	31.6	2.4	5.0	19.2	7.3	24.6
10	0.4	0.4	6.6	58.0	100	1.6	6.6	14.7	49.5	2.8	8.8	3.8	9.3	57.7
13					77.7	0	20.2	1.5	100	0	7.4	19.9	0	0

[a] Relative intensities, in per cent, refer to the lowest mass peak in each cluster. The spectra did not contain metastable peaks to determine the fragmentations leading to the C_9 and C_8 series of ions.

These, obtained with samples containing ^{13}C in its natural abundance (1.1%), are abstracted in Table II. Both **9** and **10** displayed ten peaks each of equal intensities and in three distinct regions. The frequencies farthest downfield, between 51.5 and 63.7 ppm, belong to the olefinic carbons, and the presence of four separate peaks in each isomer indicates the four nonequivalent sp^2 carbons required by the nonsymmetrical structures **9** and **10**. The second region, between 88.2 and 99.5 ppm, comprises the dichloromethylene carbons, represented by two peaks in each isomer. Frequencies belonging to the third region, between 104.0 and 109.5 ppm, are those of the four tertiary (bridgehead) carbons.

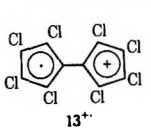
Further confirmation of the structures proposed for **9** and **10** was obtained from their mass spectra which, together with those of **7** and perchlorofulvalene, **13** (reference compound), are abstracted in Table III. Although all three $C_{10}Cl_{12}$ compounds showed the correct, but very weak, molecular ions and yielded $C_{10}Cl_8^+$ ions as the most abundant component, there was a discernible difference in the subsequent fragmentation patterns. Thus while the $C_{10}Cl_8^+$ fragment originating from **7** yielded an equally abundant $C_{10}Cl_6^+$ species, thus closely resembling the pattern of **13**, those obtained from **9** and **10** yielded less abundant $C_{10}Cl_6^+$ descendants. Unfortunately, the spectra did not contain diffuse peaks corresponding to metastable ions leading to, and revealing, skeletal fragmentation patterns; they rather indicated the gradual and extensive stripping of chlorines from the carbon framework.[37] A noteworthy difference, however was found at *m/e* 270, corresponding to $C_5Cl_6^+$; the endo $C_{10}Cl_{12}$ isomer, **10**, produced twice as abundant peaks of this species as did its exo isomer **9** and compound **7**. This indicates that **10** undergoes, expectedly, a more facile retro-Diels–Alder reaction than does its stereomer[38] and that both **9** and **7** yield fair amounts of C_5Cl_6 cleavage products, the latter presumably by a retro [2 + 2] addition. When the chlorination of **1** was carried out under conditions favorable to an ionic mechanism (in the dark and catalyzed by aluminum chloride), **9** and **10** became the major products.[40]

Much of the difference in the product distribution of the chlorination of **1** by the photochemical or by the aluminum chloride catalyzed routes can be interpreted by the probable mechanism underlying the reactions. Assuming that the light-catalyzed process involves a chlorine radical initiator which adds to the conjugated system to yield preferentially the allylic radical **1A** (Scheme I) and that the aluminum chloride catalyzed reaction involves the sequence initiated by a chloronium ion to yield preferentially **1B**, the evolvement of both reactions can be illustrated by the flow diagram outlined in Scheme I.

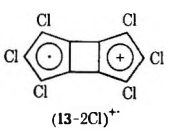
The major product of the photochlorination of **1** is **7**, which is best derived from the allylic radical involving both termini of one of the unsaturated systems, *i.e.*, **1A** (the "1,4 adduct").[41a,b] Ring closure with the other cyclopentadiene moiety, which, assuming the principle of least motion,[44] is gauche (and not trans)[45] oriented, is followed by the uptake of a second chlorine atom resulting in the formation of **7**. The change occurring on the second cyclopentadiene ring corresponds to a 1,2 addition[41a] and is probably the result of a steric effect which prevents the analogous chlorine terminated 1,4 addition[41a] to take place (*vide supra*). That addition of the latter kind, albeit not terminated directly by chlorine, can still take place is evidenced by the formation of **8**; the radical species formed on the second cyclopentadiene ring *via* a 1,4 addition,[41a] not being able to abstract or to take up chlorine, undergoes two additional cyclization steps and yields the fully saturated bishomocubane chlorocarbon.

A second possible (but unlikely) mode of cyclization of **1A** is addition of the cyclopentenyl radical to one of

(37) The similarity between **7** and **13** (which incidentally yielded, as expected, a very abundant molecular ion) in their mass spectral behavior could tentatively be rationalized by the occurrence in the $C_{10}Cl_8^+$ and $C_{10}Cl_8^+$ fragments of considerable amounts of ions **13**$\cdot^+$ and (**13**-2Cl)$\cdot^+$, presumed to be common to both compounds. Ions with the same mass numbers originating from **9** and **10** might contain tricyclic and bicyclic species other than or in addition to those shown above (*e.g.*, ions with the methanoindene and methyleneindene skeletons).



13$^{+\cdot}$



(**13**-2Cl)$^{+\cdot}$

(38) A recent, thorough analysis of the mass spectral fragmentation patterns of a variety of highly chlorinated bridged-ring compounds indicated the ready occurrence of retro-Diels–Alder fragmentation in appropriate precursors.[39]

(39) R. Binks, K. Mackenzie, and D. L. Williams-Smith, *J. Chem. Soc. C*, 1528 (1969).

(40) To avoid isomerization, a solution of **1** in methylene chloride was first saturated with chlorine in the dark and only then was aluminum chloride introduced.

(41) (a) The numbering 1,4 and 1,2 is intended to show only the relative positions of the carbon atoms directly affected in the particular steps or in the overall reaction. (b) Examples for 1,4 addition in the photochlorination of polychlorocyclopentadiene substrates are provided by 1,2,3,4-tetrachlorocyclopentadiene,[42] 5,5-dimethoxytetrachlorocyclopentadiene,[43] and perchlorofulvalene.[7]

(42) A. Roedig and L. Hornig, *Chem. Ber.*, **88**, 2003 (1955).

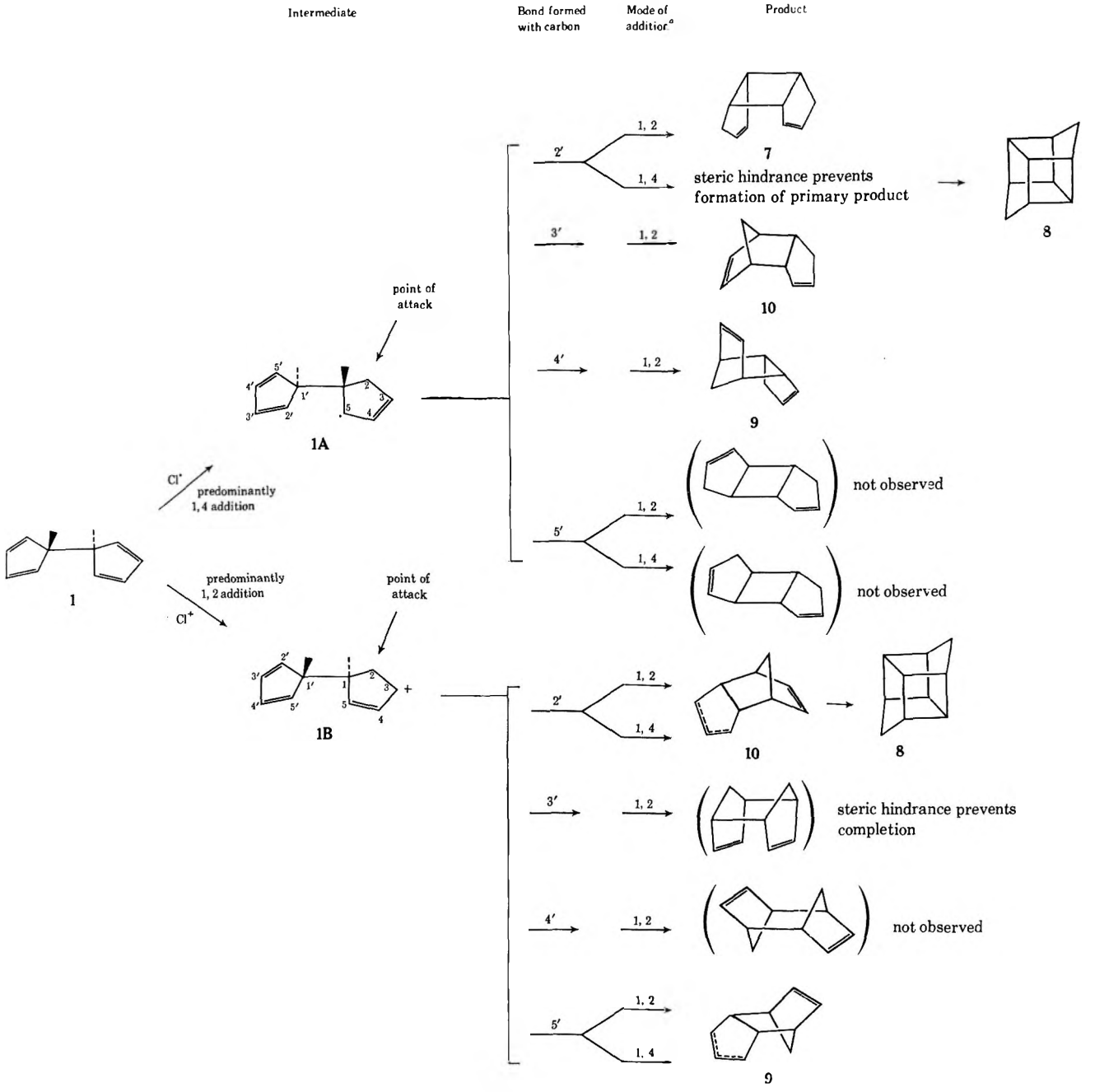
(43) E. T. McBee, D. L. Crain, R. D. Crain, L. R. Belohlav, and H. P. Braendlin, *J. Amer. Chem. Soc.*, **84**, 3557 (1962).

(44) F. O. Rice and E. Teller, *J. Chem. Phys.*, **6**, 489 (1938); *ibid.*, **7**, 199 (1939); J. Hine, *J. Org. Chem.*, **31**, 1236 (1966); J. Hine, *J. Amer. Chem. Soc.*, **88**, 5525 (1966); S. I. Miller, *Advan. Phys. Org. Chem.*, **6**, 185 (1968); O. S. Tee, *J. Amer. Chem. Soc.*, **91**, 7144 (1969).

(45) Were the cyclopentadiene rings oriented in a predominantly anti fashion to each other, cyclization would have resulted, applying the principle, in cis, anti,cis products, none of which was detected in the reaction mixture.

SCHEME I

MECHANISTIC SCHEME FOR THE CHLORINATION OF 1 (CHLORINE SUBSTITUENTS ARE OMITTED FROM STRUCTURES)



[a] 1,2 and 1,4 indicate the positions of attachment of the second chlorine reactant species (Cl^+ or Cl^-) on the second cyclopentadiene ring relative to the newly formed C–C bond.

the center carbons (3′, 4′) of the adjacent cyclopentadienyl ring to form the minor products **9** and **10**. These, however, arise more likely from the 1,2 addition of Cl· to **1**, followed by cyclization of the allylic radical with the termini of unsaturation (reaction path corresponding to that of **1B**).

The relative proportions of products **7** *vs.* **9**, **10** are reversed when the chlorination of **1** is carried out in the dark and in the presence of aluminum chloride. As before, the initiation step seems to be attack on one of the termini of unsaturation, but this time by Cl^+. In contrast to **1A**, however, the carbonium ion species seems to be localized on the carbon adjacent to the point of attack, due probably to the involvement of a cyclic chloronium ion intermediate.[46,47] The major products are thus derivable from the cyclization of ion **1B** of Scheme I, involving each of the termini of unsaturation on the adjacent ring and leading thus to the formation of **9** and **10**, *viz.* **8**. No products are feasible or were observed

(46) The occurrence of a chloronium ion could localize the electron deficiencies on carbons 2 and 3 of Scheme I. The reaction sequence initiated by carbonium ion 3 is depicted by the sequence starting with intermediate **1B** of Scheme I. The products derived from carbonium ion 2 are the same as those originating from the free radical on carbon 5 in intermediate **1A**.

(47) A similar reasoning could account also for the chlorination of the basic prototype, butadiene, which was shown to yield predominantly (3.5:1) 1,4 adducts by the radical pathway and more (1.2:1) 1,2 adducts by the polar pathway.[48] It has been suggested that a chloronium species can coordinate with only one double bond of butadiene at a time and not with both simultaneously.[49]

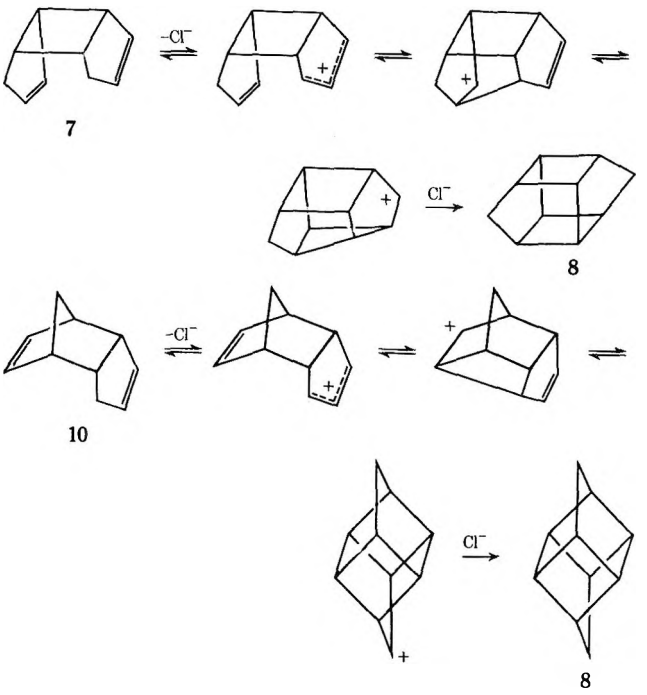
(48) M. L. Poutsma, *J. Org. Chem.*, **31**, 4167 (1966); M. L. Poutsma, *Science*, **157**, 997 (1967).

(49) K. Mislow and H. M. Heilman, *J. Amer. Chem. Soc.*, **73**, 244 (1951).

from cyclization steps involving any of the center carbons (3′, 4′) of the conjugated system.[50]

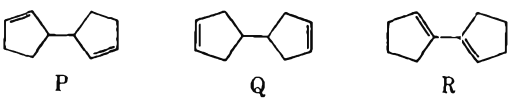
The mechanism outlined in Scheme I considers the formation of **7**, **9**, and **10** from **1** as being the result of kinetic control. The possibility of the formation of **9** and **10** from **7** in the ionic pathway due to isomerization by aluminum chloride can be excluded on the basis of control experiments, in which it was found that **9** was completely unaffected by the catalyst and that **10** yielded, under identical conditions, exclusively **8**. The total absence of **9** and the quantitative formation of **8** in the aluminum chloride catalyzed isomerization of **7** thus indicate that neither **9** nor **10** can originate from **7** in a secondary reaction. Thus kinetics seem to control not only the free-radical but the ionic chlorination mechanisms reported in this paper.

Plausible mechanisms for the cyclization of **7** and **10** to the cage structure under aluminum chloride catalysis can be outlined as follows (for clarity chlorines are omitted from structures).

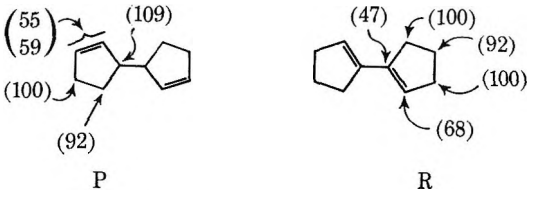


The light-catalyzed chlorination of **3**, **4**, and **5** yielded the noncyclized chlorocarbon $C_{10}Cl_{14}$ (**6**), mp 169°, as the major product. In contrast to **1**, in isomers **3**, **4**, and **5** the cyclopentadiene rings are connected through two sp^2 carbons. The geometry of the resultant linear (or planar) molecules is such that by no radical or ionic intermediates are the two rings within easy bonding distance. Hence the chlorination mechanism works on the two cyclopentadiene moieties independently and forms on each ring an analog of octachlorocyclopentene, which is known to be the end product of the chlorination of hexachlorocyclopentadiene.[52]

Although known for some time, no definite structure has so far been assigned to **6**.[2,53,54] Based on its hydrogenation under mild conditions to bicyclopentyl and on its uv spectrum [λ_{max} 224–230 mμ (ε 15,800–16,900)], it was concluded that this $C_{10}Cl_{14}$ chlorocarbon is a bi(cyclopentenyl) possessing one of the six possible structures with two nonconjugated double bonds, preferably P and Q.[2,53,54] As before, cmr was again definite in indicating a specific structure. Compound **6** exhibited five cmr peaks of equal intensities (Table II) thus indicating that the molecule is symmetrical and that of the three symmetrical structures, P, Q, and R, only P and R need to be considered.



With the help of appropriate models, including octachlorocyclopentene (**12**) and the other compounds already included in Table II, the following chemical shifts can be predicted for P and R.



The very good match between the predicted and the experimental chemical shifts (Table II) indicates rather convincingly that **6** possesses the novel structure R. The latter has not previously been considered based on the interpretation of its uv spectrum.[2,53,54] This, however, indicates only that there is no effective interaction between the two olefinic chromophores, a condition that requires coplanarity between two adjacent double bonds, as, *e.g.*, in cyclopentadiene. Two double bonds can still be adjacent and electronically nonconjugated if they are noncoplanar, especially orthogonal (type II steric effect).[55] We thus suggest that the uv datum does not conflict with the cmr evidence and that **6** has structure R in which the two cyclopentene rings are not coplanar.[10,11,56] The new structure accommodates also the chemical behavior reported[2,53,54] for **6**; its resistance to chlorination is analogous to the similar behavior of **12**,[52] and its preferential or exclusive formation under drastic, presumably thermodynamic, conditions (175–200°, liquid chlorine, sealed tube) is better accounted for by the highest branched olefinic structure R than by any of the other alternatives.[58]

(50) Since the electron density is significantly higher at the terminal carbons of a 1,3-butadiene system than at the central carbons,[51] any electrophilic reagent seeks out and reacts with carbons at the former positions.

(51) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, p 51.

(52) J. A. Krinitsky and R. W. Bost, *J. Amer. Chem. Soc.*, **69**, 1918 (1947).

(53) E. T. McBee, C. W. Roberts, and J. D. Idol, *ibid.*, **78**, 996 (1956).

(54) J. D. Idol, Thesis, Purdue University, 1955.

(55) (a) W. F. Forbes and R. Shilton, *J. Amer. Chem. Soc.*, **81**, 786 (1959), and references cited; (b) W. F. Forbes, R. Shilton, and A. Balasubramanian, *J. Org. Chem.*, **29**, 3527 (1964); (c) H. Wynberg, A. DeGroot, and D. W. Davies, *Tetrahedron Lett.*, 1083 (1963); (d) G. Vogel, *Chem. Ind. (London)*, 1954 (1964).

(56) It is becoming increasingly evident, especially with the aid of nmr spectroscopy, that even in solution multiply substituted aliphatic compounds are often present in fixed conformational states.[57]

(57) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, New York, N. Y., 1966, p 633.

(58) It is well documented that in thermodynamic equilibria the most branched olefins (*i.e.*, those substituted with the most alkyl, vinyl, phenyl, etc., groups) are favored.[59]

(59) See, *inter alia*, P. B. D. de la Mare, "Molecular Rearrangements," Vol. I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, pp 34–42.

Experimental Section

Decachloro-1,1-dihydrofulvalene (**1**),[60] mp 125°, was obtained by recrystallization of the commercially available material (Pentac, Hooker Chemical Corp.). Infrared spectra were recorded on a Perkin-Elmer 337 spectrophotometer in tetrachloroethylene and carbon disulfide solution. Ultraviolet spectra were obtained in a Cary Model 14 spectrophotometer as solutions in cyclohexane. Nuclear quadrupole resonance spectra were recorded by Dr. R. M. Smith of the University of Wisconsin on a Wilks NQR-1A commercial spectrometer and some of the low temperature spectra were obtained by Drs. J. A. S. Smith and A. Royston of the University of Warwick on a Decca Radar spectrometer with superregenerative oscillating detector and side-band suppressor. Mass spectra were determined on a GEC-AEI MS1201B spectrometer using the direct insertion probe, at a source temperature of 150–170° and electron beam energy of 70 eV. Elution chromatography was carried out on 1-in. diameter columns, using neutral alumina (507-C, Camag-A. H. Thomas Co.). Elemental analyses and molecular weights on a Mechrolab vapor pressure osmometer were carried out by Galbraith Laboratories, Knoxville, Tenn.

Thermal Isomerization of Decachloro-1,1′-dihydrofulvalene (1).—A 450.0-g sample of **1** was placed in a 500-ml round-bottomed flask, which then was evacuated to 1 mm of pressure, closed by a stopcock, and placed into an oil bath kept at 145° for 24 hr. After removal and cooling of the flask to room temperature, its contents (a red-brown viscous syrup) was dissolved in 1250 ml of glacial acetic acid and chilled, depositing 210 g of crystalline solid. This was removed by filtration and recrystallization from hot glacial acetic acid to obtain pale yellow platelets of decachloro-3,3′-dihydrofulvalene (**3**), structure D, mp 110–111°: infrared maxima are abstracted in Table I; uv (isooctane) max 274 mμ (ε 5800) and 327 (2400); cmr chemical shifts are shown in Table II.

Anal. Calcd for $C_{10}Cl_{10}$: Cl, 74.7; mol wt, 475. Found: Cl, 74.3; mol wt, 473.

The original mother liquor deposited, on standing or when it was treated with water to the point of incipient oiling-out, oily crystals, which were isolated by suction filtration. After several recrystallizations from acetic acid, pure crystalline decachloro-2,3′-dihydrofulvalene (**4**), structure E, mp 82°, was obtained:[61] infrared parameters, see Table I; uv (isooctane) max 228 mμ (shoulder) (ε 6400) and 319 (4200); cmr parameters are given in Table II.

Anal. Calcd for $C_{10}Cl_{10}$: Cl, 74.7; mol wt, 475. Found: Cl, 74.3; mol wt, 468.

The third novel $C_{10}Cl_{10}$ isomer, decachloro-2,2′-dihydrofulvalene (**5**), structure F, was isolated conveniently by elution chromatography over alumina. When a 20.0-g sample of the original mother liquor in pentane was passed over about 450–500 g of alumina and was eluted continuously with pentane, the first three 100-ml cuts of the total twenty cuts taken yielded, after stripping of the solvent, pure **3** (about 2–3 g). Subsequent cuts contained mixtures of **3** and increasing amounts of **4**, followed by cuts containing further diminishing amounts of **3** and increasing amounts of **5**, and the last 8–10 fractions, which had a yellow color, contained pure **5**, mp 114–115°: major infrared peaks of this compound are listed in Table I; uv (isooctane) max 233 mμ (ε 6900) and 352 (4650); for cmr data see Table II.

Anal. Calcd for $C_{10}Cl_{10}$: Cl, 74.7; mol wt, 475. Found: Cl, 74.5; mol wt, 466.

The spectral parameters of the parent $C_{10}Cl_{10}$ isomer **1** are as follows: ir (C_2Cl_4) 1594 vs, 1555 cm^{-1} m; ir (CS_2) 1282 w, 1252 vs, 1230 w, 1180 s, 1162 s, 1118 m, 1008 m, broad, 970 s, 952 s, 904 m, 812 s, 702 vs, 678 vs, 648 vs, 640 s, 610 s, and 502 w cm^{-1}; uv (isooctane) 235 mμ (sh) (ε 6100), 282 (2000), and 333 (2900); for cmr data see Table II.

The reference chlorocarbon, and progenitor of all of the compounds discussed in this article, hexachlorocyclopentadiene (**2**), had the following spectral data: ir (film) 1602 vs, 1570 m, 1230 vs, 1210 w, 1188 m, 1162 w, 1140 vs, 1024 w, 975 w, 962 w, 938 w, 802 vs, 708 s, 681 s, and 548 w cm^{-1}; uv (isooctane) 324 mμ (ε 1670); cmr data are shown in Table II.

Thermal Isomerization of Decachloro-1,1′-, -3,3′-, -2,3′-, and 2,2′-dihydrofulvalenes (1, 3, 4, and 5).—Approximately 0.2-g samples of **1**, **3**, **4**, and **5** were sealed in about 5-mm o.d. glass tubes, which then were placed and kept in an oil bath at 145° for 14 hr. Analysis of the resultant melts by ir indicated that they had exactly identical spectra, containing **3**, **4**, and **5** (but no **1**), in identical proportions (about 50–55% **3**, 30–35% **4**, and 10–15% **5**).

In order to determine the time needed for equilibration, 0.2-g samples of **1** were sealed in glass tubes and placed in an oil bath kept at 145°. The extent of isomerization was followed by removing tubes at hourly intervals and analyzing them by ir. It was found that the sample heated for 5 hr had already attained the equilibrium composition, whereas the tube kept in the oil bath for 4 hr contained, except for traces of **1**, nearly the final reaction mixture.

Isomerization of 1, 3, 4, and 5 by Aluminum Chloride.—To a solution of 25 g of **1** in 100 ml of methylene chloride there was added 5 g of aluminum chloride, and the resultant slurry was stirred for a period of 20 hr. The color of the slurry changed from yellow to brownish-green to deep purple. Decomposition of the reaction mixture by water yielded a yellow syrup, whose ir was identical, both qualitatively and quantitatively, with that resulting from the thermal isomerization experiment. Under similar conditions **3**, **4**, and **5** (0.3 g each) yielded reaction mixtures identical with each other and with that of the isomerization of **1**.

Chlorination of 1 Catalyzed by Light.—The procedure of McBee, Idol, and Roberts[2] was followed (method A), except that the reaction was carried out in a Pyrex flask in refluxing carbon tetrachloride solution, and heated and irradiated by a bright heating lamp (150 W). The chlorination of 10.0 g of **1** yielded 11.25 g of product, which, after trituration with pentane, left behind 7.5 g (66% of the theory) of pure **7**, mp 221–222° (lit.[2] mp 221–223°). The spectral data were as follows: ir (C_2Cl_4) 1600 cm^{-1}; ir (CS_2) 1205 s, 1182 s, 1138 w, 1122 m, 1068 m, 1040 sh, 1020 s, 957 w, 905 sh, 892 m, 884 m, 852 s, 794 w, 764 w, 709 s, 697 s, 664 s, 630 w, 605 s, 582 s, and 546 m cm^{-1}; uv, same as reported;[2] the compound was too insoluble for natural abundance cmr characterization; its nqr frequencies were of equal intensities at 37.2, 37.8, 38.0, 38.3, 39.5, and 40.0 ± 0.1 MHz; for mass spectral data see Table III.

Analysis by infrared of the residue, left behind after evaporation of pentane of the mother liquor, indicated the presence of many new bands. The mixture was redissolved in pentane and chromatographed over alumina. The earliest elution cuts contained traces of **1** followed, in order of emergence, by the cage chlorocarbon K, $C_{10}Cl_{12}$, mp 485° (**8**),[2] and the novel $C_{10}Cl_{12}$ chlorocarbons **10**, mp 237–239°, and **9**, mp 186–187°.

A second chromatography of fractions of similar composition and recrystallization led to the isolation of the pure chlorocarbons **9** and **10**.

When recrystallized from hexane, **9** had mp 186–187° and the following spectral data: ir (C_2Cl_4) 1630 s, 1615 s cm^{-1}; ir (CS_2) 1202 s, 1165 s, 1138 m, 1090 m, 1062 m, 1052 m, 1030 w, 997 m, 960 w, 922 w, 905 m, 890 s, 848 m, 805 w, 761 m, 734 w, 698 w, 674 s, 649 s, 624 m, 607 s, 580 m, 542 w cm^{-1}; uv (cyclohexane) no maximum higher than 220 mμ; for cmr and mass spectral parameters, see Tables II and III, respectively; nqr frequencies were found at 36.91 (1), 37.09 (1), 37.41 (1), 37.51 (1) 38.30 (2), 38.56 (1), 38.67 (1), 39.13 (1), 39.38 (2), and 39.60 (1) ± 0.1 MHz; numbers in parentheses indicate relative intensities.

Anal. Calcd for $C_{10}Cl_{12}$: C, 22.02; Cl, 77.98; mol wt, 545.6. Found: C, 22.2; Cl, 78.0; mol wt, 549.

The recrystallization of **10** from hexane yielded white crystals, mp 237–239°, with the following spectral parameters: ir (C_2Cl_4) 1630 s, 1600 s, cm^{-1}; ir (CS_2) 1197 s, 1174 s, 1161 s, 1088 m, 1034 s (broad), 997 s (broad), 908 s, 878 w, 836 s, 746 s, 719 m, 672 s, 662 s, 640 s, 620 w, 602 s, 568 s, 540 w, 468 w, cm^{-1}; uv showed no maximum higher than 210 mμ; for cmr and mass spectral parameters, see Tables II and III; no nqr spectrum could be secured at room or at liquid nitrogen temperature.

Anal. Calcd for $C_{10}Cl_{12}$: C, 22.02; Cl, 77.98; mol wt, 545.6. Found: C, 22.0; Cl, 78.2; mol wt, 557.

The cage chlorocarbon K, $C_{10}Cl_{12}$, mp 485° (**8**),[2] had the following infrared maxima: (CS_2) 1152 s, 1134 s, 1160 s, 968 m, 891 m, 818 s, 666 m, 655 s, and 521 s cm^{-1}; no nqr spectrum could be obtained at room or at liquid nitrogen temperature.

Chlorination of 1 Catalyzed by Aluminum Chloride.—In order to avoid the isomerization of **1** by aluminum chloride, a solution of 25.4 g of **1** in 175 ml of methylene chloride was saturated with

(60) We are adopting the nomenclature proposed[6c] for the various $C_{10}Cl_{10}$ isomers since it is simpler and easier to visualize than the corresponding IUPAC name.

(61) Neither **3** or **4** had miticidal activity comparable to that of **1**.

Cl_2 while being protected from light by aluminum foil, and only after chlorine was bubbling through was 1.0 g of aluminum chloride added to the solution. After standing at room temperature for 24 hr, during which period a slow stream of chlorine gas was introduced, the reaction mixture was added to water, and the organic layer was stripped of solvent on a rotating evaporator. Work-up of the pale yellow slush by trituration with hexane and filtration yielded 9.1 g of rather pure **9** as the insoluble component. Elution chromatography of the remainder of the mixture (23.5 g) resulted in the isolation of a small amount of **8**, followed (in order of emergence) by **10** (amounting to about a total of 10–12 g), **7**, and small amounts of **9**.

Light-Catalyzed Bromination of 1.—A solution of 40.6 g of **1** in 173 g of bromine was both irradiated and refluxed with the aid of a 100-W uv lamp (General Electric H100 A-4) for 16 hr. The excess bromine, which acted also as a solvent, was evaporated on steam bath in a well-vented hood, and the resultant crystal mass was triturated with methylene chloride and filtered by suction. The insoluble portion, 27.5 g, mp 162.0–163.5°, after recrystallization from cyclohexane, matched the properties of the $C_{10}Br_2Cl_{10}$ halocarbon, mp 147°, obtained by R. D. Crain by a similar procedure.[32] The infrared pattern of this compound (1595 s, 1205 s, 1182 s, 1138 m, 1121 m, 1069 m, 1022 s, 958 w, 892 m, 875 m, 839 m, 778 w, 742 w, 689 s, 659 w, 655 w, 604 m, 589 w, 582 w, 561 m, 552 m, and 540 m cm^{-1}) resembles very closely that of **7**, thus suggesting that the bromine adduct of **1** has the same structure as its chlorine adduct, *i.e.*, **N**.

Anal. Calcd for $C_{10}Br_2Cl_{10}$: C, 18.93; Br, 25.19; Cl, 55.88. Found: C, 19.0; Br, 25.4; Cl, 55.5.

Light-Catalyzed Chlorination of 3, 4, and 5.—The same procedure, which transformed **1** into the further cyclized products **7**, **9**, **10**, and **8**, resulted in the formation of the bicyclic $C_{10}Cl_{14}$ adduct **6**, mp 169°,[2] when applied to **3**, **4**, and **5**.

Cyclization of 7 to the Cage Chlorocarbon 8.—To a solution of 1.0 g of **7** in 20 ml of methylene chloride there was added 0.6 g of anhydrous aluminum chloride and the resultant mixture was stirred for 20 hr at room temperature. Work-up by treatment with water and stripping of the solvent resulted in 1.0 g of off-white crystalline product, shown by ir to be pure **8** by comparison with the spectrum of an authentic sample.[2]

Cyclization of 7-Br to the Cage Halocarbons 8-Br.—A slurry of 3.62 g of **7-Br** in 35 ml of methylene chloride, to which 0.5 g of anhydrous aluminum bromide was added, was stirred at room temperature for 23 hr. The resultant deep-purple reaction mixture was poured into water, the organic layer was separated and washed, and finally the solvent was stripped in a rotary evaporator. The resultant off-white solid, 3.60 g, was analyzed by ir, which indicated the complete absence of starting material or of any species with a double bond and which showed a pattern closely resembling that of **8**. Elution chromatography over alumina indicated the presence of a small amount of **8**, which was eluted first followed by several species of bromochlorocarbons.

Cyclization of 7 to 11 by Sulfur Trioxide.—A solution of 20.0 g of **7** in 200 g of liquid sulfur trioxide was kept at room temperature for 2 hr, during which period the originally deep-purple solution acquired a strong maroon color. Distillation of most of the sulfur trioxide and pouring the residue onto ice gave a white precipitate, which after washing and air-drying (18.5 g) was found by ir to be the pure hydrate of **11**.[62]

Effect of Aluminum Chloride on *endo*-Dodecachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene (10).—To a solution of 1.4 g of **10** in 10 ml of methylene chloride there was added 0.5 g of aluminum chloride, and the resultant dark greenish-gray slurry was stirred for 24 hr. Quenching by water, extraction by methylene chloride, and stripping of the solvent in a rotating vacuum evaporator resulted in the formation of a crystalline mass, the ir spectrum of which indicated it to be pure **8**. No starting material or its isomer **9** was detectable by ir.

Effect of Aluminum Chloride on *exo*-Dodecachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene (9).—When carried out with **9**, the preceding procedure resulted in the quantitative recovery of the starting material.

Registry No.—**1**, 2227-17-0; **2**, 27425-39-4; **3**, 27425-40-7; **4**, 27425-41-8; **5**, 27425-42-9; **6**, 27396-27-6; **7**, 27396-29-8; **8**, 2385-85-5; **9**, 2626-29-1; **10**, 27425-43-0; **12**, 706-78-5; bromine adduct of **1**, 27396-30-1.

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(62) E. E. Gilbert, U. S. Reissue Patent Re 24,397 (1957).

The Reaction of 1-Tetralones with Palladium/Carbon[1]

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The dehydrogenation of 1-tetralone [3,4-dihydro-1(2*H*)-naphthalenone] and similar α,β-unsaturated ketones is generally thought to give predominantly phenolic products rather than arenes. Conditions (absence of solvent, 260°, and palladium/carbon catalyst) are described that provide the arene as the major product. Steric interference to palladium/carbon dehydrogenation was observed in 4,5-dimethyl derivatives.

Dehydrogenation of cyclic ketones may lead to arenes or, with retention of oxygen, to phenolic compounds or neutral oxygen-containing condensation products. The nature of the dehydrogenation product is governed by the structure and stereochemistry, the type of dehydrogenating agent, the reaction temperature, the presence of hydrogen acceptor and/or sulfur compounds, and the solvent (if any).[3]

Exclusive formation of phenolic compounds as contrasted to conversion to arenes has been reported for the following dehydrogenations: 1-tetralone with Se[4a] or S,[4b] 3-methyl-1-tetralone with Se[4c,d] or S,[4d] 6-methyl-1-tetralone with Pd/C,[4e] 7-methyl-1-tetralone with S[4f] or Pd/C,[4g] 5,7-dimethyl-1-tetralone with Se,[4h] and 5,8-dimethyl-1-tetralone with Se[4h] or S.[4f] Other studies using Pd/C catalyst in high-boiling solvents (*p*-cymene, triethylbenzene, and phenyl ether) gave good yields of phenolic materials from di- and trialkylcyclohexenones,[3e] 1-tetralone,[5a] and 2,6-dibenzylidenecyclohexanone.[5b] The formation of 1-naphthol from 1-tetralone (**1**) during catalytic dehydrogenation has been rationalized[5a] as proceeding through the enol. We have observed that 1-naphthol also is dehydrogenated to naphthalene.

Pd/C-catalyzed dehydrogenation of 1-tetralones in the absence of solvent may give the corresponding naphthalene. Examples include reaction of **1** (77% and 37% yields)[3a,5a] and 7-methyl-1-tetralone (34%)[5c] and our earlier[1] dehydrogenation of 2,5,8-trimethyl-1-tetralone (**8**), 3,5,8-trimethyl-1-tetralone (**9**), and 4,5,8-trimethyl-1-tetralone (**10**) to the corresponding naphthalenes.

As pointed out by Linstead and Michaelis,[5a] the direct conversion of 1-tetralones to naphthalenes could be a useful synthetic route since it bypasses two steps of the usual procedure

tetralone ⟶ tetralol ⟶ dihydronaphthalene ⟶ naphthalene

With this in mind, **1** and a series of eleven methyl-substituted 1-tetralones were dehydrogenated under conditions conducive to loss of oxygen, *i.e.*, no solvent,[5a] high temperature,[5a] and a Pd/C catalyst, to determine the effect of methyl substitution on the stereochemistry and utility of the reaction. Exploration of a direct and efficient formation of arenes from 1-tetralones was of interest in our synthesis of hydrocarbons for the Standard Samples Program of the American Petroleum Institute.[6a]

The data of Table I show that the yields of naphthalenes from 1-tetralones are indeed influenced by methyl-group substitution but that significant hindrance to formation of arene results only from substituents concurrently present at positions 4 and 5 as illustrated by the decreased yields obtained from **10** and **11**. As has been pointed out, such substituents at positions 4 and 5 are believed to introduce sufficient steric crowding to cause conformational distortion of the substituted tetralone.[6c] Resistance of **10** and **11** to dehydrogenation under the conditions used is possibly due to inadequate contact with the catalyst surface or the inability of the incipient 4,5-dimethyl interaction to facilitate formation of the more planar enol form.

Steric inhibition to dehydrogenation of the monomethyl-1-tetralones **2**, **3**, and **4** appears to be absent; indeed, the presence of a methyl group actually improves the combined yield of steam-volatile dehydrogenation products for **2** and **3**. In particular, the 44% yield of 2-methylnaphthalene and the 35% yield of 2-methyl-1-naphthol from **2** shown in Table I provide an interesting contrast to the 0 and 47% yields of these products from the action of molten KOH–NaOH on **2**.[6b]

As seen from Table I, a nonsteam-volatile residue was obtained in significant yield in many cases. Attempts to identify the dimeric products existing in the tar fraction from **1** have been inconclusive. The glc analysis

(1) E. J. Eisenbraun and C. W. Hinman, *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, **10**, No. 1, 33 (1965).

(2) (a) American Petroleum Institute Graduate Research Assistantship 1965–1967; (b) NSF Graduate Trainee 1967–1968; (c) American Chemical Society Petroleum Research Fund Fellow, GF 395, 1968–1969; (d) API GRA, 1962–1965; (e) deceased.

(3) (a) P. N. Rylander and D. R. Steele, *Engelhard Ind. Tech. Bull.*, **9**, 50 (1968); (b) R. P. Linstead, K. O. A. Michaelis, and S. L. S. Thomas, *J. Chem. Soc.*, 1139 (1940); (c) R. P. Linstead, *Ann. Rep.*, **33**, 294 (1936); (d) H. Adkins, L. M. Richards, and J. W. Davis, *J. Amer. Chem. Soc.*, **63**, 1320 (1941); (e) E. C. Horning, M. G. Horning, and G. N. Walker, *ibid.*, **71**, 169 (1949); (f) E. C. Horning and M. G. Horning, *ibid.*, **69**, 1359 (1947); (g) L. M. Jackman, *Advan. Org. Chem.*, **2**, 352 (1960).

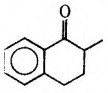
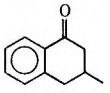
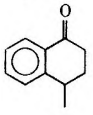
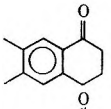
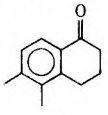
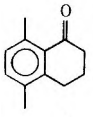
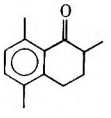
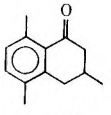
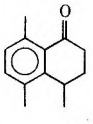
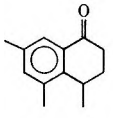
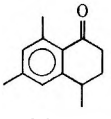
(4) (a) N. N. Vorozhtsov and V. A. Koptyug, *Zh. Obshch. Khim.*, **28**, 98 (1958); (b) G. Darzens and G. Levy, *C. R. Acad. Sci.*, **194**, 181 (1932); (c) P. P. T. Sah, *Z. Vitamin-, Hormon- Fermentforsch.*, **3**, 324 (1950); (d) M. Tishler, L. F. Fieser, and N. L. Wendler, *J. Amer. Chem. Soc.*, **62**, 2866 (1940); (e) G. Di Modica and S. Tira, *Ann. Chim. (Rome)*, **46**, 838 (1956); *Chem. Abstr.*, **51**, 6578c (1957); (f) L. Ruzicka and H. Waldmann, *Helv. Chim. Acta*, **15**, 907 (1932); (g) L. Ruzicka and E. Morgeli, *ibid.*, **19**, 377 (1936); (h) W. Cocker, B. E. Cross, J. T. Edward, D. S. Jenkinson, and J. McCormick, *J. Chem. Soc.*, 2355 (1953).

(5) (a) R. P. Linstead and K. O. A. Michaelis, *ibid.*, 1134 (1940); (b) E. C. Horning, *J. Org. Chem.*, **10**, 263 (1945); (c) J. A. Corran and W. B. Whalley, *J. Chem. Soc.*, 4719 (1958).

(6) (a) Correspondence regarding samples of the hydrocarbons mentioned in this paper should be directed to A. J. Strieff, API Samples office, Carnegie-Mellon University, Schenley Park, Pittsburgh, Pa.; (b) J. M. Springer, C. W. Hinman, E. J. Eisenbraun, P. W. K. Flanagan, and M. C. Hamming, *J. Org. Chem.*, **35**, 1260 (1970); (c) G. D. Johnson, S. Searles, and W. C. Lin, *ibid.*, **27**, 4031 (1962); (d) E. Mosettig and H. M. Duvall, *J. Amer. Chem. Soc.*, **59**, 367 (1937); (e) R. D. Haworth, *J. Chem. Soc.*, 1125 (1932); (f) E. J. Eisenbraun, C. W. Hinman, J. M. Springer, J. W. Burnham, T. S. Chou, P. W. Flanagan, and M. C. Hamming, *J. Org. Chem.*, in press.

Table I

The Reaction of 1-Tetralones with Pd/C

Structure number	Structure	Corresponding naphthalene,[a] %	Corresponding naphthol,[b] %	Nonsteam-volatile material,[c] %	Glc product ratio[d]
1		37	18	27	14
2		44	35	10	14
3		46	47	4	12
4		35	22	34	33
5		46	7	43	11
6		29	11	52	13
7		48	*e*	28	3
8		43	*e*	33	5
9		44	*e*	34	17
10		<4	*f*	7	0.05
11		13	*f*	33	0.24
12		51	*f*	28	4

[a] Determined by comparison of glc peak areas with those obtained from standard solutions. Yields are independent of unreacted tetralones (*cf.* last column of this table). [b] Yield determined gravimetrically except as noted. [c] Yield of nonsteam-volatile material determined gravimetrically after steam distillation. [d] Ratio of glc peak areas of corresponding naphthalene and the accompanying tetralone. The relative peak area of the tetralone is taken as 1. [e] The corresponding naphthol was shown to be present by glc but it was not extracted by 10% NaOH. [f] Glc studies indicated the corresponding naphthol was not present.

indicates three components represented by two minor peaks of similar retention time and a major peak several minutes removed. The mass spectrum shows a major molecular ion at m/e 268 ($C_{20}H_{12}O$) and a minor one at m/e 254 ($C_{20}H_{14}$). Finally, the glc retention times of the minor components are similar to those of authentic samples of binaphthyls (mol wt 254, $C_{20}H_{14}$). Thus, the evidence indicates the presence of such structures. The mass spectra of dimeric products from **1**, **5**, **9**, and **11** are given in Table II.

Table II

Mass Spectral Correlation of Dimeric Residues from Pd/C Dehydrogenations

Starting material	Molecular ion peak of product	Fragmentation peaks[a]
1	268[b]	269 (23), 268 (100), 254 (64), 252 (19), 239 (18)
5	326	326 (67), 156 (40), 45 (39), 31 (100), 18 (65)
9	352	352 (79), 337 (100), 176 (98), 168.5 (58), 161 (42)
11	366[c]	367 (32), 366 (100), 365 (81), 353 (43), 352 (42)

[a] 70 eV m/e (rel intensity). [b] Also m/e 254. [c] Also m/e 338.

The Pd/C dehydrogenation studies were extended to 2-tetralone, 3,4-dihydro-1(2*H*)-phenanthrenone (**13**), 1,2,3,4-tetrahydro-2,5,8-trimethyl-1-naphthol (**17**), 1,2,-3,4-tetrahydro-3,5,8-trimethyl-1-naphthol (**19**), and 1,-2,3,4-tetrahydro-4,5,8-trimethyl-1-naphthol (**20**) as shown in Schemes I and II, respectively.

The dehydrogenation (Pd/C) of 2-tetralone gave naphthalene (54%) and 2-naphthol (26%).

The Pd/C dehydrogenation of **13** (Scheme I) gave 18% of **14** and a trace of **15**. In the presence of naphthalene, Pd/C caused dehydrogenation to a mixture of 71% of **14** and 11% of **16** but **15** was not found. Dehydrogenation of **16** with Pd/C using naphthalene as solvent gave 83% of **14**. The improved yield of **14** when naphthalene was used confirms an earlier report.[6d]

The tetrahydrotrimethylnaphthols **17** and **19** are completely dehydrogenated to 1,4,6-trimethylnaphthalene (**18**) in 8 hr (Scheme II). However, **20**, with its 4,5-dimethyl substitution, is considerably more resistant to dehydrogenation to 1,4,5-trimethylnaphthalene (**21**); only 35% conversion took place in 8 hr. There was no evidence that the corresponding naphthols were formed during the dehydrogenation of **17**, **19**, or **20**.

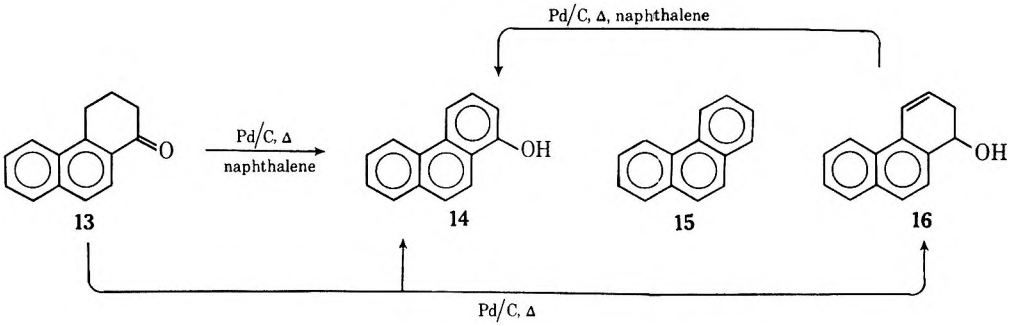
Experimental Section[7]

The tetralones used in the study were either purchased from commercial sources or prepared as described.[6b,f] 3,4-Dihydro-1(2*H*)-phenanthrenone (**13**) was prepared by Friedel–Crafts reaction of naphthalene and succinic anhydride.[6d,e] The Pd/C catalysts were purchased from Engelhard Industries.

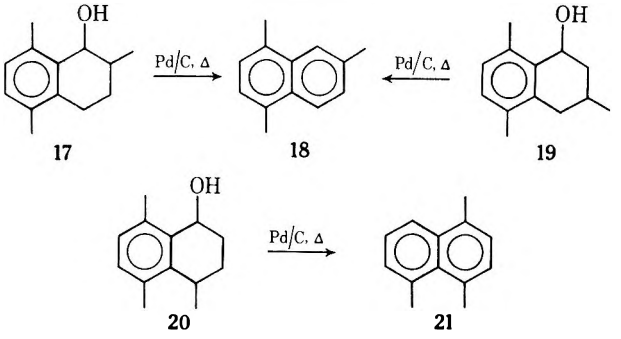
Naphthalene, 1-methylnaphthalene, 2-methylnaphthalene, 2,3-dimethylnaphthalene, and 1,4-dimethylnaphthalene were commercially available. The other naphthalenes necessary for the preparation of standard solutions for glc analyses were prepared from the corresponding 1-tetralones by Clemmensen reduction and subsequent Pd/C dehydrogenation to 1,4,5- and 1,4,6-trimethylnaphthalene; Pd/C catalytic hydrogenation to the tetralin and subsequent dehydrogenation to give 1,3,5- and 1,3,8-trimethylnaphthalene; and Pd/C dehydrogenation of 5,7-

(7) Elemental analyses were determined by Galbraith Laboratories, Knoxville, Tenn. Nmr spectra were determined on Varian HR-60 and A-60 spectrometers. Mass spectrometric data were compiled using a Consolidated Electrodynamics Corp. Model 21-103C mass spectrometer. Ir and uv spectra were obtained on Beckman IR-5A and Cary 14 spectrophotometers, respectively. Melting points are corrected. Glc studies were carried out on a 0.25-in. × 4-ft column of SE-30 on Chromosorb P and/or a 0.25-in. × 6-ft column of 5% silicone rubber on acid-washed, DMCS-treated Chromosorb W. Glc separations were done on a 10-ft × 0.25-in. column of 25% Carbowax 20M on acid-washed Chromosorb W.

SCHEME I



SCHEME II



dimethyl-1-tetralone to 1,3-dimethylnaphthalene. The physical and spectral properties of some of these naphthalenes and their tetrahydro derivatives will be published subsequently.[6f]

General Procedure for Pd/C Reactions. A. Apparatus and Procedure.—A 25-ml, three-necked, round-bottomed flask fitted with reflux condenser and a gas-inlet tube serves as the reaction vessel. Tygon tubing is attached to gas-inlet and gas-exit ports. A 5-g sample of tetralone and 0.5 g of Pd/C are used. A fast flow of helium is used initially to sweep out the system, and the helium flow then is lessened to maintain a slight positive pressure. The flask is lowered into a Wood's metal bath preheated to 70° and the bath temperature (by pyrometer and thermocouple probe as a safety measure) is raised rapidly (15–20°/min) to 260° and held stationary. After being heated for 4 hr, the reaction mixture is allowed to cool under helium atmosphere. Severe bumping due to water formed in the reaction can be lessened or eliminated by submerging the reaction flask into the bath far enough that the level of the molten metal is approximately 0.5 in. above that of the liquid in the flask.

B. Work-up for Tetralones 1, 2, 3, and 5 (Table III[8]).—The cooled reaction mixture is extracted successively with ether and chloroform and the solution is filtered through Dicalite. The filtrate is washed thoroughly with 10% NaOH solution. The alkaline wash then is back-extracted with ether and the ether solutions are combined. The alkaline solution is acidified with concentrated hydrochloric acid and extracted with ether. The extract is washed with water, dried ($MgSO_4$), filtered, and concentrated to give the phenolic material. The naphthol is purified by recrystallization from petroleum ether (bp 60–68°) and/or sublimation.

The main ethereal filtrate is washed with water, dried ($MgSO_4$), filtered, and concentrated to 50 ml by distillation. Percentage yields are determined using standard solutions as described for the KOH–NaOH reactions.[6f]

The concentrate then is thoroughly steam distilled and the nonvolatile residue dissolved in ether. The ether solution is dried ($MgSO_4$), filtered, and concentrated to yield the tar residue.

C. Modification Used for 4, 6, and 7.—Part B is modified by subjecting the alkali-washed extract to thorough steam distillation. The resulting residue is treated as before. The steam distillate is extracted with ether and the ether extract is dried ($MgSO_4$), filtered, and concentrated to 50 ml by distilling. The percentage yield of the naphthalene is determined as before.

D. Modification Used for 8, 9, 10, 11, and 12.—More chloroform than usual is needed to dissolve the reaction products from the trimethyl-1-tetralones. In order to avoid chloroform as the solvent for standard and unknown solutions, it is removed by steam distillation of the ether–chloroform filtrate. The nonvolatile residue and the steam distillate are treated as before. Washing with 10% NaOH solution does not remove the naphthol in these cases.

Pd/C Dehydrogenation of 2-Tetralone to Naphthalene and 2-Naphthol.—Dehydrogenation of 3 g of 2-tetralone for 11 hr at 250–282° gave 2.22 g of residue and a steam-volatile fraction which did not contain 2-tetralone but showed 2:1 ratio of glc peaks corresponding to naphthalene and 2-naphthol.

Deoxygenation of 1-Naphthol.—Naphthol (8.57 g) was treated with Pd/C (0.86 g) for 4 hr at 265° under He. Naphthalene was isolated by steam distillation and extraction of the steam distillate. The nonvolatile residue (5.85 g) of brown oil was recrystallized from 1:3 benzene–ethanol to yield a yellow powder: mp 165–175°; mass spectrum (70 eV) *m/e* (rel intensity) 268 (11), 255 (21), 254 (100), 252 (29), and 28 (44).

Pd/C Dehydrogenation of 3,4-Dihydro-1(2*H*)-phenanthrenone (13).—A 2-g sample of **13** was dehydrogenated with 0.067 g of 5% Pd/C at 220–225° for 24 hr. The products were isolated (*cf.* part B above) and yielded 0.36 g (18% yield) of 1-phenanthrol (**14**): mp 154.5–156° [lit.[6d] 153–154°]; mass spectrum (70 eV) *m/e* (rel intensity) 194 (95), 165 (78), 43 (100), 29 (24), 28 (26), and 15 (37). The material extracted from the basic solution gave 0.56 g of a mixture of **13** and **15**. This mixture was identified by glc on a 0.25-in. × 4-ft column of SE 30 on Chromosorb P at 190°. Considerable tar remained in the sublimation tube.

Pd/C Dehydrogenation of 3,4-Dihydro-1(2*H*)-phenanthrenone (13) in the Presence of Naphthalene.—A 2-g sample of **13**, 20 g of naphthalene, and 0.067 g of 5% Pd/C were treated as described in the previous experiment except that the filtered product was steam distilled to remove naphthalene. The base-soluble product

TABLE III

PROPERTIES OF NAPHTHOLS[a] PRODUCED IN Pd/C DEHYDROGENATION OF 1-TETRALONES

	Mp, °C	Mass spectrum[b]
1-Naphthol	95–96.5[c]	144 (100), 116 (42), 115 (94), 89 (12), 39 (13)
2-methyl-	62–63.5[d]	158 (100), 157 (23), 129 (38), 128 (36), 115 (21)
3-methyl-	90.5–93.5[e]	158 (100), 157 (23), 129 (29), 128 (28), 115 (22)
4-methyl-	75–78[f]	158 (100), 157 (46), 144 (35), 115 (40), 128 (30)
5,7-dimethyl-	55–59[g,h]	172 (100), 157 (30), 129 (24), 128 (22), 115 (14)
6,7-dimethyl-	138.5–140[i]	172 (100), 171 (13), 157 (27), 129 (23), 128 (22)

[a] Isolated by extraction of Pd/C dehydrogenation reaction mixtures with 10% NaOH. [b] 70 eV *m/e* (rel intensity). [c] Lit.[8a] 94°. [d] Lit.[8b] 64–65°. [e] Lit.[8c] 92.5–93.5°. [f] *Anal.* Calcd for $C_{11}H_{10}O$: C, 83.51; H, 6.37. Found: C, 83.44; H, 6.47. Lit.[8b] 84–85°. [g] Monohydrate, lit.[4b] 58–59°. [h] Lit.[8a] 79–80°. [i] Lit.[8d] 140°.

(8) (a) "Dictionary of Organic Compounds," 4th ed, I. Heilbron, Ed. Oxford University Press, New York, N. Y., 1965, p 2378; (b) J. W. Cornforth, R. H. Cornforth, and R. Robinson, *J. Chem. Soc.*, 168 (1943); (c) B. R. Baker and G. H. Carlson, *J. Amer. Chem. Soc.*, **64**, 2657 (1942); (d) E. A. Coulson, *J. Chem. Soc.*, 1305 (1938).

was sublimed to give 1.44 g (71% yield) of **14**. The ether-soluble and alkali-insoluble fraction gave 0.23 g of solid 1,2-dihydro-1-phenanthrol (**16**): mp 115–116.5°, mass spectrum (70 eV) *m/e* 196 (M^+).

Anal. Calcd for $C_{14}H_{12}O$: C, 85.71; H, 6.12. Found: C, 85.52; H, 6.06.

Pd/C Dehydrogenation of 1,2,3,4-Tetrahydro-2,5,8-trimethyl-1-naphthol (17) and 1,2,3,4-Tetrahydro-3,5,8-trimethyl-1-naphthol (19) to 1,4,6-Trimethylnaphthalene (18).—The tetrahydronaphthols **17**, bp 95° (0.4 mm), mp 79–81°, and **19**, mp 76–77°, were prepared by $LiAlH_4$ reduction of **8** and **9**.[6f] Dehydrogenation of **17** and **19** with Pd/C at 270° was followed with glc studies and shown to be complete in about 8 hr. There was no evidence of naphthol formation. Both alcohols gave about 98% yield of **18**,[6f,9] bp 91° (0.9 mm).

The orange picrate of **18**, mp 134–135° [lit.[9] 133°], was prepared.

Pd/C Dehydrogenation of 1,2,3,4-Tetrahydro-4,5,8-trimethyl-1-naphthol (20) to 1,4,5-Trimethylnaphthalene (21).—The tetrahydronaphthol **20**, bp 110° (0.5 mm) [lit.[9] bp 106–107° (0.1 mm)], obtained by $LiAlH_4$ reduction of **10** was treated with Pd/C in the same procedure as was used for **17** and **19**. At the end of 8 hr, the glc analysis showed the presence of four peaks. The largest was due to unreacted **20** and the second major peak represented **21**. This peak increased with time and was approximately 35% of the total peak area at the end of 8 hr.

(9) L. Ruzicka and L. Ehman, *Helv. Chim. Acta*, **15**, 140 (1932).

Registry No.—**1**, 529-34-0; **2**, 1590-08-5; **3**, 14944-23-1; **4**, 19832-98-5; **5**, 19550-57-3; **6**, 13621-25-5; **7**, 5037-63-8; **8**, 10468-59-4; **9**, 10468-60-7; **10**, 10468-61-8; **11**, 27410-97-5; **12**, 27310-98-6; **16**, 27410-99-7.

Acknowledgment.—We thank the American Petroleum Institute for partial support of this work through API Research Project 58A and the Research Foundation of Oklahoma State University for their assistance. Grateful acknowledgment is made also to the National Science Foundation and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We thank Dr. O. C. Dermer for having read the manuscript.

The Reaction of Formaldehyde with Deactivated Benzoic Acids. An Ester-Directed Electrophilic Aromatic Substitution Process[1]

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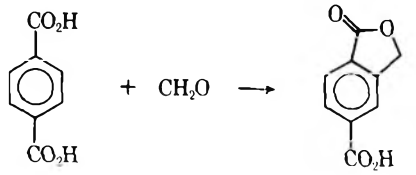
The reaction of formaldehyde with benzoic acids bearing electron-withdrawing groups has been shown to provide phthalide derivatives. The reaction media must contain sulfur trioxide. Evidence is presented to show that an intermediate is formed prior to the electrophilic attack which involves the carboxyl group. It is suggested that this intermediate is a methylene ester, stabilized by sulfur trioxide.

Terephthalic acid in strong acid media undergoes several electrophilic substitution reactions, such as nitration,[2] halogenation,[3] and mercuration.[4] The reaction of terephthalic acid and formaldehyde in sulfur trioxide-containing media to give 5-carboxyphthalide (**1**) has recently been reported.[5] 5-Carboxyphthalide can be nitrated and halogenated to yield 6-nitro- or 6-halo-5-carboxyphthalide. The $-CH_2O-$ substituent of 5-carboxyphthalide should activate the material toward electrophilic attack, relative to terephthalic acid.[6] But while terephthalic acid reacts easily with formaldehyde,[5] 5-carboxyphthalide does not, and only small amounts of the diadduct, **2**, can be detected from treatment of 5-carboxyphthalide with formaldehyde, even under forcing conditions.



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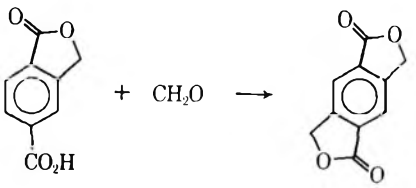

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These observations suggested that the reaction of terephthalic acid and formaldehyde may involve more than direct electrophilic substitution by a protonated or sulfated formaldehyde species and prompted our further investigation of the system. We have since studied the scope of the reaction and extended it to other deactivated aromatic substrates. In this paper we propose that the terephthalic acid reaction represents one example of a class of electrophilic aromatic substitutions involving deactivated benzoic acids. These reactions are characterized by an ortho-directing effect which results from an esterification occurring prior to ring attack.

Results

Electrophilic substitution reactions are generally sensitive to changes in acid strength. Therefore, a number of known Lewis acids were added to the formaldehyde–

(1) Presented, in part, before the Division of Petroleum Chemistry, American Chemical Society, Houston Meeting, Feb 22–27, 1970.

(2) (a) G. A. Burkhardt, *Ber.*, **10**, 144 (1877); (b) R. Wegscheider, *Monatsh. Chem.*, **21**, 621 (1900).

(3) S. Akiyosi, M. Okamura, and S. Hashimoto, *J. Chem. Soc. Jap., Ind. Chem. Sect.*, **57**, 214 (1954); *Chem. Abstr.*, **49**, 2774a (1955).

(4) F. C. Whitmore and L. L. Isenhour, *J. Amer. Chem. Soc.*, **51**, 2785 (1929).

(5) L. S. Forney, *J. Org. Chem.*, **35**, 1695 (1970).

(6) The effect of a $-CH_2O-X$ group on the activation of aromatic systems toward electrophilic attack has not been reported. However, the σ_p^+ for phenylacetic acid toward nitration is -0.164 which means the $-CH_2CO_2H$ group is activating relative to H.[7] In contrast, the CH_3O-CH_2- group has been found to have a positive σ^* (0.64) relative to H (0.49).[8] Generally, it is thought that σ^* represents ground-state effects, and as a result the $-CH_2O-X$ is a moderate activator toward electrophilic aromatic substitution.

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

(8) P. Ballinger and F. A. Long, *ibid.*, **82**, 795 (1960).

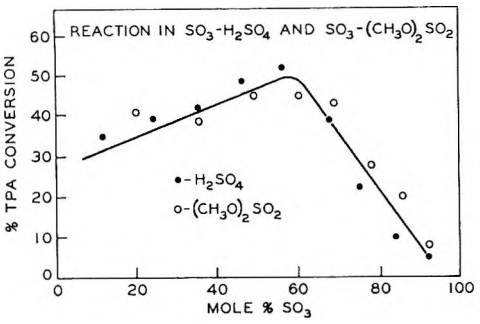


Figure 1.—Yield of 5-carboxyphthalide in sulfuric acid (black dots) and methyl sulfate (open circles) solutions containing varying amounts of SO_3. Conditions were: 1 *M* terephthalic acid and 1 *M* formaldehyde, reacted in sealed glass tubes for 1 hr at 150 ± 0.2°.

terephthalic acid reaction. The results are shown in Table I. Without added metal salts, a 61% conversion

TABLE I
EFFECT OF ADDED SALTS ON THE REACTION OF FORMALDEHYDE AND TPA

Salt	% TPA	% 5-CP
None	39	61
$ZnBr_2$	19	55[a]
$FeCl_3$	47	53
$AlCl_3$[b]	46	54
$TiCl_4$	64	36
SbF_5	75	25
NaCl	42	58
LiF	40	60

[a] The products included 26% of a mixture of brominated carboxyphthalides, which was not characterized. [b] The $AlCl_3$ was not completely soluble at the concentration used (0.5 g/5 ml of mixture).

to 5-carboxyphthalide was achieved in 2 hr. Addition of Lewis acids gave lower conversions. The results with added Lewis acids are not in accord with a direct electrophilic substitution mechanism, *i.e.*, dependent upon the acid strength of the medium. Were such a system operative, the highest conversion would have been observed with SbF_5, contrary to the observed effect.

Addition of the neutral salts, NaCl and LiF, did not affect the conversion. Since the highly ionic nature of the oleum medium would be only slightly changed by additional neutral ionic species, no great effect on conversion was expected or observed.

The conversion was quite sensitive to the nature of the solvent used for the reaction. As shown by Table II, the conversions in 30% SO_3–H_2SO_4 and 30% SO_3–dimethyl sulfate were nearly equivalent and much greater than those observed in other media. A moderate conversion was found in 30% SO_3–HSO_3F. On the other hand, 100% HSO_3F, 98% H_2SO_4 (aqueous), HSO_3F–SbF_5 (the so-called "Magic Acid"[9]), and methanesulfonic acid gave uniformly poor results. If the condensation was facilitated by high acid strength, then the fastest rate, and presumably the greatest conversion in 2 hr, would have been observed in HSO_3F–SbF_5.

The unifying features of the solvents listed in Table II seemed to be that relatively high conversions were observed in solvents characterized by their free SO_3 content, with the single exception of methanesulfonic acid.

(9) G. A. Olah and R. H. Schlosberg, *J. Amer. Chem. Soc.*, **90**, 2726 (1968).

TABLE II
SOLVENT EFFECT ON THE REACTION OF FORMALDEHYDE AND TPA AT 150° FOR 2 HR

Run	Solvent	% conversion to 5-CP
1	30% SO_3–H_2SO_4	95
2	30% SO_3–dimethyl sulfate	92
3	30% SO_3–HSO_3F	20
4	HSO_3F	3
5	98% H_2SO_4 aqueous	1[a]
6	30% SO_3–methanesulfonic acid	0
7	SbF_5–HSO_3F (1:1)	0
8	100% SO_3	94[b]

[a] Product work-up indicated 12% terephthaloyloxyacetic acid (isolated as the dimethyl ester). [b] The reaction solution was more concentrated than in the other cases (about 6 *M* in TPA and formaldehyde). As a result, this run cannot be directly compared for conversion data.

This implies that SO_3 is a critical factor for the condensation. This was confirmed by a reaction in 100% SO_3. The reactant concentration was not comparable with runs 1–7, since the use of 100% SO_3 required a more concentrated reaction medium to prevent a phase separation. However, these conditions provided an excellent conversion (>90%) to 5-carboxyphthalide.

A comparison of the formaldehyde–terephthalic acid condensation in sulfuric acid and dimethyl sulfate media with varying amounts of SO_3 is presented in Figure 1. Two features of the graph are apparent: in both media, equivalent conversions are found at any given SO_3 concentration, despite the great contrast in the nature of these media; the conversion in both solvents reaches a maximum at 60 mol % SO_3 content.

The dependence of the conversion on the SO_3 content of the media strongly suggests that the same mechanism is operative in both sulfuric acid and dimethyl sulfate. In view of the differences in the highly protic (sulfuric acid) and aprotic (dimethyl sulfate) media, this supports the assertion that the condensation is not a direct electrophilic substitution process by a protonated or sulfated formaldehyde species. It must be noted, however, that proton catalysis of the reaction cannot be excluded on the basis of these data, since even in the dimethyl sulfate media some protons were introduced by the dissociation of terephthalic acid in solution.

The formaldehyde condensation was extended to *m*- and *p*-nitrobenzoic acids. The *m*-nitrobenzoic acid is the more reactive to direct electrophilic attack, since its 5 position is not as deactivated as reactive sites in *p*-nitrobenzoic acid.[10] However, no reaction occurred, and *m*-nitrobenzoic acid was recovered unchanged. Formaldehyde condensation with *p*-nitrobenzoic acid under analogous conditions gave a 47% yield of 5-nitrophthalide. This initially was unexpected, since all ring positions of *p*-nitrobenzoic acid are deactivated, as each position is either ortho to a carboxy or nitro group. Thus, the condensation with nitrobenzoic acids does not occur *via* a direct electrophilic attack.

Discussion

From the foregoing results, a mechanistic interpretation of the condensation of formaldehyde with highly

(10) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N.Y., 1959, p 428.

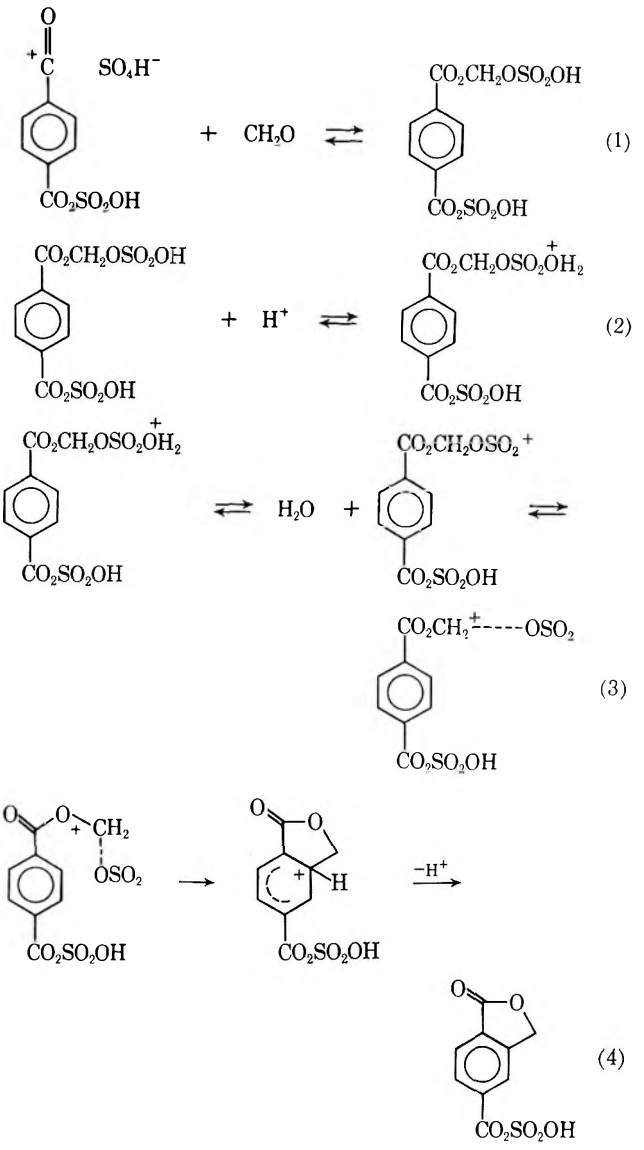
deactivated aromatic substrates, such as terephthalic acid, must include the following features: (a) the same mechanism is operative in both oleum and dimethyl sulfate–SO_3 media; (b) the reaction of nitrobenzoic acids does not occur through attack by some free electrophilic formaldehyde species; (c) SO_3 must be intimately involved in the condensation in a role which cannot be played by other Lewis acids such as SbF_5 or $AlCl_3$, etc; and (d) reaction is retarded in fluorosulfonic acid and methanesulfonic acid.

These criteria can be satisfied by formation of an intermediate complex involving the carboxyl function prior to attack on the aromatic nucleus. A hydroxymethyl ester is proposed, formed *via* reaction of formaldehyde with a TPA species as shown in eq 1. Formaldehyde has been suggested to form hydroxymethyl esters with carboxylic acids. Although such products have not been isolated, their postulation aids in understanding the chemistry of formaldehyde in solution.[11] It is worth noting that the electrophilic metalations of benzoic acid and derivatives have been found to occur subsequent to interaction with the carboxyl group. Thus, the thallation of benzoic acid and its esters was recently suggested to occur by initial formation of a thallium–carbonyl complex, followed by intramolecular substitution of thallium into the ortho position of the acid.[12] Similarly, mercuration of terephthalic acid produces the mercurophthalide.[4]

The nature of the aromatic acid, formaldehyde, and proposed formaldehyde ester intermediate cannot be conclusively specified under our reaction conditions. However, acids and esters would certainly be rapidly sulfated in SO_3 media.[13] Indeed, since formaldehyde itself forms a stable complex with SO_3,[14] it is probable that the esterification is a result of a reaction between a formaldehyde–sulfur trioxide complex and the aromatic acid, present as the sulfate or corresponding acylium ion. The acid sulfate of acetic acid in sulfuric acid–SO_3 is converted to the acylium ion at 13–17% SO_3 content at 35°.[15] Under still more acidic conditions, such as SbF_5–HSO_3F mixtures, the diacylium ion of terephthalic acid can be prepared.[16] If the monoacylium ion of terephthalic acid is the reactive species for the esterification, then the rate increase up to 60 mol % SO_3 in either sulfuric acid or dimethyl sulfate may correspond to increasing acylium ion concentrations at higher SO_3 levels. As a consequence of eq 1, this would increase the concentration of the hydroxymethyl ester in solution, and the reaction rate would be enhanced, as shown in Figure 1.

Once formed, the formaldehyde–ester may undergo protonation and loss of water to provide a primary carbonium ion stabilized by association with SO_3, as shown in eq 2 and 3.

Primary carbonium ions are extremely reactive. Therefore, reversal of the stabilized ester species formed in eq 3 to re-form an acylium ion and formaldehyde must



be a major reaction pathway. However, proximity to the nucleophilic oxygen of SO_3 should stabilize this primary oxycarbonium ion. Lewis acids lacking nucleophilic oxygens would not be expected to facilitate the reaction because they cannot stabilize this positively charged ester. This is in accord with our results of Table II. Indeed, primary oxycarbonium ions have been found to possess greatly enchanced stabilities, relative to primary carbonium ions in the hydrocarbon series.[17]

Alternative explanations[18] for the lack of catalytic effect from added Lewis acids cannot be ruled out from the experimental data. Thus, the added acid may preferentially form a complex with formaldehyde, decreasing its availability. Or, the Lewis acid may complex with the carboxyl group para to the site of formaldehyde esterification, deactivating the aromatic nucleus toward electrophilic attack. However, we prefer the argument based on the absence of oxygen in the Lewis acids, as noted above. This reasoning is in accord with the decreased reactivity in fluorosulfonic acid and methanesulfonic acid media.

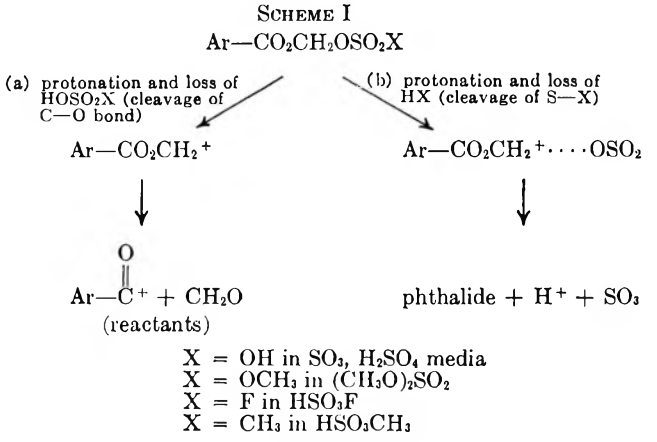
The SO_3 stabilization of the primary oxycarbonium ion allows it to participate in a second reaction pathway,

(11) J. F. Walker, "Formaldehyde," ACS Monograph Series, No. 159, American Chemical Society, Washington, D. C., 1964.
(12) E. C. Taylor, F. Kiezle, R. L. Robey, and A. McKillop, *J. Amer. Chem. Soc.*, **92**, 2175 (1970).
(13) E. E. Gilbert, *Chem. Rev.*, **62**, 575 (1962).
(14) E. E. Gilbert, "Sulfonation and Related Reactions," Interscience, New York, N. Y., 1965, p 370.
(15) N. C. Deno, C. U. Pittman, Jr., and M. J. Wisotsky, *J. Amer. Chem. Soc.*, **86**, 4370 (1964).
(16) G. A. Olah and M. B. Comisarow, *ibid.*, **88**, 3313 (1966).
(17) B. G. Ramsey and R. W. Taft, *ibid.*, **88**, 3058 (1966).
(18) Private communication with Min-Hon Rei.

in addition to reversion to reactants. This pathway involves attack on the aromatic ring and leads to phthalide formation (eq 4) by electrophilic attack of the stabilized oxycarbonium ion.

The mechanism described above will reconcile the solvent effects noted in Table I. Formation of the SO_3-stabilized primary carbonium ion (eq 2 and 3) can be generalized to include other solvents as shown below (Scheme I). When X = CH or OCH_3, protonation of

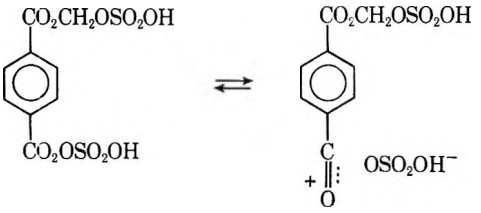
SCHEME I



these groups followed by their loss as neutral species competes favorably with protonation and loss of $HOSO_2X$ (regeneration of starting materials). Since protonation of F with loss of HF is relatively less likely, the rate of phthalide formation would be expected to decrease in fluorosulfonic acid. Cleavage of the SX bond seems quite unlikely when X = methyl, and as a consequence, little if any phthalide formation is anticipated in methanesulfonic acid.

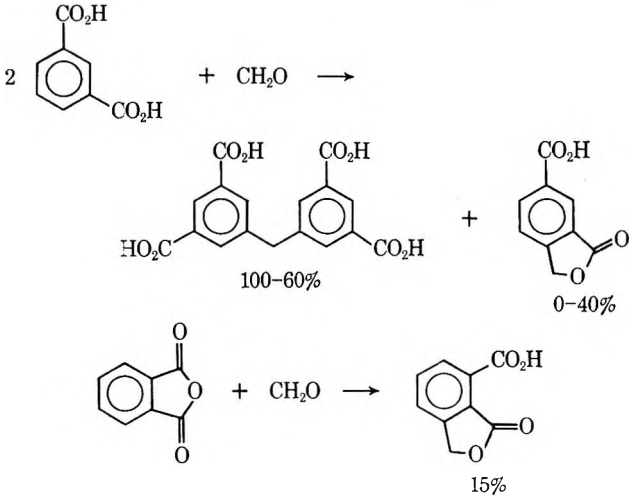
The nitrobenzoic acid condensations can also be understood in terms of a mechanism in which an electrophilic attack on the aromatic ring is preceded by esterification. The carboxyl group must now control the course of the reaction, so that attack occurs only at the 2 and 6 positions. Since a *m*-NO_2 substituent strongly deactivates both these positions, electrophilic attack from an intermediate ester or carboxyl complex should be decreased or prevented in the case of *m*-nitrobenzoic acid. On the other hand, the 2 and 6 positions of *p*-nitrobenzoic acid are less deactivated by the nitro group, relative to the meta isomer. Hence, electrophilic attack on *p*-nitrobenzoic acid by a complex of formaldehyde and a carboxyl group is more likely to occur than attack by the equivalent complex formed from *m*-nitrobenzoic acid. Had the reaction of nitrobenzoic acids not proceeded through a preliminary esterification, the meta isomer should have been the more reactive. Furthermore, the expected product would have been 3,3′-dicarboxy-5,5′-dinitrodiphenylmethane, by analogy of the formaldehyde condensations with benzoic acid to provide 3,3′-dicarboxydiphenylmethane,[19] and with isophthalic acid to provide 3,3′,5,5′-tetracarboxydiphenylmethane.[20]

The decreased conversion at SO_3 levels greater than 60 mol %, as shown in Figure 1, can be explained by the formation of an acylium ion of the formaldehyde–ester. Such a reaction will powerfully deactivate the aromatic nucleus toward an electrophilic attack according to eq 4, since this would require an intermediate aromatic dicarbonium ion. Thus the conversion decreases at SO_3 concentrations above 60 mol %.



The mechanistic pathway presented in the foregoing section accounts for the experimental observations on the condensation of formaldehyde with highly deactivated substrates. However, a direct electrophilic substitution reaction of formaldehyde is sufficient to explain diarylmethane formation from benzoic or isophthalic acids, or phthalide formation from activated benzoic acids.[21] Given that a choice of reaction pathways exists for reaction of formaldehyde with more or less deactivated benzoic acids, it should be possible to find intermediate cases where a competition between these reaction pathways can be observed. In this event, some diarylmethane derivatives should be formed by attack of a free electrophilic formaldehyde species, along with some phthalide derivatives derived from a formaldehyde–ester species. Therefore, we reinvestigated the reaction of phthalic and isophthalic acids with formaldehyde.

The reaction of isophthalic acid and formaldehyde was reported to yield only tetracarboxydiphenylmethane.[20] However, we found that with suitable control of conditions, 6-carboxyphthalide was also formed in yields up to 40%. We believe that this substrate represents an intermediate case which can form products by either a "direct" electrophilic substitution reaction (leading to a diarylmethane) or by a substitution reaction involving carboxyl participation (leading to phthalide). As would be expected in such intermediate cases, the partitioning of material between the two reaction pathways is sensitive to experimental conditions. The formaldehyde condensation with phthalic anhydride may represent yet another such intermediate case, as a



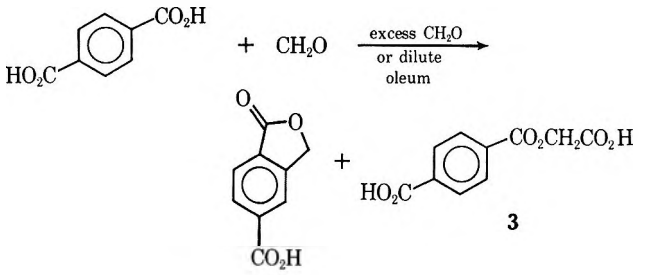
(19) R. W. Beattie and R. H. Manske, *Can. J. Chem.*, **42**, 223 (1964).

(20) J. R. LeBlanc, D. B. Sharp, and J. G. Murray, *J. Org. Chem.*, **26**, 4731 (1961).

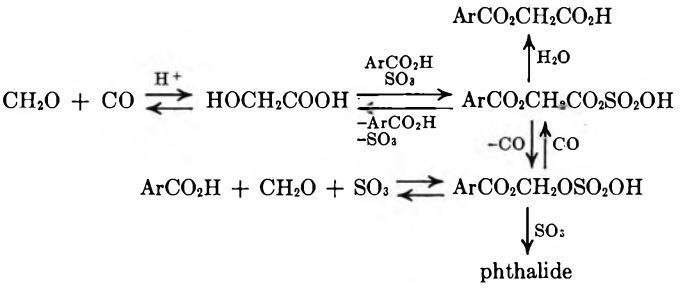
(21) E. H. Charlesworth, R. P. Rennie, J. E. Sinder, and M. M. Yan, *Can. J. Res.*, **23B**, 17 (1945).

15% yield of 7-carboxyphthalide results from this reaction.

When the 5-carboxyphthalide synthesis is run with a large excess of formaldehyde, or in dilute oleum mixtures, terephthaloyloxyacetic acid (**3**) appears as a product of the reaction. The isolation of terephthaloyloxyacetic acid under conditions similar to those which provide 5-carboxyphthalide strongly suggest that terephthalic acid is undergoing esterification during the reaction. The formation of **3** indicates that some of the formaldehyde was oxidized to carbon monoxide under



the reaction conditions. Two reaction pathways involving CO can be envisaged which would lead to terephthaloyloxyacetic acid, as shown below.



No distinction can be made at this time between a reaction involving CO attack on the hydroxymethyl ester and a reaction involving esterification with hydroxyacetic acid formed previously by attack of CO and CH_2O under the reaction conditions. The latter process is similar to the synthesis of hydroxyacetic acid by the acid-catalyzed carbonylation of formaldehyde.[22] Although much higher temperatures and CO pressures are required in that process than we observe during 5-carboxyphthalide synthesis, the yields of terephthaloyloxyacetic acid are improved by reaction under CO pressure.

Recently, cyclohexanecarboxylic acid was shown to undergo decarbonylation in fuming sulfuric acid at 25°.[23] This agrees with our observation that hydroxyacetic acid reacts with terephthalic acid in fuming sulfuric acid to give a small yield of 5-carboxyphthalide. Since this reaction could only occur with decarbonylation, it indicates that the carbonylation of the terephthalic acid–formaldehyde ester is reversible, as indicated.

(22) D. J. Loder, U. S. Patent 2,152,852 (1939).

(23) M. I. Vinnik, R. S. Ryabova, and V. I. Ganina, *Zh. Fiz. Khim.*, **42**, 2916 (1968); *Chem. Abstr.*, **70**, 46570 (1969).

Experimental Section

Materials.—Aromatic substrates, formaldehyde (trioxane), cosolvents, and sulfur trioxide (Sulfan-B) were commercial products of the highest purity attainable.

The sulfur trioxide was stored in a vessel jacketed in boiling pentane (36°) to prevent crystallization catalyzed by traces of water.

Methods.—The preparation of phthalides from phthalic acids and nitrobenzoic acids was carried out according to the method described for the reaction with terephthalic acid.[5]

The effect of added salts on the 5-carboxyphthalide synthesis (Table I) was obtained from reactions conducted in sealed glass tubes. Solutions (5 ml) of 30% oleum, containing 1 *M* terephthalic acid and 1 *M* formaldehyde, and 0.5 g of salts were placed in a bath at 150 ± 0.2° for 2 hr. The products were converted to methyl esters and analyzed by gas chromatography. Material balances based on aromatics were all above 76%, and in most cases, 86–94%.

The experiments in various solvents (Table II) also were conducted for 2 hr at 150 ± 0.2°, in sealed glass tubes. Except as noted, the solutions were 1 *M* in terephthalic acid and 3 *M* in formaldehyde and were worked up as described above. Material balances, based on aromatics, were 79–90%.

Effect of CO on Preparation of Terephthaloyloxyacetic Acid (3).—Terephthalic acid (8.3 g, 0.05 mol) and formaldehyde (4.5 g, 0.30 mol of Trioxane) in 50 ml of 98% sulfuric acid were placed under 1000 psi of CO in a glass-lined pressure vessel.

After heating to 150° for 2 hr the contents of the vessel were poured into ice water, converted to methyl esters ($MeOH-BF_3$), and analyzed by gas chromatography. The product mixture contained 94% dimethyl terephthalate and 5% dimethyl terephthaloyloxyacetic acid. When this procedure was carried out in the absence of CO, only dimethyl terephthalate could be isolated.

Registry No.—Formaldehyde, 50-00-0; terephthalic acid, 100-21-0; 1, 4792-29-4; 2, 16776-76-4.

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Alkali Metals as Hydrogenation Catalysts for Aromatic Molecules[1]

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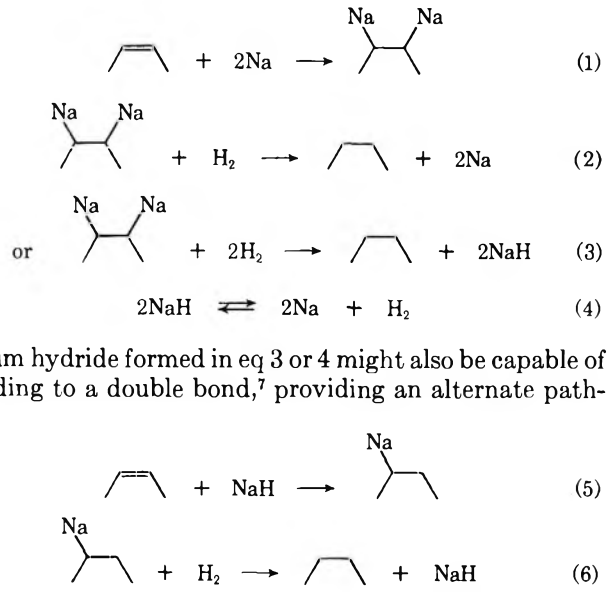
Alkali metals are hydrogenation catalysts for aromatic compounds at high temperatures and pressures. Catalytic activity increases from lithium to rubidium. It is unnecessary to use the more active metals as the free metal; mixtures of sodium metal and potassium carbonate produce results equivalent to those obtained with NaK alloy. The extent of hydrogenation depends on temperature and the metal used. Below 250°, polycyclics and polyphenyls can be reduced readily in benzene as solvent to compounds containing isolated benzene rings at initial hydrogen pressures of 1400 psig and temperatures of 180–250° with Na + Rb_2CO_3; above 250°, benzene forms hydrogenated dimers and higher polymers. *o*-Terphenyl hydrogenates and cyclizes to dodecahydrotriphenylene. Ethers are cleaved by the alkali metals as are some polycyclic heteroaromatic compounds. The use of amines as solvents permits hydrogenation at lower temperatures than with benzene.

Sodium in liquid ammonia has been used for many years as a reducing agent for aromatic systems,[2] and more recently both sodium and lithium in amines have become increasingly important.[3,4] In these reductions, the amines serve as proton donors; in liquid ammonia, an alcohol is usually added to furnish the hydrogen.[2]

There are also some instances known where ethers are used as solvents for reductions with alkali metals;[5] here, the alkali metal salt of the hydrocarbon is formed. Addition of water or alcohol then provides the necessary hydrogen to decompose the salt and form the reduced hydrocarbon. In these reactions, the alkali metal participates noncatalytically and is eventually converted to $M^+ B^-$, where M = Na or Li and B = OH, OR, or NR_2. The equivalent of an ionic carbon–metal bond is formed at some stage of the reaction.

Carbon–metal bonds, such as those formed in alkali metal reductions in nonpolar solvents, are known to hydrogenate readily.[6] Thus, if such a bond is formed in an atmosphere of hydrogen, reduction can take place to regenerate the metal or to form its hydride. The sodium hydride formed in eq 3 or 4 might also be capable of adding to a double bond,[7] providing an alternate pathway to the reduction product. In either case, these reactions would constitute a catalytic hydrogenation.



Several investigations have explored this catalytic system for hydrogenating aromatics, using alkali metals[8] and sodium hydride[7,9] as the initial catalysts, and in all cases hydrogenations have been achieved. However, most of the reported work has been confined to the reduction of naphthalene to tetrahydronaphthalene. We have investigated the system in more detail, studied the effects of other alkali metals and of other solvents, and applied it to compounds other than naphthalene, especially compounds of the type one might find in coal or coal tar.

Discussion

Initially, a series of reactions was conducted in which sodium metal, an aromatic hydrocarbon, and a solvent (benzene or toluene) were heated with hydrogen in a rocking autoclave to a specified temperature. The reaction product contained some white solid in suspension. Addition of isopropyl alcohol caused considerable reaction, with evolution of gas, presumably hydrogen from decomposition of NaH. Examination of the products by mass spectrometry and gas chromatography gave the results shown in Table I. These results indicated that sodium (or NaH) was a hydrogenation catalyst, and that careful control of temperature and pressure might allow stepwise hydrogenation to be carried out.

Similar experiments showed that lithium, which is a better reducing agent than sodium in metal–amine systems,[4] is a much poorer catalyst than sodium for hydrogenation of naphthalene. Lithium, due to its low density, floats on the surface of the reaction mixture and appears to be poorly dispersed during the reaction. Even at 325°, only 4% of the naphthalene is reduced. Limitations of the equipment prevented going to higher temperature.

Liquid sodium–potassium alloy (NaK), which probably behaves like potassium, was more active than sodium. As shown in Tables I and II, most of the hydrocarbons tried were hydrogenated to mixtures of products, with a few exceptions. The reductive cyclization of *o*-terphenyl to give *sym*-dodecahydrotriphenylene as a major product is one of the best available methods for

(1) Presented before the Division of Fuel Chemistry, 148th National Meeting of the American Chemical Society, Chicago, Ill., Aug 30–Sept 4, 1964.

(2) A. J. Birch, *Quart. Rev.*, **4**, 69 (1950).

(3) G. W. Watt, *Chem. Rev.*, **46**, 317 (1950).

(4) (a) R. A. Benkeser, *Advan. Chem. Ser.*, **23**, 58 (1959). (b) L. Reggel, R. A. Friedel, and I. Wender, *J. Org. Chem.*, **22**, 891 (1957).

(5) S. E. Hunt and A. S. Lindsey, *J. Chem. Soc.*, 2227 (1958); H. Mohler and J. Sorge, *Helv. Chim. Acta*, **22**, 229 (1939).

(6) H. Gilman, A. L. Jacoby, and H. Ludeman, *J. Amer. Chem. Soc.*, **60**, 2336 (1938).

(7) S. M. Blitzer and T. H. Pearson, U. S. Patent 2,987,558 (1961).

(8) F. W. Bergstrom and J. F. Carbon, *J. Amer. Chem. Soc.*, **63**, 2934 (1941). Guyot, *Chim. Ind. Spec.*, No. 410 (1928); *Chem. Abstr.*, **22**, 4522 (1928). N. A. Orlov and N. D. Likhachev, *Ber.*, **63B**, 2179 (1930).

(9) G. Hugel and Friess, *Bull. Soc. Chim. Fr.*, **49**, 1042 (1931); G. Hugel, *Can. Chem. Met.*, **13**, 5 (1929).

TABLE I

ALKALI METAL CATALYZED HYDROGENATIONS OF POLYCYCLIC AROMATIC HYDROCARBONS

Compd	Catalyst	Temp, °C	Principal products[a] (%)
Naphthalene	Li	325	Naphthalene (96)
			1,2,3,4-Tetrahydronaphthalene (4)
	Na	300	Naphthalene (30)
			1,2,3,4-Tetrahydronaphthalene (62)
	NaK	250	1,2,3,4-Tetrahydronaphthalene (91)
			1,1′,2,2′,3,3′,4,4′-Octahydro-2,2′-dinaphthyl (8)
	NaRb	180	1,2,3,4-Tetrahydronaphthalene (99)
	NaCs	200	1,2,3,4-Tetrahydronaphthalene (88)
Anthracene	Na	250	9,10-Dihydroanthracene (53)
			1,2,3,4-Tetrahydroanthracene (38)
	NaK	250	1,2,3,4-Tetrahydroanthracene (37)
			Octahydroanthracene (53)[b]
	NaK	350	Octahydroanthracene (85)[b]
	NaRb	220	Octahydroanthracene (70)[b]
Phenanthrene	Na	250	9,10-Dihydrophenanthrene (23)
			1,2,3,4-Tetrahydrophenanthrene (72)
	NaK	250	9,10-Dihydrophenanthrene (10)
			Octahydrophenanthrene (80)[b]
	NaRb	180	9,10-Dihydrophenanthrene (82)
			1,2,3,4-Tetrahydrophenanthrene (5)
	NaRb	200	9,10-Dihydrophenanthrene (10)
			Octahydrophenanthrene (78)[b]
	NaCs	220	9,10-Dihydrophenanthrene (50)
			Octahydrophenanthrene (36)[b]
Naphthacene	NaK	250	5,12-Dihydronaphthacene (99)
	NaRb	300	5,12-Dihydronaphthacene (25)
			Hexahydronaphthacene (18)
			Octahydronaphthacene (36)
Chrysene	NaK	250	Hexahydrochrysene (40)
			Octahydrochrysene (24)
			Dodecahydrochrysene (23)
	NaRb	250	Dodecahydrochrysene (85)
Triphenylene	NaK	250	Triphenylene (12)
			sym-Dodecahydrotriphenylene (70)
Pyrene	NaK	250	Pyrene (45)
			4,5-Dihydropyrene (42)
	NaK	350	Pyrene (50)
			Hexahydropyrene (10)
			Decahydropyrene (32)
	NaRb	250	Pyrene (43)
			Decahydropyrene (22)
			Dodecahydropyrene (14)
Perylene	NaRb	250	Perylene (10)
			Octahydroperylene (47)
			Dodecahydroperylene (30)
Fluorene	NaRb	250	Fluorene (60)
			1,2,3,4-Tetrahydrofluorene (10)
			1,2,3,4,4a,9a-Hexahydrofluorene (25)

[a] Percentage yields, based on recovered material, in parenthesis. [c] Approximately 2:1 mixture of symmetrical (1,2,3,4,5,6,7,8-octahydro) isomer and unsymmetrical (1,2,3,4,4a,9,9a,10-octahydroanthracene; 1,2,3,4,4a,9,10,10a-octahydrophenanthrene) isomer. All other unnumbered products were identified by mass spectral peaks and were not further characterized.

preparation of the latter compound.[10] The starting material is readily available, and the product is easily crystallized from the reaction mixture.

In the reduction of the polyaryls, scission of the bonds between the rings is indicated by the formation of traces

(10) D. A. Scola, *J. Chem. Eng. Data*, **9**, 405 (1964).

TABLE II

ALKALI METAL CATALYZED HYDROGENATIONS OF POLYARYL HYDROCARBONS

Compd	Catalyst	Temp, °C	Principal products[a]
Biphenyl	NaK	350	Biphenyl (20)
			Phenylcyclohexane (70)
			Benzene[b]
	NaRb	250	Biphenyl (20)
			Phenylcyclohexane (70)
			Benzene[b]
o-Terphenyl	NaK	350	o-Terphenyl (30)
			sym-Dodecahydrotriphenylene (50)
	NaRb	250	Biphenyl (60)
			Hexahydroterphenyl (10)
			sym-Dodecahydrotriphenylene (20)
			Benzene[b]
p-Terphenyl	NaK	350	Biphenyl (10)
			trans-1,4-Diphenylcyclohexane (40)
			Dodecahydroterphenyl (40)
1,3,5-Triphenylbenzene	NaRb	250	Hexahydroterphenyl (10)
			Hexahydrotriphenylbenzene (50)
			Dodecahydrotriphenylbenzene (30)
			Octadecahydrotriphenylbenzene (5)

[a] Percentage yields, based on recovered material, in parenthesis. [b] Yield not determined.

of benzene, biphenyl, phenylcyclohexane, and traces of higher polyaryls. When benzene is heated to 250° with NaK and hydrogen, some biphenyl is formed; at 350°, hydrogen is absorbed with formation of hydrogenated dimers and higher polymers, as well as chars.[11] Toluene, though less reactive than benzene, reacts in a similar manner; there is some migration of methyl groups, with formation of benzene and small amounts of material with molecular weights corresponding to xylene, phenylcyclohexane, methylbiphenyl, and methylphenylcyclohexane. Because of this, tetralin or decalin was used as solvent for hydrogenations carried out above 250°, though they resulted in less extensive hydrogenation when compared to benzene at 250°.

Alkali Metal–Salt Combination Catalysts.—Since the reaction of alkali metals and alkali metal salts is an equilibrium reaction (eq 7), it was felt that NaK

$$\mathrm{Na} + \mathrm{KX} \rightleftharpoons \mathrm{NaX} + \mathrm{K} \qquad (7)$$

could be formed *in situ* in a reaction vessel at elevated temperatures by using Na and the appropriate potassium salt. Potassium chloride–sodium mixtures fail to give results comparable to NaK at 250°; instead the mixture behaves like sodium. When K_2CO_3 or KOH is used with Na, however, hydrogenation of naphthalene,[12] phenanthrene, and pyrene proceeds to give products and yields similar to those obtained with NaK. In the absence of sodium, K_2CO_3 gives no hydrogenation.

The success of the potassium salt–sodium metal system suggested that the use of rubidium salts might allow the catalytic behavior equivalent to sodium–rubidium (NaRb) to be studied without the inconvenience of handling metallic rubidium. Experiments indicate this to be valid. Substitution of Rb_2CO_3 for K_2CO_3 results in lowering the temperature of a given hydrogenation

(11) L. H. Slaugh, *Tetrahedron*, **24**, 4525 (1968). This reference incorrectly quotes the authors (ref 1) as stating that benzene does not react in the presence of alkali metals and hydrogen.

(12) G. L. O'Connor, H. E. Fritz, and M. A. Eccles, U. S. Patent 2,968,681 (1961). This patent, which covers the use of sodium with potassium salts for hydrogenation of naphthalene, appeared during the course of this work.

by 50° to 100°. In some cases, NaRb (prepared *in situ* from Na and Rb_2CO_3 in all experiments) causes more extensive hydrogenation than is observed with NaK. Varying the ratio of Na to Rb_2CO_3 from 1:2 to 2:1 had no observable effect on results. A single experiment using rubidium formate with sodium gave results comparable to those obtained with sodium itself.

Some of the observations reported in this paper may be the result of the heterogeneity of the system and the difficulty in obtaining reaction between a solid salt and a solid or molten metal immersed in a passive liquid phase, rather than to the chemistry of the materials themselves.

Hydrogenation of Heteroatom Compounds.—The presence in an aromatic molecule of oxygen-containing functional groups necessitates that sufficient catalyst be present to allow for the formation of an alkali metal salt of the hydroxyl group which may be formed. The results shown in Tables III and IV indicate that aromatic C–O bonds are readily hydrogenolyzed by NaRb; the products are predominantly those expected from hydrogenation of the deoxygenated compounds. Decarboxylation also occurs readily.

TABLE III

NaRb-CATALYZED HYDROGENATIONS OF OXYGENATED AROMATIC COMPOUNDS

Compd	Catalyst	Temp, °C	Principal products[a]
2-Methoxynaphthalene	NaRb	250	1,2,3,4-Tetrahydronaphthalene (80) 2-Naphthol (10) Dihydro- and tetrahydronaphthol (5)
2-Naphthol	NaRb	220	1,2,3,4-Tetrahydronaphthalene (50) 5,6,7,8-Tetrahydro-2-naphthol (45)
p-Phenylphenol	NaRb	250	Phenylcyclohexane (90)
2-Naphthoic acid	NaRb	250	1,2,3,4-Tetrahydronaphthalene (80)
Anthraquinone	NaRb	250	Octahydroanthracene (70)[b] *sym*-Octahydroanthranol (20)

[a] Percentage yields, based on recovered material, in parenthesis. [b] Approximately 2:1 mixture of symmetrical and unsymmetrical isomers.

TABLE IV

NaRb-CATALYZED HYROGENATIONS OF HETEROCYCLIC AROMATIC COMPOUNDS

Compd	Catalyst	Temp, °C	Principal products[a]
Dibenzofuran	NaRb	250	Phenylcyclohexane (80) Biphenyl (10) Hexahydroterphenyl (5)
Dibenzothiophene	NaRb	250	Dibenzothiophene (50) Phenylthiophenol (20) Biphenyl (20)
Quinoline	NaRb	220	5,6,7,8-Tetrahydroquinoline (60) Dimers (30)
Acridine	NaRb	250	Acridine (30) 9,10-Dihydroacridine (30) Tetrahydroacridine (9) Octahydroacridine (25)[b]
Phenanthridine	NaRb	250	Octahydrophenanthridine (77)[b]

[a] Percentage yields, based on recovered material, in parenthesis. [b] Only unsymmetrical isomers detected.

Dibenzofuran (Table IV) at 250° is reductively cleaved; small amounts of hexahydroterphenyl are formed indicating reaction with the solvent, benzene. By contrast, dibenzothiophene is relatively inert toward both hydrogenation and cleavage in the presence of NaRb. This contrasts with Raney nickel or lithium–ethylenediamine reductions,[13] both of which bring about desulfurization. Added thianaphthene did not affect the NaRb-catalyzed hydrogenation of naphthalene, which indicates that the presence of sulfur compounds does not poison the alkali metal catalysts. Ring cleavage and decomposition are observed with nitrogen-containing heterocyclic aromatic compounds. Pyridine, when used as a solvent, forms a variety of products, including tar.

Several experiments to evaluate cesium as a catalyst were carried out in a manner similar to those involving rubidium (Table I), using cesium carbonate and sodium metal. Cesium proved to be a less active hydrogenation catalyst than rubidium and slightly more active than potassium in catalytic activity.

Effect of Solvents.—Initially, benzene and toluene were used as solvents because of their lack of reactivity toward alkali metals at room temperature. Since the work was directed primarily toward reductions of coal, it was apparent that a better coal solvent would be useful. Amines, which are good coal solvents, react with alkali metals to form amides.

$$M + RNH_2 \rightleftharpoons RNH^- + M^+ + {}^1/_2H_2$$

However, the reaction is probably reversible, so that, in the presence of hydrogen, some metal remains, probably in solution. In any event, the catalytic hydrogenation does proceed in amine and in benzene–amine solvents. Whereas 180° is the lowest temperature at which measurable hydrogen uptake occurs in benzene, in ethylenediamine or in butylamine–benzene (1:1) at 120°, phenanthrene is hydrogenated to octahydrophenanthrene with Na + Rb_2CO_3 (Table V). By lowering the initial hydrogen pressure to 100 psig, it is possible to prepare 1,2,3,4-tetrahydrophenanthrene in 80% yield in butylamine–benzene at 120°.

Similarly, other polycyclic hydrocarbons can be reduced at temperatures up to 200° in ethylenediamine and in ethylenediamine–benzene (1:1). The results are roughly comparable to those obtained at 250° when benzene is used as solvent.

Preliminary investigations have been carried out on coal and coal tar fractions. As many as 15 hydrogens per 100 C atoms have been added to a 90% carbon coal. The H_{arom}/H_{aliph} ratio (nmr) of a coal tar pitch was reduced from an initial 4.26 to 0.61 by hydrogenation with NaRb at 350°.

Experimental Section

Reagents.—The hydrocarbon solvents were dried over sodium. The ethylenediamine was refluxed with Na and freshly distilled before use. The reactants were obtained from standard suppliers. Where possible, reagent grade material was used.

The NaK (containing 76% potassium by weight, approximately 1:2 mol ratio) was a gift of the Mine Safety Appliance Research Corp. The liquid NaK was kept under N_2 and transferred by means of a hypodermic syringe. All NaRb was prepared *in situ* using sodium–Rb_2CO_3 weight ratios of 1:2 to 2:1.

Analyses of Products.—Products were analyzed by gas–liquid chromatography where possible, and by low-voltage mass spec-

(13) L. Reggel, C. Zahn, I. Wender, and R. Raymond, *Bull. U. S. Bur. Mines*, No. 615, 36 (1965).

TABLE V

NaRb-CATALYZED HYDROGENATIONS IN AMINE SOLVENTS

Compd	Catalyst	Temp, °C	Solvent	Principal products[a]
Phenanthrene	NaRb	120	Ethylenediamine	Octahydrophenanthrene (91)
	NaRb	120	Butylamine–benzene (1:1)	Octahydrophenanthrene (97)
	NaRb	120[b]	Butylamine–benzene (1:1)	Dihydrophenanthrene (12) 1,2,3,4-Tetrahydrophenanthrene (80)
Pyrene	NaRb	200	Ethylenediamine	Tetrahydropyrene (28) Hexahydropyrene (23) Decahydropyrene (18)
Naphthacene	NaRb	200	Ethylenediamine–benzene (1:1)	Dihydronaphthacene (32) Hexahydronaphthacene (22) Octahydronaphthacene (29)
Fluoranthene	NaRb	200	Ethylenediamine	Dihydrofluoranthene (80) Tetrahydrofluoranthene (7)
o-Terphenyl	NaRb	120	Ethylenediamine	Hexahydroterphenyl (75) Dodecahydrotriphenylene (13)

[a] Percentage yields, based on recovered material, in parenthesis. [b] Gas pressure, 100 psi.

trometry routinely. This latter procedure provides a molecular weight distribution of products. In certain experiments, it was possible to isolate a specific component and identify it by infrared and ultraviolet spectrometry. In these instances, the products are suitably described.

When a product is identified without specific numbering of the substituted hydrogen, identification has been inferred from the molecular weight (obtained from mass spectral measurements).

Procedure.—The procedure for all experiments was similar. Two examples will be given to illustrate the procedure. Initial pressures were between 1200 psi and 1400 psi. Temperatures shown in Tables I to V represent minimum temperatures at which appreciable yields of the indicated products were observed. Benzene or toluene was used as solvent for all reactions up to 250°. In a few cases, reductions were carried out above 250° to achieve more extensive reaction. In those experiments, tetralin and decalin served as solvents. All runs were held at temperature for 4.5–5 hr. The quantity of reactants was 5 g, except for naphthalene (30 g) and the tetra- and pentacyclic hydrocarbons which were used in 2-g amounts due to limited solubility. Recoveries ranged between 80 and 100%, physical losses being proportionately greater for runs containing smaller amounts of substrate. All analytical results are reported on the basis of the percentage of the total recovered, isolated product.

Hydrogenation of Naphthalene.—A solution of 30 g of naphthalene in 150 ml of toluene was placed in a 0.5-l. Aminco[14] rocking autoclave with 2 g of NaK. Hydrogen was introduced into the autoclave at 1250 psi, and it was then heated to 250°. It took 2.5 hr for the autoclave to reach this temperature. The autoclave was kept at 250° for 4.5 hr and then allowed to cool overnight. The reaction mixture consisted of a white solid in suspension in the toluene solution. The solid reacted vigorously with the isopropyl alcohol added to dispose of excess NaK. The solution was extracted with water to remove the alkali hydroxides, and the organic layer was extracted with ether. The ether solution was distilled through a helix-packed column to remove all solvents. The residue, containing naphthalene and its reduction products, was examined by mass spectrometry and gas chromatography. It was found to consist of 91% tetrahydronaphthalene and 8% of dimeric product with mol wt 262, and a small amount with mol wt 260.

The dimer was isolated by chromatography on alumina after removal of the lower boiling material by distillation. The recrystallized material, mp 105–108°, had a tetralin-like ultraviolet spectrum and infrared and nmr spectra consistent with a structure of 1,1′,2,2′,3,3′,4,4′-octahydro-2,2′-dinaphthyl.[15,16] Dehydrogenation with palladium on charcoal gave 2,2′-dinaphthyl.

Hydrogenation of Phenanthrene.—A solution of 5 g of phenanthrene in 80 ml of benzene was placed in an Aminco rocking autoclave with 1.5 g of sodium and 2.0 g of rubidium carbonate. Hydrogen was introduced into the autoclave at 1400 psi, and it was then heated to 200°. It took 2 hr for the autoclave to reach this temperature, which was maintained for 5 hr. The autoclave was allowed to cool overnight, and isopropyl alcohol was added to decompose the metal hydrides. The solution was extracted with water to remove the metal hydroxides, and the organic layer was extracted with ether. The ether and benzene were removed by distillation and the residue was examined by mass spectrometry. The product contained 10% 9,10-dihydrophenanthrene and 78% octahydrophenanthrene, as well as smaller amounts of 1,2,3,4-tetrahydrophenanthrene and phenanthrene. Traces of dimeric products were also present. Gas chromatographic analysis of the octahydrophenanthrene indicated an approximate 2:1 ratio of 1,2,3,4,5,6,7,8-octahydrophenanthrene to 1,2,3,4,4a,9,10,10a-octahydrophenanthrene.

Registry No.—Naphthalene, 91-20-3; anthracene, 120-12-7; phenanthrene, 85-01-8; naphthacene, 92-24-0; chrysene, 218-01-9; triphenylene, 217-59-4; pyrene, 129-00-0; perylene, 198-55-0; fluorene, 86-73-7; biphenyl, 92-52-4; *o*-terphenyl, 84-15-1; *p*-terphenyl, 92-94-4; 1,3,5-triphenylbenzene, 612-71-5; 2-methoxynaphthalene, 93-04-9; 2-naphthol, 135-19-3; *p*-phenylphenol, 92-69-3; 2-naphthoic acid, 93-09-4; anthraquinone, 84-65-1; dibenzofuran, 132-64-9; dibenzothiaphene, 132-65-0; quinoline, 91-22-5; acridine, 260-94-6; phenanthridine, 229-87-8; fluoranthene, 206-44-0.

Acknowledgment.—We thank Miss Janet Shultz for mass spectral determinations.

(14) Reference to specific trade names is made for identification only and does not imply endorsement by the Bureau of Mines.

(15) E. J. Eisenbraun, D. V. Hertzler, R. C. Bansal, P. W. K. Flanagan, and M. C. Hamming, Preprints of Papers, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, PETR 017. The same compound is also reported in ref 12.

(16) L. Reggel, H. W. Sternberg, and I. Wender, *Nature*, **81**, 190 (1961), report what is apparently a diastereomer.

The Nuclear Magnetic Resonance Spectra of Cyclic 1,3-Diphenylallyl Cations. Some Observations on 1,3-Orbital Interaction[1a]

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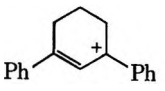
The possibility of 1,3-orbital overlap stabilization in the 1,3-diphenylcyclobutenyl cation (**3**) is explored by comparison of the nmr spectra of cycloalkenyl cations 1–4. It is concluded that 1,3-electrostatic repulsion results in charge dispersion in cation **3**. Extensive charge dispersion onto the phenyls in diphenylcyclopropenium ion (**4**) is found, accompanied by an unusually low barrier to rotation in accord with extended Hückel calculations. Several useful syntheses of cyclobutane and cyclobutene derivatives are described.

In some earlier papers we suggested that the para-proton resonance of phenyl-substituted carbonium ions was a reasonable quantitative measure of the stability or electron demands of the carbonium ion center.[2] We had hoped to use this method to look for stabilization by 1,3-orbital overlap in the series of allyl cations: 1,3-diphenylcyclohexenyl (**1**), 1,3-diphenylcyclopentenyl (**2**), 1,3-diphenylcyclobutenyl (**3**), and 1,3-diphenylcyclopropenyl (**4**) cations. Normally, if there were stabil-



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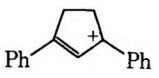

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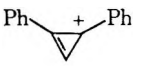

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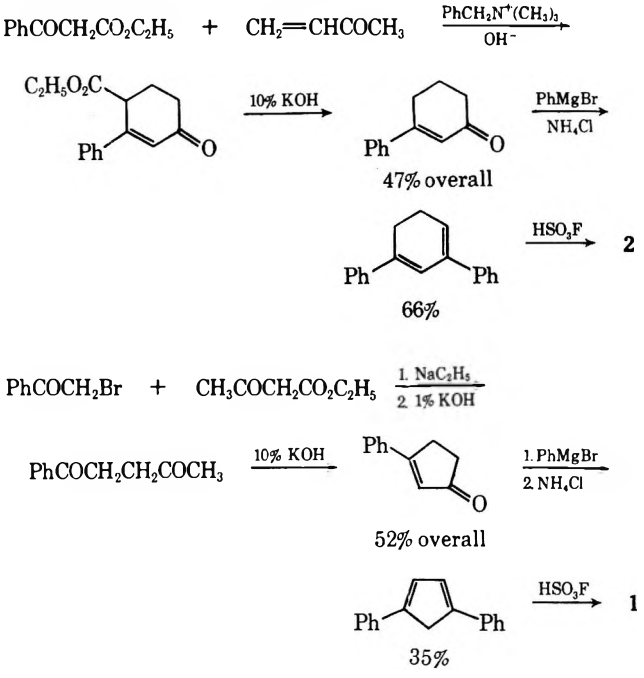
ization of the cations by 1,3 overlap, one would expect the stabilization to increase as ring size decreased. One would therefore expect the para-proton resonance of the phenyl substituents on these cations to move upfield as one moved to smaller and smaller ring sizes. Although we have since shown that the para-proton resonance is in fact a very insensitive measure of carbonium ion stability,[2b] and Taft has shown that the fluorine resonance is orders of magnitude more sensitive,[3] we nonetheless believe that the unexpected results of our investigation of the cyclic allyl cations, as well as some interesting synthetic methods developed in their preparation, warrant publication at this time.

The diphenylcyclopropenium ion (**4**), has, of course, been known for some time.[4,5] The diphenylcyclohexenyl (**1**) and diphenylcyclopentenyl (**2**) cations were prepared by solution of the corresponding dienes in cold fluorosulfonic acid. The dienes were synthesized in an unexceptional way as indicated in Scheme I.

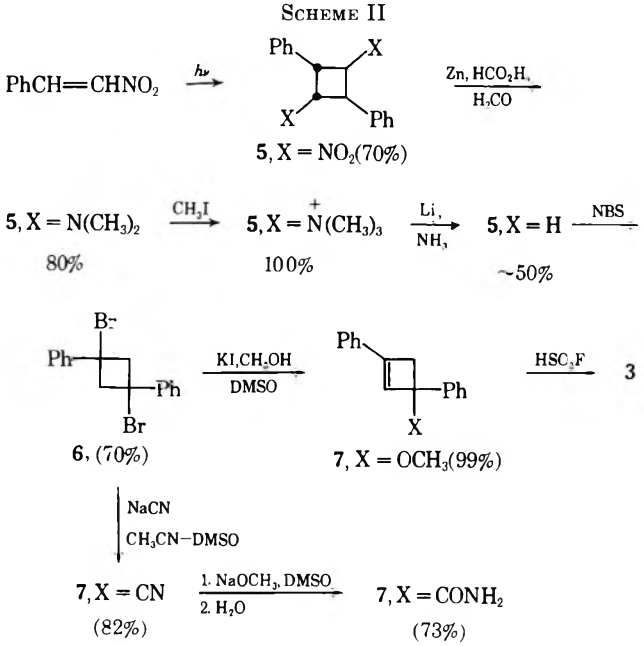
The attempted synthesis of 1,3-diphenylcyclobutenyl cation caused unexpected aggravation but was finally accomplished as indicated in Scheme II.

Several points in Scheme II deserve comment. The first step, photodimerization of β-nitrostyrene, has been reported in the literature.[6] The reaction, however, was conducted on solid material by spreading a thin film of

SCHEME I



SCHEME II



(1) (a) This work was supported by the National Science Foundation under Grant GP 10734. (b) This author acknowledges financial assistance from the people of Iran, as administered by the Ministry of Science and Higher Education.

(2) (a) D. G. Farnum, *J. Amer. Chem. Soc.*, **89**, 2970 (1967); (b) D. G. Farnum and G. Mehta, *ibid.*, **91**, 3256 (1969).

(3) R. W. Taft and L. D. McKeever, *ibid.*, **87**, 2489 (1965).

(4) D. G. Farnum and M. Burr, *ibid.*, **82**, 2651 (1960).

(5) R. Breslow and H. Höver, *ibid.*, **82**, 2644 (1960).

(6) R. D. Campbell and R. F. Ostead, *Proc. Iowa Acad. Sci.*, **71**, 197 (1964).

Table I

Chemical Shifts for 1,3-Diphenylcycloalkenyl Cations (τ Values)

Cation	Ortho H	Meta H	Para H	Methine H	Other H
Cylcohexenyl 1	1.77	2.41	2.14	1.46	6.42 (4 H) 7.64 (2 H)
Cyclopentenyl 2	1.76	2.35	2.10	1.51	6.04
Cyclobutenyl 3	1.75	2.18	1.98	1.87	5.82
Cyclopropenyl 4	1.55	2.10	1.92	−0.45	

the crystals at the bottom of a crystallizing dish and irradiating this film with occasional stirring over a period of several days or weeks. We find that the yield and quantity of material obtained in this reaction can be markedly enhanced by the simple expedient of conducting the reaction in a vigorously stirred concentrated slurry of the finely powdered crystals in water suspension. This technique has also been applied to the photodimerization of cinnamic acid and will be described elsewhere.[7] The second step in the sequence, reductive methylation of dimer **5** (X = NO_2) to give **5** [X = $N(CH_3)_2$], was originally accomplished in the usual two-step method. That is, the nitro groups were first reduced with zinc and acetic acid and the resulting unstable diamine was then methylated with formaldehyde and formic acid. The modified one-step procedure, involving reduction of the nitro groups with zinc and formic acid, and concomitant reductive methylation of the resulting diamine with formaldehyde works extremely well. The method gives high yields in a convenient procedure and may be a general method for the conversion of nitro compounds to dimethylamino compounds. The final step in the synthesis, the conversion of the dibromocyclobutane **6** to the methoxycyclobutene **7** (X = OCH_3) is an interesting example of the competition between dehydrobromination and nucleophilic displacement on the dibromide. The reaction conditions are apparently quite critical and took some time to work out. Several methods for this type of conversion were attempted, including a variety of bases in methanolic solution and dimethyl sulfoxide (DMSO) solution, a variety of nucleophiles in different solvent systems, and sulfuric acid, fluorosulfonic acid, and a mixture of fluorosulfonic acid and antimony pentafluoride. Only the reagent indicated in Scheme II, potassium iodide in DMSO with a limited amount of methanol, proved to be successful. One other reagent combination, sodium cyanide in acetonitrile–DMSO, was found to give a related reaction—conversion of dibromide **6** to the cyclobutenyl cyanide **7** (X = CN). However, we could not convert the product to the cyclobutenyl cation **3**, nor could we hydrolyze it to the carboxylic acid **7** (X = CO_2H), although we were able to obtain the amide **7** (X = $CONH_2$) from the cyanide **7** (X = CN) with sodium methoxide in DMSO (see Scheme II).

An alternative four-step synthesis of *trans*-1,3-diphenylcyclobutane (**5**, X = H) in about 20% overall yield from *α-trans*-cinnamic acid was also developed and is diagrammed in Scheme III.

All of the 1,3-diphenylcycloallyl cations thus prepared were stable in fluorosulfonic acid at room temperature, although the cyclobutenyl and cyclopropenyl cations could be kept much longer than the other two without deterioration. The structures of the cations

Scheme III

$$\mathrm{PhCH{=}CHCO_2H} \xrightarrow{h\nu} \mathbf{5},\ \mathrm{X} = \mathrm{CO_2H}\ (60\%) \xrightarrow{\mathrm{SOCl_2}}$$
$$\mathbf{5},\ \mathrm{X} = \mathrm{COCl}\ (80\%) \xrightarrow{(\mathrm{CH_3})_3\mathrm{COOH}}$$
$$\mathbf{5},\ \mathrm{X} = \mathrm{CO_3C(CH_3)_3}\ (80\%) \xrightarrow[150^\circ]{p\text{-cymene}} \mathbf{5},\ \mathrm{X} = \mathrm{H}\ (50\%)$$

were confirmed both by their nmr spectra and also by quenching the cations to give the starting dienes or ethers with sodium methoxide in methanol.

The chemical shifts of the para protons in the several cations were determined as we described previously.[2a] τ values for the several key protons in the cations are given in Table I. Note that, although the differences are small, the τ values for the para protons fall in the reverse order from that expected for increasing 1,3-overlap stabilization with decreasing ring size. This fact is particularly surprising for the 1,3-diphenylcyclopropenium ion, for which we know there is large delocalization stabilization in the cyclopropenium ion, and for which we expect, therefore, much less charge dispersion onto the attached phenyl rings.[8,9] The meta-proton chemical shifts parallel the para shifts and are slightly larger, in accord with an *inductive* dispersal of charge to the attached phenyl. The ortho- and methine-proton chemical shifts are much less susceptible to reliable interpretation because of the proximity of the magnetically anisotropic phenyl and allyl cation systems and the different geometries of the cations.[2a,9] However, the dramatic low-field shift of the cyclopropenium ion ortho and methine protons must reflect the ring current effect of this 2-π-electron system.[4,5,8,9]

We can suggest two factors which were ignored in our original expectations and which could conspire to produce the unexpected results which we observe. The first factor is the electrostatic repulsion engendered by bringing the two ends of the allyl system, each with about one-half a positive charge, closer together in the small ring system. This repulsion would be a destabilizing factor and would cause the positive charge to disperse onto the phenyl rings. Such inductive charge dispersal would also be in accord with the larger downfield shift of the meta than para protons with decreasing ring size.

We suggest the second factor in order to account at least in part for the anomalous low-field shift of the para proton in diphenylcyclopropenium ion. In comparing this ion with the cyclobutenyl cation, we have replaced the alkyl substituents on the cyclobutenyl cation, that is, the ring methylene group, by a direct bond between the trigonal carbon atoms in the system. We have therefore lost the large inductive stabilizing effect of the methylene group. In other words, we suggest that the

(7) D. G. Farnum and A. Mostashari, "Photochemical Syntheses," R. Srinivasan, Ed., in press.

(8) R. Breslow, H. Hover, and H. W. Chang, *J. Amer. Chem. Soc.*, **84**, 3168 (1962).

(9) D. G. Farnum and C. F. Wilcox, *ibid.*, **89**, 5379 (1967).

cyclopropenyl cation is not a good system for comparison with the cyclobutenyl cation because it is less substituted. In fact, it is difficult to see how one could obtain a good model for the cyclopropenyl cation. We have tried to prepare the unsubstituted 1,3-diphenylallyl cation as a compromise model but find that under our conditions this cation cyclizes much too rapidly to enable its nmr spectrum to be determined.

An interesting point emerges from observation of the variable temperature nmr spectra of cations **1**–**4**. Thus the cyclohexenyl and cyclopentenyl cations **1** and **2** give essentially no change in the nmr other than viscosity broadening down to −50°. In particular, the four ortho protons seem to remain equivalent appearing as a doublet of doublets, indicating essentially free rotation about the *C*-phenyl bonds on an nmr time scale for these cations. In contrast, the nmr spectrum of cyclobutenyl cation **3** begins a reversible broadening of the ortho-proton doublet of doublets as the temperature is lowered to 0°. Below −40° the spectrum sharpens again with two ortho protons appearing as a broad low-field doublet at τ 1.46 and the remaining two ortho protons lost in the higher field 9-proton multiplet. Thus there is onset of restricted rotation in cation **3** near 0°. The higher barrier to rotation in cation **3** than in cations **1** and **2** is in complete accord with the observed greater dispersal of charge to the phenyl groups in cation **3**, and contrary to expectations based on steric grounds.

On the basis of the preceding arguments and observations alone, cyclopropenium ion **4** would be expected to exhibit restricted rotation at a temperature higher than 0°, since its para-proton resonance indicates still more dispersal of positive charge onto the phenyl groups than in **3**. Therefore, the observation of *equivalence of ortho protons in the nmr of cyclopropenium ion* **4** *down to* −50° is especially surprising. However, a low barrier to rotation, nonetheless accompanied by significant charge dispersal onto the phenyl groups, is exactly what has been predicted for the cation **4** on the basis of extended Hückel calculations.[10] Our observation provides a convincing test of this suggestion.

We conclude, then, that these results suggest that a 1,3-electrostatic repulsive interaction in the cyclobutenyl cation must also be considered as a contributer to destabilization and charge dispersion in the cation. This effect may be superimposed upon a 1,3-attractive or -bonding interaction which makes its contribution to stabilization and charge dispersion in the cations. We have no way at present of telling which of these two factors, the destabilizing or stabilizing, is more important in the 1,3-diphenylcyclobutenyl cation **3**. We also conclude that the diphenylcyclopropenium ion **4** exhibits an unusually low barrier to rotation about the *C*-phenyl bonds inconsistent with intuitive expectations based upon the extent of positive charge dispersal onto the phenyl groups but consistent with extended Hückel calculations.[10]

Experimental Section

General.—Melting points and boiling points are uncorrected. Spectroscopic data were determined on a Perkin-Elmer Infracord ir spectrophotometer, a Beckman DK uv spectrophotometer, a Perkin-Elmer Hitachi RMU-6 mass spectrometer, and a Varian A-60 or JEOLCO C-60H nmr spectrometer. The nmr spectra are recorded in τ values relative to tetramethylsilane internal standard unless otherwise indicated. The following format is used: τ value (multiplicity, coupling constant values, number of H's) with the following abbreviations, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

Determination of Nmr Spectra of the Carbonium Ions.—Solutions of the carbonium ions for nmr study were prepared by dissolving the appropriate precursor in a small amount of Freon 114B and adding the solution dropwise to stirred fluorosulfonic acid maintained at Dry Ice–acetone bath temperature. Solutions were made up to 5–10% precursor, and a small amount of tetramethylammonium fluoroborate (τ 6.87[2a]) was added as internal reference when needed. For recovery studies, solutions were quenched by pouring slowly into excess sodium methoxide in methanol at ice bath temperatures. Products were then isolated by extraction with pentane after swamping with water. The pentane extracts were dried over magnesium sulfate and evaporated to dryness. The residues were compared spectroscopically (nmr, ir) with starting materials and found to be virtually identical in every case.

3-Phenylcyclopent-2-enone. A. Condensation.—Ethyl acetoacetate (26 g, 0.2 mol) in dry benzene (250 ml) was added to sodium hydride (9.6 g of 50% dispersion in oil) in benzene with stirring under a nitrogen atmosphere. After the completion of the reaction (indicated by cessation of bubbling of hydrogen), phenacyl bromide (40 g, 0.20 mol) was added at once and the mixture was refluxed for 6 hr. The reaction mixture was then washed with cold water twice (total of 800 ml). The benzene solution was dried over magnesium sulfate and evaporated to give an oil, the nmr spectrum of which exhibited peaks characteristic of ethyl benzoylpropionate and 1-phenyl-3-carbethoxypentane-1,4-dione.

B. Saponification and Decarboxylation.—The product of the above reaction was placed in a 3-l. flask, an 0.8% solution of potassium hydroxide (2.5 l.) was added, and the mixture was refluxed under a nitrogen atmosphere for 2.5 hr. The reaction mixture was then cooled and extracted with ether. The ether solution was washed with water and dried over magnesium sulfate. Evaporation of the ether gave a brownish oil which was chromatographed over alumina. The diketone (1-phenylpentane-1,4-dione) (7 g) was eluted first with ethyl acetate–benzene (20:80). A mixture of the diketone and 3-phenylcyclopent-2-enone (7.5 g) followed by the cyclopentenone (4.5 g) was eluted with ethyl acetate. The diketone was separated from the mixture by distillation: bp 104° (0.35 mm); ir (neat) 1720, 1695 cm^{-1}; nmr (CCl_4) τ 2.2 (m, 2 H), 2.68 (m, 3 H), 7.16 (A_2B_2, q, 4 H), 7.97 (s, 3 H). 3-Phenylcyclopent-2-enone (2 g) was obtained from the residue by crystallization from hexane–ether.

C. Ring Closure.—The combined diketone crop (12 g) was refluxed in aqueous potassium hydroxide (250 ml of a 10% solution) under a nitrogen atmosphere for 2 hr to give 9.5 g of a light brownish phenylcyclopentenone isolated by chromatography as above, giving a total overall yield of 52%. The pure ketone was obtained by sublimation of the crude product: mp 83.5–84.5° (lit.[11] 83–84°); ir (CCl_4) 1705–1695 cm^{-1}; nmr ($CDCl_3$) τ 2.6 (m, 5 H), 3.6 (t, J = 1.5 cps, 1 H), 7.05 (m, 2 H), 7.55 (m, 2 H).

1,4-Diphenyl-1,3-cyclopentadiene.—3-Phenylcyclopentenone (3.16 g, 0.02 mol) in ether (20 ml) was added to phenyl Grignard reagent prepared from bromobenzene (3.3 g, 0.021 mol) and magnesium turnings (50 mg) in ether under an argon atmosphere. After 3 hr the reaction was worked up by adding concentrated ammonium chloride solution. The ether solution was washed with water and evaporated to give an oil, which was dissolved in methanol with warming. When the methanolic solution was chilled, 2.9 g (35%) of solid was obtained: mp 155.5–157° (lit.[12] 155–157°); nmr ($CDCl_3$) τ 2.6 (m, 10 H), 3.12 (t, J = 1 cps, 2 H), 6.27 (t, J = 1 cps, 2 H).

3-Phenylcyclohex-2-enone. A. Michael Condensation.—This reaction was done according to Walker.[13] A 40% methanol solution of Triton B (60 ml) was added with stirring to a solution of ethyl benzoylacetate (56.8 g, 0.30 mol) and methyl vinyl ketone (20.8 g, 0.30 mol) in *tert*-butyl alcohol (75 ml) at 0°. The solution became brownish and then green. After 5 hr the reaction was worked up according to Walker to give a mixture of

(10) R. Hoffmann, R. Bissell, and D. G. Farnum, *J. Phys. Chem.*, **73**, 1789 (1969).

(11) W. Borsche and W. Menz, *Ber.*, **41**, 209 (1908).

(12) N. L. Drake and J. R. Adams, *J. Amer. Chem. Soc.*, **61**, 1326 (1939).

(13) G. Walker, *ibid.*, **77**, 3664 (1955).

crystalline material and oil. The mixture was triturated with ether and filtered to give 39.5 g of a crystalline compound, mp 122–125°, which, when recrystallized from methanol, had mp 125–127° (lit.[13] 128–130°); ir (Nujol) 3400, 1707, 1693 cm^{-1}; nmr ($CDCl_3$) τ 2.7 (m, 10), 5.79 (br s, 1 H), 6.05 (q, 2 H), 7.4 (s, 2 H). 7.55 (m, 4 H), 9.02 (t, 3 H). The filtrate when evaporated yielded 29.7 g of a yellow brown oil, **9**.

B. Decarboxylation of the Condensation Products.—The solid obtained from above (31.5 g) was treated with an 8% aqueous potassium hydroxide solution (250 ml) and refluxed for 12 hr. The mixture was then cooled and extracted with ether, which was then washed with water and dried over magnesium sulfate. Evaporation of the solvent resulted in 19.1 g of the product which was recrystallized from hexane–ether (80:20) to give 17.5 g of 3-phenylcyclohex-2-enone: mp 64.5–65.5° (lit.[13] 63–66°); ir 1665 cm^{-1}; nmr ($CDCl_3$) τ 2.7 (m, 5 H), 3.64 (t, J = 1.5 cps, 1 H), 7.13–8.1 (complex m, 6 H). The brown oil (29.1 g) obtained in A was refluxed in 8% potassium hydroxide (250 ml) to give the desired ketone (7.5 g) as a brownish solid. This crude product when recrystallized from hexane–ether (80:20) gave 6.1 g of the pure ketone. The total yield of pure ketone was 23.6 g (46.5%).

1,3-Diphenyl-1,3-cyclohexadiene.—3-Phenylcyclohex-2-enone (6 g) in dry tetrahydrofuran was added to a Grignard reagent prepared from bromobenzene (18.3 g) and magnesium turnings (2.8 g) in dry ether (150 ml) under an argon atmosphere. The reaction was allowed to go on overnight and then worked up by addition of a concentrated solution of ammonium chloride. The organic layer, after drying over magnesium sulfate, was evaporated to give 5.7 g of a thick yellow oil which was taken up in 95% ethanol, and the solution was chilled to give white platelets, mp 89–93°. Recrystallization from 95% ethanol resulted in 4.9 g (66%) of the same type of crystals: mp 95–97° (lit.[14] 98–99°); nmr ($CDCl_3$) τ 2.67 (m, 10 H), 3.33 (sextet, J = 1.5 cps, 1 H), 3.9 (dt, J = 1.5 cps, J = 4.5 cps, 1 H), 7.4 (m, 4 H).

Truxilloyl Chloride.—This compound was prepared according to White.[15] Treatment of α-truxillic acid (29.6 g, 0.1 mol) with thionyl chloride (300 ml) yielded crystalline acid chloride. Recrystallization from benzene–petroleum ether (60:40) gave white prisms (26.7 g, 81%): mp 121–123° (lit.[15] 127–128°); ir (Nujol) 1785 cm^{-1}.

Di-*tert*-butyl Pertruxillate.—Truxilloyl chloride (22 g) was mixed with *tert*-butyl hydroperoxide (40 ml) in dry benzene, under a nitrogen atmosphere. The mixture was cooled in an ice–salt bath to 0°, and dry pyridine (25.0 ml) was added dropwise. The reaction mixture was allowed to stir for 12 hr. The contents of the flask were then washed with 5% hydrochloric acid in ice water to remove the excess of pyridine. The unreacted acid and traces of hydrochloric acid were removed by washing with potassium hydroxide solution (150 ml of a 5% solution). The organic layer was dried over magnesium sulfate and the solvent was evaporated under reduced pressure at room temperature. The solid residue (25.5 g) was recrystallized from ether–hexane (1:2) (150 ml). The resulting needles weighed 23.7 g (81.5%): mp 142–142.5°; ir 1750 cm^{-1}. Titration of the perester[16] indicated that it was 95.7% active perester.

***trans*-1,3-Diphenylcyclobutane (5, X = H). A. By Pyrolysis of Di-*tert*-butyl Pertruxillate.**—The perester (22.5 g) was suspended in *p*-cymene (600 ml of solvent, distilled at 207.5–208.5°), and the suspension was heated under a stream of nitrogen with stirring. The perester dissolved at around 55°. At 130° the solution turned yellowish and effervescence began which became vigorous at around 150°. After 1.5 hr the bubbling stopped, but heating was continued for 12 hr more. The reaction vessel containing a yellowish solution was then attached to a 36-in. Vigreux column and the bulk of the *p*-cymene was distilled (at 35°, 0.5 mm). The yellow pasty residue was taken in ethanol and chilled. The *p*-cymene dimer which crystallized was filtered off and the mother liquor was stripped of solvent and distilled through a 4-in. Vigreux column. *p*-Cymene was distilled first. The fraction which distilled at 125–140° (1.0 mm) was rich in the desired product (70–80% as judged by nmr). The residue of distillation also contained 20–30% of the product. The above-mentioned fraction and the residue were combined and redistilled to give 5.8 g of an oil [110–123° (0.25 mm)] containing *ca.* 90% of the cyclobutane **5**, (X = H) as judged by nmr. Column chromatography over silicic acid yielded 4.5 g (42%) of purer hydrocarbon as a thick oil. Recrystallization from methanol yielded needles: mp 40–41°; ir (film) 3030, 2980, 1610, 1500, 1450 cm^{-1}; nmr (CCl_4) τ 2.8 (m, 10 H), 6.4 (q, J = 7 cps, 2 H), 7.48 (t, J = 7 cps, 4 H).

Anal. Calcd for $C_{16}H_{16}$: C, 92.26; H, 7.74; mol wt, 208. Found: C, 92.07; H, 7.60; mol wt, 208 (mass spectrum, parent peak).

B. By Reductive Deamination of Dimethiodide 5 [X = $^+N(CH_3)_3$].—Dimethiodide (14 g, 0.024 mol) (see below) was added to distilled liquid ammonia (400 ml) at −78°. Isopropyl alcohol (3.6 ml) was added and lithium ribbon (washed with petroleum ether to remove the oil) was cut and added in pieces until the blue color persisted for 2 min. The mixture was then allowed to stir at −78° for 30 min more and then ammonium chloride (10 g) was added. The ammonia was then allowed to evaporate, and the residue was taken in ether and washed with water and then hydrochloric acid solution. The ether solution was dried and evaporated to give a yellow fluorescent oil. The oil was distilled [91° (0.15 mm)] to give 3 g (60%) of a clear liquid. The nmr spectrum showed peaks characteristic of 1,3-diphenylcyclobutane plus some other peaks. However, 90–95% of the phenyl absorption was due to the diphenylcyclobutane based on the ratio of its methylene peak (τ 7.48) to the phenyl peak (τ 2.8). The mixture could not be separated by vpc, column chromatography, or fractional distillation but was successfully used in the preparation of dibromide **6**.

1,3-Dibromo-1,3-diphenylcyclobutane (6).—1,3-Diphenylcyclobutane (2.2 g, 0.0105 mol) was dissolved in carbon tetrachloride (50 ml), and *N*-bromosuccinimide (4.3 g, 0.023 mol) and benzoyl peroxide (0.2 g) were added. The mixture was brought to reflux by means of an oil bath. When all of the *N*-bromosuccinimide was consumed, the succinimide was filtered and the solvent was removed at reduced pressure. The residue was taken up in ether. The ethereal solution yielded needles (800 mg): mp 145–145.5° dec; nmr ($CDCl_3$) τ 2.6 (m, 10 H), 5.85 (s, 4 H).

Anal. Calcd for $C_{16}H_{14}Br_2$: C, 52.46; H, 3.83; Br, 43.71. Found: C, 52.62; H, 3.94; Br, 43.65.

Addition of hexane to the ethereal mother liquor and cooling gave a solid (1.9 g) (total yield 69%) whose nmr spectrum showed peaks for the solid previously obtained and others at τ 2.7 (10 H) and 6.0 (s, 4 H). Both isomers decompose when allowed to stay in air.

Anal. Calcd for $C_{16}H_{14}Br_2$: C, 52.46; H, 3.83; Br, 43.71. Found: C, 52.62; H, 3.82; Br, 43.62.

1,3-Diphenyl-2,4-bis(dimethylamino)cyclobutane [5, X = N(CH$_3$)$_2$].—The β-nitrostyrene photodimer (**5**, X = NO_2) (45 g, 0.15 mol) was placed in a 3-l. round-bottom flask, and zinc dust (300 g) and formaldehyde (250 ml of a 37% aqueous solution) were added. The suspension was warmed on a steam bath and formic acid (550 ml of a 88% aqueous solution) was added dropwise over a period of 4 hr with vigorous stirring. As soon as the reaction started, the external heat was discontinued since heat of reaction was sufficient to maintain the temperature at about 80–90°. *Caution! In one run the formic acid accumulated without reacting and the reaction suddenly took off with explosive violence.* After the addition was completed, the reaction was heated over a steam bath again for 6 hr more, and formic acid (two 200-ml portions) was added to ensure completion of the reaction. The insoluble material was then filtered and the filtrate was concentrated under reduced pressure at 60°. The concentrated solution was washed with benzene and the aqueous phase was made basic with sodium hydroxide solution. A white precipitate formed which was filtered, and the solid was washed with ether. The filtrate was also extracted with ether. The combined ethereal solution was washed with water and dried over magnesium sulfate. Evaporation of the ether yielded 38.5 g of a white solid which was recrystallized from ether–hexane (20:80) to give 35.5 g (79.9%) of pure **5** [X = $N(CH_3)_2$]: mp 125–127° (lit.[15] 122–123°); ir ($CHCl_3$) 2990, 2950, 2850, 2800 cm^{-1}; nmr ($CDCl_3$) τ 2.75 (m, 10 H), 6.7 (A_2B_2 q, 4 H), 8.25 (s, 12 H).

1,3-Diphenyl-2,4-bis(dimethylamino)cyclobutane Dimethiodide [5, X = $^+N(CH_3)_3$].—2,4-Diphenyl-1,3-bis(dimethylamino)-cyclobutane (6.7 g) was dissolved in anhydrous acetone (50 ml) with a little warming. Methyl iodide (10 ml) was added and the mixture was warmed for 2 min. The flask was stoppered and allowed to stand for 0.5 hr. The dimethiodide was filtered and proved to be pure without any need for recrystallization, mp 222–225° (lit.[15] 215–217°).

(14) G. F. Woods and I. W. Tucker, *J. Amer. Chem. Soc.*, **70**, 2176 (1948).
(15) E. H. White and H. C. Dunathan, *ibid.*, **78**, 6055 (1956).
(16) L. Silbert and D. Swern, *Anal. Chem.*, **30**, 385 (1958).

1,3-Diphenylcyclobut-2-enyl Cyanide (7, X = CN).—1,3-Dibromo-1,3-diphenylcyclobutane (6) (2 g, 5 mmol) was dissolved in acetonitrile (150 ml) and DMSO (60 ml) under a nitrogen atmosphere. Sodium cyanide (2 g) was added to the solution and the mixture was stirred at room temperature for 10 hr. The milky yellow solution was then poured into 1 l. of water and extracted with ether (two 300-ml portions). The ethereal solution was washed with water several times and then with saturated sodium chloride solution and was dried over magnesium sulfate. Evaporation of the solvent yielded a brownish oil which was chromatographed on Florisil. The desired product was eluted with hexane as a yellow oil (1.03 g, 82%): ir (neat) 2220 cm^{-1}; nmr (CCl_4) τ 2.70 (m, 10 H), 3.72 (s, 1 H), 6.79 (A_2B_2 q, J = 13 cps, 2 H); mass spectrum m/e 231 (parent peak). The substance decomposed rapidly on standing at room temperature and was not analyzed.

1,3-Diphenylcyclobut-2-ene-1-carboxamide (7, X = $CONH_2$).—Sodium methoxide (commercial powder, 1.2 g, 22 mmol) was dissolved in DMSO (50 ml). Cyanide 7 (X = CN) (1.1 g, 4.7 mmol) in DMSO (5 ml) was added. The solution was stirred at room temperature under a nitrogen atmosphere. After 48 hr, the solution was poured into 800 ml of ice water and extracted with ether. The ether solution was washed with water several times and dried over magnesium sulfate. When the ether solution was concentrated to 15 ml and hexane was added, a white precipitate formed which was filtered and recrystallized from hexane–ether to give 0.872 g (73%) of a white solid: mp 143–145°; ir ($CHCl_3$) 3500, 3360, 1685 cm^{-1}; nmr ($CDCl_3$) τ 2.7 (m, 10 H), 3.31 (s, 1 H), 4.25 (br s, 2 H), 6.68 (A_2B_2 q, J = 13.1 cps, 2 H); mass spectrum m/e 249 (parent peak). The compound decomposed rapidly at room temperature and was not analyzed.

1-Methoxy-1,3-diphenylcyclobutene (7, X = OCH_3).—Sodium iodide (3 g) was dissolved in DMSO (50 ml), and absolute methanol (1.5 ml) was added to the solution. Dibromide 6 (1.5 g of the mixture of isomers) was dissolved in 5 ml of DMSO and added to the solution. After a while a yellow color developed which gradually turned red-brown (iodine). After 12 hr the solution was added to ice water (800 ml), and the cloudy solution was extracted with ether. The ether solution was washed with a dilute sodium sulfite solution to remove the iodine and washed several times with water to remove the DMSO. The ether solution was dried and evaporated to give 0.953 g (98.5%) of an oil: ir ($CHCl_3$) 1117 cm^{-1}; nmr (CCl_4) τ 2.75 (m, 10 H), 3.35 (s, 1 H), 6.82 (s, 3 H), 7.02 (A_2B_2 q, J = 13 cps, 2 H) (there were no other peaks evident in the nmr spectrum, and integration ratios were within 5% of the calculated values); mass spectrum m/e 236. The compound was unstable at room temperature and was not analyzed.

Registry No.—**1**, 27617-85-2; **2**, 27396-85-6; **3**, 27396-86-7; **4**, 27396-87-8; *trans*-**5** (X = H), 25558-23-0; **5** [X = $N(CH_3)_2$], 19043-28-8; *cis*-**6**, 27396-24-3; *trans*-**6**, 27396-25-4; **7** (X = CN), 27396-88-9; **7** (X = $CONH_2$), 27396-89-0; **7** (X = OMe), 27396-90-3; 1-phenylpentane-1,4-dione, 583-05-1; 3-phenylcyclopent-2-enone, 3810-26-2; 1,4-diphenyl-1,3-cyclopentadiene, 4982-34-7; 3-phenylcyclohex-2-enone, 10345-87-6; 1,3-diphenyl-1,3-cyclohexadiene, 10345-94-5; di-*tert*-butyl pertruxillate, 27396-96-9.

Application of the Linnett Electronic Theory to Organic Chemistry. IV. The SN2 Transition State

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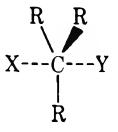
Linnett structures for the SN2 transition state are proposed which differ from conventional dotted-bond structures $X\cdots CR_3\cdots Y$ in that the three C–R bonds are weakened by L strain. Valence shell expansion is not required. Walden inversion is accounted for, and the energy price for retention is estimated at 11 kcal/mol for R = H and 16 kcal/mol for R = CH_3. The pattern of activation energies in alkyl halide exchanges is discussed in terms of secondary L strain, which also explains the rate accelerations brought about by conjugated unsaturation, α heteroatoms, and the α effect. The effect of L strain on entering and leaving groups is also assessed. The discussion includes proton transfer and displacements on heteroatoms. Hydrogen bonds and trihalide ions are presented as examples of reactions with negative activation energy, or "frozen transition states," existing when L strain is exceptionally low. Deviations from simple kinetic–thermodynamic relationships, such as the Brønsted equation, are stressed. The E2C mechanism is critically discussed.

One of the most common devices in chemistry is the transition state picture in which dotted bonds are used to represent normal ones that are in a state of either formation or dissolution. The dots are meant to express our ignorance of the structures of transition states as compared to stable molecules but are frequently taken to mean much more than that, in particular a state intermediate in properties between reactant and product. However, in opposition to this simple picture, for many reactions, is the disparity between the kinetic and thermodynamic products and, most significantly, the need for activation energy.

It is possible, by means of the Linnett electronic theory,[1,2] to replace many dotted-bond structures with better defined, yet simple, ones with unique properties that are not derived immediately from reactants or products. One such property is L strain,[3,4] a type of angle strain not yet recognized in conventional molecular representations, but clearly derived form Linnett's double-quartet theory. L strain must nevertheless be latent in conventional theory also, since the Linnett theory is based upon the same underlying quantum mechanical postulates. In contrast with an ordinary bent bond, an L-strained bond suffers from lack of coincidence of the two spin sets about one or more atoms, which weakens the bond in the same way that bending does, namely by forcing the bonding electrons away from their optimum positions. L-Strained bonds are not bent, however. This topic is fully discussed in papers I and II of this series. The policy will be continued here of limiting the discussion to first row elements for the most part.

A prominent example of a dotted-bond transition state is that for the SN2 reaction, depicted universally

(1) J. W. Linnett, *J. Amer. Chem. Soc.*, **83**, 2643 (1961).
(2) J. W. Linnett, "The Electronic Structure of Molecules," Methuen and Co. Ltd., London, 1964.
(3) R. A. Firestone, *Tetrahedron Lett.*, 971 (1968).
(4) R. A. Firestone, *J. Org. Chem.*, **34**, 2621 (1969).



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as 1. Associated with this structure are two problems which are often ignored. One is the requirement for activation energy[5] in the exothermic direction, if the formation of the new bond is synchronous with the dissolution of the old. The other is the question of how many electrons are in the outer shell of the carbon atom; although its capacity is at most eight, the sum of the electrons in the three C–R bonds and those in both sets of dots is ten. In the case of a displacement on hydrogen, four electrons are associated with a shell that can hold only two.

These problems have occasionally been brought into the open. Grunwald says that "the intermediate states never conform to the Lewis rule of the octet" for displacement reactions on a saturated carbon atom.[6] Coulson identifies the two dotted bonds as "localized electron-pair bonds,"[7] invoking $d_\sigma p_\sigma$ hybridization at the central carbon atom, a theory endorsed by Gillespie[8] and Dewar[9] as well. Streitwieser,[10] however, places only two of the dotted electrons in a bonding MO, and the other two in a nonbonding one. Ingold's description[11] seems similar.

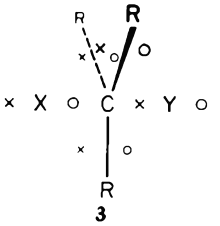
For related reactions, Linnett has proposed transition states of definite structure in place of the dotted bonds.[12] When his principles are applied to 1, the structure 2 is

2

obtained. It is meant to represent the midpoint of the reaction coordinate, which may be a transition state or else a metastable intermediate flanked by two less symmetrical transition states. While there are cases to be discussed subsequently in which true intermediates exist, for ordinary SN2 displacements at saturated carbon it is safe to say that, if 2 lies in a potential well, it must be a very shallow one, and consequently 2 will be taken as a transition state in this paper.

It is apparent at once that promotion of electrons to d orbitals is unnecessary and that the Lewis octet rule[13] may be retained intact, provided that the habit of pairing electrons whenever possible—and it is no more than a habit—be abandoned.[14] If promotion is denied, then the octet rule prohibits the involvement of the odd electrons on X and Y.

The number of bonding electrons is constant throughout the transformation, raising the question of why activation energy is required in the exothermic direction.[5] One obvious answer is that a one-electron bond is not necessarily one-half as strong as a two-electron bond. There is, however, another more subtle source of an activation requirement which lies in the three nonreacting C–R bonds. Their bond energies in 2 are lower than they are in either XCR_3 or YCR_3 owing to L strain[3,4] by an amount which is probably more than half the activation energy for many SN2 reactions, exclusive of solvation and ion-pairing effects. The participation in the reaction of bonds that have hitherto been considered to be merely bystanders is not apparent in either the dotted-bond formula 1 or the condensed Linnett structure 2. However, the full involvement of all the carbon atom's valence electrons at the transition state is brought to light in the double quartet representation of the transition state, 3.[15] Each C–R bond suffers



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from 40° of L strain. The published L-strain curve,[4] which though crude is serviceable, assigns 3.6 kcal/mol to a C–C bond L strained by this amount. The estimate for a C–H bond, augmented by the ratio of their bond energies,[16] is 4.3 kcal/mol. Thus, for SN2 displacements on methyl about 13 kcal/mol of L strain in the three C–H bonds is anticipated. From this must be deducted 4 kcal/mol for the fourth electron pair around carbon,[17] which is well correlated in the transition state but was closely paired in the starting molecule (a correlation correction has already been made[4] for the electrons in the L-strained bonds). The net energy demand from this source, then, is about 9 kcal/mol when R = H.

How does this number compare with activation energies in the literature? For proper comparison, reactions must be chosen in which solvation factors are at a minimum, and which are symmetrical along the reaction coordinate in order that the transition state occur at the point of maximum L strain, *i.e.*, midway. Experimental figures in acetone are 15.8 kcal/mol for Br–Br exchange on methyl[18] and 13.5 for I–I exchange.[19] For $CH_3Br + I^-$ in acetone, the activation energy is 15.1 kcal/mol,[20] and the data in that paper allow an estimate of *ca.* 12 to be made for I–I exchange; desolvation of the anion was reckoned an insignificant factor in the activation energy. For $CH_3Br + Cl^-$, E_a's are 17.9 kcal/mol

(5) In his classic paper on the quantum mechanical interpretation of the process of activation, in *Z. Electrochem.*, **35**, 552 (1929), F. London states "In general . . . . a vanishingly small activation energy is expected for reactions of the type XY + Z → X + YZ."

(6) E. Grunwald, *Progr. Phys. Org. Chem.*, **3**, 350 (1965).

(7) C. A. Coulson, *Nature*, **221**, 1106 (1969).

(8) R. J. Gillespie, *J. Chem. Soc.*, 1002 (1952).

(9) M. J. S. Dewar, *ibid.*, 2885 (1953).

(10) A. Streitwieser, Jr., *Chem. Rev.*, **56**, 571 (1956); see especially p 577.

(11) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, p 424.

(12) See ref 2, pp 74–75, 103.

(13) G. N. Lewis, *J. Amer. Chem. Soc.*, **38**, 762 (1916).

(14) It is indeed a general feature of the Linnett theory that structures with odd-electron bonds are often advantageous, even when reasonable even-electron counterparts are available.

(15) Heretofore there has been perhaps no essential difference between the description offered by Streitwieser, Ingold, and others, and that outlined here. It is in the complete Linnett array **3** and its consequences that the real novelty lies.

(16) T. L. Cottrell, "The Strengths of Chemical Bonds," 2nd ed, Butterworths, London, 1958.

(17) See ref 2, pp 66 and 91.

(18) P. B. D. de la Mare, *J. Chem. Soc.*, 3180 (1955).

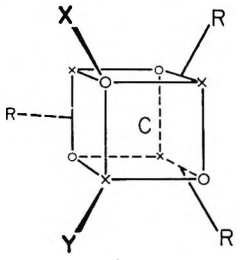
(19) E. R. Swart and L. J. LeRoux, *ibid.*, 406 (1957).

(20) Farhat-Aziz and E. A. Moelwyn-Hughes, *ibid.*, 1523 (1961).

in DMF[21] and 15.7 in acetone.[22] It is likely that these numbers are all on the high side of hypothetical solvation-free values, since the existence of residual external effects even in typical dipolar aprotic solvents is indicated by the report that activation energies for SN2 reactions can be lowered still further by changing from DMSO, DMF, and the like to the newest supersolvent, hexamethylphosphoramide.[23]

It is apparent, therefore, that L strain in the three nonreacting bonds contributes significantly to the energy requirements of the SN2 transition state at saturated carbon.[24]

Walden Inversion.—The requirement for inversion during each act of displacement is an old and apparently rigid rule. We account for it by comparing the transition state for inversion, **3**, with that for retention, **4**.



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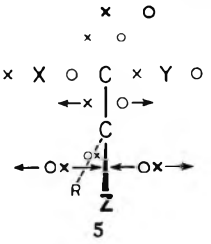
Both L strain and the intrusion of unwanted electrons on the valence shells of X and Y are minimized in the cubical array. Nevertheless, L strain in the three C–R bonds in **4** has risen to 70.5°. Thus the activation energy for retention will be greater than that for inversion by *ca.* 11 kcal/mol for R = H,[4] or 16 kcal/mol[25] for R = CH_3.[26] Retention then competes very unfavorably with inversion, although it is not altogether forbidden and should indeed be detectable under the proper circumstances.

Secondary L Strain.—In transition state **3**, L strain is higher when R is hydrogen than when it is carbon because C–H bonds are stronger than C–C bonds.[16] However, when R is saturated carbon there are three other bonds attached which must also suffer from L strain. Secondary L strain is expected to be less important than primary because spin sets are not completely rigid. Nevertheless, it is sufficient to increase the activation energy by about 1–2 kcal/mol for each R group in **3** that is changed from hydrogen to methyl. The best data on this topic are in the recent report of Cook and Parker[21] on the reaction of alkyl bromides with Cl^- in DMF where these activation energies are given: Me, 17.9 kcal/mol; Et, 19.2; *i*-Pr, 20.9; *tert*-Bu, 21.2. A similar series is reported by Ingold's group[27] for isotopic bromide exchange in acetone: Me, 15.8 kcal/mol; Et, 17.5; *i*-Pr, 19.7; *tert*-Bu, 21.8.[28]

If, as we propose, tertiary and higher orders of L strain are negligible, then the effect of substituting methyl for hydrogen in an ethyl group undergoing SN2 displacement should depend on where it is put. At the 1 carbon, an extra methyl changes ethyl into isopropyl and increases secondary L strain, as seen above, but at the 2 carbon the change is to *n*-propyl and does not increase secondary L strain. Thus, *n*-propyl halides should exhibit activation energies similar to ethyl, as indeed they do. In the first reaction series above, the figures for ethyl and *n*-propyl are 19.2 and 19.8 kcal/mol,[21] respectively, and in the second, 17.5 and 17.5.[18] Even isobutyl, which though still primary is beginning to suffer from steric hindrance, stands even with or slightly higher than *n*-propyl and well below isopropyl, with activation energies of 19.7[21] and 18.9[18] kcal/mol for the two cited reactions, compared to 20.9[21] and 19.7[18] for isopropyl.

Turning from activation energies to rates, we find that the general pattern is Me > Et > *n*-Pr and all other *n*-alkyl > *i*-Pr and all other secondary alkyl > *tert*-Bu and all other tertiary alkyl.[29]

α-Halo Ketones and Allylic Halides.—Secondary L strain can be reduced if a carbon atom attached to the reaction center is unsaturated. This comes about in the following way. Creating L strain at one bond of a saturated carbon atom affects all the other six bonding electrons in an adverse way because they were already in optimum bonding positions beforehand, *i.e.*, on their respective internuclear lines. In contrast, the four bonding electrons about olefinic carbon that form the double bond are far off the internuclear line, and secondary L strain at this bond, if applied in the proper direction as in **5**, moves only two electrons into inferior



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bonding positions, while the other two actually increase their binding energies by moving *toward* the internuclear line.

To a first approximation, let it be assumed that the gain and loss in binding energy for these four electrons are equal (actually the loss must slightly exceed the gain because the L-strain curve is concave upward),[4] with the result that two-thirds of the secondary L strain normally present at saturated carbon is absent; the last third still affects the other single bond. Cancellation of even more than two-thirds might be anticipated because secondary L strain will tend to concentrate at the point of least resistance, the double bond. For 40° primary L strain, the magnitude of secondary L strain at saturated carbon has been crudely estimated at 1–2

(21) D. Cook and A. J. Parker, *J. Chem. Soc., B*, 142 (1968).

(22) E. D. Hughes, C. K. Ingold, and J. D. H. Mackie, *J. Chem. Soc.*, 3173 (1955).

(23) J-J. Delpuech, *Tetrahedron Lett.*, 2111 (1965).

(24) The structure **3** (X, Y, and R = H) is consonant with the calculated electron distribution and bond populations in CH_5^-: T. Yonezawa, H. Nakatsuji, and H. Kato, *J. Amer. Chem. Soc.*, **90**, 1239 (1968).

(25) The figure of 14 kcal/mol for R = CH_3 given in ref 4 was based on an estimated ~1 kcal/mol of secondary L strain per methyl, which is herein revised to 1–2 kcal/mol, *vide infra*.

(26) According to a recent calculation for CH_5^- by the PNDO–SCF method, inversion is preferred to retention by 14.9 kcal/mol: N. L. Allinger, J. C. Tai, and F. T. Wu, *J. Amer. Chem. Soc.*, **92**, 579 (1970).

(27) P. B. D. de la Mare, L. Fowden, E. D. Hughes, C. K. Ingold, and J. D. H. Mackie, *J. Chem. Soc.*, 3169 (1955).

(28) Ingold has reviewed a large body of his group's work in *Quart. Rev., Chem. Soc.*, 11, 1 (1957), concluding, as we do, that the stepwise increments in activation energy in the series of alkyl groups arise from properties within the carbon skeleton and not from variations in the entering or leaving halogens. Cook and Parker[21] add that most of the polar and steric effects of alkyl substituents are accounted for by the activation energy, not by the log B term. Of course, their analyses take cognizance of factors other than L strain.

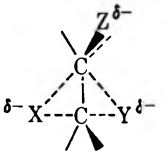
(29) See ref 11, pp 431–436.

kcal/mol more than the difference in primary L strain between C–C and C–H (*vide supra*), or *ca.* 2.2 kcal/mol. Two-thirds of this is 1.5 kcal/mol, worth about one order of magnitude in rate at ordinary temperatures. Rate increases are thus predicted of tenfold or more for allylic halides *vis-á-vis* their saturated counterparts. The observed increases are about a 100-fold.[30] Clearly, secondary L strain is a quantitatively reasonable phenomenon.

When Z in **5** is oxygen instead of CR_2, rate accelerations are much greater, reaching as high as 10^5 compared to saturated carbon.[31,32] This comes about because the other four electrons around Z are bonding when Z = CR_2 but nonbonding when Z = oxygen. In either case these electrons are closely paired in the ground state, and when Z = CR_2 they tend to remain so in the transition state. However, when Z is O the four nonbonding electrons are free to spread in the transition state, giving rise to a reduction in interelectronic repulsion which could be as great as 4 kcal/mol per electron pair.[17] At maximum, the corresponding rate factor expected for α-halo carbonyl compounds beyond that for allylic halides is 10^5–10^6.

The very high reactivity of α-halo carbonyl compounds cannot be ascribed to the electronegativity of the carbonyl group, because electronegative substituents powerfully diminish the rates of SN2 reactions. For example, toward iodide ion in acetone, the purely inductively[33] withdrawing α-CF_3 group reduces the reactivity of alkyl halides and tosylates[32] by a factor of about 10^4; α-halo sulfoxides and sulfones have low SN2 reactivity;[32,34] and, in general, β substitution in alkyl halides by electronegative groups exerts a rate-retarding effect.[35]

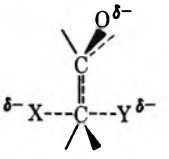
Current theory is divided as to the origin of the rate enhancements[30,32,36,37] by α-phenyl, α-vinyl, and α-carbonyl. The most widely accepted representation, **6**, is



6

certainly a poor one since it predicts that the reactivities of benzyl halides will be increased markedly by electron-withdrawing substituents in the phenyl ring and diminished by electron-releasing ones, contrary to experiment.[38] Thus, in displacements on para-substituted benzyl halides by oxygen, sulfur, nitrogen, and halide nucleophiles, both nitro and methoxy, as well as other less powerful groups, impose a rate effect compared to hydrogen that ranges from weakly positive to nil.

A modification of **6**, in which no direct bonding exists between the incoming nucleophile and the carbonyl carbon, but in which the reacting orbital of the α carbon overlaps with the C=O π bond, is represented by **7**. In



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addition to sharing the drawback of **6** mentioned above, **7** clashes with other observations as well. If it were valid, one would expect a parallel to exist between the ability of a substituent S to facilitate SN2 displacement of X in SCH_2X and the addition of base to olefins CH_2=CHS. However, for the first reaction reactivity decreases in the order S = COR > CN > COOR > alkyl > SO_2R,[32] while for the second, S = COR > SO_2R > CN > COOR[39] (> alkyl).

It is significant that the accelerating effect of α-phenyl over α-*n*-butyl (300 times) in SN2 displacement on saturated carbon disappears almost entirely (1.9 times) in displacement on divalent sulfur[40] where secondary L strain is negligible.[41]

The geometrical requirements of the α-halo ketone effect depicted in **5** have been found to be precisely in accord with experiment. The nucleophile is required to approach along a line perpendicular to the >C=O plane.[36]

α **Heteroatoms.**—The reactivity of substrates RCH_2X (relative to CH_3X) is reduced by the effects of secondary L strain when R is saturated alkyl. If now R is changed into an atom bearing unshared electrons, secondary L strain diminishes, disappearing entirely if the unshared electrons number four or more. However, four other factors must be taken into account in addition to secondary L strain: (a) bond energy, (b) electronegativity, (c) electron correlation, and (d) steric hindrance.

(a) L strain has been taken[4] as proportional to the energy[16] of the C–R bond. For 40°, L strain varies with R in the following way (in kcal/mol): C, 3.6; H, 4.3; O. 3.7; N, 3.3; F, 4.6–5.0;[16,45] Cl, 3.5; Br, 3.0; S, 2.8.

(b) Since electron withdrawal at the reaction site inhibits SN2 reactions, the effect from this source of varying R in **3** should be to diminish reactivity in the order H; C, S; Br; N, Cl; O; F.[46]

(30) See ref 10, p 585.

(31) J. B. Conant, W. R. Kirner, and R. E. Hussey, *J. Amer. Chem. Soc.*, **47**, 488 (1925).

(32) F. G. Bordwell and W. T. Brannen, Jr., *ibid.*, **86**, 4645 (1964).

(33) (a) S. Andreades, *ibid.*, **86**, 2003 (1964); (b) S. F. Campbell, R. Stephens, and J. C. Tatlow, *Chem. Commun.*, 134 (1965); (c) A. Streitwieser, Jr., A. P. Marchand, and A. H. Pudjaatmaka, *J. Amer. Chem. Soc.*, **89**, 693 (1967); (d) D. Holtz, A. Streitwieser, Jr., and R. G. Jesaitis, *Tetrahedron Lett.*, 4529 (1969).

(34) R. L. Loeppky and D. C. K. Chang, *ibid.*, 5415 (1968).

(35) See ref 10, p 589.

(36) P. D. Bartlett and E. N. Trachtenberg, *J. Amer. Chem. Soc.*, **80**, 5808 (1958).

(37) "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, pp 103–106.

(38) (a) See ref 10, p 591; (b) R. F. Hudson and G. Klopman, *J. Chem. Soc.*, 1062 (1962); (c) E. P. Grimsrud and J. W. Taylor, *J. Amer. Chem. Soc.*, **92**, 739 (1970).

(39) R. N. Ring, G. C. Tesoro, and D. R. Moore, *J. Org. Chem.*, **32**, 1091 (1967).

(40) W. A. Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill, New York, N. Y., 1962, p 63.

(41) The admissibility of divalent sulfur to the discussion is questionable in view of its low-lying d orbitals, for which no analogy exists in **3**. There is, however, evidence that divalent sulfur does not utilize its d orbitals when undergoing SN2 reactions.[42,43] Pryor[44] has criticized one of Fava's arguments but the others still stand, namely (1) the weak effect of *p*-NO_2 on the rate of nucleophilic attack on ArSX,[42] and (2) the Brønsted β for entering (0.25) and leaving (−0.97) groups in the reaction $ArOSCPh_3 + Ar'O^-$.[43]

(42) E. Ciuffarin and A. Fava, *Progr. Phys. Org. Chem.*, **6**, 81 (1968).

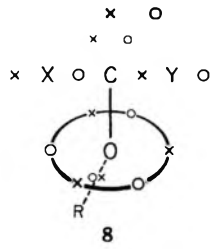
(43) L. Senatore, E. Ciuffarin, and A. Fava, *J. Amer. Chem. Soc.*, **92**, 3035 (1970).

(44) W. A. Pryor and K. Smith, *ibid.*, **92**, 2731 (1970).

(45) L. N. Ferguson, "The Modern Structural Theory of Organic Chemistry," Prentice-Hall, Englewoods Cliffs, N. J., 1963, p 48.

(46) (a) See ref 45, p 179; (b) L. Pauling, "The Chemical Bond," Cornell University Press, Ithaca, N. Y., 1967, p 64.

(c) Unusual effects are predicted here. If the atom R has *two* unshared electrons, their correlation will of course improve as L strain is imparted to the C–R bond, a favorable circumstance; however, the presence of the other two bonds to R will tend to keep both spin sets about R in coincidence, resulting in secondary L strain, though much reduced compared to R = CH_3. If R has *six* unshared electrons, they will already be well correlated in the ground state and will stand neither to gain by way of electron correlation, nor to lose by way of secondary L strain, in the transition state. If R has *four* unshared electrons, they must be closely paired, *i.e.*, poorly correlated, in the ground state, because the two bonds compel both spin sets to coincide. In this instance, however, the imposition of L strain on the C–R bond in the transition state results in no secondary L strain, owing to the ability of both spin sets about R to pivot in a circle around the axis of the other single bond to R. In the example **8**, R = OCH_3. There is



8

further advantage in that spreading of the unshared pairs in **8** lowers the energy relative to the ground state. As much as 4.7 kcal/mol of stabilization is potentially available to the transition state from this source, based on the sin θ relationship proposed in paper II of this series.[4]

(d) The most common heteroatoms from which steric hindrance is to be expected are the halogens except fluorine, increasing in the order Cl, Br, I. The type of hindrance is that encountered in neopentyl systems.

Bearing these considerations in mind, let us consider reactivities in heteroatom-substituted methyl halides RCH_2X. When X = Br, and R is the series of halogens, the relative reactivities toward iodide ion in acetone are F, 0.79, Cl, 0.13, Br, 0.041, and I, 0.059, where ethyl bromide is set at 1.0.[47] Since methyl halides react about 10–100 times faster than ethyl halides in polar aprotic solvents,[21,30] fluorine is seen to be mildly deactivating at the reaction site, compared to hydrogen. This is expected because the two elements differ little in electron correlation change at the transition state and in steric requirements, while fluorine exceeds hydrogen in electronegativity and also slightly in primary L strain. The diminution in reactivity with the other halogens is, of course, no surprise in view of their bulk.

The most important divalent α heteroatoms are oxygen and sulfur. Compared to hydrogen, they both create less primary L strain, but they exceed hydrogen in electronegativity; using fluorine as a gauge for these two factors, reactivity comparable to hydrogen would be anticipated. Secondary L strain, as with the halogens, is still absent. Sterically, groups such as methoxy and thiomethoxy both exceed hydrogen but are comparable to alkyl. However, the electron correlation factor, discussed above, is especially large and favorable for divalent elements.[48] On balance, rate accelerations relative to hydrogen, and large ones relative to alkyl, are expected. In confirmation, the following series of relative rates can be constructed: R = alkyl, 1; methoxy, 900; thiophenoxy, 540; acetoxy, 270; benzyloxy, 59.[32,47]

With nitrogen, a trivalent α heteroatom, secondary L strain will appear, but probably little. Primary L strain will also be less than for either O or C, owing to differences in bond strength,[16] and steric effects will be about the same. There is a gain in electron correlation at the transition state, though less than with O. On the other hand, N is inferior to O in electronegativity.[46] Overall, anticipated rates with α-amino groups are greater than with F or alkyl, but less than with O. We are not aware of any quantitative experimental data on this point, although α-halamines are known to be exceptionally reactive to nucleophiles.[49]

In contrast to the theory just outlined, the "neighboring orbital overlap" theory of α-heteroatom effects[47] suffers from the fact that neighboring O and S activate S_N2 displacements much more than do neighboring F and Cl. One would have expected it the other way around, since the halogens have a greater number of neighboring orbitals. A more recent assessment[50] asserts that there is no good explanation in current theory.

Displacement at Atoms Other than Carbon.—The simplest way to do away with L strain in the nonreacting bonds of **3** is to do away with the nonreacting bonds themselves. Reactions at heteroatoms are therefore expected to be more facile than at saturated carbon, which as a rule they are.

The high reactivity to nucleophiles of halogen molecules, hypochlorites, and chloramines are among the oldest known chemical facts. Hypochlorites are reactive at both heteroatoms.[51] Peroxy bonds are very easily attacked by nucleophiles.[52] The enormous disparity in reactivity at oxygen *vs.* carbon, with matching entering and leaving groups, has been emphasized.[53] Divalent sulfur, too, is subject to very facile S_N2 displacement with a large variety of nucleophiles and leaving groups.[4]

The cases cited so far have a flaw with regard to the L-strain theory, which is that the bonds broken during the reaction are all relatively weak ones, since heteroatoms generally form weaker bonds to each other than they do to carbon.[16] Of course, the bonds being formed are usually weak ones also, but it might be said that the simultaneous making and breaking of bonds must somehow be faster with weak bonds than with strong ones. However, this cannot be so, because the fastest S_N2 reactions of all are those in which the strongest bonds are involved. Proton transfer is an extremely rapid process despite the fact that hydrogen forms stronger bonds to all typical nucleophiles *and* leaving groups than carbon or any of the above-mentioned heteroatoms do.[16] Thus, the strengths of the bonds being made and broken

(47) See ref 10, p 598.

(48) More favorable for oxygen than for sulfur because the comparatively large valence shell of the second-row element accommodates some spreading of the unshared pairs even in the ground state.

(49) H. Gross and E. Höft, *Angew. Chem., Int. Ed. Engl.*, **6**, 335 (1967).

(50) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 284.

(51) C. Walling and M. J. Mintz, *J. Org. Chem.*, **32**, 1286 (1967).

(52) K. M. Ibne-Rasa and J. O. Edwards, *J. Amer. Chem. Soc.*, **84**, 763 (1962), and references cited therein.

(53) E. J. Behrman and J. O. Edwards, *Progr. Phys. Org. Chem.*, **4**, 93 (1967); see specifically p 117.

is not an overriding factor in symmetrical displacements. What hydrogen does have in common with the other heteroatoms is that it suffers from no L strain in the transition state. This topic will come up again in later sections of this paper.

Entering and Leaving Groups.—In the transition state **3**, L strain is not limited to the carbon atom at the center. Both X and Y, the entering and leaving groups, are also subject to its influence, accounting for a wide range of phenomena.

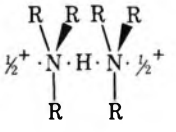
From what has been said before, it is clear that heteroatoms must be better than saturated carbon in either role, and the more nonbonded electrons, the better. For displacements at CH_3, one would ideally like to compare activation energies in series such as $(CH_3)_3N + (CH_3)_4N^+$, $(CH_3)_2O + (CH_3)_3O^+$, $CH_3F + (CH_3)_2F^+$ and $(CH_3)_3C^- + (CH_3)_4C$, $(CH_3)_2N^- + (CH_3)_3N$, $CH_3O^- + (CH_3)_2O$, $F^- + CH_3F$, all in some dipolar aprotic solvent. Although exact data are not yet available, some comparisons may be made. In the first series, it may safely be said that the first two members are in the expected order, since oxonium cations are known to be extremely reactive alkylating agents to (among others) ethers,[54] while ammonium cations are comparatively stable to nucleophilic attack. The substrates $R_2\overset{+}{N}PR'_3$ have much less susceptibility to nucleophilic attack on R than the corresponding oxygen analogs $ROPR'_3$.[55,56] Even the neutral halogens in alkyl halides are better leaving groups than positive nitrogen in ammonium cations,[57] despite the vastly greater electronegativity of the latter moiety. The further prediction that dimethylfluoronium cation, when prepared, will be a methylating agent of fantastic reactivity, even to methyl fluoride, is not a startling one in view of the already facile substitution in the neutral methyl halides as a class.[58]

As for the second series, little can be said at present except that the last two items are probably in the correct order; the severe conditions required for dealkylation of phenyl ethers with alkoxide anions, *ca.* 200°,[59] may be contrasted with the relatively mild 25° that is not uncommon for halide–halide exchange.[20,21] Note that the known vulnerability of SN2 reactions to electron withdrawal at the central carbon atom[32,34,35] would lead to reversal of both the above series if it were the dominant factor.

When displacement on hydrogen is considered, heteroatoms are again expected to be favored over carbon as both entering and leaving groups, and this has long been known to be the case. Proton transfer between atoms with unshared electrons is much faster than between atoms with no unshared electrons,[60] and reprotonation of ambident anions kinetically favors heteroatoms over carbon even when carbon protonation is thermodynamically favored, *e.g.*, $EtNO_2^-$[61] and CHN_2^-.[62] The situation is nicely summarized by Ingold's rule that the less stable tautomer is always most quickly formed.[63] Usually this means that heteroatom protonation is kinetically favored over carbon, and it is significant that the rule holds even when both competing anionic sites are carbon, as in cyclopentylidene malonate anion,[63] when only the kinetically favored site is substituted with groups (COOEt) of exceptionally low secondary L-strain susceptibility, but that the rule fails in another all-carbon system, cumene anion,[64] where the two sites are less unequal in this respect.

Similarly, aliphatic nitro compounds and β diketones (CH acids) have Brønsted catalytic constants $^1/_{20}$th those of phenols (OH acids) of comparable acidities,[65] which means that there is a kinetic factor favoring oxygen over carbon as a leaving group which is not fully accounted for by the thermodynamic differences in acidity. As a general rule, rates of proton transfer follow the expected order O > N > C,[66] and amines, when protonated, transfer hydrogen at exceptionally low rates,[67] showing that their special status as heteroatoms is lost when their complement of L-strain-reducing unshared electrons is depleted.

Yet another example of the imposition of a kinetic factor by L strain upon an otherwise thermodynamically controlled situation is provided by the reaction $R_3\overset{+}{N}H + R_3N$.[68] Two types of proton transfer can be distinguished, one through intervening water and the other directly from one nitrogen atom to another. In the first type, where both partners are solvated all around at all times, the rate response to changing R's from hydrogen to methyl one at a time is small, fitting the relative basicities of the various amines. However, in the second type the transition state may be written as **9**. Solvation effects are reduced in magnitude, and secondary L strain increases progressively as R's are changed from hydrogen to methyl. This is expressed in the rates for the second type of process, which fall rapidly as secondary L strain increases, and which now do *not* reflect the relative basicities. Thus basicity, a



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(54) (a) S. Kahuss, *Angew. Chem., Int. Ed. Engl.*, **5**, 675 (1966); (b) K. Dimroth and P. Heinrich, *ibid.*, **5**, 676 (1966).

(55) R. F. Hudson, "Structure and Mechanism in Organo-Phosphorus Chemistry," Academic Press, London, 1965, pp 136–137.

(56) In keeping with this concept, decomposition of tetraalkylammonium salts with bases typically requires comparatively severe conditions, with substitution even then usually outdone by the well-known Hofmann elimination, while decomposition of $(CH_3)_4N^+$ with strong bases such as NH_2^- and OH^- often occurs by an ylide mechanism rather than SN2: W. K. Musker, *J. Org. Chem.*, **32**, 3189 (1967); *J. Amer. Chem. Soc.*, **86**, 960 (1964).

(57) See ref 11, p 339.

(58) Dialkyl chloronium and bromonium ions have recently been prepared. They are more reactive than Meerwein oxonium salts and alkylate *inter alia* nitriles, ethers, carbonyl compounds, and nitro compounds: G. A. Olah and J. R. DeMember, *J. Amer. Chem. Soc.*, **92**, 2562 (1970); P. E. Peterson, P. R. Clifford, and F. J. Slama, *ibid.*, **92**, 2840 (1970).

(59) S. M. Shein and A. D. Khmelinskaya, *J. Org. Chem. USSR*, **4**, 2084 (1968).

(60) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, p 112.

(61) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 33.

(62) G. W. Cowell and A. Ledwith, *Quart. Rev., Chem. Soc.*, **24**, 119 (1970).

(63) See ref 11, p 565.

(64) G. A. Russell, *J. Amer. Chem. Soc.*, **81**, 2017 (1959).

(65) See ref 50, p 113.

(66) See ref 61, p 122.

(67) (a) A. I. Brodskii and L. V. Sulima, *Dokl. Akad. Nauk SSSR*, **74**, 513 (1950); *Chem. Abstr.*, **45**, 424a (1951). (b) L. Kaplan and K. E. Wilzbach, *J. Amer. Chem. Soc.*, **76**, 2593 (1954). (c) C. G. Swain, J. T. McKnight, M. M. Labes, and V. P. Kreiter, *ibid.*, **76**, 4243 (1954); C. G. Swain and M. M. Labes, *ibid.*, **79**, 1084 (1957); C. G. Swain, J. T. McKnight, and V. P. Kreiter, *ibid.*, **79**, 1088 (1957).

(68) E. Grunwald and A. Y. Ku, *ibid.*, **90**, 29 (1968).

thermodynamic and solvent-related phenomenon, dominates the picture when solvation is complete throughout the reaction but gives way to L strain, a kinetic phenomenon, when the transition state excludes solvent molecules.

It is, in fact, a general rule that good Brønsted linear relationships are observed, even for oxygen acids alone, only for acids of closely related structure, and these limitations on the simple kinetic–thermodynamic parallelism are even more severe for carbon acids.[69] A "geometric factor" has been uncovered which contributes to the activation energies for carbon but not for oxygen acids;[70] this factor is here identified as L strain.

In an earlier discussion of deviations from the Brønsted relation,[71] it was pointed out that these deviations could be expressed as variations in the shape of the Morse curve describing proton loss from the acid, with greater steepness of the potential well on the dissociation side identified with lowered rate toward a standard base. The L-strain theory accounts for the shapes of these curves in a natural way.

The kinetics of proton exchange at saturated carbon are also governed by L-strain considerations. The relative rates of exchange at C–H in *N*-alkylanilines with butyllithium, and in alkylbenzenes with both lithium and cesium cyclohexylamide in cyclohexylamine, with potassium *tert*-butoxide in DMSO, and with KND_2 in ND_3, all diminish similarly with increasing alkyl substitution, providing the series methyl, 1.0, methylene, 0.1–0.5, methine, 0.01–0.1.[72] In unactivated aliphatic hydrocarbons, the same general pattern of kinetic C–H acidity is observed: methane > methyl > methylene > methine.[73] Exchange rates in the series HCH_3, HCH_2CH_3, $HCHAlk_2$ fall in the relative order 2300, 34, *ca.* 0.6,[74] corresponding to a stepwise increase in activation energy at 50° of about 2.7 kcal/mol for each hydrogen replaced by alkyl. This figure for secondary L strain in the *leaving* group is quite similar to that assigned earlier, about 1.5 kcal/mol, for secondary L strain at the *seat* of substitution in the halide–halide exchange series.

All these data fit the sequence anticipated by the L-strain theory, since secondary L strain increases as alkyl groups replace hydrogen. It is interesting that hydrogen itself, a Brønsted acid that is free from L strain, displays much greater kinetic acidity than saturated hydrocarbons.[73]

While it is conceded that these rate differences might be said to reflect the as yet unknown thermodynamic acidities[75] rather than any important kinetic phenomenon, the next example is not subject to this qualification. In the series CH_3NO_2, $MeCH_2NO_2$, Me_2CHNO_2, thermodynamic acidity *increases* toward the right, with pK_a's of 10.2, 8.5, and 7.7, respectively,[76] as one would anticipate for the effect of substitution on the double bond in the anions $R_2C{=}NO_2^-$, but the rate of proton abstraction *diminishes* toward the right in the ratio 113:18:1.[77] Thus the existence of a kinetic effect on alkyl substitution cannot be doubted. This cannot be simply steric because proton abstraction is virtually insensitive to steric hindrance.[78]

The foregoing phenomenon is not limited to nitro compounds. The rate of base-catalyzed ionization at the α carbon of esters in ethanol[79] and in liquid ammonia[80] is reduced by successive replacement of the other α hydrogens by alkyl groups. It is likely, however, that the thermodynamic stability of the enolate anions is increased by alkyl substitution, as it is with nitronate anions.[81]

α Effect.—Entering and leaving groups, like the atom that is the seat of substitution, may suffer from not only primary L strain but also secondary L strain at atoms adjacent to those forming or breaking bonds. Consequently, the replacement of carbon adjacent to the nucleophilic center by a heteroatom should enhance nucleophilicity over and above whatever pK_b changes also are effected. This is the well-known α effect[82,83] and is analogous to the α-heteroatom effect presented earlier. In most examples of SN2 displacements, the nucleophilic atom is a heteroatom itself, subject to reduced primary L strain, and therefore almost negligible secondary L strain. As a result, the α effect is expected to be of small magnitude.

The experimental facts support this conclusion. The α effect is a real phenomenon but quantitatively a minor one and varies from case to case. The widespread attention it has received apparently stems from its hitherto mysterious nature[83,84] rather than from its experimental importance.

Typical examples are the enhanced nucleophilicity of OOH^- relative to OH^- toward *p*-nitrophenyl diethyl phosphate,[85] benzyl bromide,[86] isopropyl methylphosphonofluoridate,[87] tetraethyl pyrophosphate,[88] and benzonitrile,[89] despite the fact that OH^- is by far the stronger base. The α effect also operates in aminol-

(69) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 9.

(70) C. D. Ritchie, *J. Amer. Chem. Soc.*, **91**, 6749 (1969).

(71) See ref 61, p 173.

(72) A. Streitwieser, Jr., and J. H. Hammons, *Progr. Phys. Org. Chem.*, **3**, 63 (1965), and references cited therein; (b) A. R. Lepley and W. A. Khan, *Chem. Commun.*, 1198 (1967).

(73) See ref 69, p 21.

(74) Relative exchange rates with cesium cyclohexylamide in cyclohexylamine at 50° are CH_4, 2300; C_2H_6, 34; cyclohexane, 1 (preliminary unpublished data kindly related by Professor A. Streitwieser, Jr.). Rates for $(CH_2)_n$ rings large enough to minimize steric and annular effects are *ca.* 0.6 relative to cyclohexane: A. Streitwieser, Jr., R. A. Caldwell, and W. R. Young, *J. Amer. Chem. Soc.*, **91**, 529 (1969). Steric effects, associated perhaps with accessibility of the cation, are not responsible for these rate differences since even very bulky groups lower the rate for CH_2R but little, the relative rates in the same study being CMe_4, 8, and C_2Me_6, 5.

(75) It is, in fact, likely that the *intrinsic* acidities of C–H bonds follow the sequence methine > methylene > methyl, because in the gas phase the acidities of N–H bonds increase progressively with alkyl substitution: J. I. Brauman and L. K. Blair, *J. Amer. Chem. Soc.*, **91**, 2126 (1969).

(76) D. Turnbull and S. H. Maron, *ibid.*, **65**, 212 (1943).

(77) F. G. Bordwell, W. J. Boyle, Jr., J. A. Hautala, and K. C. Yee, *ibid.*, **91**, 4002 (1969).

(78) H. C. Brown and B. Kanner, *ibid.*, **88**, 986 (1966).

(79) W. G. Brown and K. Eberly, *ibid.*, **62**, 113 (1940).

(80) C. R. Hauser, R. Levine, and R. F. Kibler, *ibid.*, **68**, 26 (1946).

(81) Malonate anions are somewhat unusual, compared with simple esters, in that an α-phenyl slows base-catalyzed protium–deuterium exchange,[76] and also in that ethylmalonic ester may be less acidic than malonic ester: R. G. Pearson, *ibid.*, **71**, 2212 (1949). However, these anomalies clearly stem from steric inhibition of coplanarity in the highly crowded anions and do not detract from the main argument.

(82) J. O. Edwards and R. G. Pearson, *ibid.*, **84**, 16 (1962).

(83) For a thorough recent discussion, see T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *ibid.*, **89**, 2106 (1967).

(84) See ref 55, p 106.

(85) J. Epstein, M. M. Demek, and D. H. Rosenblatt, *J. Org. Chem.*, **21**, 796 (1956).

(86) R. G. Pearson and D. N. Edgington, *J. Amer. Chem. Soc.*, **84**, 4607 (1962).

(87) See ref 55, p 107.

(88) G. Aksnes, *Acta Chem. Scand.*, **14**, 1515 (1960).

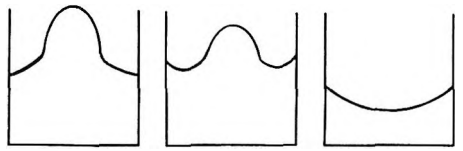
(89) K. B. Wiberg, *J. Amer. Chem. Soc.*, **77**, 2519 (1955).

ysis[90] and base-catalyzed hydrolysis[91] of *p*-nitrophenyl acetate, in displacement on oxygen in AcOOH (where PhNHOH is 6 times more reactive than $PhNH_2$),[52] and in displacement on hydrogen in base-catalyzed reactions; thus ketoxime anions exhibit >20 times positive deviations from the Brønsted catalysis law.[65] This case, like the one cited earlier, illustrates a kinetic factor overriding thermodynamic ones. Many other examples have been given.[83,87]

On the other hand, no α effect was seen in the aminolysis of alkyl iodides in water[90] or acetonitrile,[92] or in attack of amines on the acidic α hydrogen of nitroethane.[93] Clearly, there is much concerning the α effect that is not understood.[94]

The data on the α effect presently obtainable suffer from the facts that many of the reactions were run in hydroxylic solvents with their attendant complications; not all of the examples involve SN2 displacement at a saturated atom (although all of those cited are relevant to this discussion); and few, if any, have the transition state at the midpoint of the reaction coordinate. From the standpoint of the L-strain theory, the α effect ought to be maximized when (1) solvation effects are minimized; (2) the reaction is symmetrical; (3) the attacking atom has few nonbonded electrons, *i.e.*, suffers most from primary L strain; and (4) α atoms are compared that differ greatly in the expected degree of secondary L strain they suffer in the transition state. Typical examples might be $Me_3N + CH_3\overset{+}{N}Me_3$ *vs.* $PhONMe_2 + CH_3\overset{+}{N}Me_2OPh$, or $Me_3N + HNMe_3^+$ *vs.* $XNMe_2 + HNMe_2X$, where X is methoxy or halogen.

Frozen Transition States. Hydrogen Bonds and Trihalide Ions.—If L strain at atoms X, C, and Y in transition state 2 indeed plays an important role in its properties, then, if we were to gradually change the nature of all the atoms and attached groups in such a way that L strain progressively becomes altogether abolished, we might anticipate a gradual sinking of the reaction coordinate diagram to an ultimate form representing a completely L-strain-free reaction. In cases of the latter type, the transition state, having the same number of bonding electrons but better electron correlation than the reactants, could be lower in energy than they are and thus exist as a stable species. This phenomenon will clearly be most pronounced in SN2 displacements on univalent atoms such as hydrogen and the halogens.[96]



Normal SN2 10 11

Hydrogen bonds and trihalide ions are immediately recognized as examples of such frozen transition states.[97] Their Linnett structures are **12** and **13**, first proposed by Linnett.[98] Trihalide ions **13**, having good electron cor-

12 **13**

relation and no L strain whatever, fit well into category **11**. They are linear[99] and have two half bonds,[100] as expected. Almost all combinations of halogens form X_3^- ions,[99] and the absence of F_3^- from the list is undoubtedly owing to the extremely great reactivity of F_2; F_3^- will presumably be found when a system is devised in which F_2 and free F^- can coexist in solution without attacking the solvent. In least interacting media the order of stability is $Cl_3^- > Br_3^- > I_3^-$,[101] indicating that higher orbitals[102] are not involved in trihalide ion formation.

The cations Hal_3^+ offer an interesting contrast. Having two fewer valence electrons, they may adopt the configuration $:\ddot{X}:\ddot{X}:\ddot{X}:$, whose Linnett structure has two-electron bonds and an angle of about 109.5°. The species ClF_2^+ fit the overall picture well. Valence force constants in millidynes/Å follow: ClF_2^+, 4.6–4.8,[103] 4.8;[104] ClF_2^-, 2.35;[100] *cf.* ClF, 4.36.[105] Bond angles are as follows: ClF_2^+, 95–110°,[103] 90–120°;[104] ClF_2^-, 180°.[100]

Hydrogen-bonded molecules exhibit more structural variety because the groups Y and Z in **12** are frequently not entirely free of L strain. Thus, typical hydrogen bonds have the proton closer to one side than the other, as in **10**,[106] corresponding to resonance between **12** and **14**. However, symmetrical hydrogen bonds of type **11**

12 **14**

are known, and it is significant that in all cases the groups Y and Z are capable of forming one-electron bonds, as in **12**, without suffering any increase in L strain. Examples are HF_2^-,[107] HCl_2^-[107] (and probably HBr_2^- and HI_2^-),[107] $H(NO_3)_2^-$,[107,108] $H(OCOR)_2^-$ (R = CH_3, CF_3, Ar).[109]

The hydrogen-bond phenomenon, as an aspect of proton transfer, must represent equilibrium basicity as well as L strain. Basicity effects cancel when Y and Z are the same, and in these cases we expect hydrogen bond strengths to diminish in the order Y, Z = F > O > N >

(90) M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 4400 (1967).

(91) W. B. Gruhn and M. L. Bender, *ibid.*, **91**, 5883 (1969).

(92) S. Oae, Y. Kadoma, and Y. Kano, *Bull. Chem. Soc. Jap.*, **42**, 1110 (1969).

(93) M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 2327 (1967).

(94) From a recent study of the α effect in oxazolone reactions with nucleophiles,[95] good evidence was adduced that these nucleophiles acted as biphilic reagents; *i.e.*, that the α heteroatom bore a proton which acted as an acid catalyst in the transition state. The biphilic and L-strain interpretations of the α effect are, however, not necessarily exclusive, since each may apply under different circumstances.

(95) M. Goodman and C. B. Glaser, *J. Org. Chem.*, **35**, 1954 (1970).

(96) The possibility that these diagrams also have shallow dips at the centers is acknowledged (*vide supra*) but plays no part in the discussion.

(97) Frozen transition states are by definition intermediates, and not true transition states. The expression is used because it is uniquely descriptive for our present purpose.

(98) See ref 2, p 118.

(99) K. O. Christe and J. P. Guertin, *Inorg. Chem.*, **4**, 905 (1965), and references cited therein.

(100) K. O. Christe, W. Sawodny, and J. P. Guertin, *ibid.*, **6**, 1159 (1967).

(101) R. Alexander, E. C. F. Ko, and A. J. Parker, *J. Amer. Chem. Soc.*, **89**, 3703 (1967).

(102) R. F. Hudson, *Angew. Chem., Int. Ed. Engl.*, **6**, 749 (1967).

(103) R. J. Gillespie and M. J. Morton, *Inorg. Chem.*, **9**, 616 (1970).

(104) K. O. Christe and W. Sawodny, *ibid.*, **6**, 313 (1967).

(105) A. H. Nielsen and E. A. Jones, *J. Chem. Phys.*, **19**, 1117 (1951).

(106) (a) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman Co., San Francisco, Calif., 1960, p 259; (b) see ref 46b, p 223.

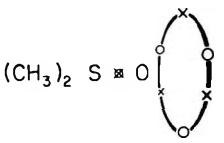
(107) G. A. Sim, *Ann. Rev. Phys. Chem.*, **18**, 67 (1967).

(108) B. D. Faithful and S. C. Wallwork, *Chem. Commun.*, 1211 (1967).

(109) J. C. Speakman, *ibid.*, 32 (1967).

C, since L strain in 12 ↔ 14 increases with the number of groups borne by Y and Z. Although the experimental data must be viewed against a background of solvent effects poorly understood, they clearly are in accord with this expectation.[110] This is also the order of relative rates of proton transfer.[66]

The clash between thermodynamic and kinetic effects, presented earlier, appears here also. It has become increasingly apparent in recent years that hydrogen bonds are subject to a powerful influence which sometimes runs counter to trends in basicity. Dimethyl sulfoxide, though a very weak base, should be a potent hydrogen-bond acceptor, in keeping with the structure 15. The unshared electrons on the oxygen



15

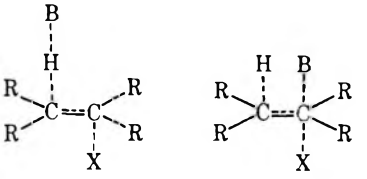
atom are not closely paired and consequently can accept a hydrogen bond with no increase in L strain. Hexamethylphosphoramide is alike in this respect. Divalent oxygen is less favored because both spin sets are formally coincident.[4] However, doubly bonded oxygen can separate its spin sets more easily than ether oxygen for reasons given earlier (*cf.* α-halo ketones), with amides better than ketones owing to their pronounced resonance. Trivalent nitrogen suffers still more L strain in 12 ↔ 14 than divalent oxygen, offsetting its greater basicity. As with oxygen, ease of accepting hydrogen bonds should increase with multiplicity, countering the concurrent decrease in basicity.

Dimethyl sulfoxide, even in the presence of proton donors, profoundly increases the reactivity of bases and nucleophiles,[111] which we ascribe to its role as hydrogen-bond acceptor.[112] In activating piperidine to nucleophilic attack on nitroaromatic substrates by coordinating with NH, DMSO far outstrips dioxane and the much more basic pyridine.[113]

Recent comprehensive studies of hydrogen bonding provide strong confirmation of the L-strain theory. Toward phenylacetylene, hydrogen bond strengths diminish in the sequence HMPA > DMSO > DMF > acetone, ethers > acetonitrile,[114] in accord with the theory but not with their relative basicities. In a comparison of 62 bases toward *p*-fluorophenol,[115] no correlation between basicity and hydrogen bond strength was found. The trends, however, were precisely as predicted above, with DMSO, HMPA, and DMF unusually potent hydrogen bond acceptors for their basicity, and amines unusually weak. Carbonyl compounds and ethers, in that order, were intermediate. In a second paper,[116] a plot for all bases of log K_f (H bond) *vs.* pK_a (H_2O) fit no one line but could be resolved into a series of roughly parallel lines, each representing a family of compounds of the same type in the order just given. Within each family, log K_f was proportional to pK_a, but some factor other than pK_a operated to separate the various classes. We identify this factor as L strain.

The theory of hydrogen bonding and trihalide ions outlined above does away with the problem of hypervalency[102] previously associated with these phenomena. An MO description of the hydrogen bond by McClellan and Pimentel[117] may be equivalent to ours, although it makes no provision for L strain.

The E2C Mechanism.—Related to the problem of basicity *vs.* hydrogen bonding ability is the theory of bimolecular elimination called the E2C mechanism. In the E2 reaction, as in neutralization by a protic acid, a Lewis base forms a new bond to hydrogen, while in the SN2 reaction the new bond is to carbon. Because the logarithms of E2 reaction rates of cyclohexyl tosylate with various bases were related randomly toward their pK_a's, but linearly toward the logarithms of the concurrent SN2 reaction rates of the same substances, it was proposed[118] that E2 transition states be categorized as E2H (16) or E2C (17), or a combination



16 17

of the two. Further studies have appeared,[111e,119] as well as opposed views.[120]

It had been noted[118] that the poor Brønsted relationship was markedly improved if hydrogen-bonding ability were considered in place of equilibrium basicity. In the light of the discussion above on hydrogen bonding, it becomes clear that the tendency for a base to attack on hydrogen *vs.* carbon ought to be compared with its hydrogen-bonding ability, not its basicity. The latter measures its states before and after complete proton transfer has occurred, but it is the former which relates to the contrast between the ground and transition states. Thus those factors, such as L strain, which cause differences to arise between pK_a and hydrogen bond basicity will also be operative in transition state 16, making the consideration of unusual forms such as 17 less imperative.

Conclusion

The Linnett electronic theory and its corollary, L strain, account for a wide variety of phenomena

(110) See ref 106a, pp 212, 224.

(111) (a) E. C. Steiner and J. M. Gilbert, *J. Amer. Chem. Soc.*, **85**, 3054 (1963); (b) C. A. Kingsbury, *J. Org. Chem.*, **29**, 3262 (1964); (c) D. Bethell and A. F. Cockerill, *J. Chem. Soc. B*, 913 (1966); (d) A. F. Cockerill and S. Rottschaefer, *J. Amer. Chem. Soc.*, **89**, 901 (1967); (e) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969); (f) K. Kalliorinne and E. Tommila, *Acta Chem. Scand.*, **23**, 2567 (1969).

(112) The authors of the papers cited are not always in agreement with this point of view.

(113) C. F. Bernasconi, M. Kaufmann, and H. Zollinger, *Helv. Chim. Acta*, **49**, 2563 (1966).

(114) C. Agami and M. Caillot, *Bull. Soc. Chim. Fr.*, 1990 (1969).

(115) D. Gurka and R. W. Taft, *J. Amer. Chem. Soc.*, **91**, 4794 (1969).

(116) R. W. Taft, D. Gurka, L. Joris, P. v. R. Schleyer, and J. W. Rakshys, *ibid.*, **91**, 4801 (1969).

(117) See ref 106a, p 236.

(118) A. J. Parker, M. Ruane, G. Biale, and S. Winstein, *Tetrahedron Lett.*, 2113 (1968).

(119) (a) D. J. Lloyd and A. J. Parker, *ibid.*, 5183 (1968); (b) D. Cook, A. J. Parker, and M. Ruane, *ibid.*, 5715 (1968); (c) D. Cook and A. J. Parker, *ibid.*, 4901 (1969); (d) G. Biale, A. J. Parker, S. G. Smith, I. D. R. Stevens, and S. Winstein, *J. Amer. Chem. Soc.*, **92**, 115 (1970).

(120) (a) D. Eck and J. F. Bunnett, *ibid.*, **91**, 3099 (1969); (b) D. J. McLennan and R. J. Wong, *Tetrahedron Lett.*, 881 (1970).

dealing with SN2 reactions on carbon, hydrogen, and heteroatoms. No other valence theory presently makes allowance for L strain although this may come about in the future, since the Linnett theory is complementary to, and not incompatible with, the valence bond and molecular orbital viewpoints. A strong point of the new method is the facility with which it can be applied. Definite structures are easily assigned to molecules and transition states with no need to invoke dotted-bond forms with vague properties. The systematic application of Linnett's theory to other organic reactions will follow in due course.

The 12α,13β-Etiojervane Analog of Testosterone

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The 3-keto-17α-acetoxyetiojervane **1f** was converted *via* the 2,4-dibromide to the unsaturated ketone **5f**; room-temperature formation of the ethylenedioxy ketal **6e** followed by successive saponification, oxidation, and hydride reduction afforded the 17β-hydroxy derivative **6a** (R′ = $-CH_2CH_2-$) which was hydrolyzed to the title compound. Attempts to prepare and use the 2,4-dibromide **4b** in the 17β-acetoxy series were unsuccessful. The corresponding 12β-etiojervanes were prepared from jervine by modification and extension of known methods.

The objective of the research described here was to synthesize, starting from hecogenin, simple etiojervane derivatives which would display some of the potent physiological characteristics of the Veratrum alkaloids.[1] The initial group of etiojervanes (12α, 13α)[2] prepared had both a C/D cis ring fusion and a 13α substituent (methyl) in analogy to the Veratrum alkaloids. These derivatives had no noteworthy physiological activity. The serendipitous preparation[3] (by fermentation) of the corresponding 13β-methyldione **5d** (Δ^1), however, led to the syntheses of a series of compounds with good potency as antialdosterone agents.[4]

The primary target of our research was a practicable synthesis of the title compound **5a**. One starting material was the saturated 3-ketone **1b**, obtained by rearrangement of hecogenin and subsequent degradation of the sapogenin side chain.[5] The 2-monobromide **2b** was investigated as a possible intermediate to be used in the introduction of the C-4 double bond. The bromide **2b**, a crystalline compound prepared by direct bromination of the ketone **1b**, had both gross structure (C-2 bromine) and configuration (α-bromine) in analogy to the steroidal bromination product, as suggested by nmr and ORD measurements.[6] A chemical confirmation was obtained by zinc–acetic acid reduction to starting material **1b** and by magnesium oxide dehydrohalogenation to give preponderantly the Δ^1 ketone **3b**. A minor by-product of the latter reaction was the Δ^4 ketone **5b** which was separated and characterized. The monobromide **2f** (17α-acetate) underwent analogous reactions, although neither the 17α-acetate **3f** nor its alcohol **3e** was obtained in a crystalline form.

Dehydrobromination of 2-bromo steroids with lithium chloride in dimethylformamide proceeds vinylogously to yield 45% of the Δ^4 derivative.[7] With the etiojervane monobromide **2f**, the same reagent afforded, rather than an elimination product, a displacement product, the monochloride **2f** (X = Cl). The same chloride was produced readily from the monobromide over a wide range of temperatures. Similarly, treatment of the bromide with sodium iodide provided an iodo derivative (**2f**, X = I). The position of the chlorine atom in **2f** was not readily determined because of its stability to relatively vigorous dehydrohalogenation conditions; treatment of the compound in boiling collidine for 7 hr effected little change in the starting material. With magnesium oxide in boiling dimethylformamide, the monochloride **2f** slowly yielded mixtures from which the Δ^1 derivative **3f** could be isolated. In contrast, the iodide underwent a facile elimination to give mainly the Δ^1 ketone, thus supporting directly the assigned position of the iodine atom in the iodo ketone **2f** and indirectly the position of the chlorine atom in the chloro ketone **2f**. The configuration of the chlorine atom in **2f** was determined by ORD and nmr measurements.[8]

The behavior of the 2-monobromo-17β-acetate **2b** on treatment with lithium chloride differed markedly from that of the corresponding 17α-acetate, reacting very slowly in this case and producing an intractable chlorine-containing mixture. Under conditions vigorous enough to remove halogen, the product lacked an unsaturated ketone component (ir analysis). Several other reagents also failed to generate an unsaturated ketone from the lithium chloride product. The difference in behavior between the 17α-acetate and the more strained 17β-acetate[9] on treatment with lithium chloride may be attributed either to a long-range effect (transmission of strain through the carbon–carbon bonds) or to a steric effect (produced by the cupping of the D ring toward the β face of the A ring). Molecular models imply the former to be the more important cause.

Direct dibromination of the 3-keto-17α-acetate **1f** led to the 2,4-dibromide **4f** in good yield. Treatment of this compound sequentially with sodium iodide, acid,

(1) S. M. Kupchan and A. W. By in "The Alkaloids," Vol. X, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1968, Chapter 2.

(2) W. F. Johns and I. Laos, *J. Org. Chem.*, **30**, 123 (1965).

(3) W. F. Johns, *ibid.*, **35**, 3524 (1970).

(4) The physiological activity of the compounds reported will appear in a forthcoming publication.

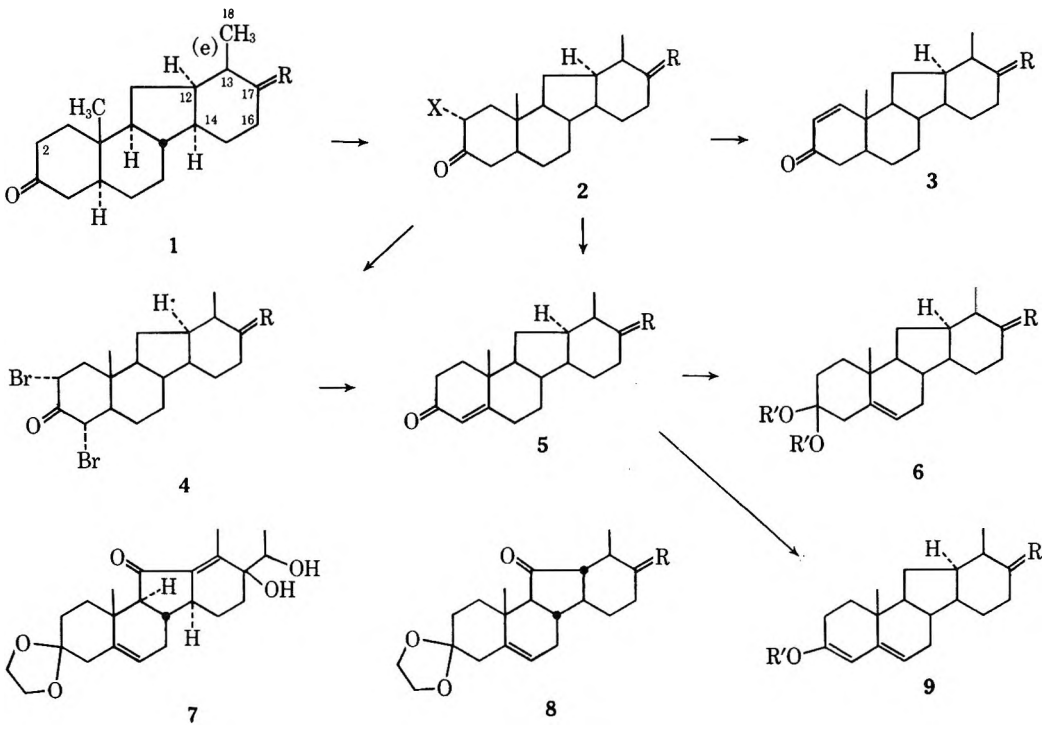
(5) W. F. Johns, *J. Org. Chem.*, **29**, 2545 (1964).

(6) Professor W. Klyne, Westfield College, University of London, kindly supplied this data and its interpretation.

(7) B. J. Magerlein, *J. Org. Chem.*, **24**, 1564 (1959).

(8) Preparation of 2-iodocholestanone from the 2-bromide has been recorded: G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi, *J. Amer. Chem. Soc.*, **72**, 4077 (1950). The displacement by chloride, however, leads to elimination (ref 7). For displacement of halo ketones at other positions, *cf.*, *inter alia*, G. P. Mueller and W. F. Johns, *J. Org. Chem.*, **26**, 2403 (1961).

(9) The 17β derivatives are more strained because of the interaction of the 17β substituents with C-19. See ref 2 for a further discussion of this point.



a, R = β-OH; b, R = β-OAc; c, R = β-OCOPh; d, R = O; e, R = α-OH; f, R = α-OAc

and zinc–acetic acid[10] produced the Δ^4 derivative **5f** in good yield. The dibromide also underwent dehydrohalogenation with magnesium oxide to afford the 1,4-dienone (**5f**, Δ^1). The Δ^4-acetate **5f** was saponified to its alcohol **5e**, and this in turn was oxidized to the ketone **5d**.

Dibromination of the 17β-acetoxy 3-ketone **1b** led to the formation of an amorphous, heterogeneous product. Although the elemental analysis was acceptable, the spectral data were ambiguous as were the subsequent chemical reactions. Direct dehydrobromination of the dibromide with magnesium oxide gave intractable mixtures instead of the expected 1,4-dienone. The sodium iodide procedure gave a nonpolar mixture which crystallized in part to yield a component with an empirical formula of $C_{19}H_{30}O$ (elemental analysis, mass spectrum). The exact structure of this compound was unclear from its spectra, but it is thought to represent D-ring deoxygenated material.

Inversion of the 17α-hydroxy group in the available unsaturated ketone **5e** to provide the desired 17β isomer **5a** was attempted by tosylate formation followed by formolysis. The product was largely olefinic. Inversion by oxidation of the 17α-hydroxyl to a ketone and subsequent reduction to the 17β-hydroxyl had been demonstrated in the A-ring saturated etiojervanes[3] but was complicated in the present case by the unsaturated 3-ketone. Lithium tri-*tert*-butoxyaluminohydride reduction of the 17-carbonyl of **5d** proceeded at a rate slow enough to cause partial reduction of the 4,5 double bond. Lithium aluminum hydride reduction of **5d** afforded the unsaturated diol (**5a**, 3β-OH), but manganese dioxide oxidation to regenerate the unsaturated ketone proceeded only in moderate yields.

Attempts to protect the unsaturated ketone moiety while inverting the 17α-hydroxyl function uncovered a marked instability of the Δ^4-etiojervene in contrast to the normal steroid, presumably due to inherently greater bond strain in the former. Thus acetic anhydride–toluenesulfonic acid treatment of **5f** gave intractable tars instead of the desired enol acetate **9f** (R′ = Ac). Enol ether formation with trimethyl orthoformate provided mixture of dienol ether **9f** (R′ = Me) and ketal **6f** (R′ = Me). Purification of the mixture was abandoned when it was discovered that the dienol grouping was oxidized with the Sarett reagent.[11] Preparation of the ethylenedioxy ketal was successful only through use of a room temperature procedure employing ethylene glycol and triethyl orthoformate.[12] Subsequent oxidation of the 17α-hydroxyl, reduction of the resulting ketone with lithium tri-*tert*-butoxyaluminohydride, and hydrolysis of the ketal group gave the desired 17β-hydroxy compound **5a** in good overall yield.

Despite the modest yields obtained of the 1,4-dienone (**5b**, Δ^1) by direct selenium dioxide oxidation of the saturated ketone **1b**,[2] investigations were also made into the selective reduction of its Δ^1 bond. Brief lithium–ammonia treatment[13] gave the desired 3-keto-4-ene contaminated with appreciable amounts of the saturated ketone. Hydrogenation of the dienone in the presence of tristriphenylphosphorhodium catalyst[14] was highly erratic and very slow, giving in the best instance, less than 30% of the desired 4-ene after a 28-hr period.

The need for biological comparisons between the

(10) K. Schreiber, A. Walther, and H. Rönsch, *Tetrahedron*, **20**, 1939 (1964). Also see ref 8.

(11) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

(12) This procedure was developed by H. L. Dryden, Jr., and G. Webber of these laboratories for use on steroidal 17-ketones; *cf.* also British Patent 850,386 (1960); *Chem. Abstr.*, **56**, 8800*b* (1962).

(13) R. E. Schaub and M. J. Weiss, *Chem. Ind. (London)*, 2003 (1961); E. Shapiro, T. Legatt, L. Weber, M. Steinberg, and E. P. Oliveto, *ibid.*, 300 (1962).

(14) (a) A. J. Birch and K. A. M. Walker, *J. Chem. Soc.*, 1894 (1966); (b) C. Djerassi and J. Gutzwiller, *J. Amer. Chem. Soc.*, **88**, 4537 (1966).

C/D *cis*- and *trans*-etiojervanes dictated the synthesis of the latter. The route chosen involved modification and extension of the known degradation of jervine.[15] Among the changes made was the replacement with manganese dioxide of the chromium trioxide used in the cleavage of the 17,20-glycol **7**, affording a yield of 76% of the crystalline enedione **8d** (Δ^{12}). At a subsequent step, the efficiency of the Wolff–Kishner reduction of the 11-ketone was improved by use of hydrazine dihydrochloride in triethylene glycol to form the hydrazone as a discrete step before the addition of potassium hydroxide. Each of the isomers prepared was hydrolyzed to give the free 12β,13β-testosterone analogs (**5a**, **5e**; 12β-H). Chromic acid oxidation provided the 17-keto derivative **5d** (12β-H).

Experimental Section[16]

2α-Bromo-17β-acetoxy-12α-etiojervan-3-one (2b, X = Br).—Pyridinium bromide perbromide (1.11 g) was added in four portions over a 5-min period to a solution of 0.99 g of the acetate **1b**[3] in 50 ml of acetic acid containing a trace of hydrogen bromide. After 2 min more, the solution was diluted with water and aqueous sodium thiosulfate. The resultant precipitate was collected, washed with water, dried, and recrystallized from acetone–hexane to yield 0.50 g of the bromide **2b**: mp 153–155°; λ_{max} 5.78 μ; Δν 52 and 59 (18-Me), 66 (19-Me) 288 (q, CHBr) Hz; ORD (in 2:1 MeOH/dioxane) $[\phi]^{pk}_{306\ m\mu}$ 2940; $[\phi]^{tr}_{263\ m\mu}$ −3170°; $a = +62$.[6]

Anal. Calcd for $C_{21}H_{31}BrO_3$: C, 61.31; H, 7.60; Br, 19.43. Found: C, 61.63; H, 7.58; Br, 19.36.

Treatment of the monobromo compound **2b** with zinc dust in acetic acid at room temperature for 3 hr gave a good yield of the saturated 3-ketone **1b**.

The 17-benzoate **1c** was prepared by benzoyl chloride–pyridine treatment of the alcohol **1a**.[3] The resulting amorphous compound was monobrominated to provide a chromatographically and spectrally homogeneous, but amorphous, bromide **2c**.

Anal. Calcd for $C_{25}H_{33}BrO_3$: Br, 16.88. Found: Br, 17.04.

17β-Hydroxy-12α-etiojerv-1-en-3-one (3a).—A solution of 0.17 g of the crystalline bromide **2b** in 20 ml of dimethylformamide was added to a stirred, boiling mixture of 1.0 g of magnesium oxide in 30 ml of dimethylformamide under an atmosphere of nitrogen over a 10-min period. After 3 hr the cooled solution was filtered and concentrated to dryness. The residue was chromatographed but failed to crystallize. Similar treatment of the 2α-bromo 17-benzoate **2c** gave again an amorphous product.

A solution of 0.81 g of the benzoate **2c** in 30 ml of *tert*-butyl alcohol containing 5 ml of 10% aqueous potassium hydroxide was boiled in an atmosphere of nitrogen with stirring for 25 hr. The solvent was removed in a stream of nitrogen and the product was extracted with methylene chloride. Chromatography[17] yielded first, by elution with 15% ethyl acetate–benzene, material recrystallized from acetone–hexane to yield the alcohol **3a** as a hemiacetonate: mp 84–87°; λ_{max} 2.72, 5.95 μ; Δν 59 and 68 (18-Me), 62 (19-Me), 350 (d, 1-H), 422 (d, 2-H) Hz.

Anal. Calcd for $C_{19}H_{28}O_2 \cdot {}^1/_2C_3H_6O$: C, 77.56; H, 9.84. Found: C, 77.71; H, 9.81.

The Δ^4 derivative (**5a**, 45 mg), identical with the material prepared below, was obtained by further elution of the column with 20% ethyl acetate–benzene.

Lithium Chloride Treatment of the 2α-Bromo-17β-acetate 2b.—Treatment of the bromide **2b** in dimethylformamide containing lithium chloride at 80° for 2 hr returned 90% of starting material unchanged and no chloro derivatives (halogen analysis). After 20 hr at 95°, an amorphous product was isolated.[18]

Anal. Calcd for $C_{21}H_{31}ClO_3$: Cl, 9.66. Found: Cl, 6.14 (no bromine).

Raising the temperature to the boiling point of dimethylformamide for 2 hr gave a dark product lacking halogen and lacking unsaturated ketone absorption in the ir. Use of lithium chloride–lithium carbonate in the same solvent offered similar results.

Among the reagents used in an attempt to convert the bromide **2b** to the Δ^4 ketone **5b** were ethanolic acid at reflux, collidine at reflux, and semicarbazone formation followed by pyruvic acid reversal. In each of these instances the yield of the desired unsaturated ketone was negligible.

2α-Bromo-17α-acetoxy-12α-etiojervan-3-one (2f).—A solution of bromine in acetic acid (41.4 ml, 0.38 *M*) was added over a 20-min period to a stirred solution of 4.75 g of the ketone **1f** in 200 ml of acetic acid containing a trace of hydrogen bromide at 15°. After an additional 5 min, the solution was diluted with water, and the resulting precipitate was collected, washed with water, dried, and recrystallized from methylene chloride–hexane to yield 4.4 g of the bromide **2f**: mp 142–147°; λ_{max} 5.78 μ; Δν 52 and 58 (18-Me), 64 (19-Me), 287 (q, CHBr) Hz.

Anal. Calcd for $C_{21}H_{31}BrO_3$: C, 61.31; H, 7.60; Br, 19.43. Found: C, 60.44; H, 7.65; Br, 19.60.

Dehydrohalogenation of Bromo Ketone 2f.—Lithium chloride–lithium carbonate dehydrohalogenation of bromide **2f** in boiling dimethylformamide for 1 hr gave an amorphous olefin with the proper spectral characteristics for the Δ^1 ketone **3f**: λ_{max} 232 mμ (ε 5350); λ_{max} 5.78, 5.95 μ; Δν 53 and 59 (18-Me), 60 (19-Me), 350 (d, 1-H), 427 (d, 2-H) Hz.

Saponification of this material in methanol with aqueous potassium hydroxide gave only an amorphous product.

2α-Chloro-17α-acetoxy-12α-etiojervan-3-one (2f).—The bromo ketone **2f** (0.75 g) was added to a solution of 1.0 g of lithium chloride in 20 ml of dimethylformamide with stirring. After 7 hr at room temperature, the solution was diluted with water. The resulting precipitate was collected and dried, yielding 0.55 g of essentially pure chloride **2f**, mp 147–152° (found: 9.44% Cl). Recrystallization of this sample from methylene chloride–hexane gave the pure material: mp 163–167°; λ_{max} 5.78 μ; Δν 52 and 58 (18-Me), 65 (19-Me), 279 (q, CHCl) Hz; ORD[19] (*c* 1.05, dioxane) $[\phi]^{pk}_{312\ m\mu}$ +2720; $a = +71$.

Anal. Calcd for $C_{21}H_{31}ClO_3$: C, 68.74; H, 8.52; Cl, 9.66. Found: C, 68.76; H, 8.35; Cl, 9.64.

Dehydrohalogenation of the Chloro Ketone 2f.—The chloro ketone **2f** was essentially inert to lithium chloride in dimethylformamide at 95° for 3 days or to refluxing collidine for 7 hr. Magnesium oxide in boiling dimethylformamide transformed the chloro ketone **2f**, after 6 hr, into a product containing 20% starting material and the rest a mixture of the Δ^1 ketone **3f** mixed with a small amount of the Δ^1 ketone **5f**. The chloro ketone **2f** displayed a slightly lower stability with lithium chloride and lithium carbonate in boiling dimethylformamide.

Attempts to dehydrochlorinate the chloro ketone **2f** by treatment of its semicarbazone with pyruvic acid[20] were unsuccessful.

Formation and Dehydroiodination of 2α-Iodo-17α-acetoxy-12α-etiojervan-3-one (2f).—Potassium iodide (0.2 g) was added to a solution of 0.20 g of the bromo ketone **2f** in 2 ml of acetone at 5°. After 3 hr at an ambient temperature, the solution was diluted with water and the precipitate collected. The product was recrystallized from aqueous methanol to yield 0.12 g of the iodo ketone: mp 125–134°; λ_{max} 5.75 μ.

Anal. Calcd for $C_{21}H_{31}IO_3$: I, 27.59. Found: I, 29.30 (no bromine).

Treatment of this product with lithium carbonate in hot dimethylformamide afforded the Δ^1 ketone **3f** as the major product (by nmr analysis).

2α,4α-Dibromo-17α-acetoxy-12α-etiojervan-3-one (4f). A. Direct Bromination (Procedure A).—A bromine–acetic acid solution (250 ml, 0.38 *M*) was added over a 25-min period to a solution

(15) (a) S. M. Kupchan and S. D. Levine, *J. Amer. Chem. Soc.*, **86**, 701 (1964). (b) See also an alternate route described in the more recent work of T. Masamune and K. Orito, *Tetrahedron*, **25**, 4551 (1969).

(16) The infrared spectra were determined in chloroform, ultraviolet spectra in methanol, optical rotations in chloroform, and nmr spectra in deuteriochloroform (TMS as an internal standard, Δν = 0 Hz on a Varian A-60 spectrometer). We are indebted to Dr. J. W. Ahlberg and staff for these results as well as for the elemental analyses reported. Melting points were taken on a Fisher–Johns apparatus and are uncorrected.

(17) The chromatographies described in this section were uniformly run on a weight of Davison silica gel 60 times the weight of the compound involved. We thank Mr. R. T. Nicholson and staff for the competent execution of this work.

(18) The isolation procedure used throughout this work involved dilution of the reaction mixture with water, evaporation of water-soluble solvents more volatile than water, and extraction with an immiscible solvent. The extract was routinely dried over magnesium sulfate and the solvent removed under reduced pressure ($T < 50°$).

(19) This ORD was run by N. L. McNiven, Worcester Foundation for Experimental Biology, Shrewsbury, Mass.

(20) E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

at 15° of 14.5 g of the ketone 1a in 200 ml of acetic acid containing a trace of hydrogen bromide. The solution was stirred 2 hr more during which time the dibromide precipitated. The mixture was diluted with 2 l. of water and the crystals were collected on a filter, washed with water, and dried, yielding 20.6 g of the dibromide, mp 160–161°. Recrystallization of a portion of this material from aqueous acetone afforded the pure compound 4f: mp 168–169°; λ_{max} 5.71 (m), 5.80 (s) μ; $\Delta\nu$ 52 and 58 (18-Me), 68 (19-Me), 285 (m, 17-H, 2β-H, 4β-H) Hz.

Anal. Calcd for $C_{21}H_{30}Br_2O_3$: Br, 32.60. Found: Br, 32.75.

Addition of 100 mg of the dibromide 4f to 0.2 g of lithium carbonate and 0.1 g of lithium chloride in 10 ml of refluxing dimethylformamide led, after 4 hr, to formation of the dienone ($\Delta^{1,4}$ derivative of 1f) separated by chromatography and identified by its nmr spectrum.[3]

B. Bromination of the Bromide 2f.—Bromination of the 2-bromo compound 2f (4.3 g) in 90 ml of acetic acid containing 10 g of potassium acetate with 1.3 equiv of bromine in acetic acid at 90° for 10 min caused a disappearance of the bromine color. The resulting product could not be obtained in a crystalline form however. Treatment of this material with hydrogen bromide in acetic acid (2 hr, room temperature) led to a moderate yield of the above crystalline 2,4-dibromide 4f.

17α-Acetoxy-12α-etiojervan-4-en-3-one (5f, Procedure B).—Iodoacetone[10] was prepared by dropwise addition of 20 ml of bromine over 15 min to 0.6 l. of acetone with cooling. The decolorized solution was stirred well with 200 g of potassium carbonate and filtered into a solution of 2 l. of acetone containing 400 g of sodium iodide. The solution was boiled under nitrogen for 15 min. The dibromo ketone 4f (45 g) was then added and the solution was distilled slowly for a 2-hr period to a 1.5-l. volume. Oxalic acid (30 g) was added in several portions and the heating continued for an additional 30 min. The reaction mixture was diluted with 2 l. of ethyl acetate and was filtered. The filtrate was washed with water, bicarbonate solution, and water. The combined extracts, after drying, were diluted with 50 ml of acetic acid and then, with stirring and cooling, 100 g of zinc dust was added in several portions. After 0.5 hr, the mixture was filtered and the filtrate washed with water and bicarbonate. The dried extract was concentrated to dryness. Tlc indicated that it was largely the desired unsaturated ketone 5f contaminated with the starting saturated ketone 1f. Attempts to purify the product by crystallization or by formation of its sodium bisulfite adduct were unsuccessful. Chromatography of the product yielded first the saturated ketone 1f, eluted with 3% ethyl acetate–benzene. Eluted shortly after this were fractions which were combined and recrystallized from ether–cyclohexane to yield the pure unsaturated ketone 5f: mp 84–85°; λ_{max} 5.79, 6.01 μ; λ_{max} 239 mμ (ϵ 17,000); $\Delta\nu$ 52 and 59 (18-Me), 70 (19-Me), 123 (OAc), 346 (C=CH) Hz.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.26; H, 9.34.

More polar fractions contained heterogeneous, amorphous, materials which proved intractable.

17α-Hydroxy-12α-etiojerv-4-en-3-one (5e).—A solution of 100 mg of the acetate 5f in 2 ml of methanol containing 0.2 ml of 10% aqueous potassium hydroxide was boiled in an atmosphere of nitrogen for 1 hr. The methanol was distilled and the remaining mixture was diluted with water. The resulting precipitate was collected, dried, and recrystallized from acetone–hexane to afford 45 mg of the alcohol 5e: mp 136–138°; λ_{max} 2.75, 6.02 μ; λ_{max} 239 mμ (ϵ 16,700); $\Delta\nu$ 60 and 67 (18-Me), 70 (19-Me), 347 (4-H) Hz; $[\alpha]_D$ 73°.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.23; H, 9.82.

This compound formed an amorphous tosylate which on treatment with sodium formate in hot dimethylformamide led to intractable products.

12α-Etiojerv-4-ene-3,17-dione (5d, Procedure C).—The 17α alcohol 5e (0.20 g) was oxidized with the Sarett ragent[11] prepared from 0.2 g of chromium trioxide and 2 ml of pyridine. The reaction mixture was diluted with water after 6 hr at room temperature. The product was isolated by ether extraction and afforded, after recrystallization from ether–cyclohexane, 0.14 g of the diketone: mp 169–172°; λ_{max} 239 mμ (ϵ 16,000); λ_{max} 5.83, 6.00 μ; $\Delta\nu$ 57 and 64 (18-Me), 66 (19-Me) Hz; $[\alpha]_D$ −39°.

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.46; H, 9.31.

Attempted Formation of 2,4-Dibromo-17β-acetoxy-12α-etiojervan-3-one (4b).—The dibromination procedure A given above, when applied to the 17β-acetate 1b, afforded an amorphous mixture (I). Treatment of mixture I with sodium iodide according to procedure B led to an amorphous nonpolar mixture from which was isolated, after chromatography, a small amount of crystalline material: mp 103–110°; λ_{max} 5.80 μ; $\Delta\nu$ 57 Hz (broad methyl signal). The mass spectrum of this component showed a molecular ion of 274, implying the compound has an empirical formula of $C_{19}H_{30}O$.

Direct dehydrobromination of the "dibromide" (mixture I) with magnesium oxide led to intractable mixtures in which the desired dienone (1b, $\Delta^{1,4}$) was a negligivele component.

When the dibromination and sodium iodide sequence (procedures A, B) were carried out on the 17β-benzoate 1c, a nonpolar fraction was again produced, but in this case it was accompanied by a small amount of the desired unsaturated ketone 5c and the saturated ketone 1c.

12β-Etiojerv-4-ene-3β,17β-diol (5a, 3β-OH).—A solution of 0.57 g of the dione 5d in 100 ml of ether and 5 ml of tetrahydrofuran was added to a solution of 0.30 g of lithium aluminum hydride in 100 ml of ether over a 30-min period maintaining the temperature at −10°. After an additional 20 min, excess ethyl acetate was added dropwise followed by 2 ml of 10% aqueous potassium hydroxide. The mixture was filtered through Super-cel and the filtrate was concentrated to dryness. The resulting crystalline residue was recrystallized from ethyl acetate to yield 0.21 g of the diol: mp 187–191°; λ_{max} 3.02, 6.03 (w) μ (KBr); $\Delta\nu$ 51 and 58 (18-Me), 57 (19-Me), 312 (C=CH, 4-H) Hz [$(CD_3)_2SO$].

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.78; H, 10.64.

Oxidation of the diol 5a (3β-OH) with MnO_2 in chloroform for 22 (or 40 hr) gave the desired unsaturated ketone 5a in 55% yield.

The reduction of 5d with lithium tri-*tert*-butoxyaluminohydride was less than half complete after 4 hr at room temperature.

3,3-Ethylenedioxy-12α-etiojerv-5-en-17α-ol (6e, R′ = $-CH_2CH_2-$).—Concentrated sulfuric acid (0.5 ml) was added to a slurry of 1.35 g of the unsaturated ketone 5e in 15 ml of ethylene glycol (redistilled) and 1 ml of trimethyl orthoformate (redistilled). The mixture became homogeneous, turned darker in color, and afforded a new precipitate within 1 min. After 5 min, 1 ml of tetramethylguanidine was added followed by dilution of the reaction mixture with water. The crystalline product was collected, washed, dried, and recrystallized from acetone–hexane (darco) to yield 1.16 g of the ethylenedioxy ketal 6e: mp 163–166°; λ_{max} 2.75 μ; $\Delta\nu$ 61 and 67 (18-Me), 67 (19-Me), 237 (OCH_2CH_2O-), 325 (m, 6-H) Hz.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.02; H, 9.84.

Treatment of the ketal with acidified aqueous acetone afforded a good yield of the starting material (5e).

Treatment of the unsaturated ketone 5e using the normal ketal procedure (refluxing benzene, ethylene glycol, and toluenesulfonic acid) gave after a short time a dark mixture of intractable products. Use of adipic acid in boiling benzene containing ethylene glycol effected no reaction after 24 hr.

3,3-Ethylenedioxy-12α-etiojerv-5-en-17-one (6d, R′ = $-CH_2CH_2-$).—The ketal 6e (R′ = $-CH_2CH_2-$) (1.2 g) was oxidized according to procedure C for 7 hr at room temperature. The product was recrystallized from acetone hexane to afford 0.97 g of the product: mp 170–173°; λ_{max} 5.82 μ; $\Delta\nu$ 57 and 64 (18-Me), 57 (19-Me), 322 (m, 6-H) Hz.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.15; H, 9.06.

3,3-Ethylenedioxy-12α-etiojerv-5-en-17β-ol (6a, R′ = $-CH_2CH_2-$).—Lithium tri-*tert*-butoxyaluminohydride (15 g) was added to a solution of 6.9 g of 6d (R′ = $-CH_2CH_2-$) in 250 ml of tetrahydrofuran at 5°. After 20 hr at ambient temperature, the solution was diluted with 2% aqueous acetic acid. The product was extracted with methylene chloride and was recrystallized from ether–hexane, yielding 4.23 g of the ketal 6a (R = $-CH_2CH_2-$): mp 113–115°; λ_{max} 2.75 μ; $\Delta\nu$ 62 (19-Me), 59 and 66 (18-Me), 237 (OCH_2CH_2O), 326 (m, 6-H) Hz; $[\alpha]_D$ −56°.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 76.36; H, 9.15. Found: C, 76.05; H, 9.08.

Less than 10% of the 17α-ol was present in the mother liquors (tlc analysis).

17β-Hydroxy-12α-etiojerv-4-en-3-one (5a). A. Hydrolysis of the Ketal 6a (R′ = $-CH_2CH_2-$).—The ketal 6a (R′ = $-CH_2CH_2-$) (3.0 g) in 100 ml of acetone and 10 ml of water was boiled for 1 hr under an atmosphere of nitrogen. The solution was diluted

with water and the acetone distilled. The resulting precipitate was collected and washed with water. Recrystallization gave the pure unsaturated ketone **5a**: mp 159–160°; λ_{max} 239 mμ (ε 16,300); λ_{max} 2.72, 5.98 μ; Δν 58 and 66 (18-Me), 71 (19-Me), 347 (4-H) Hz; $[\alpha]_D$ +111°.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.03; H, 9.81.

B. Reduction of the Dienone (1a, $\Delta^{1,4}$; Procedure D).—A solution of 0.90 of the dienone **1a** ($\Delta^{1,4}$) in 20 ml of tetrahydrofuran was added to a solution of 0.30 g of lithium metal in 200 ml of distilled ammonia at −70° over a 40-sec period. After an additional 1 min, 2 g of ammonium chloride was added causing discharge of the color within 1 min. The ammonia was distilled and the mixture diluted with water. The product, isolated by ether extraction, crystallized and was recrystallized from ether–hexane to yield 0.55 g of the unsaturated ketone **5a**, mp 148–150°.

The mother liquors consisted of unreduced starting material (**1a**, $\Delta^{1,4}$) and the saturated ketone **1a**.

Several hydrogenations of the dienone (**1a**, $\Delta^{1,4}$) in the presence of tristriphenylphosphorhodium catalyst afforded at best 30% of the monounsaturated ketone **5a** after 28 hr. (The same batch of catalyst reduced Δ^1-testosterone efficiently.)

17β-Acetoxy-12α-etiojerv-4-en-3-one (5b) was an amorphous compound obtained either by acetylation of the corresponding alcohol **5a** with acetic anhydride–pyridine or by use of the lithium reduction (procedure D) on the dienone acetate (**1b**, $\Delta^{1,4}$). The acetate **5b** could be hydrolyzed in good yield with potassium hydroxide to yield the free alcohol **5a**.

Trimethyl Orthoformate Treatment of the Unsaturated Ketone 5e.—Concentrated sulfuric acid (0.2 ml) in 2 ml of methanol was added to a slurry of 1.0 g of the unsaturated ketone **5e** in 8 ml of methanol and 2 ml of trimethyl orthoformate with stirring. The reaction mixture quickly became homogeneous and dark. After 0.5 hr, 1 ml of pyridine was added and the mixture was extracted with methylene chloride. The oily product (mixture II) showed a maximum at 239 mμ (6280), 188 and 193 (OMe:ketal), and 215 Hz (OMe:enol ether) indicating the product was approximately 30% enol ether **9e** (R′ = Me) and 70% ketal **6e** (R′ = Me). In other runs, variations in proportions of solvents and reagents, length of reaction time, or change in the acid used led to no significant change in the relative proportion of products. Triethyl orthoformate gave comparable results. Acid hydrolysis of these mixtures yielded a maximum of 75% of the starting material **5e**.

Use of the Sarett reagent (procedure C) on mixture II at 5° for 5 hr gave a product lacking enol ether absorption but containing the ketal bands: Δν 187 and 193 Hz (OMe), 55 (19-Me), 58 and 66 (18-Me) Hz.

Manganese Dioxide Oxidation of 3-Ethylenedioxy-17,20-dihydroxypregnajerva-5,12-dien-11-one (7).—The diol **7**[21] (2 g) in 100 ml of chloroform was stirred with 4.0 g of activated manganese dioxide (Beacon Chemical Industries) for 3 hr. The mixture was filtered and the solvent distilled, yielding a yellow oil which was crystalled from acetone–cyclohexane to yield 1.35 g, mp 174–177°, and 0.24 g, mp 168–173°, of the 3-ethylenedioxyetiojerva-5,12-diene-11,17-dione, (**8d**, Δ^{12}) with ir and nmr spectra identical with those of an authentic sample.[21]

17β-Hydroxyetiojerv-4-en-3-one (5a, 12β-H; Procedure D).—A solution of 0.5 g of the ketal **8a**, 0.8 g of hydrazine dihydrochloride, and 3.5 ml of hydrazine hydrate in 20 ml of triethylene glycol was distilled slowly until the temperature of the vapors reached 165°. A reflux condenser was then installed above the reaction mixture (care). The temperature was held at 160–165° for 1.5 hr more, the mixture was cooled to 100°, and 1.5 g of potassium hydroxide was added. The reaction mixture was heated to 210° with slow distillation and held at 210–220° for a total of 2 hr. The mixture was cooled and then diluted with ice water. The product, isolated by ether extraction, was hydrolyzed by boiling for 16 hr in 30 ml of acetone, and 3 ml of water containing 35 mg of *p*-toluenesulfonic acid. Water was added, the acetone was distilled, and the product was extracted with ether. The crude extract was recrystallized twice from acetone–cyclohexane to yield the alcohol solvated with 0.25 mol equiv of acetone (**5a**, 12β-H): mp 176–178°; λ_{max} 2.75, 6.02 μ; Δν 57 and 62 (18-Me), 68 (19-Me), 344 (4-H) Hz.

Anal. Calcd for $C_{19}H_{28}O \cdot {}^1/_4C_3H_6O$: C, 78.30; H, 9.82. Found: C, 78.45; H, 9.46.

17α-Hydroxyetiojerv-4-en-3-one (5e, 12β-H).—The ketal **8e**[21] was treated according to procedure D and provided, after recrystallization from acetone–hexane, the unsaturated ketone (**5e**, 12β-H): mp 144–146°; λ_{max} 2.74 and 6.00 μ.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.77; H, 9.67.

12β-Etiojerv-4-ene-3,17-dione (5d, 12β-H).—The alcohol **5e** (12β-H) was oxidized with Sarett reagent (procedure C) for 1 hr. The product was isolated and recrystallized from acetone–hexane, affording 0.13 g of the dione **5d** (12β-H): mp 164–170°; λ_{max} 5.85, 6.00 μ; λ_{max} 239 mμ (ε 16,600); Δν 58 and 65 (18-Me), 69 (19-Me), 346 (4-H) Hz.

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.68; H, 8.96.

Registry No.—**2b** (X = Br), 27141-96-4; **2f** bromide, 27141-97-5; **2f** chloride, 27141-98-6; **2f** iodide, 27141-99-7; **3a**, 22785-16-6; **3f**, 27142-01-4; **4f**, 27142-02-5; **5a**, 22782-07-5; **5a** (3β-OH), 27142-04-7; **5a** (12β-H), 3818-35-7; **5d**, 22785-18-8; **5d** (12β-H), 24174-46-7; **5e**, 27142-08-1; **5e** (12β-H), 3818-36-8; **5f**, 22785-15-5; **6a** ketal, 27142-11-6; **6d** ketal, 27141-91-9; **6e** ketal, 27142-12-7; **8d** (Δ^{12}), 27142-13-8.

Acknowledgment.—The author gratefully acknowledges the competent assistance of Mrs. Barbara Tucker, Mr. R. Salzmann, and Mr. G. Plume in various phases of this work.

(21) This sample was obtained by following exactly the procedure in ref 15a.

The Rearrangement of 20-Substituted Bisnorallocholanes and Derivatives[1]

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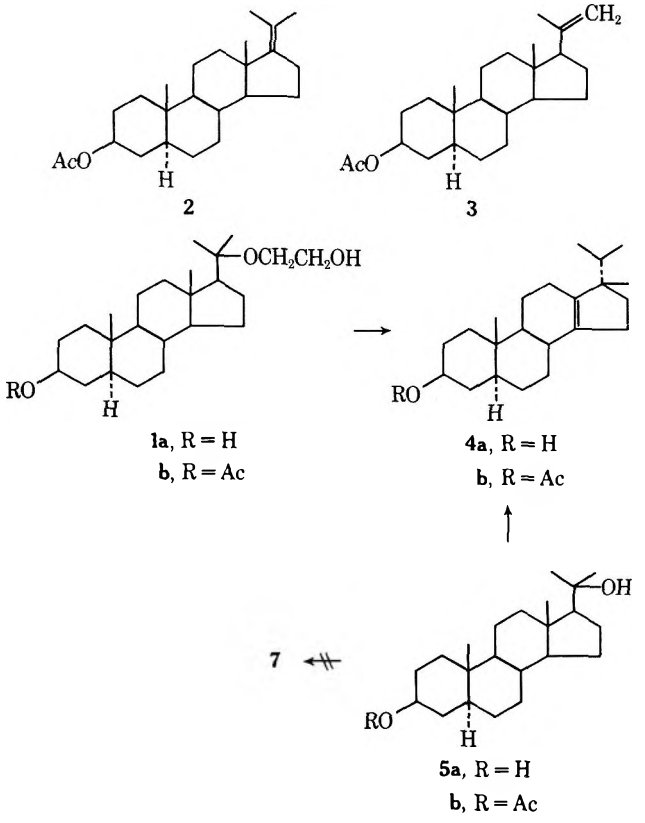
Dehydration of bisnorallocholane-3β-20-diol (**5a**) in refluxing acetic acid solution containing a catalytic amount of iodine or acid cleavage of 20-(2-hydroxyethoxy)bisnorallocholan-3β-ol (**1a**) gave a rearranged product which was shown to be 18-nor-17β-methyl-17α-isopropylandrost-13(14)-en-3β-ol (**4a**). On the other hand, dehydration of the *D*-homo alcohol **6** afforded two *D*-homo products, **8b** and **7**. Chemical degradation and mass spectral analysis confirmed the proposed structures.

The rearrangement of 17-deoxy 20-substituted steroids under acidic conditions is of interest both from a mechanistic viewpoint and as a pathway to structurally modified steroid hormones. Previous studies have indicated that the products formed upon dehydration depend largely on the reaction conditions and the substituents at the 3 position. For example, dehydration of bisnorallocholane-3β,20-diol (**5a**) in acetic acid, followed by acetylation of the reaction product, afforded three isomeric rearranged products. The major product was identified as the isopropylidene derivative **2**, one of the minor products as the isopropenyl derivative **3**, while the other minor product remained unidentified (Scheme I).[2] However, dehydration of **5b** in acetic acid gave mainly **3**.[3] On the other hand, Uskoković, *et al.*, carried out the dehydration of **5a** in refluxing acetic acid containing a catalytic amount of iodine and obtained a product, in nearly quantitative yield, which they formulated as the *D*-homo derivative **8a**.[4] In the same work the dehydration of the *D*-homo alcohol **6** with acetic acid containing a catalytic amount of *p*-toluenesulfonic acid was also reported to give **8b**[4] which upon hydrolysis afforded **8a**.

SCHEME I



In the course of studies on the synthesis of tertiary glycol ethers[5] from the corresponding ketals, we examined the dehydration products of 20-(2-hydroxyethoxy)bisnorallocholan-3β-ol (**1a**) and the corresponding 5,6-unsaturated derivative (**12**). Refluxing a solution of **1a** in acetic acid containing a catalytic amount of iodine gave after chromatography only one rearranged product (*ca.* 80% yield), with the empirical formula $C_{22}H_{36}O$, which was identical in all respects (melting point, specific rotation, infrared comparison, and R_f values) with the product obtained under the same conditions by the dehydration of **5a** and formulated as **8a** by Uskoković, *et al.*[4] (Scheme II).

We sought further evidence for the postulated structure **8a** by nmr examination of the rearranged product. Structure **8a** would require the presence of two vinyl methyl groups near δ 1.7. The nmr spectrum of the rearranged product showed the presence of four methyl groups between the region of δ 0.75 and 0.99, two of them being secondary and attributable to an isopropyl group, the remaining two being tertiary. There was no indication of the presence of vinyl methyl groups. The postulated *D*-homo system (**8a**) is consequently untenable, and we suggest the structure **4a**, an 18-nor-17α-isopropyl-17β-methyl-13-androstene system, which may be envisaged as formed by a hydride shift from C-17 to the initially formed C-20 carbonium ion, followed by a 1,2 shift of the C-18 methyl group to C-17, and loss of a proton at C-14. The nmr signals at δ 0.75 (J = 7.5 cps) and 0.85 (J = 6.5 cps) are attributable to the methyl protons on the isopropyl group at C-17. The remaining singlets at δ 0.81 and 0.99 are assigned to the C-19 and C-17 methyl protons, respectively. Structure **4a** was further substantiated by mass spectral analysis. The spectrum exhibited the proper molecular ion peak at m/e 316, loss of methyl (m/e 301), and an intense fragment at m/e 273 due to the loss of 43 mass units (C_3H_7) attributable to the removal of the isopropyl group at C-17.[6]

Since the *D*-homo alcohol **6** was also reported to give the *D*-homo product **8b**,[4] we reexamined this re-

(1) A preliminary account of this work has appeared: F. Kohen, R. A. Mallory, and I. Scheer, *Chem. Commun.*, 1019 (1967).

(2) A. Butenandt and H. Cobler, *Z. Physiol. Chim.*, **234**, 218 (1935).

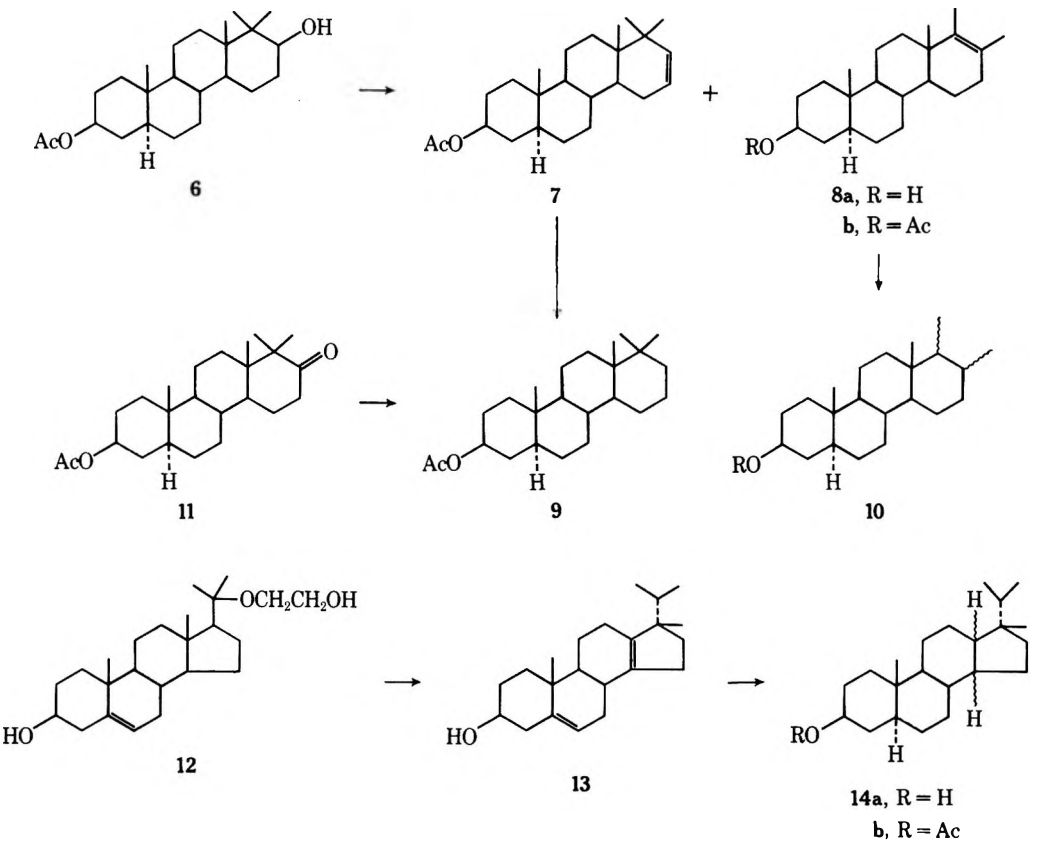
(3) B. Koechlin and T. Reichstein, *Helv. Chim. Acta*, **27**, 549 (1944).

(4) M. Uskoković, M. Gut, and R. I. Dorfman, *J. Amer. Chem. Soc.*, **82**, 3668 (1960).

(5) R. A. Mallory, S. Rovinski, F. Kohen, and I. Scheer, *J. Org. Chem.*, **32**, 1417 (1967).

(6) Similar rearrangements have been reported recently by B. Krieger and E. Kaspar [*Chem. Ber.*, **100**, 1169 (1967)], and by H. Laurent, H. Muller, and R. Wiechert [*ibid.*, **99**, 3836 (1966)].

SCHEME II



action. Reduction of the *D*-homo ketone **11** with LiAlH(*tert*-OBut)$_3$ gave the corresponding axial alcohol **6**, since attack from the less hindered α side is expected. Dehydration of **6** in acetic acid containing *p*-toluenesulfonic acid gave an oil which upon chromatography afforded a crystalline solid, mp 84–86°. However, the complexity of the methyl region in the nmr indicated that this product was a mixture. This was further substantiated by tlc examination on silica gel G impregnated with $AgNO_3$. Two spots of equal intensity were observed. Separation of this mixture was achieved by chromatography on silicic acid impregnated with $AgNO_3$. In this way, two isomeric olefinic products, **7** and **8b**, were obtained.

The more mobile component **8b**, mp 122–123°, $[\alpha]D$ +35.7°, analyzed for $C_{24}H_{38}O_2$ and displayed two vinyl methyl peaks at δ 1.55 in the nmr. The C-18 and C-19 methyl groups appeared at δ 0.87 and 0.82, respectively. The absence of vinyl protons in the nmr indicated that the double bond formed upon dehydration was tetrasubstituted. Structure **8b** was readily assigned to this product, and this was further confirmed by chemical transformation. Hydrogenation of **8b** gave the dihydro derivative **10** whose nmr spectrum showed the presence of two secondary methyl peaks at δ 0.92 and 0.90 in addition to the C-18 and C-19 methyl peaks. The formation of **8b** can be viewed as a 1,2 shift of one of the methyl groups at C-17a to the initially formed carbonium ion at C-17 followed by a loss of proton at C-17.

The more polar component **7**, mp 134–135°, $[\alpha]D$ −66°, also analyzed for $C_{24}H_{38}O_2$. The nmr spectrum showed two vinyl protons at δ 5.40, attributable to C-16 and C-17 protons. The C-17a methyl groups appeared at δ 0.94 and 0.82. The peaks at δ 0.87 and 0.82 were attributed to C-18 and C-19, respectively. The correctness of the assignment of structure **7** to this product was further confirmed by chemical reduction. Hydrogenation of **7** gave the dihydro derivative **9**, identical in all respects with the product obtained by Wolff–Kishner reduction, followed by acetylation, of the *D*-homo ketone **11**.

In the 20-(2-hydroxyethoxy)bisnorchol-5-en-3β-ol (**12**) series, we found that the action of acetic acid containing a catalytic amount of iodine resulted in the formation of 18-nor-17β-methyl-17α-isopropylandrosta-5,13(14)-dien-3β-ol (**13**), with appropriate nmr signals at δ 0.74 (doublet, J = 7 cps), 0.86 (doublet, J = 7 cps) (the isopropyl protons at C-17), and 1.00 (the C-19 and C-17 methyl protons).

Hydrogenation of **13** with platinum oxide in acetic acid resulted in an uptake of 2 mol of hydrogen with formation of the tetrahydro derivative **14a**, with unassigned configuration at C-13 and C-14. A mixture of geometrical isomers may be present in this compound. Mass spectral examination of **14a** revealed the presence of a molecular ion peak at *m/e* 318, a peak at *m/e* 303, due to the loss of a methyl group, and an intense fragment at *m/e* 275, due to the removal of the isopropyl group at C-17.

Experimental Section[7]

18-Nor-17β-methyl-17α-isopropylandrost-13(14)-en-3β-ol (4a). A.—A solution of 20-(2-hydroxyethoxy)bisnorallocholan-3β-ol

(7) Specific rotations were determined in $CHCl_3$ solution at a concentration of approximately 1%. All melting points were determined using a Fisher-Johns melting point apparatus. Nmr spectra were determined using a Varian A-60 spectrophotometer. Mass spectra were carried out by Morgan-Schaffer Corporation in Montreal, Canada. Petroleum ether refers to the fraction of bp 30–60°.

(1a, 0.8 g) in HAc (50 ml) was refluxed with a catalytic amount of I_2 (7 mg) for 30 min. After cooling the solution, the I_2 was reduced with saturated $NaHSO_3$ solution, and a large amount of H_2O was added. The mixture was extracted with $CHCl_3$, and the extract was washed with $NaHCO_3$, H_2O, dried ($MgSO_4$), and evaporated. The dark red residue (0.7 g) was chromatographed on Woelm neutral Al_2O_3 (activity II). Elution with benzene gave **4a**[8] (550 mg, 82% yield): mp 144.5–146° (from acetone); $[\alpha]D$ −64° (lit.[4] mp 144.5–145.5°); nmr ($CDCl_3$) δ 0.75 (d, 3, J = 7.5 cps, a methyl group at C-20), 0.85 (d, 3, J = 6.5 cps, a methyl group at C-20), 0.81 (s, 3, C-19 CH_3), and 0.99 (s, 3, C-17 CH_3); mass spectrum (70 eV) m/e (rel intensity) 316 (4) (M^+), 301 (6) (M − 15), 273 (98) (M − 43, loss of the ispropyl chain), and 255 (83) (M − 43 and loss of H_2O).

Anal. Calcd for $C_{22}H_{36}O$: C, 83.48; H, 11.47. Found: C, 83.36; H, 11.18.

Acetylation with pyridine and Ac_2O gave the **acetate 4b**, mp 70–71° (from CH_3OH), $[\alpha]D$ −57° (lit.[4] mp 62–64°, $[\alpha]D$ −58°).

Anal. Calcd for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.27; H, 10.59.

B.—A solution of bisnorallocholane-3β,20-diol[4] (**5a**, mp 182–183°) (3.0 g) in HAc (150 ml) was refluxed with a catalytic amount of I_2 (15 mg) for 30 min and worked up as in A above. The product thus obtained was recrystallized from acetone to give **4a**, 2.2 g, mp 143–145°. This material was identical in all respects (melting point, ir, nmr, and R_f) with that obtained in A above.[9]

17a,17a-Dimethyl-*D*-homoandrostane-3β,17β-diol 3-Acetate (6).—To a solution of the *D*-homo ketone 11[10] (1 g) in dry THF (50 ml) was added LiAlH(*tert*-OBut)$_3$ (3 g), and the reaction mixture was stirred overnight. Dilute HCl was then added, and the organic phase separated, dried, and evaporated. Recrystallization from CH_3OH gave **6** (0.8 g): mp 194–195°; $[\alpha]D$ 0.0° (lit.[4] mp 193–195°; $[\alpha]D$ −13.9°); nmr ($CDCl_3$) δ 0.83 (s, 3, C-19 CH_3), 0.88 (s, 3, C-18 CH_3), 0.97 (s, 3, C-17a CH_3), and 1.1 (s, 3, C-17a CH_3).

Dehydration of 17a,17a-Dimethyl-*D*-homoandrostane-3β,17β-diol 3-Acetate.—A solution of **6** (0.5 g) in HAc (25 ml) was refluxed with *p*-toluenesulfonic acid (25 mg) for 1 hr. The reaction mixture was poured into a large excess of H_2O, the mixture extracted with $CHCl_3$, and the extract washed with $NaHCO_3$ solution, H_2O, dried ($MgSO_4$), and evaporated. The residue (0.4 g) was first chromatographed on Woelm neutral Al_2O_3 (activity II). Elution with hexane–chloroform gave a solid (0.4 g), mp 84–85° (from methanol). However, the complexity of the methyl region in the nmr indicated that this product was a mixture. Furthermore, tlc examination of this product on silica gel G impregnated with $AgNO_3$ showed the presence of two spots of R_f 0.2 and 0.34, respectively, benzene being used as a developing solvent. This mixture was then rechromatographed on silicic acid (Mallinckrodt) impregnated with 5% $AgNO_3$.

Elution with hexane–benzene (9:1) (100 ml) gave **17,17a-dimethyl-*D*-homoandrost-17(17a)-en-3β-ol 3-acetate (8b)** (100 mg): mp 122–123° (from CH_3OH); $[\alpha]D$ +35.7°; nmr ($CDCl_3$) δ 0.82 (s, 3, C-19 CH_3), 0.87 (s, 3, C-18 CH_3), and 1.55 (s, 6, vinyl methyl groups at C-17 and C-17a).

Anal. Calcd for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.15; H, 10.48.

Further elution with the same solvent system (400 ml) gave a mixture of **7** and **8b** (200 mg). Elution with hexane–benzene (1:1) (100 ml) gave **17a,17a-dimethyl-*D*-homoandrost-16(17)-en-3β-ol 3-acetate (7)** (55 mg): mp (from CH_3OH) 134–135°; $[\alpha]D$ −66°; nmr ($CDCl_3$) δ 0.82 (s, 6, C-19 CH_3 and a methyl group at C-17a), 0.87 (s, 3, C-18 CH_3), and 0.94 (s, 3, C-17a CH_3).

Anal. Calcd for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.25; H, 10.59.

17ξ,17aξ-Dimethyl-*D*-homoandrostan-3β-ol 3-Acetate (10).—A solution of **8a** (80 mg) in HAc (50 ml) was hydrogenated using PtO_2 as catalyst. After hydrogen uptake had ceased, the catalyst was filtered, and the filtrate was poured into a large excess of H_2O, and the product was filtered and crystallized from CH_3OH to give **10** (60 mg): mp 110–111°; $[\alpha]D$ 0°; nmr ($CDCl_3$) δ 0.90 (d, 3, J = 6 cps, C-17a CH_3) and 0.92 (d, 3, J = 6 cps, C-17 CH_3).

Anal. Calcd for $C_{24}H_{40}O_2$: C, 79.94; H, 11.18. Found: C, 80.02; H, 11.22.

17a,17a-Dimethyl-*D*-homoandrostan-3β-ol 3-Acetate (9). A.—A solution of **7** (40 mg): in HAc (25 ml) was hydrogenated using PtO_2 as catalyst and worked up as above. Recrystallization from CH_3OH gave **9**: mp 180–181°; $[\alpha]D$ −21°; nmr ($CDCl_3$) δ 0.78 (s, 6, C-18 CH_3 and C-17a CH_3), 0.83 (s, 3, C-19 CH_3), and 0.94 (s, 3, C-17a CH_3).

Anal. Calcd for $C_{24}H_{40}O_2$: C, 79.94; H, 11.18. Found: C, 79.89; H, 11.09.

B.—A mixture of the *D*-homo ketone **11** (200 mg), 99% hydrazine hydrate (2 ml), and diethylene glycol (15 ml) was heated at 150° for 10 min, KOH (2 g) then added, and heating continued at 150° for 45 min. Solvent was then distilled off until a solution temperature of 210° was reached, and the mixture was refluxed for a further 6 hr, cooled, poured into H_2O, and extracted with $CHCl_3$. The washed and dried extract was evaporated, and the residue was acetylated with pyridine and acetic anhydride. After the usual work-up, the product was crystallized from CH_3OH to give **9** (100 mg) identical in all respects with that obtained in A above.

18-Nor-17β-methyl-17α-isopropylandrost-5,13(14)-dien-3β-ol (13).—A solution of 20-(2-hydroxyethoxy)bisnorchol-5-en-3β-ol[5] (**12**, mp 190–192°, 3.0 g) in HAc (150 ml) was refluxed with a catalytic amount of I_2 (15 mg) for 0.5 hr and worked up in the usual way. The red oily residue was chromatographed on Woelm neutral Al_2O_3 (activity II). Elution with benzene (600 ml) afforded **13** (2.1 g) which crystallized from CH_2Cl_2–petroleum ether as needles: mp 134–135°; $[\alpha]D$ −197°; nmr ($CDCl_3$) δ 0.74 (d, 3, J = 7 cps, one of the methyl groups at C-20), 0.86 (d, 3, J = 7 cps, a methyl group at C-20), and 1.00 (s, 6, C-19 and C-17 methyl protons).

Anal. Calcd for $C_{22}H_{34}O$: C, 84.01; H, 10.90. Found: C, 83.91; H, 10.73.

Hydrogenation of 18-Nor-17β-methyl-17α-isopropylandrost-5,13(14)-dien-3β-ol.—A solution of **13** (500 mg) in HAc (75 ml) was hydrogenated using PtO_2 (100 mg) as catalyst. When H_2 uptake ceased (80 ml, 2 hr), the catalyst was removed by filtration, and a large volume of H_2O was added to the filtrate. The resultant white precipitate (350 mg) was filtered off and recrystallized from acetone to afford the tetrahydro derivative **14a** as prisms: mp 115–117°; $[\alpha]D$ +8.8°; nmr ($CDCl_3$) δ 0.80, 0.84, and 0.95 (methyl groups); mass spectrum (70 eV) m/e (rel intensity) 318 (5) (M), 303 (7) (M − 15), 275 (97) (M − 43, loss of the isopropyl side chain), and 257 (90) (M − 43 and loss of H_2O).

Anal. Calcd for $C_{22}H_{38}O$: C, 82.95; H, 12.03. Found: C, 83.09; H, 12.00.

Acetylation with acetic anhydride and pyridine gave the derived acetate **14b** which crystallized from acetone–water as needles, mp 75–76°, $[\alpha]D$ −1°.

Anal. Calcd for $C_{24}H_{40}O_2$: C, 79.94; H, 11.18. Found: C, 79.98; H, 11.27.

Registry No.—**4a**, 27390-93-8; **6**, 27390-94-9; **7**, 27390-95-0; **8b**, 27390-96-1; **9**, 27390-97-2; **10**, 27390-98-3; **13**, 27390-99-4; **14a**, 27391-00-0; **14b**, 27391-01-1.

Acknowledgment.—The authors wish to acknowledge the experimental assistance of Mr. S. Rovinski. We are indebted to Mrs. E. Kaffitz for the determination of the nmr spectra. We would also like to thank Dr. G. Karmas for his valuable suggestions.

(8) The homogeneity of this compound was confirmed by tlc on silica gel G impregnated with $AgNO_3$, a method that is commonly used for the separation of double bond isomers. Only one spot was observed with different developing solvents.

(9) We wish to thank Dr. Marcel Gut of the Worcester Foundation for Experimental Biology for supplying us with a sample of material obtained from the dehydration of **5a**.

(10) M. Uskoković, M. Gut, and R. I. Dorfman, *J. Amer. Chem. Soc.*, **81**, 4561 (1959).

Chemistry of Coelenterates. XXI.[1a] Lactones from the Gorgonian *Pterogorgia guadalupensis*[1b,c]

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Two lactones isolated from the marine coelenterate *Pterogorgia guadalupensis*, a gorgonian, are described. One of these is a bisbutenolide, ancepsenolide (**3**); the other lactone is shown on the basis of spectroscopic data and conversion to ancepsenolide to be 2-(13-carboxy-14,15-diacetoxyhexadecanyl)-2-penten-4-olide (**1**).

The octocoral *Pterogorgia guadalupensis* Duchassaing & Michelin belongs to a group of sessile tropical reef invertebrates classified as gorgonians but more commonly known as sea fans and sea whips.[2] The fact that these stationary organisms can flourish in an environment inhabited by numerous potential predators has been attributed at least in part to the presence of endogenous organic compounds which endow these animals with a chemical means of defense.[3] Biological screening of the total extracts of various gorgonians has demonstrated[4] the presence of antimicrobial materials in these animals, and chemical investigations have resulted in the isolation and identification of various terpene hydrocarbons,[5a,b] diterpene lactones[5a-d] prostaglandins,[5e] and unusual dodecane-1,2-dilactones[5f,g] from this group of organisms. We wish herewith to report the isolation of two crystalline lactones from the gorgonian *Pterogorgia guadalupensis*. One of these exhibited mild antibiotic activity[6] against *Staphylococcus aureus* and *Mycobacterium smegmatis*, and evidence cited in this paper permits this lactone to be formulated as **1**; the other lactone, **3**, has been isolated previously[5f] from a related species of gorgonian, *Pt. anceps*.

Brief hexane extraction of a large, single, air-dried colony of *Pt. guadalupensis* afforded in 3.1% yield a white solid, mp 90.5–92.0°, which was identified as ancepsenolide (**3**) by comparison of its physical and spectral properties to those of material isolated previously (see Experimental Section)[5f]. Prolonged hexane extraction afforded in 1% yield a second compound, **1**, mp 81.1–82.9°, for which elemental and mass spectral analysis confirmed the formula $C_{26}H_{42}O_8$ (*m/e* 482).

The infrared spectrum of **1** exhibited strong, broad absorption centered at 1740 cm^{-1} (1700–1770 cm^{-1} at half peak intensity), consistent with the presence of butenolide, acetate, and carboxyl functionalities. The presence of a butenolide ring in **1** was confirmed by the uv absorption (λ_{max} 204 nm, ϵ 17,436) and one-proton multiplets in the nmr spectrum at δ 5.0 (well resolved at 220 MHz) and 7.02 ppm identical with those present in ancepsenolide (**3**).[5f] Strong, sharp absorption at δ 1.27 ppm confirmed the presence of a long methylene chain, and two partially resolved singlets at 2.08 ppm suggested the presence of two acetate residues in **1**. A neutralization equivalent verified that **1** contained a free carboxyl group, and acetyl analysis confirmed the presence of two acetate moieties.

The position of the acetate moieties in **1** was suggested by the structure of the compounds **3** and **4a** which had been isolated previously from *Pt. anceps*.[5f,g] This tentative assignment was corroborated by the presence of two distinct doublets at δ 1.17 (J = 6 Hz) and 1.35 ppm (J = 7 Hz) in the 220-MHz nmr spectrum[7] of **1** (chloroform–acetone-d_6) ascribable to the pentenolide methyl group and another methyl group in a very similar structural environment, *i.e.*, $CH_3CH(OAc)$. Confirmation of the structure **1** (without stereochemistry) was achieved by conversion of **1** *via* acid-catalyzed methanolysis to the lactone **2a** which underwent dehydration upon treatment with phosphorus oxychloride in pyridine to give ancepsenolide (**3**) in good yield (see Scheme 1). These conversions establish the overall carbon skeleton of **1** and confirm the assignment of one of the acetate moieties to the penultimate (C-15′) in the hexadecanyl residue in **1** (lactone formation).

Although the nmr signals of the protons attached to carbons bearing oxygen atoms in both **1** and **2a** overlap to give complex multiplets which do not lend themselves to facile interpretation, the corresponding absorptions in the acetate **2b**, derived from the lactone **2a** by routine acetylation, are well resolved (see Table I) and provide confirmation of the presence of three single protons on carbons bearing oxygen in **2b** and

TABLE I

LACTONE PMR ABSORPTIONS AND COUPLING CONSTANTS[a]

	Compd 2b			Compd 4b[b]		
Proton	δ	J $H_{14',15'}$	J	δ	J $H_{14',15'}$	J
$H_{14'}$	5.62	3	5 ($H_{14',13'}$)	5.15	0.5–1	6 ($H_{14',13'}$)
$H_{15'}$	4.59	3	6.5 ($H_{15'\text{-Me}}$)	4.50	0.5–1	6 ($H_{15'\text{-Me}}$)
H_4	5.0			5.0		

[a] Measured in $CDCl_3$ at 60 MHz. [b] See ref 5 g.

(1) (a) Papers XIX–XX in this series are, respectively, M. B. Houssain and D. van der Helm, *Recl. Trav. Chim. Pays-Bas*, **88**, 1413 (1969); R. L. Hale, J. Leclerq, B. Tursch, C. Djerassi, R. A. Gross, Jr., A. J. Weinheimer, K. Gupta, and P. J. Scheuer, *J. Amer. Chem. Soc.*, **92**, 2179 (1970). (b) Presented in part at the Food-Drugs from the Sea Symposium, Marine Technology Society, Kingston, R. I., 1969, and at the 15th Oklahoma Tetrasectional Meeting of the American Chemical Society, March 15–16, 1969. (c) This investigation was supported by NIH Training Grant 5675 from the National Heart Institute. (d) Sabbatical leave, Woods Hole Oceanographic Institution, 1969–1970; NIH Special Fellowship GM 13941.

(2) F. M. Bayer, "The Shallow-Water Octocorallia of the West Indian Region," Martinus Mijhoff, The Hague, Netherlands, 1961, pp 272–277.

(3) See, for example, R. F. Nigrelli, *Trans. N. Y. Acad. Sci.*, **24**, 496 (1962), and ref 4.

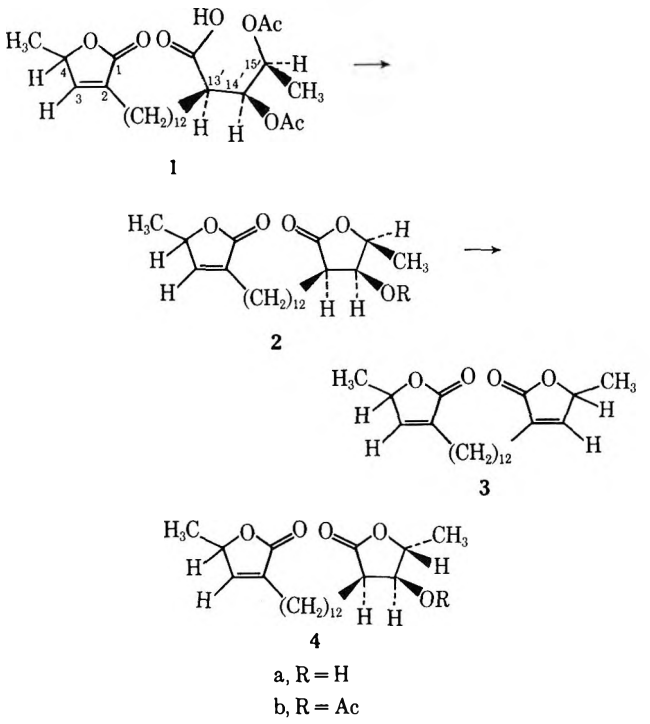
(4) L. S. Ciereszko, *ibid.*, **24**, 502 (1962).

(5) (a) A. J. Weinheimer, F. J. Schmitz, and L. S. Ciereszko, Transactions of the Drugs from the Sea Symposium, Aug 1967, Marine Technology Society, pp 135–141; (b) L. S. Ciereszko, D. H. Sifford, and A. J. Weinheimer, *Ann. N. Y. Acad. Sci.*, **90**, 917 (1960); (c) A. J. Weinheimer, R. E. Middlebrook, J. O. Bledsoe, W. E. Marsico, and T. K. B. Karns, *Chem. Commun.*, 384 (1968); (d) M. B. Hossain and D. van der Helm, *Recl. Trav. Chim. Pays-Bas*, **88**, 1413 (1969); (e) A. J. Weinheimer and R. L. Spraggins, *Tetrahedron. Lett.*, 5185 (1969); (f) F. J. Schmitz, K. W. Kraus, L. S. Ciereszko, D. H. Sifford, and A. J. Weinheimer, *ibid.*, 97 (1966); (g) F. J. Schmitz, E. D. Lorance, and L. S. Ciereszko, *J. Org. Chem.*, **34**, 1989 (1969).

(6) We thank Dr. P. Burkholder for the antimicrobial testing.

(7) Kindly provided by Dr. N. Bhacca, Louisiana State University.

SCHEME I



hence in **2a** and **1**. Thus both acetate groups in **1** must be secondary. Since an endocyclic double bond is formed upon dehydration of **2a**, the hydroxyl group in the latter and its acetate progenitor in **1** must be located at C-14′ in the hexadecanyl moiety.

The transesterification of **1** leading to the formation of **2a** is not expected to effect the carbon–oxygen bonds at C-14′ or C-15′, and hence we propose the relative stereochemistry shown for **1** and **2a** from a comparison of the coupling constant data of the acetate **2b** with that observed for the acetate **4b** (see Table I). The resonance signals for protons at C-4, -14′, and -15′ are sufficiently separated in the acetates **2b** and **4b** to permit a first-order analysis of the coupling constants. Since $J_{H_{15'}\text{-}Me}$ in **2b** can be determined from the spacing of the methyl doublet (J = 6.5 Hz), the second coupling of H-15′ (J = 3 Hz) must be due to $J_{H_{15',14'}}$. Hence it follows that the 5-Hz splitting in H-14′ must be due to $J_{H_{14',13'}}$. The large value of $J_{H_{14',13'}}$ is consistent with a small dihedral angle[8] and hence the cis stereochemistry for H-14′,13′ in **2b** just as in **4b**. The much larger value of $J_{H_{15',14'}}$ in **2b** in comparison to **4b** argues for a cis H-15′,14′ arrangement in **2b** as opposed to the trans H-15′,14′ assignment in **4b**.[5g]

Experimental Section

Melting points were determined in capillary tubes with a Thomas-Hoover melting apparatus and are corrected. Ultraviolet spectra were measured in 95% ethanol on Beckman DK-1 and Hitachi Perkin-Elmer Model 124 spectrophotometers under nitrogen sweep. Nmr spectra were determined using tetramethylsilane as an internal standard with Varian A-60 and HR-220 spectrometers. Elemental analyses were performed by Alfred Bernhardt, Mülheim, Germany. Infrared spectra were obtained on a Beckman IR-8 spectrophotometer. Mass spectra were obtained on Hitachi RMU-6A (Purdue University) and RMU-6E (University of Arkansas) spectrometers at 75 and 80 eV.

Isolation of Ancepsenolide (3) and 2-(13-Carboxy-14,15-diacetoxyhexadecanyl)-2-penten-4-olide (1).—A single colony of dried, coarsely ground *Pt. guadalupensis*, 115 g, collected near Port Royal, Jamaica, June 1967, was extracted in a continuous percolator–extractor[9] sequentially as follows (solvent, duration of extraction periods): (1) hexane, 18 hr, 48 additional hr, 96 additional hr; (2) benzene, 28 hr, 72 hr; (3) methanol, 48 hr, 72 hr. Ancepsenolide precipitated from the first hexane extract in nearly pure form (3.2 g, 3.5% crude). After chromatography over alumina (activity III) and recrystallization from a mixture of chloroform and hexane, ancepsenolide was obtained as a white solid: mp 90.5–92°; $[\alpha]_D$ +47.8°;[10] uv max (95% EtOH) 207 nm (ϵ 29,850) [lit.[5f] mp 91.5–92.0°; uv max (95% EtOH) 208 nm (ϵ 28,000)]. The nmr and ir spectra of this material were identical with those of authentic ancepsenolide.[5f]

The lactone **1** precipitated from the third hexane extract, 1.14 g, and after chromatography on silicic acid (eluent, benzene followed by benzene–ethyl acetate mixtures in which the ethyl acetate concentration was gradually increased to 10%) and recrystallization from aqueous isopropyl alcohol, it was obtained as a white solid: mp 81.1–82.9°; $[\alpha]_D$ −8.3° (0.47, $CHCl_3$); uv max (95% EtOH) 204 nm (ϵ 17,436); ir ($CHCl_3$) 3500 (w, broad), 1740 (s, broad, width at half intensity, 1700–1770), 1215 cm^{-1} (s, broad); nmr ($CHCl_3$) δ 7.02 (q, 1, J = 1.5 Hz, H-3), 4.78–5.42 (complex multiplet, 4, CO_2H, H-4, 15′,14′), 2.08 (two partially resolved singlets, acetates), 1.40 (d, J = 7 Hz, C-4 methyl), 1.28 ppm (methylene protons and C-15′ methyl partially visible as a shoulder at 1.2). Essentially the same spectrum was obtained in deuteriodimethyl sulfoxide and addition of D_2O to the sample in this solvent resulted in the loss of absorption amounting to one proton in the region of 5.4–6.1 ppm.[11]

At 220 MHz ($CDCl_3$/deuterioacetone) the following peaks were observed: 7.02 (q, J = 1.5 Hz, H-3), 5.15 (m, 2, H-14′,15′), 5.0 (dq, 1, J = 6.5, 1.5 Hz, H-4), 2.21 (t, J = 7.5 Hz, allylic methylene), 2.00, 2.02 (singlets, acetates), 1.35 (d, J = 6.5 Hz, C-4 methyl), 1.28 (s, methylene protons), 1.17 (d, J = 6 Hz, C-15′ methyl).

Anal. Calcd for $C_{26}H_{42}O_8$: C, 64.73; H, 8.71; neut equiv, 482. Found: C, 64.85; H, 8.82; neut equiv, 478. Acetyl analysis. Calcd for two acetates: 17.84. Found: 16.91.

Conversion of 1 to 2a.—A solution of 0.198 g of **1** (0.411 mmol) in 30 ml of methanol containing a few drops of concentrated hydrochloric acid was heated under reflux for 8 hr and then allowed to stand at room temperature for 5 days. Most of the methanol was removed at reduced pressure (aspirator) and the residue was dissolved in ether. The ether solution was washed with bicarbonate solution, then water, and finally dried over anhydrous sodium sulfate. Evaporation of the ether afforded **2a** in quantitative yield: mp (after recrystallization from aqueous isopropyl alcohol) 115.4–115.9°; *m/e* 380; ir ($CHCl_3$) 3320–3540 (broad peak, OH), 1752 cm^{-1} (strong, broad, lactone C=O); uv (95% EtOH) λ_{max} 209 nm (ϵ 16,694); nmr ($CDCl_3$) δ 7.03 (q, H-3), 5.0 (m, H-4); 4.25–4.85 (superimposed m's, H-14′,15′), 1.42 (pr of d, C-4,15′ methyls), 1.27 (s, polymethylene).

Acetylation of 2a.—Treatment of 78 mg (0.206 mmol) of **2a**, mp 113.6–115.1°, with pyridine–acetic anhydride (10 ml/1 ml) at room temperature for 24 hr followed by the usual work-up produced **2b** in quantitative yield: mp 55.4–56.5° after recrystallization from aqueous isopropyl alcohol; ir ($CHCl_3$) 1745 (acetate and pentenolide carbonyls), 1772 cm^{-1} (satd lactone); uv (95% EtOH) λ_{max} 209 nm (ϵ 18,840); nmr ($CDCl_3$) 7.02 (q, 1, H-3), 5.62 (dd, 1, J = 3, 5 Hz, H-14′), 5.0 (poorly resolved dq, 1, H-4), 4.59 (dq, 1, J = 3, 6.5 Hz, H-15′), 2.13 (s, acetate), 1.40 [pr of d, partially obscured by methylene peak; in benzene a pr of d at 1.03, J = 6.5 Hz (each), lactone methyls], 1.28 ppm

(8) See, for example, R. H. Bible, "Interpretation of NMR Spectra," Plenum Publishing Co., New York, N. Y., 1965, p 35 ff.

(9) L. S. Ciereszko, *J. Chem. Educ.*, **43**, 252 (1966).

(10) See, however, footnote 7, ref 5 g.

(11) This rather high field position for carboxyl proton absorption may be accounted for in part by the dilute solutions used for determining the spectrum of **1** owing to its limited solubility in $CDCl_3$: see F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York and London, 1969, pp 82–85. Factors similar to those responsible for the upfield shift of the carboxyl protons in oospolide and related structures may also be operative in the case of **1**; see K. Nitta and Y. Yamamoto, *Tetrahedron Lett.*, 4231 (1968).

(s, polymethylene). This material is isomeric with the hydroxyancepsenolide acetate reported earlier.[5g]

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.25; H, 9.24. Found: C, 68.39; H, 9.16.

Dehydration of 2a.—Phosphorous oxychloride–pyridine dehydration of 129 mg of **2a** in the manner described for hydroxyancepsenolide[5g] afforded 96 mg (78%) of ancepsenolide: mp 91.5–94.0° after recrystallization from chloroform–hexane, $[\alpha]^{27}_{589}$ +43.3° (2.98, $CHCl_3$); infrared and nmr spectra for this product were identical with those reported for ancepsenolide;[5f,g] mmp [with an authentic sample of ancepsenolide (mp 89.5–91.5°)] 89.5–92.0°.

Registry No.—**1**, 27261-77-4; **2a**, 27261-78-5; **2b**, 27261-79-6; **3**, 27261-80-9.

Acknowledgments.—We are pleased to acknowledge the use of the collecting facilities of the Port Royal Marine Laboratory of the University of the West Indies, Port Royal, Jamaica. We wish to thank Dr. W. Meyer and Mrs. P. Schroeder, University of Arkansas, and the NIH mass spectral center at Purdue University for providing us with mass spectra.

Notes

The Synthesis of (−)-$\Delta^{9(11)}$-*trans*-Tetrahydrocannabinol

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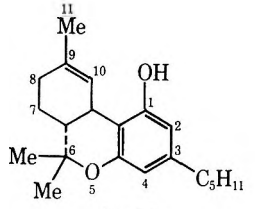
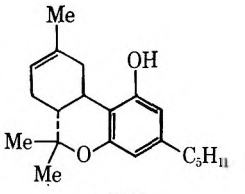
Received August 14, 1970

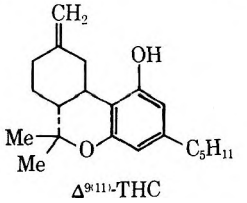
The growing interest in the chemistry and pharmacology of cannabinoids,[1] which include the active constituents of marijuana and hashish, has created a need for new methods of synthetically altering the basic dibenzopyran skeleton. We wish to describe the preparation and properties of $\Delta^{9(11)}$-*trans*-tetrahydrocannabinol ($\Delta^{9(11)}$-THC), which provides a key intermediate for the introduction of new functionalities at either C-9 or C-11.



Δ^9-THC



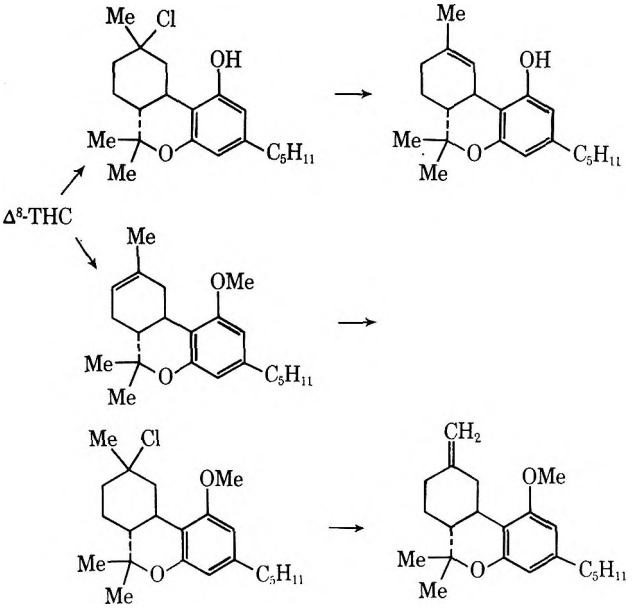
Δ^8-THC



$\Delta^{9(11)}$-THC

Although a total synthesis of racemic $\Delta^{9(11)}$-THC has been reported,[2] for biochemical studies it is desirable to have a ready source of the optically active isomer of the natural configuration. We therefore sought a method for the conversion of the readily available Δ^8 or Δ^9 isomers to $\Delta^{9(11)}$-THC. This contrathermodynamic conversion was accomplished by E2 elimination of the hydrogen chloride adduct of Δ^8- (or Δ^9-) THC (Scheme I), using the sterically hindered base potassium tricyclopentylcarbinolate, following the procedure recently described by Acharya and Brown.[3] It was first necessary, however, to protect the phenolic hydroxyl group, thus blocking any intramolecularly assisted elimination involving the phenolate anion (Scheme I. This intramolecular process has previously been ingeniously exploited in the conversion of Δ^8- to Δ^9-THC[2,4]).

SCHEME I



The methyl ether was selected as a protecting group because of its stability to both the acidic and basic conditions employed in the reaction sequence and was readily obtained[5] in greater than 90% yield. Conversion of the methyl ether to the hydrogen chloride

(1) For a review, see R. Mechoulam and Y. Gaoni, *Fortschr. Chem. Org. Naturst.*, **25**, 175 (1967).

(2) K. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *J. Amer. Chem. Soc.*, **89**, 5934 (1967).

(3) S. P. Acharya and H. C. Brown, *Chem. Commun.*, 305 (1968).

(4) T. Petrzilka and C. Sikemeier, *Helv. Chim. Acta*, **50**, 1416 (1967).

(5) G. Brieger, D. Hachey, and T. Nestrick, *J. Chem. Eng. Data*, **13**, 581 (1968).

adduct with zinc chloride and hydrogen chloride in chloroform at 0°, followed by refluxing a toluene solution of this product with an excess of potassium tricyclopentylcarbinolate for 12 hr afforded a 65:35 mixture of the methyl ethers of $\Delta^{9(11)}$- and Δ^{8}-THC, plus a trace of the Δ^{9} isomer. Elution from silver nitrate–silica gel with a benzene–hexane mixture provided quantitative separation, the more strongly adsorbed $\Delta^{9(11)}$ isomer being isolated in approximately 45% overall yield.

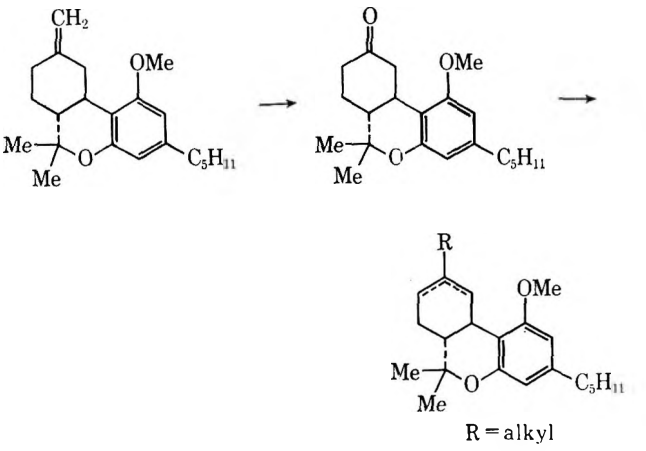
A number of reagents have been described which conceivably might be used for the final conversion of the methyl ether to the free phenol. Excluding acidic reagents (*e.g.*, boron tribromide) which would obviously cause double bond migration, lithium iodide,[6] pyridine hydrochloride,[7] methylmagnesium iodide,[8] and potassium hydroxide (in diethylene glycol) were examined. Surprisingly, with all of these reagents isomerization of the $\Delta^{9(11)}$ double bond to the Δ^{8} and Δ^{9} positions was competitive with demethylation. However, demethylation with only *ca.* 10% isomerization was successfully accomplished using potassium thiophenoxide in diethylene glycol. Thiophenoxide has commonly been used to affect dequaternization of amines,[9] but there is only one brief, unelaborated report[10] of its use with a phenol. Its successful use may be attributed to its high nucleophilicity and to the absence of any radical processes which are probably responsible for isomerization observed with reagents based on iodide nucleophilicity. Yields have varied between 75 and 100% in different experiments. Longer reaction times caused substantial isomerization of $\Delta^{9(11)}$-THC to the more stable Δ^{8} isomer.

Partial isomerization also occurred on bulb-to-bulb distillation at 200° and *p*-toluenesulfonic acid effected quantitative conversion to Δ^{8}-THC.

$\Delta^{9(11)}$-THC exhibits relatively weak psychotomimetic properties, showing approximately $^{1}/_{20}$th of the activity of Δ^{8}- and Δ^{9}-THC when administered intravenously to mice.[11] It has been recently demonstrated[12] that the major metabolic degradation of Δ^{8}- and Δ^{9}-THC involves hydroxylation of the vinylic 11-methyl group to produce physiologically active metabolites; this metabolic pathway is not available to the $\Delta^{9(11)}$ isomer.

$\Delta^{9(11)}$-THC promises to be a useful synthetic intermediate in cannabinoid chemistry. For example, oxidation with potassium permanganate–periodate quantitatively affords the 9-ketone,[2] which may then be used to obtain tritium or ^{14}C-labeled Δ^{9}-THC[13] or, alternatively, higher homologs of the cannabinoids (Scheme II, R = alkyl, CT_3, or $^{14}CH_3$).

SCHEME II



R = alkyl

Experimental Section

Δ^{8}-THC 1-Methyl Ether.—A procedure described by Brieger, Hackey, and Nestrick[5] was employed. Anhydrous potassium carbonate (4.95 g) and methyl iodide (14.0 ml, 0.225 mol) were added to a solution of Δ^{8}-THC (4.84 g, 15.4 mmol) in dimethylformamide (24 ml), and the mixture was stirred and refluxed for 20 hr. At this time glc of an aliquot showed that the reaction was virtually complete. The mixture was poured into water (100 ml) and extracted with hexane (three 100-ml portions). The combined organic extracts were washed with Claisen's alkali[14] to remove unchanged Δ^{8}-THC and then with water and dried over magnesium sulfate. Removal of the solvent gave 5.04 g of the methyl ether as a brown oil, shown by glc to be 98% pure.

An analytial sample was prepared by silica gel thick layer chromatography. The nmr spectrum showed a singlet at τ 6.26 (3 H, OCH_3) in addition to the typical absorption observed for Δ^{8}-THC.[1]

Anal. Calcd *m/e* for $C_{22}H_{32}O_2$: 328.240. Found: 328.239.

$\Delta^{9(11)}$-THC 1-Methyl Ether.—To the methyl ether of Δ^{8}-THC (2.05 g) in chloroform (60 ml) was added fused zinc chloride (1.1 g), and anhydrous hydrogen chloride was then passed through the stirred mixture for 2 hr at 0°. The mixture was was then kept at room temperature overnight, before diluting with chloroform (40 ml) and washing with water (two 50-ml portions), aqueous sodium bicarbonate (25 ml), and water (10 ml). After drying over magnesium sulfate, the solvent was evaporated *in vacuo* to leave 2.25 g of the hydrogen chloride adduct as a light brown oil. The formation of this adduct was confirmed by mass spectroscopy (Calcd *m/e* for $C_{22}H_{33}ClO_2$: 364.217. Found: 364.218.) and nmr spectroscopy, which showed the absence of olefinic protons.

The hydrochloride adduct (3.94 g, 10.8 mmol) was dissolved in 65 ml (32.5 mmol) of 0.5 *M* potassium tricyclopentylcarbinolate in toluene, and the solution was refluxed under nitrogen for 23 hr. The mixture was washed with water (three 50 ml portions) and dried over magnesium sulfate. Concentration *in vacuo*, followed by elution of the crude product from 22% silver nitrate–silica gel with a solvent gradient of 10% benzene in hexane to 25% benzene in hexane, gave 1.67 g of $\Delta^{9(11)}$-THC 1-methyl ether of 97% purity, as well as 0.24 g of 73% purity: nmr τ ($CDCl_3$) 5.26 (2 H, s, $W_{1/2}$ = 8 Hz, C=CH_2), 9.22 (t, *J* = 7 Hz, CH_3-$(CH_2)_4$), 8.97, 8.61 (6 H, s, $C(CH_3)_2$), 7.50 (t, *J* = 7.5 Hz, Ar CH_2), 6.36 (1 H, d, *J* = 12 Hz, Ar CH), 6.21 (3 H, s, OCH_3), 3.77, 3.71 (2 H, s, Ar H); ir $\nu_{max}^{CCl_4}$ 890 cm^{-1}.

Anal. Calcd *m/e* for $C_{22}H_{32}O_2$: 328.240. Found: 328.240.

$\Delta^{9(11)}$-THC.—A (50:50) mixture of $\Delta^{9(11)}$-THC and Δ^{8}-THC 1-methyl ethers (3.10 g, 9.45 mmol), potassium thiophenoxide 15.8 g, 107 mmol), thiophenol (2.0 ml, 19.5 mmol), and diethylene glycol (160 ml) was refluxed under nitrogen for 30 min. The mixture was then diluted with water (200 ml) and extracted with hexane (two 200-ml portions). The combined organic extracts were washed with 3 *M* aqueous potassium hydroxide to

(6) I. T. Harrison, *Chem. Commun.*, 616 (1969).

(7) V. Prey, *Chem. Ber.*, **75**, 445 (1942).

(8) A. L. Wilds and W. B. McCormack, *J. Amer. Chem. Soc.*, **70**, 4127 (1948).

(9) M. Shamma, N. C. Deno, and J. F. Remar, *Tetrahedron Lett.*, 1375 (1966); J. McKenna, B. G. Hutley, and J. White, *J. Chem. Soc.*, 1729 (1965).

(10) G. K. Hughes and E. O. P. Thompson, *Nature*, **164**, 365 (1949).

(11) The evaluation of the activity of cannabinoids is based on the comprehensive procedure of S. Irwin, *Psychopharmacologia*, **13**, 222 (1968).

(12) M. E. Wall, D. R. Brine, G. A. Brine, C. G. Pitt, R. I. Freudenthal, and H. D. Christensen, *J. Amer. Chem. Soc.*, **92**, 3466 (1970); S. H. Burstein, F. Menezes, E. Williamson, and R. Mechoulam, *Nature*, **225**, 87 (1970); Z. Ben-Zvi, R. Mechoulam, and S. Burstein, *J. Amer. Chem. Soc.*, **92**, 3468 (1970); R. L. Foltz, A. F. Fentiman, E. G. Leighty, J. L. Walter, H. R. Drewes, W. E. Schwartz, T. F. Page, and E. B. Truitt, *Science*, **168**, 845 (1970); I. M. Nilsson, S. Agurell, J. L. G. Nilsson, A. Ohlsson, F. Sandberg, and M. Wahlqvist, *ibid.*, **168**, 1228 (1970).

(13) For a recent example of radiolabeling using the racemic ketone obtained by total synthesis, see J. L. G. Nilsson, I. M. Nilsson, and S. Agurell, *Acta Chem. Scand.*, **23**, 2209 (1969).

(14) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 153.

remove thiophenol and then extracted with Claisen's alkali (three 100-ml portions). The latter extracts were diluted with water, neutralized with carbon dioxide, and then extracted with hexane. The combined hexane extracts were dried and concentrated to give 2.68 g (91%) of a 43:57 mixture of $\Delta^{9(11)}$-THC and Δ^{8}-THC.

An analytically pure sample was obtained by elution from silver nitrate–silica gel: nmr τ ($CDCl_3$) 9.12 (t, J = 7 Hz, $CH_3(CH_2)_4$), 8.95, 8.82 (s, $C(CH_3)_2$), 7.56 (t, J = 7 Hz, Ar CH_2), 6.26 (d, J = 12 Hz, Ar CH), 5.22 (s, 2 H, $C{=}CH_2$), 3.92, 3.83 (s, 2 H, Ar H); ir $\nu_{max}^{CCl_4}$ 3600 (OH), 890 cm^{-1} ($C{=}CH_2$); $[\alpha]^{25}D$ −38.5° (c 1.03, 95% EtOH).

Anal. Calcd *m/e* for $C_{21}H_{30}O_2$: 314.225. Found: 314.225.

11-Nor-9-ketohexahydrocannabinol 1-Methyl Ether.—$\Delta^{9(11)}$-THC 1-methyl ether (1.48 g, 4.51 mmol) in *tert*-butyl alcohol (742 ml) was treated with potassium carbonate (1.88 g) in water (100 ml), potassium permanganate (0.233, g, 1.48 mmol) in water (100 ml), and sodium metaperiodate (7.74 g, 35.4 mmol) in water (150 ml). After stirring at room temperature for 75 min, the mixture was extracted with benzene (three 500-ml portions) and the combined organic extracts were washed with saturated aqueous sodium bicarbonate (250 ml) and water (250 ml). After drying and concentrating, there remained 1.36 g of the desired product as a pale yellow oil of 99% purity. This product crystallized with difficulty from hexane: mp 87–88.2° (capillary); ir $\nu_{max}^{CCl_4}$ 1715 cm^{-1}; nmr τ ($CDCl_3$) 9.12 (t, J = 7 Hz, $CH_3(CH_2)_4$), 8.92, 8.78 (s, $C(CH_3)_2$), 7.48 (t, J = 7 Hz, Ar CH_2), 6.24 (s, 3 H, OCH_3), 3.78, 3.69 (s, 2 H, Ar H).

Anal. Calcd *m/e* for $C_{21}H_{30}O_3$: 330.219. Found: 330.220.

Registry No.—*trans*-$\Delta^{9(11)}$-THC, 27179-28-8; *trans*-$\Delta^{9(11)}$-THC 1-methyl ether, 27179-29-9; 11-nor-9-ketohexahydrocannabinol 1-methyl ether, 27179-30-2.

Acknowledgments.—This work was carried out under Contract No. PH-43-68-1452 of the National Institute of Mental Health, National Institutes of Health. We are grateful to Dr. H. D. Christensen for determining the pharmacological properties of $\Delta^{9(11)}$-THC.

Synthesis of 7-Dimethylamino-6-demethyl-6-deoxytetracycline (Minocycline) *via* 9-Nitro-6-demethyl-6-deoxytetracycline

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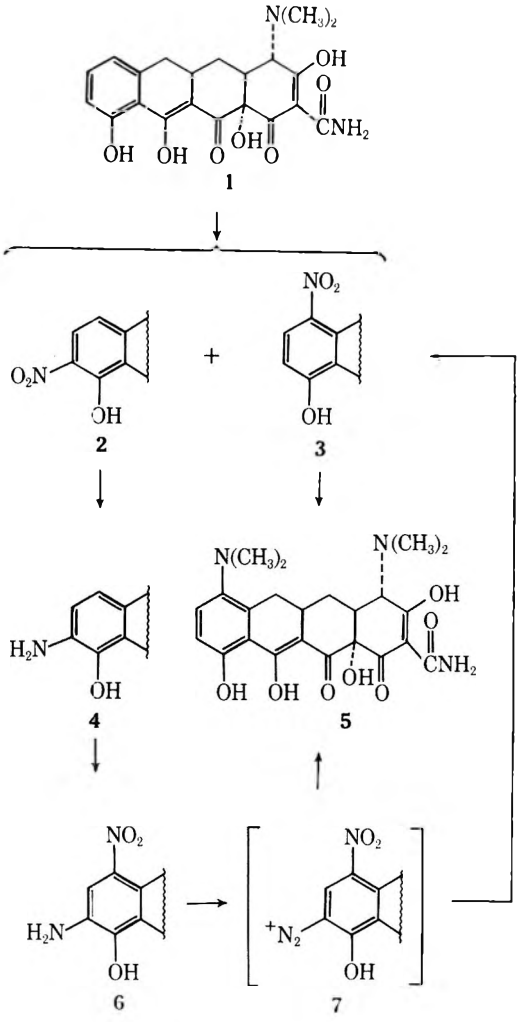
Recently it has been established that minocycline (7-dimethylamino-6-demethyl-6-deoxytetracycline, **5**) is a unique tetracycline derivative in that it is effective against tetracycline-resistant *staphylococci* in mice.[1,2] This important compound was originally prepared[1] by reductive methylation of 7-nitro-6-demethyl-6-deoxytetracycline (**3**) obtained by nitration of the accessible[3] 6-demethyl-6-deoxytetracycline (**1**). Unfortunately, the nitration of **1** affords a preponderance of the undesired 9-nitro isomer **2**, from which the 7-nitro isomer **3** must be separated.[4] Obviously, the efficiency of this process would be enhanced by the utilization of the 9-nitro isomer **2**.

The conversion of **2** to **5** has now been achieved *via* the previously reported[5] 9-amino-7-nitro intermediate **6**, obtained by catalytic reduction of **2** to the 9-amino derivative **4** followed by nitration.[6] The key feature of this sequence is the transformation of **6** to **5** by deamination at the 9 position *via* diazotization (butyl nitrite, sulfuric acid)[7] followed by reductive cleavage. Heating of the isolated diazonium salt **7** in ethanol affords the 7-nitro intermediate **3**,[8] convertible to the product **5** as previously described. This transformation, as well as reductive methylation, was accomplished in one operation by submitting **7**, prepared *in situ*, to hydrogenation with palladium catalyst in the presence of formaldehyde.[9]



(1) M. J. Martell and J. H. Boothe, *J. Med. Chem.*, **10**, 44 (1967).

(2) G. S. Redin, *Antimicrob. Ag. Chemother.*, 371 (1966); J. Federko, S. Katz, and H. Allnoch, *Amer. J. Med. Sci.*, **255**, 252 (1968); N. H. Steigbigel, C. W. Reed, and M. Finland, *ibid.*, **255**, 179, 296 (1968).

(3) J. R. D. McCormick, E. R. Jensen, P. A. Miller, and A. P. Doerschuk, *J. Amer. Chem. Soc.*, **82**, 3381 (1960).

(4) J. Petisi, J. L. Spencer, J. J. Hlavka, and J. H. Boothe, *J. Med. Chem.*, **5**, 538 (1962).

(5) J. L. Spencer, J. J. Hlavka, J. Petisi, H. M. Krazinski, and J. H. Boothe, *ibid.*, **6**, 405 (1963).

(6) A study of this reaction confirmed the reported conditions[5] as optimal. It may be noted that a twofold excess of nitrating agent resulted in much lower yields. Furthermore, nitration in liquid hydrogen fluoride gave apparently poorer results.

(7) J. J. Hlavka, A. Schneller, H. Krazinski, and J. H. Boothe, *J. Amer. Chem. Soc.*, **84**, 1426 (1962).

(8) For an earlier example of this reaction in the tetracycline series, see ref 7.

(9) The replacement of the diazonium group by hydrogen by this procedure is due either to hydrogenolysis or to reduction by formaldehyde. In either case it is unusual. Reduction of diazonium salts by formaldehyde is normally carried out in alkaline medium: R. Q. Brewster and J. A. Poje, *J. Amer. Chem. Soc.*, **61**, 2418 (1939). Hydrogenolysis of aromatic diazonium groups in the presence of palladium catalyst, a reaction first noted with another tetracycline by Dr. J. J. Hlavka of these laboratories, has no literature precedence of which we are aware.

The overall yield of the 7-dimethylamino product **5** from the 9-nitro isomer is 34%, and the yield obtainable directly from the 7-nitro isomer is 54%. Thus the efficiency of the nitration process for the preparation of **5** is dependent upon two factors: (1) the ratio of the nitro isomers, and (2) their total yield. We have been unable to improve the 7- to 9-nitro isomer ratio (about 1:2) although the nitration of **1** has been studied rather extensively. However, we have been able, by nitrating in liquid hydrogen fluoride,[10] to increase the total yield of separated nitro isomers to almost quantitative from the less than 50% observed when nitration is carried out in concentrated sulfuric acid. This procedure affords an 11.7% average yield (9.5–14.9%) of the 7-nitro isomer and 77.4% (73.5–80.6%) of the 9-nitro isomer, both of high purity.[11] The lower 7 to 9 isomer ratio is more than offset by the much higher total yield. Duplicate conversions of 6-demethyl-6-deoxytetracycline (**1**) to **5** using this procedure gave an average overall yield of 6.3% *via* the 7-nitro isomer and 26.4% *via* the 9-nitro isomer for a respectable total yield of 32.7%.

Experimental Section

All hydrogenations were carried out on a Parr hydrogenation apparatus at pressures of 5–35 psig. Solutions were dried over sodium sulfate and evaporations were carried out at reduced pressure. See ref 11 for bioassay data.

Nitration of 6-Demethyl-6-deoxytetracycline (1) in Liquid Hydrogen Fluoride.—A solution of 20.7 g (50 mmol) of 6-demethyl-6-deoxytetracycline (**1**) in 170 ml of liquid hydrogen fluoride was cooled in Dry Ice–acetone and treated with 5.06 g (50 mmol) of potassium nitrate. Nitrogen was blown over the solution while warming in a water bath for 30 min, and the black residue was evacuated (water aspirator) until no further gas evolution was noted. Cold acetone (80 ml) was added and the mixture was shaken to effect solution of the residue. After filtering and washing the acetone-insoluble material (KF·HF, 3.09 g, 78% of theoretical), the filtrate was poured into 2 l. of stirred ether. The mixture was stirred 35 min and filtered. The filtrate immediately developed additional precipitate; it was filtered again and combined with the previously obtained solid, and the entire yellow mass was washed with *ca.* 100 ml of ether. The crude nitration product weighed 26 g.

Separation of the Crude Mixed Nitro Isomers.—This method is a modification of the documented procedure.[4] The crude nitro product was suspended in 160 ml of methanol, and triethylamine was added with stirring to adjust the pH to 7.5. The mixture was stirred 45 min, maintaining (with triethylamine or sulfuric acid) the pH at 7.5 ± 0.2, and then filtered. The filter cake was washed with *ca.* 50 ml of methanol (the combined filtrates were saved for recovery of the 7-nitro isomer) and resuspended in 120 ml of methanol. The pH was adjusted to 6.5 with sulfuric acid, and the mixture was stirred 3 hr and filtered. The filter cake was washed with a small amount of methanol and dried *in vacuo* to constant weight to afford 18.21 g (79.0%) of a yellow solid (bioassay[11] 421).

The filtrate, after removal of the 9-nitro isomer **2**, was immediately treated with sulfuric acid to pH 1.0 and stirred at room temperature for 3 hr. The 7-nitro isomer **3** crystallized as the sulfate salt; it was filtered and washed with a few milliliters of methanol, and then dried *in vacuo* to constant weight to afford 2.99 g (10.6%) of a pale yellow powder (bioassay[11] 4254).

The results of four such experiments are given in Table I.

TABLE I

Expt no.	9-NO_2 isomer 2 Yield, %	9-NO_2 isomer 2 Bioassay[11]	7-NO_2 isomer 3 Yield, %	7-NO_2 isomer 3 Bioassay[11]
1	79.0	421	10.6	4254
2	73.5	594	14.9	3587
3	80.6	774	9.5	4360
4	76.6	665	11.8	3868
	Av 77.4		Av 11.7	

Reductive Methylation of 7-Nitro-6-demethyl-6-deoxytetracycline (3) to Minocycline (5) Hydrochloride Dihydrate.—The procedure described by Martell and Boothe[1] was used. All of the 7-nitro-6-deoxytetracycline, obtained from the four experiments described above, was blended and divided into two portions which were treated separately. The yields of 7-dimethylamino-6-demethyl-6-deoxytetracycline (**5**) disulfate obtained from the two preparations were 89.4 and 89.8% (bioassay[11] 509 and 469, respectively).

The disulfate salt was converted to the monohydrochloride dihydrate[12] by the following procedure.[13] A solution of 5.67 g of 7-dimethylamino-6-demethyl-6-deoxytetracycline (**5**) disulfate in 68 ml of water containing 0.226 g of sodium sulfite was adjusted to pH 6.5 at 25° by dropwise addition of 5 *N* sodium hydroxide. The solution was extracted successively with 145, 115, 115, and 115 ml of chloroform. The combined extracts were washed with 6 ml of saturated sodium chloride solution, dried, and evaporated to dryness (25° bath) to afford 4.5 g of a glass. The material was suspended in 8 ml of 1 *N* hydrochloric acid and the pH was adjusted to 1.1–1.3 with 6 *N* hydrochloric acid. The resulting solution was stirred for about 5 min with activated charcoal and filtered through acid-washed Celite,[14] and the filter cake was washed with 3 ml of 5% sodium chloride solution. The mother liquor was stirred, the pH was adjusted to a constant 4.0 with 5 *N* sodium hydroxide, and the mixture was then stirred at 5° for several hours. The product was collected by filtration and washed with 5 ml of 5% sodium chloride and 1.5 ml of 0.001 *N* hydrochloric acid. Drying at room temperature under reduced pressure for 24 hr afforded the crude hydrochloride of **5**.

The product was recrystallized as follows. A solution of 1.52 g of the hydrochloride was dissolved in 3.2 ml of 1 *N* hydrochloric acid, and the resulting solution was treated with 16 mg of activated charcoal for 10 min, followed by filtration through acid-washed Celite.[14] The cake was washed with 0.4 ml of 5% aqueous sodium chloride. The combined filtrate and wash was adjusted to pH 4.0 with 5 *N* sodium hydroxide. The suspension was stirred at 0° for several hours and then aged in the refrigerator overnight. The solid was collected, washed with 1 ml of 0.001 *N* hydrochloric acid, and dried at 40° *in vacuo* for several hours to give 1.43 g (94%) of product.

By this procedure, conversion of the two samples of the disulfate salt of 7-dimethylamino-6-demethyl-6-deoxytetracycline (**5**) gave the corresponding monohydrochloride dihydrate in yields of 59.4 and 60.2% (bioassay[11] 893 and 892, respectively). This product was identical by spectral and chromatographic analysis with an authentic sample of minocycline monohydrochloride dihydrate.

Reduction of 9-Nitro-6-demethyl-6-deoxytetracycline (2) to 9-Amino-6-demethyl-6-deoxytetracycline (4).—The 9-nitro-6-demethyl-6-deoxytetracycline (**2**) obtained from the four experiments described above was blended, and the combined material was then divided into two portions and hydrogenated as described previously.[5] The products of the two experiments were purified by conversion of the isolated disulfate salt to the neutral form[5] followed by reconversion to the disulfate in overall yields of 82.8 and 84.7% (bioassay[11] 1096 and 985, respectively).

Nitration of 9-Amino-6-demethyl-6-deoxytetracycline (4).—The procedure previously described was used.[5] The yields, in duplicate experiments, of 9-amino-7-nitro-6-demethyl-6-deoxytetracycline (**6**) obtained from the above-described **4** were 98.0 and 99.0% (bioassay[11] 3000 and 2734, respectively).

Conversion of 9-Amino-7-nitro-6-demethyl-6-deoxytetracycline (6) to Minocycline (5) Hydrochloride Dihydrate.—To 120 ml of ice-cold methanol containing 0.54 ml of concentrated sulfuric

(10) A preliminary study of this reaction was carried out by P. Bitha of these laboratories.

(11) Bioassays were measured by the turbidimetric assay of E. Pelcak and A. G. Dornbush, *Ann. N. Y. Acad. Sci.*, **51**, 218 (1948), using *Staphylococcus aureus* as the test organism. Results are compared to neutral tetracycline standard (1000), except for the case of minocycline (**5**) which was compared to minocycline neutral (1000). Standard *in vitro* biological activities for the other compounds discussed in this paper are as follows: 9-nitro-6-demethyl-6-deoxytetracycline (**2**), 200; 7-nitro-6-demethyl-6-deoxytetracycline (**3**), 6000; 9-amino-6-demethyl-6-deoxytetracycline (**4**), 1400; 7-nitro-9-amino-6-demethyl-6-deoxytetracycline (**6**), 4000.

(12) This salt was first prepared by Dr. J. Krueger and Mr. W. Barringer (Belgian Patent 696,488) and is recorded in ref 1.

(13) We wish to thank Dr. M. Tobkes for this procedure.

(14) Celite is the trademark of the Johns Manville Co. for diatomaceous earth silica products.

acid was added with stirring 6 g of 9-amino-7-nitro-6-demethyl-6-deoxytetracycline (6). To the resulting solution was added 2.03 ml (2 mol equiv) of *n*-butyl nitrite, and stirring was continued for 1.75 hr during which time a red solid separated. Urea[15] (540 mg) was added and stirring was continued for 15 min. After the addition of 19 ml of 40% aqueous formaldehyde, the solution was added to a suspension of 1.5 g of 10% palladium-on-carbon catalyst in 7 ml of ethylene glycol monomethyl ether. After an apparent induction period of about 1 hr, hydrogen uptake could be observed and was complete in about 45 min. The filtered solution was poured into 2 l. of ether and aged in the refrigerator overnight. The supernatant liquid was decanted and the residual solid taken up in 125 ml of methanol and reprecipitated from 1400 ml of ether to give 5.4 g (92.0%) of crude minocycline disulfate.

A duplicate experiment afforded 91.0% of product **5** disulfate. These products were then converted by the procedure described above to once-recrystallized minocycline monohydrochloride dihydrate in yields of 43.8 and 46.4% (bioassay[11] 960 and 930, respectively), identical by spectral and chromatographic analysis with an authentic sample.

Registry No.—**2**, 27298-24-4; **5**, 27179-27-7.

Acknowledgments.—The authors are indebted to Mr. L. Brancone and staff for microanalyses, and to Mr. A. Dornbush and Dr. J. J. Corbett and their staffs for biological assays. We are grateful to Drs. J. J. Hlavka, M. J. Martell, and R. Winterbottom, and to Miss P. Bitha for useful conversations. We also wish to acknowledge that the 9-nitro route to minocycline was first suggested by Dr. R. G. Wilkinson.

(15) The presence of a large excess of butyl nitrite was found to inhibit the subsequent hydrogenation.

Structure of Murrayacine[1]

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Bose Institute, Calcutta 9, India

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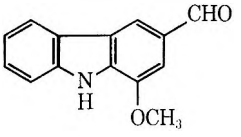
Since the report of the first carbazole alkaloid murrayanine[4] (I) from the stem bark of *Murraya koenigii*



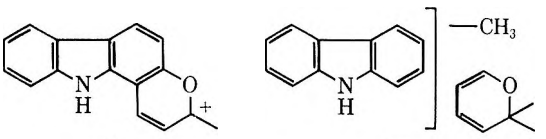
I

Spreng. (Family *Rutaceae*), study of carbazole alkaloids from the taxonomically related genera, *Murraya*, *Glycosmis*,[5,6] and *Clausena*[7] of the family *Rutaceae* has resulted in isolation of different carbazole alkaloids.[8,9]

The present communication relates to the structure of one of these, murrayacine (II), which was isolated from the stem bark of *Murraya koenigii* Spreng. in poor yield.

Murrayacine (II), $C_{18}H_{15}NO_2$, mp 244–245° (M^+ 277), gave a 2,4-dinitrophenylhydrazone and reduced ammoniacal silver nitrate solution showing the presence of an aldehyde function. Its ir spectrum (KBr) showed peaks at 3250 (NH function), 1675 (carbonyl function), 1640, 1600 (unsaturation and aromatic group), and 895, 865, 740 cm^{-1} (substituted benzene derivative). Its uv spectrum [$\lambda_{max}^{ethanol}$ 226 mμ (log ϵ 4.60), 282 (4.57), 301 (4.58)] was very similar to those of 3-formylcarbazole,[10] murrayanine, and 1,4-dimethyl-3-formylcarbazole.[4] This suggested the presence of a 3-formylcarbazole chromophore in II.

The nmr spectrum of II (60 Mc in DMSO) showed signals at δ 10.68 (for an aldehyde function) and at δ 12.0 (for the NH function). One of the aromatic protons appeared as a singlet at δ 8.4 while the other four appeared as multiplets centered around δ 8.15 and 7.35. The sharp singlet for the six protons together with the doublets for one proton each at δ 7.00 and 5.95 (J = 10 cps/sec) revealed the presence of a 2,2-dimethyl-Δ^3-pyran ring. The high intensity mass spectral peak at m/e 262 (M − 15) was suggestive of the formation of the carbazolopyrilium ion (III) during mass spectral fragmentation. The mass spectrum also showed peaks at m/e 234 (M − 15 − 28) due to loss of mass 28 from III. All these data were consistent with the presence of a 3- or 6-formyl-2′,2′-dimethyl-$\Delta^{3'}$-pyranocarbazole skeleton. The isolation of carbazole by zinc dust distillation confirmed the carbazole skeleton in II.



III VI

An alcohol (IV), obtained by sodium borohydride reduction of II, had a uv spectrum strikingly similar to that of girinimbine (V), the first 2,2-dimethyl-Δ^3-pyranocarbazole from a plant source.[11] This suggested that an identical chromophore was present in the two compounds. Because murrayacine was obtained only in small quantity, information regarding the fusion of the pyran ring to the carbazole ring in II was based on the structure elucidation of girinimbine which was formulated by Chakraborty, *et al.*,[11] as VI.

We previously reported that ozonolysis of V furnished an α-hydroxyaldehyde (VII). Structure elucidation of this aldehyde would settle the structure of girinimbine. In the course of the present work, we isolated not only the aldehyde VII but also the corresponding α-hydroxy acid (VIII), in better yield. Zinc dust distillation of VIII furnished 3-methylcarbazole. This showed that the methyl group of V, VII, and VIII was attached to C-3 or C-6 of the carbazole nucleus.

(1) Part XXVI in the series Chemical Taxonomy. Part XXV: B. K. Chowdhury and D. P. Chakraborty, *J. Indian Chem. Soc.*, in press. A short communication on the subject appeared in *Chem. Commun.*, 967 (1968).

(2) Participated as a National Institute of Sciences (India) Research Fellow.

(3) Participated as a Junior Research Fellow in the C.S.I.R. (India) scheme entitled "Studies on Chemical Taxonomy in Relation to the Family *Rutaceae*."

(4) D. P. Chakraborty, B. K. Barman, and P. K. Bose, *Tetrahedron*, **21**, 681 (1965).

(5) D. P. Chakraborty, *Phytochemistry*, **8**, 769 (1969).

(6) D. P. Chakraborty and B. P. Das, *Sci. Cult.* (*Calcutta*), **32**, 181 (1966).

(7) D. P. Chakraborty, K. C. Das, and A. Islam, *J. Indian Chem. Soc.*, in press.

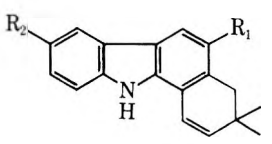
(8) B. K. Chowdhury and D. P. Chakraborty, *Chem. Ind.* (*London*), 549 (1969).

(9) D. P. Chakraborty, A. Islam, S. P. Basak, and R. Das, *ibid.*, 593 (1970).

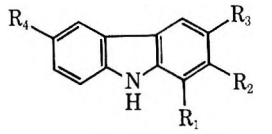
(10) G. Büchi and E. W. Warnhoff, *J. Amer. Chem. Soc.*, **81**, 4433 (1959). The uv data of the formyl carbazoles provided by Professor G. Büchi is gratefully acknowledged.

(11) D. P. Chakraborty, B. K. Barman, and P. K. Bose, *Sci. Cult.* (*Calcutta*), **30**, 445 (1964).

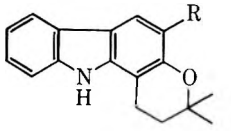
Furthermore, VII gave an *o*-acetate (IX), the uv spectrum of which [$\lambda_{max}^{ethanol}$ 226 mμ (log ε 4.56), 253 (4.09), 292 (4.22), 330 (3.74), and 372 (3.89)] was characteristic of a 1-formylcarbazole. Decarbonylation of VII resulted in a phenolic carbazole which could be methylated with diazomethane to the corresponding methoxycarbazole. The methoxy compound had a uv spectrum [$\lambda_{max}^{ethanol}$ 237 mμ (log ε 4.69), 258 (ε 4.36), 300 (4.15)] characteristic for 2-methoxycarbazole.[12] This showed that the phenol had the hydroxyl group at C-2 and could be formulated either as 2-hydroxy-3-methylcarbazole (X)[13] or 2-hydroxy-6-methylcarbazole (XI).[14] On comparison with synthetic specimens of X and XI, it has been found identical (mixture melting point, tlc, and uv) with X. On this basis, the hydroxyaldehyde could be formulated as VII and girinimbine as V.[15,16] The alcohol IV would, therefore, be IVa or IVb.



II, R_1 = CHO; R_2 = H
IVa, R_1 = CH_2OH; R_2 = H
IVb, R_1 = H; R_2 = CH_2OH
V, R_1 = CH_3; R_2 = H



VII, R_1 = CHO; R_2 = OH; R_3 = CH_3; R_4 = H
VIII, R_1 = CO_2H; R_2 = OH; R_3 = CH_3; R_4 = H
IX, R_1 = CHO; R_2 = $OCOCH_3$; R_3 = CH_3; R_4 = H
X, R_1 = R_4 = H; R_2 = OH; R_3 = CH_3
Xa, R_1 = R_4 = H; R_2 = OCH_3; R_3 = CH_3
XI, R_1 = R_3 = H; R_2 = OH; R_4 = CH_3



XII, R = CHO
XIII, R = CH_3

Dihydromurrayacine (XII) (M^+ 279; ν_{max}^{KBr} 3328, 1665, 1600, 872, 755 cm^{-1}) yielded dihydrogirinimbine (XIII) on $LiAlH_4$ reduction. Hence murrayacine was II, a structure which accounts for the deshielded one-proton singlet at δ 8.40 as being due to H-4. The alcohol IV was therefore IVa.

Experimental Section[17]

Isolation of Girinimbine and Murrayacine. Girinimbine (V).—Air-dried finely powdered stem bark of *Murraya koenigii* Spreng. was extracted with petroleum ether (bp 40–60°). The residue after removal of solvent, was taken up in dry benzene and chromatographed over alumina (500 g). Eluents were collected in fractions (~50 ml each). The residue from the 16th to 21st fraction on washing with petroleum ether gave yellowish crystals (1 g), mp 171–172°. On further crystallizations from a mixture of benzene and petroleum ether (bp 40–60°) and subsequent sublimation, a substance melting at 176° was obtained. This was identical with girinimbine.[11]

Murrayacine (II).—On removal of eluents from fractions 76–85 (benzene–chloroform mixture), a yellowish brown semisolid residue was obtained which on crystallization from ethyl acetate furnished light yellow crystals (50 mg), mp 235–240°. This on sublimation [180° (0.05 mm)] and further crystallization from ethyl acetate melted at 244–245°.

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.98; H, 5.41; N, 5.37. Found: C, 78.41; H, 5.67; N, 5.37.

2,4-Dinitrophenylhydrazone of II.—2,4-Dinitrophenylhydrazone was obtained in the usual way. The resulting product was washed with methanol. The residue melted at 280°.

Anal. Calcd for $C_{24}H_{19}N_5O_5$: N, 15.31. Found: N, 15.1.

Sodium Borohydride Reduction of Murrayacine to IV.—A solution of murrayacine (15 mg) in methanol (20 ml) was reacted with an excess of sodium borohydride at room temperature for 20 hr. Water and 10% hydrochloric acid were added to the mixture. It was extracted with ether, made acid free, and dried. On removal of the solvent, a compound, mp 200°, was obtained. It was recrystallized from methanol and was found homogeneous by paper chromatography: $\lambda_{max}^{ethanol}$ 238 mμ (log ε 4.56), 288 (4.16), and 330 (3.64).

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.0. Found: C, 77.10; H, 5.93; N, 5.29.

Dihydromurrayacine (XII).—A mixture of murrayacine (30 mg), PtO_2 (50 mg), and absolute ethanol (20 ml) was stirred at room temperature for 3 hr in the presence of hydrogen. The mixture was filtered. On removal of the solvent, a solid product was obtained which on crystallization from methanol furnished a colorless compound, mp 176°.

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.25; H, 5.83; N, 5.34.

Zinc Dust Distillation of Murrayacine. Isolation of Carbazole.—Murrayacine (100 mg) was thoroughly mixed with dry zinc dust (10 g) and was distilled[4] when a solid was obtained. The solid was dissolved in benzene and chromatographed over alumina (3 g). From the benzene eluent of the chromatogram, a compound, $C_{12}H_{19}N$, mp 225°, was obtained. This was identical with carbazole in all respects (mixture melting point, uv, and tlc).

Ozonolysis of Girinimbine.—Through the solution of V (1 g) in carbon tetrachloride (120 ml) was passed ozonized oxygen for 1.5 hr at −10° when no further uptake of ozone was noticed. Ice-cold water was added to the reaction mixture and heated on a water bath for 30 min to decompose the ozonide. The phenolic fraction isolated from the reaction mixture as a brown mass was dissolved in benzene. This was chromatographed over silica gel and 25 ml of each fraction was collected using benzene as an eluent. Fractions 5–9 yielded a compound, mp 186°, and fractions 9–16 gave a compound, mp 250°. The compound (50 mg) melting at 186° on recrystallization from benzene melted at 193°, identical with the hydroxyaldehyde VII previously obtained[11] (mixture melting point and uv). The compound VIII (100 mg) melting at 250° on recrystallization from benzene, melted at 255°: ν_{max}^{KBr} 3390, 1700 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.43; H, 4.60; N, 5.89.

Acetylation of VII to IX.—The aldehyde VII (25 mg) was dissolved in pyridine and acetic anhydride (2 ml) and refluxed for

(12) D. P. Chakraborty, J. Dutta, and A. Ghosh, *Sci. Cult. (Calcutta)*, **31**, 529 (1965).

(13) D. P. Chakraborty, D. Chatterjee, and S. Ganguli, *Chem. Ind. (London)*, 1662 (1969).

(14) D. P. Chakraborty, D. Chatterjee, and B. K. Chowdhury, *J. Indian Chem. Soc.*, in press.

(15) A preliminary announcement of the structure of girinimbine (Proceedings of the IUPAC Symposium on the Chemistry of Natural Products, London, 1968, p 418) was made; the identity of the decarbonylated product, $C_{13}H_{11}NO$, had not yet been established by synthesis. On the basis of the spectral analogy between girinimbine and mahanimbine, Dutta and Quasim [*Indian J. Chem.*, **7**, 307 (1969)] advanced the same structure of girinimbine.

(16) (a) B. S. Joshi, *et al.*, came to the same conclusion in connection with some other work (Proceedings of the Indo-Soviet Symposium on the Chemistry of Natural Products, New Delhi, India, Feb 1970). Their approach and some experimental results are different. (b) The structure has also been confirmed by synthesis: A. Islam, Dr. of Philosophy Thesis, Calcutta University, Jan 1970; *J. Indian Chem. Soc.*, in press.

(17) Melting points were determined on a Kofler block. For chromatography, alumina by Sarabhai-Merck Co, and Merck silica gel were used. Ultraviolet spectra (95% ethanol as solvent) were recorded on Beckman DK-2 and Hilger and Watts uv spectrophotometers.

1 hr. The reaction mixture was poured into crushed ice and an almost colorless substance separated. On crystallization of the substance from benzene, IX, mp 217°, was obtained (20 mg): ν_{max}^{KBr} 3400, 1750, 1660 cm^{-1}.

Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.78; H, 4.82; N, 5.37.

Decarbonylation of VII.—The aldehyde VII (40 mg) was mixed with Pd/C (20 mg) and heated in a sealed tube with 1 ml of dry alcohol for 15 min at 270° under vacuum. The residue obtained, after removal of solvent from the alcoholic extract of the reaction product, on crystallization from benzene furnished crystals of X melting at 243°. The compound was soluble in 1% alkali and gave an olive green color with alcoholic ferric chloride solution. This was found identical with 2-hydroxy-3-methylcarbazole (mixture melting point, uv) and different from 2-hydroxy-6-methylcarbazole (mixture melting point 210–220°): $\lambda_{max}^{ethanol}$ 236 mμ (log ε 4.72), 258 (4.31), 302 (4.24).

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10. Found: C, 79.03; H, 5.57; N, 7.10.

Methylation of X.—The phenol X (40 mg) in methanol (15 ml), on treatment with diazomethane and keeping in a refrigerator for 16 hr, furnished a semisolid mass. This was dissolved in benzene and chromatographed over alumina (3 g). From the fractions collected with benzene as eluent, a colorless solid (Xa) was obtained which on crystallization from a mixture of benzene and petroleum ether melted at 225° (yield, 15 mg).

Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.54; H, 6.08; N, 6.81.

Reduction of Dihydromurrayacine to XIII.—A solution of XII (5 mg) in tetrahydrofuran (10 ml) was slowly added to a suspension of $LiAlH_4$ (1 gm) in tetrahydrofuran (7 ml). The mixture was refluxed for 3 hr. The $LiAlH_4$ was decomposed and the reaction mixture was extracted with ether. The ether layer was washed with water and dried, and solvent was removed from it. A solid, mp 176°, identical with dihydrogirinimbine (mixture melting point, tlc, uv) was obtained. No analysis was possible.

Zinc Dust Distillation of an α-Hydroxy Acid VIII. Formation of 3-Methylcarbazole.—The compound VIII (100 mg) was mixed with zinc dust (7.5 g) and distilled by the method and procedure described previously.[4] On working up the reaction product, a compound, mp 207°, was obtained. This was identified as 3-methylcarbazole[5] (mixture melting point, uv).

Registry No.—II, 27300-29-4; II 2,4-DNP, 27300-30-7; IVa, 27300-31-8; V, 23095-44-5; VIII, 27300-33-0, IX, 27300-34-1; X, 24224-30-4; Xa, 24224-28-0; XII, 17750-37-7.

Acknowledgment.—The authors thank Professor S. M. Sircar, Director, Dr. D. M. Bose, and Dr. A. Sen, Head of Department of Chemistry, for their interest in the work. The financial supports partly by C.S.I.R. and partly by NIS (India) are gratefully acknowledged, The authors acknowledge their indebtedness to Dr. B. C. Das of the Institute-de-Chimie des Substances, Gif-Sur-Yvette, France, for nmr and mass spectra.

The Preparation and Properties of Some Cytosine Derivatives

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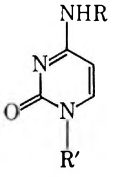
Received July 6, 1970

In order to develop a method for the preparation of some O-acylated derivatives of cytosine, in particular, 2′,3′,5′-tri-*O*-benzoylcytidine (IV), a study was made of some 4-N-acylated cytosines in an attempt to obtain a derivative which could be deacylated at 4 N using conditions under which the sugar benzoyl groups would be stable. The only methods available for obtaining partially acylated derivatives of cytidine give the 4-*N*-acyl derivative as the final product[1] or partially O-acylated derivatives.[2] A preliminary communication of part of this work has already appeared,[3] and from this study it was apparent that in aqueous media, of the derivatives investigated (4-*N*-trifluoroacetyl-, trichloroacetyl-, dichloroacetyl-, monochloroacetyl-, and acetylcytosine), only the latter two would be of use as a protecting group for 4 N because of the lability of the other derivatives.

4-*N*-Chloroacetylcytosine (I) was prepared as previously described.[3] This was easily converted into cytosine under mild acidic conditions, the time for 50% hydrolysis in 0.1 *N* HCl at 20° being 13.5 min, compared with 130 min for the hydrolysis of 4-*N*-acetylcytosine (I). The compound was indefinitely stable in dry ethanol and dry pyridine. It has previously been reported[4] that the acidic deacylation of 4-*N*-acetylcytosine (80% acetic acid) gave a mixture of cytosine and uracil in equal amounts. In the present study, no chromatographic evidence was found for the presence of any uracil (<5%) in the acidic hydrolysate of either 4-*N*-chloroacetyl- or 4-*N*-acetylcytosine.

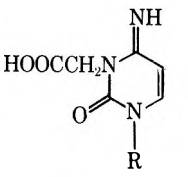


I, R^1 = H; R = $CH_2ClC(=O)-$

II, R^1 = 2′,3′,5′-tri-o-chloroacetylribose; R = $CH_2ClC(=O)-$

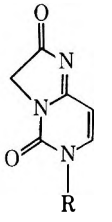
III, R^1 = 2′,3′,5′-tri-*o*-benzoylribose; R = $C_6H_5C(=O)-$

IV, R^1 = 2′,3′,5′-tri-*o*-benzoylribose; R = H



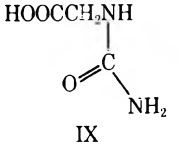
V, R = H

VI, R = ribose

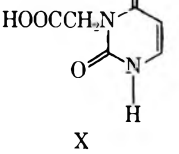


VII, R = H

VIII, R = 2′,3′,5′-tri-o-chloroacetylribose



IX



X

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The normal method for the removal of the 4-*N*-acetyl group from cytosine is to use alkaline conditions, the time for 50% hydrolysis in 0.01 *N* KOH at 20° being 340 min; and in 15% NH_3 in methanol, 57 min.[3] It was hoped that the 4-*N*-chloroacetyl group would be removed even faster under these conditions, particularly as it had been shown that this was sufficient to instantaneously deacylate the trifluoroacetyl-, trichloroacetyl-, and dichloroacetylcytosines. However, a product was isolated in fair yield which was shown by its uv and nmr spectra and elemental analysis to be the imidazopyrimidine (VII), 1*H*-2,3-dihydro-2,5-dioxo[1,2-*c*]pyrimidine, formed by a cyclization reaction between N^3 of the pyrimidine ring and the chloroacetyl group with the elimination of hydrogen chloride. Confirmation of the identity of this compound was obtained from its acidic hydrolysis to 3-carboxymethylcytosine (V) and its alkaline hydrolysis to 3-carboxymethyluracil (X). Ueda and Fox[5] have observed a similar cyclization with 4-*N*-chloropropionylcytosine. The bicyclic product gave only cytosine on acidic or alkaline hydrolysis, which is surprising in view of the results obtained here. The same paper[5] described the synthesis of several pyrimido[1,2-*c*]pyrimidines and those which contained the 4-*N*-acyl-N^3-alkylcytosine structure were easily hydrolyzed to 3-(2-carboxyethyl)-cytosine and the corresponding uracil derivative. Similar derivatives of some *C*-alkylcytosines[6] and some purines[7] have been reported.

Thus the chloroacetyl group might be of use as an amino blocking group for cytosine, where a group which is more readily removed under acidic conditions than acetyl is required; however, the cyclization of 4-*N*-chloroacetylcytosine under basic conditions is a serious disadvantage to its use because it is impossible to regenerate cytosine from the cyclized product.

The corresponding acylated nucleoside was investigated in order to see whether the same properties were present. 4-*N*-chloroacetyl-2′,3′,5′-tri-*O*-chloroacetylcytidine (II) was prepared by reacting cytidine with chloroacetic anhydride in DMF in the presence of potassium carbonate. The product, which was isolated in 80% yield, could not be obtained in a crystalline form but was chromatographically pure and had the elemental analysis and uv spectrum required for the tetrachloroacetylcytidine. As the compound was insoluble in water, the cyclization had to be done in DMF, but the cyclized product was less stable than the cytosine derivative. Very dilute alkali (0.001 *N* KOH) or acid (0.01 *N* HCl) gave 3-carboxymethylcytidine (VI), and the presence of the cyclized compound (VIII) could only be demonstrated by the uv spectrum of the solution. Acidic hydrolysis of the cyclized compound, followed by a mild alkaline hydrolysis to remove any *O*-acyl groups remaining, resulted in the isolation of 3-carboxymethylcytidine (VI) in fair yield (27%). No evidence for the production of any cytosine, uracil, or their 3-carboxymethyl derivatives was obtained. Thus no deamination or glycosyl bond cleavage had occurred during the acidic hydrolysis. Alkaline hydrolysis (1 *N* KOH at 100°) of the cyclized product gave 3-carboxymethylcytidine which, in turn, rapidly decomposed. The only product which could be detected in the hydrolysate apart from a small amount of 3-carboxymethycytidine was a compound which gave a positive reaction with Ehrlich's reagent when subjected to tlc and was therefore considered to be a urea derivative. This compound was also an acid and was thought likely to be *N*-carboxymethylurea (IX), formed from the typical alkaline degradation of 1,3-disubstituted pyrimidines.[8,9]

All attempts to selectively 4-N-acylate cytidine with chloroacetic anhydride failed, under conditions which have been used to selectively acetylate or benzoylate cytidine[2] or deoxycytidine.[10]

It appeared from the properties of the derivatives so far described that the best route to a 2′,3′,5′-tri-*O*-acylcytidine with the amino group unprotected would be the selective acid 4-N-deacylation of a 4-*N*-acyl-2′,3′,5′-tri-*O*-acylcytidine. It was found that the *O*-benzoyl group of 2′,3′,5′-tri-*O*-benzoyluridine[11] was stable to 0.1 *N* HCl at room temperature for up to 3 weeks, and thus the 4-N-debenzoylation of tetrabenzoylcytidine was attempted using 0.1 *N* HCl. The deacylation was followed by the changing uv spectrum of the solution and was seen to be almost complete in 12 days at room temperature. 2′,3′,5′-Tri-*O*-benzoylcytidine (IV) was isolated in 40% yield (32% overall yield from cytidine), and, in contrast to results obtained with the deoxycytidine derivative,[12] only 10% deamination to 2′,3′,5′-tri-*O*-benzoyluridine was detected in the reaction solution. No glycosyl bond cleavage was found.

2′,3′,5′-Tri-*O*-benzylcytidine was more readily prepared by the selective 4-N-deacylation of 4-*N*-acetyl-2′,3′,5′-tri-*O*-benzoylcytidine (III) which was made by the benzoylation of cytidine which had been selectively 4-N-acetylated by the method of Watanabe and Fox.[2] Only traces of 4-*N*-benzoyl-2′,3′,5′-tri-*O*-benzoylcytidine were produced, and the pure product (III) (53% overall yield from cytidine) was obtained after recrystallization from ethanol. This method is quicker and gives a better yield than the method of Fox, *et al.*,[13] which involves the condensation of 1-chloro-2,3,5-tri-*O*-benzoyl-D-ribofuranose with the mercury derivative of 4-*N*-acetylcytosine.

The acidic hydrolysis of 4-*N*-acetyl-2′,3′,5′-tri-*O*-benzoylcytidine was achieved in 0.1 *N* HCl at room temperature for 3 days. At the end of this time, the uv spectrum of the solution showed that no 4-N-acylated product was left. 2′,3′,5′-Tri-*O*-benzoylcytidine (IV) was isolated in almost quantitative yield (40% overall yield from cytidine), and no deaminated product or products formed by glycosyl bond cleavage were detected.

Experimental Section

4-*N*-Acetylcytosine was prepared by the method of Wheeler and Johnson.[14] 2′,3′,5′-Tri-*O*-benzoyluridine was prepared by

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(12) H. G. Khorana, A. F. Turner, and J. P. Vizsolyi, *ibid.*, **83**, 686 (1961).
(13) J. J. Fox, N. Yung, I. Wempen, and I. L. Doerr, *ibid.*, **79**, 5060 (1957).
(14) W. L. Wheeler, and T. B. Johnson, *Amer. Chem. J.*, **29**, 492 (1903).

the method of Fox, *et al.*[11] 4-*N*-Benzoyl-2′,3′,5′-tri-*O*-benzoylcytidine was prepared by the method of Brown, *et al.*[4] 4-*N*-Chloroacetylcytosine was prepared as previously described.[3]

Acidic Hydrolysis of 4-*N*-Chloroacetylcytosine (I).—I was dissolved in 0.1 *N* HCl to give a solution with an optical density at 244 nm of about 1.0. The uv spectrum of the solution at 20° was followed by observing the appearance of a new peak at 275 nm and the disappearance of the maximum at 298 nm. In this way the time taken for 50% hydrolysis was determined. The value was 13.5 min compared with 130 min for 4-*N*-acetylcytosine, as determined under the same conditions.

Mild Alkaline Hydrolysis of 4-*N*-Chloroacetylcytosine (I).— I (1.6 g) was heated in distilled water (200 ml) on a boiling water bath. The mixture was stirred vigorously and the pH of the solution was kept at 8 by the addition of 1 *N* KOH. When complete solution had been achieved and the pH was constant, the solution was concentrated to 80 ml and allowed to stand at room temperature. The crystals which formed were removed by filtration, washed with a little cold water, and dried to give a slightly brown crystalline product (0.7 g). The product was further decolorized and recrystallized from hot water using decolorizing charcoal to give a white crystalline product which was 1*H*-2,3-dihydro-2,5-dioxoimidazo[1,2-*c*]pyrimidine (VII): darkens rapidly above 80°, does not melt below 300°; λmax (at pH 1) 300 nm (ε 20,800); λmin (at pH 1) 260 nm (ε 3600); λmax (at pH 5) 302 nm (ε 21,000); λmin (at pH 5) 242 nm (ε 2600); λmax (at pH 14) 318 nm (ε 27,000); λmin (at pH 14) 270 nm (ε 1600); nmr spectrum (in trifluoroacetic acid) τ 5.31 (singlet, two protons), 3.4 (doublet, 5 H of pyrimidine ring), 1.8 (doublet, 4 H of pyrimidine ring) ($J_{4H,5H}$ = 7 cps). The compound did not move on electrophoresis at pH 3.5. *Anal.* Calcd for $C_6H_5N_3O_2$: C, 47.67; H, 3.34; N, 27.81. Found: C, 47.56; H, 3.10; N, 27.40.

Hydrolysis of 1-*H*-2,3-Dihydro-2,5-dioxoimidazo[1,2-*c*]pyrimidine (VII). A. Acidic.—VII (0.4 g) was dissolved in 1 *N* HCl (20 ml) and the solution allowed to stand at 37° for 14 hr. The solvent was removed by evaporation and the remaining crystalline solid redissolved in water and evaporated to dryness several times to remove most of the hydrochloric acid. The residue was dissolved in a small volume of water and acetone was added to give a slightly turbid solution. The solution, on standing at room temperature, deposited fine needles of 3-carboxymethylcytosine (V, 0.21 g) (as the hydrochloride): mp >300°; λmax (at pH 1) 277 nm (ε 7960); λmin (at pH 1) 242 nm (ε 2030); λmax (at pH 10.5) 297 nm (ε 9640); λmin (at pH 10.5) 250 nm (ε 1590);[5] nmr spectrum (in [$^2H_6$] dimethyl sulfoxide) τ 5.32 (singlet, two protons), 3.8 (doublet, 5 H), 2.3 (doublet, 4 H) ($J_{4H,5H}$ = 7 cps). The compound did not move on electrophoresis at pH 3.5. *Anal.* Calcd for $C_6H_7N_3O_3 \cdot HCl$: C, 35.04; H, 3.93; N, 20.44. Found: C, 35.20; H, 4.11; N, 20.82.

B. Alkaline.—VII (0.6 g) was dissolved in 1 *N* NaOH (20 ml), and the solution was heated at 100° for 1 hr and was passed down a column of Dowex 50 (H^+ form) which was washed with water until no more uv-absorbing material was eluted. The combined washings were evaporated to dryness, the residue was dried and dissolved in dry ethanol, and *n*-hexane added slowly to the solution. Crystals of 3-carboxymethyluracil (X, 0.3 g) were obtained: mp 222–224°; λmax (at pH 5.0) 260 nm (ε 7120); λmin (at pH 5.0) 229 nm (ε 2280); λmax (at pH 14) 285 nm (ε 10,730); λmin (at pH 14) 245 nm (ε 2280);[8,9] nmr spectrum (in [$^2H_6$] dimethyl sulfoxide) τ 5.68 (singlet, two protons), 4.45 (doublet, 5 H), 2.64 (triplet, 4 H), 1.08 (doublet, 3 H). The compound had a mobility of 4.2 cm/hr on electrophoresis at pH 3.5. *Anal.* Calcd for $C_6H_6N_2O_4$: C, 42.36; H, 3.56; N, 16.47. Found: C, 42.20; H, 3.50; N, 16.80.

4-*N*-Chloroacetyl-2′,3′,5′-tri-*O*-chloroacetylcytidine (II).—Anhydrous cytidine (1 g) and chloroacetic anhydride (10 g) were dissolved in dry DMF (30 ml). Anhydrous potassium carbonate (10 g of a finely divided powder) was added to the stirred solution which was cooled in an ice bath. After the initial reaction had subsided, the mixture was allowed to stand at room temperature for 15 min. The potassium salts were removed by filtration, and the filtrate was poured into water (300 ml). After stirring for 1 hr, the mixture was extracted with chloroform, the extract dried with anhydrous magnesium sulfate, and the chloroform removed by evaporation to yield an oil which on repeated evaporation with dry methanol gave a stable dry foam. The foam was washed with ether and dried to give II (1.77 g) as a pale yellow powder. The product could not be obtained crystalline: λmax (in ethanol) 248 nm (ε 14,500) and 299 (5850); λmin (in ethanol) 227 nm (ε 2150) and 274 (1560). *Anal.* Calcd for $C_{17}H_{17}N_3O_9Cl_4$: C, 37.18; H, 3.13; N, 7.65; Cl, 25.81. Found: C, 37.76; H, 3.45; N, 8.00; Cl, 25.86.

An attempt was made to prepare 4-*N*-chloroacetylcytidine by the selective 4-N-acylation of cytidine. Cytidine (0.1 g) was dissolved in hot methanol (10 ml) and chloroacetic anhydride (0.1 g) was added. The solution was heated under reflux and examined at intervals by tlc and uv spectroscopy. No evidence for the presence of any uv-absorbing material other than cytidine was obtained at any time. More anhydride (0.3 g) was added and the experiment was repeated at room temperature, but no reaction was obtained.

Preparation of the Imidazopyrimidine VIII.—II (0.25 g) was dissolved in dry DMF (10 ml) and the solution heated at 90°. After 5 hr tlc on silica (2% ethanol in chloroform) showed the presence of only two uv-absorbing components. The slower components (70% of the total product) had the uv spectrum expected for 4-*N*-acyl-N^3-alkylcytidine with a λmin 258 nm and λmax 305 nm and was presumably the imidazopyrimidine VIII. The other faster component (30% of the total product) was unchanged starting material. All attempts to isolate VIII failed, as it partially decomposed on taking the solution to dryness and also decomposed on a silica plate to a compound which had the properties of 3-carboxymethyl-2′,3′,5′-tri-*O*-chloroacetylcytidine, which on treatment with ammonia gave 3-carboxymethylcytidine (VI) (see below).

Hydrolysis of the Imidazopyrimidine VIII. A. Acidic.—4-*N*-Chloroacetyl-2′,3′,5′-tri-*O*-chloroacetylcytidine (II, 1 g) was dissolved in DMF (20 ml) and heated for 5 hr at 90°. The solution was taken to dryness, the residue dissolved in acetone (40 ml), and 4 *N* HCl added to make the solution 1 *N* with respect to acid, and the solution was left at 37° for 24 hr. The solvent was removed by evaporation under reduced pressure and the HCl was removed by repeated evaporation to dryness with acetone. The residue was dissolved in water, ammonia (sp gr 0.880, 1 ml) was added, and the solution was allowed to stand for 1 hr, after which time the uv spectrum of the solution showed a maximum (pH 1) at 280 nm only. The solution was evaporated to dryness, redissolved in water (50 ml) which was adjusted to pH 9 with ammonia and applied to a column of Deacidite FF (Cl^- form), and eluted with water (pH 5) until no more cytidine was obtained. The column was then eluted with 0.01 *N* acetic acid. One major uv-absorbing component was present in the eluate and this was further purified on a column (22 × 3 cm) of microcrystalline cellulose eluted with propan-2-ol–water (70:30). The fractions containing the major component were combined and evaporated to dryness, and the residue recrystallized from aqueous acetone to give 3-carboxymethylcytidine (VI) as colorless platelets (0.2 g, 27%): mp 225–227° dec; λmax (at pH 1) 279 nm (ε 8040); λmin (at pH 1) 240 nm (ε 2420); λmax (at pH 14) 266 nm (ε 7020); λmin (at pH 14) 245 nm (ε 2470).[15] *Anal.* Calcd for $C_{11}H_{15}N_3O_7$: C, 43.84; H, 5.03; N, 13.95. Found: C, 43.76; H, 5.09; N, 14.27. No evidence for the presence of cytosine, uracil, uridine, or 3-carboxymethyluridine was obtained.

B. Alkaline.—II (50 mg) was dissolved in DMF, heated at 90° for 5 hr, and then made 0.01 *N* with respect to NaOH. The compound (VIII) with a uv absorption spectrum characteristic of a 4-*N*-acyl-N^3-alkylcytidine was immediately replaced by a compound identified as 3-carboxymethylcytidine (V). In 1 *N* NaOH at 100° for 30 min, this compound rapidly decomposed in a manner typical of an N^1,N^3-disubstituted pyrimidine,[8] and the only compound which would be detected in the hydrolysate apart from a trace of 3-carboxymethylcytidine was a compound which gave a positive reaction with Ehrlich's reagent and which on electrophoresis in formate buffer (pH 4) exhibited the mobility of a monocarboxylic acid (5.5 cm/hr). The compound was likely to be *N*-carboxymethylurea (IX).

Acidic Hydrolysis of 2′,3′,5′-Tri-*O*-benzoyluridine and 4-*N*-Benzoyl-2′,3′,5′-tri-*O*-benzoylcytidine.—2′,3′,5′-Tri-*O*-benzoyluridine[14] (10 mg) was dissolved in ethanol (10 ml), 1 *N* HCl (1.1 ml) was added, and the solution was allowed to stand at room temperature. The material could be recovered unchanged after 3 weeks.

4-*N*-Benzoyl-2′,3′,5′-tri-*O*-benzoylcytidine[4] (0.5 g) was dissolved in a solvent containing chloroform (20 ml), ethanol (150 ml), and 1 *N* HCl (19 ml). The solution was allowed to stand at

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room temperature for 12 days and then evaporated to dryness under reduced pressure, and the ethyl benzoate present was removed by repeated evaporation with ethanol. Tlc on silica (10% ethanol in benzene) showed the presence of three uv-absorbing components in the mixture. Two minor compounds accounting for about 10% of the total product were unchanged starting material and 2′,3′,5′-tri-*O*-benzoyluridine. The third compound was isolated in a pure state by recrystallization of the hydrolysis products from boiling chloroform–ethanol (1:4) to which petroleum ether (60–80° fraction) had been added to incipient cloudiness, and the solution was allowed to cool. A flucculent white precipitate of 2′,3′,5′-tri-*O*-benzoylcytidine (IV) (as the hydrochloride) was collected and dried (0.22 g, 32% overall yield from cytidine): mp 226–227° dec; λmax (in ethanol) 230 nm (ε 29,500) and 280 (9500); λmin (in ethanol) 253 nm. *Anal.* Calcd for $C_{30}H_{25}N_3O_8 \cdot HCl$: C, 60.87; H, 4.44; N, 7.10. Found: C, 60.80; H, 4.43; N, 7.11. No evidence for any glycosyl bond cleavage was obtained.

4-*N*-Acetyl-2′,3′,5′-tri-*O*-benzoylcytidine (III).—Cytidine was selectively 4-N-acylated using acetic anhydride in methanol as described by Watanabe and Fox,[2] and the product was benzoylated as follows. 4-*N*-Acetylcytidine (0.9 g) was suspended in dry pyridine (25 ml) and benzoyl chloride (2 ml) was added. The mixture was stirred at room temperature for 2 hr and then poured into 200 ml of 0.01 *N* HCl. After stirring for 1 hr, the sticky precipitate was extracted with chloroform, washed with sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and evaporated to dryness. The residue was dissolved in hot chloroform and *n*-hexane was added to give a slightly turbid solution. On standing, the product crystallized to give a mixture which was mainly the desired compound III but which contained traces of 4-*N*-benzoyl-2′,3′,5′-tri-*O*-benzoylcytidine. Recrystallization from ethanol gave the chromatographically pure product III (1.3 g, 45% overall yield from cytidine): mp 191–192°; λmax (in ethanol) 231 nm (ε 40,400) and 284 (7500), shoulder at 295 nm. *Anal.* Calcd for $C_{32}H_{27}N_3O_9$: C, 64.30; H, 4.56; N, 7.03. Found: C, 64.64; H, 4.42; N, 6.50.

Acid Hydrolysis of 4-*N*-Acetyl-2′,3′,5′-tri-*O*-benzoylcytidine (III).—III (1.3 g) was dissolved in chloroform–ethanol (3:1, 100 ml) and 1 *N* HCl (11 ml) was added. The solution was allowed to stand at room temperature for 3 days, at the end of which time the uv absorption of the solution at 300 nm had dropped to zero. The solvent was removed under reduced pressure and ethanol was added to the residue which was evaporated to dryness several times to remove the HCl. Tlc on silica (10% ethanol in benzene) showed the presence of a single uv-absorbing compound which had the same R_f as a marker of IV, prepared as described above. The product was recrystallized as described before to give 2′,3′,5′-tri-*O*-benzoylcytidine (1.1 g, 40% overall yield from cytidine) (as the hydrochloride): mp 226–227° dec; λmax (in ethanol) 230 nm (ε 29,700) and 280 (9650); λmin (in ethanol) 253 nm. *Anal.* Calcd for $C_{30}H_{25}N_3O_8 \cdot HCl$: C, 60.87; H. 4.44; N, 7.10. Found: C, 60.54; H, 4.41; N, 7.10.

Registry No.—II, 27391-02-2; III, 27391-03-3; IV HCl, 20649-51-8; V HCl, 27415-59-4; VI, 27391-05-5; VII, 14630-99-0; X, 14383-43-8.

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Nucleophilicities toward *n*-Propyl Tosylate in Dimethyl Sulfoxide

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An important contribution to the understanding of solvent effects on reaction rates has been the recent calculation of solvent activity coefficients[1,2] ($^{O}\gamma^{S}_{\pm}$) and enthalpies of transfer[3] ($\Delta\Delta H_{ts}$) of transition states. $^{O}\gamma^{S}_{\pm}$ for SN2 reactions can be calculated[1] from the rates in the two solvents of interest (O and S)

$$\log k^S/k^O = \log {}^{O}\gamma^{S}_{Y^-} + \log {}^{O}\gamma^{S}_{RX} - \log {}^{O}\gamma^{S}_{\pm}$$

provided that the solvent activity coefficients for the transfer of each reactant from solvent S to the reference solvent O have been measured. Parker[1] has found that, in the transfer from methanol to dipolar aprotic solvents, the rate increase may be assisted or resisted by the change in transition state solvation.

The purposes of the present study are (1) to establish the relative reactivities of a series of nucleophiles toward *n*-propyl tosylate under sufficiently similar experimental conditions to permit comparisons, and (2) to estimate $^{O}\gamma^{S}_{YRX\pm}$ values for the reactions where possible. Attention has been given to the small anions hydroxide, methoxide, and fluoride, for which few rate data are available under comparable conditions.

Experimental Section

The nucleophile sources were tetrabutylammonium thiosulfate, hydroxide, fluoride, chloride, bromide, and iodide, sodium methoxide, phenoxide, and thiocyanate, and *N*-methylaniline. The substrate was *n*-propyl tosylate in all reactions except that with fluoride, where *n*-hexyl tosylate was used. Nucleophile concentrations were about 0.03 *M*, and the tosylate was about 0.015 *M*, except in the case of fluoride, and the chloride rate at −4.5°, in which concentrations were 0.45 *M* in the nucleophile and 0.25 *M* in the substrate (to facilitate gas chromatographic determination of hexyl fluoride). Rate measurements were made at −4.5, 20, 30, or 40°. The solvent in each case was dimethyl sulfoxide containing no more than 0.05% water, except that the rates at −4.5° were measured in 45% DMSO–55% tetramethylene sulfoxide (v/v).

The reaction rates were followed by potentiometric titration of aliquots (*vs.* standard iodine, sulfuric acid, or silver nitrate solutions). In the fluoride reaction the appearance of hexyl fluoride was followed by gas chromatography (DC 710 on Chromosorb W).

Tetrabutylammonium thiosulfate (mp 60.1°) and tetrabutylammonium fluoride (mp 58°) were prepared from the bromide by anion exchange. The other nucleophile sources are commercially available.

The rates of reaction of the chloride ion were measured under each condition of temperature, substrate, concentration, and solvent. The slightly inexact assumption has been made that other nucleophiles are affected by these experimental differences to the same extent as is the chloride reaction, and corrections have been made on this basis. The rates of the bromide runs with Bu_4NBr and KBr are, within experimental error, the same. The effect of cation variation is insignificant with this anion, and this is probably true also for the majority of the other nucleophiles. With the small anions, OH^-, F^-, and CH_3O^-, appreciable differences in rate would be anticipated as a function of the cation, due to ion-pair association of the salts in nonaqueous media. It is extremely difficult to obtain Bu_4NF free from water and $NaOCH_3$ free from methanol. The low melting point of Bu_4NF (58°) suggests that the sample is a hydrate, probably with 3–5 molecules of water. Solvation of the anions by hydroxylic solvents should decrease nucleophilic reactivity. Our rates should be considered only as establishing for OH^-, F^-, and CH_3O^- the *lower limit* of the reactivity which would be observed at infinite dilution in the absence of water or methanol. The rates of reaction with chloride in DMSO and in 45% DMSO–55% tetramethylene sulfoxide are substantially the same. In the hydroxide reaction with *n*-propyl tosylate, 48% of the product (by gc) is 1-propanol, and the remainder is the E2 product propylene. The rate of substitution by hydroxide was taken as 0.48 × the overall rate of disappearance of hydroxide as de-

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termined by potentiometric titration of aliquots. The methoxide solution after completion of the reaction contained methyl propyl ether (74%) and methanol (26%). Neither propylene nor 1-propanol was present, which indicates that the methanol detected by gc was present in the original sodium methoxide. Had methanol been formed by methoxide hydrolysis, the hydroxide ion also produced would have yielded 1-propanol with propyl tosylate.

Values of the solvent activity coefficient differences between methanol and DMSO ($^{M}\gamma^{D}_{Y^-}$) for anions have been published.[1] Values of $^{M}\gamma^{D}_{PrOTs}$ and the rates of reaction of *n*-propyl tosylate with nucleophilies in methanol are not available but have been estimated from Parker's data[1] for methyl tosylate. The uncertainties of these estimates are probably no greater than that for the anions (±0.3 log units[1]). Log $^{M}\gamma^{D}$ was estimated in the following way: $\log {}^{M}\gamma^{DMF}_{MeOTs} = -0.6$; $\log {}^{M}\gamma^{DMF}_{MeCl} - \log {}^{M}\gamma^{DMF}_{t\text{-BuCl}} = +0.2$, and $\log {}^{M}\gamma^{DMF}_{MeBr} - \log {}^{M}\gamma^{DMF}_{n\text{-BuBr}} = +0.2$; $\log {}^{DMF}\gamma^{D} =$ 0.0 to +0.2 (MeI, *n*-BuBr, *t*-BuCl). We have therefore made corrections of +0.2 for the larger alkyl group of *n*-PrOTs, and +0.1 for the DMF to DMSO transfer, to give an estimated value of $\log {}^{M}\gamma^{D}_{PrOTs} = -0.3$.

From our unpublished rate data for the reactions of MeOTs with Cl^-, Br^-, and I^- in aqueous DMSO (70, 80, and 85% DMSO by volume), we have estimated $\log k_{MeOTs} - \log k_{PrOTs} = 1.4$ (a comparison of values[1] for MeX and *n*-BuX with five nucleophiles in MeOH affords an average value of 1.1). Transfer values for some of the anions in Table I, or appropriate rates in methanol, are not available; these have been omitted from Table II.

TABLE I

RATES OF TOSYLATE DISPLACEMENT IN DMSO

Nucleophile	Tosylate	Temp, °C	$10^5 k_{obsd}$, l. mol^{-1} sec^{-1}	Corrections[a]	Est $10^5 k_2$ PrOTs, 25°
$S_2O_3^{2-}$	Pr	20	5.60×10^4	t_1	9.4×10^4
OH^-	Pr	20	3.67×10^4	t_1, p_1	2.9×10^4
CH_3O^-	Pr	20	1.63×10^4	t_1	2.7×10^4
F^-	Hex	−4.5	7.34×10^2	t_2, s[b]	2.0×10^4
$C_6H_5O^-$	Pr	20	1.57×10^3	t_1	2.6×10^3
N_3^-	Pr	30	3.89×10^2	t_4	2.7×10^2
Cl^-	Pr	20	5.68×10		
	Pr	30	1.37×10^2	t_4	9.5×10
	Pr	40	3.54×10^2		
	Hex	20	4.64×10		
	Hex	−4.5	3.54	*b*	
	Pr	60	3.03×10^3	*b*	
	Pr	60	2.90×10^3		
Br^-	Pr	30	5.26×10	t_4	4.1×10
	Pr	50	4.88×10^2	(Bu_4NBr)	
	Pr	50	4.78×10^2	(KBr)	
I^-	Pr	40	4.33×10	t_3	1.2×10
SCN^-	Pr	40	1.26×10	t_3	3.4
C_6H_5NHMe	Pr	40	1.20×10	t_3	3.2

[a] Temperature: t_1, $k_{25}/k_{20} = 1.67$; t_2, $k_{25}/k_{-4.5} = 22.0$; t_3, $k_{25}/k_{40} = 0.268$; t_4, $k_{25}/k_{30} = 0.692$; k_{25}, obtained from Arrhenius plot for PrOTs with chloride ion. Product (fraction of total rate leaing to expected substitution product): p_1, $k_S/(k_T + k_E) = 0.48$. Substrate(s), $k_{Pr}/k_{Hex} = 1.22$. [b] At higher concentration in 45% DMSO–55% tetramethylene sulfoxide (v/v) (see text). All rates are the average of two or more determinations.

The relative nucleophilicities of anions toward alkyl tosylates are reasonably consistent among protonic solvents, and among aprotic solvents, but not between the two groups. The orders of decreasing nucleophilicity follow: EtOTs in H_2O,[4] $S_2O_3^{2-} > N_3^- > OH^- > SCN^- \sim I^-$; MeOTs in MeOH,[1] $N_3^- > I^- > SCN^- > Br^- > Cl^-$; MeOTs in DMF,[1] $N_3^- \sim Cl^- > I^- > SCN^-$; PrOTs in DMSO (Table I), $S_2O_3^{2-} > OH^- \sim CH_3O^- \sim F^- > C_6H_5O^- > N_3^- > Cl^- > Br^- > I^- > SCN^-$. In both aprotic solvents the now familiar order of halide reactivity is observed. In DMSO azide ion is distinctly more nucleophilic than chloride. Thiosulfate is most nucleophilic in water and in DMSO. However, if OH^-, CH_3O^-, and F^- were free of hydroxylic solvation and ion association in DMSO, it is probable that these anions would be more reactive than thiosulfate. There is a tendency for the small basic anions to be highly nucleophilic in DMSO, whereas strong hydrogen bonding greatly decreases the relative reactivity of these ions in protonic solvents. Larger more polarizable anions undergo relatively small changes in solvation in the transfer from aprotic to protic solvents.[1,5] The slightly increased solvation of propyl tosylate and the decreased solvation of the transition states in DMSO (relative to methanol) both have a rate decreasing effect. But the more important factor (in this system) of anion desolvation leads to the observed rate increases, which are most striking for small nucleophiles.

(4) R. E. Davis, R. Nehring, W. J. Blume, and C. O. Chuang, *J. Amer. Chem. Soc.*, **91**, 91 (1969).

TABLE II

SN2 REACTIONS OF ANIONS AND *n*-PROPYL TOSYLATE AT 25° IN METHANOL AND DIMETHYL SULFOXIDE

Nu$^-$	Log k^{D}_{PrOTs}[a]	Log k^{D}/k^{M}[b]	Log $^{M}\gamma^{D}_{PrOTs}$	Log $^{M}\gamma^{D}_{Y^-}$	Log $^{M}\gamma^{D}_{\ddagger}$[c]	MeOTs,[d] Log $^{M}\gamma^{DMF}_{\ddagger}$
N_3^-	−2.6	2.1	−0.3	3.5	1.1	2.3
Cl^-	−3.0	3.5	−0.3	5.5	1.7	2.1
Br^-	−3.4	2.6	−0.3	3.6	0.7	1.2
I^-	−3.9	0.9	−0.3	1.3	0.1	0.6
SCN^-	−4.5	0.8	−0.3	1.4	0.3	1.3

[a] Rate of reaction of *n*-PrOTs in DMSO at 25° with indicated nucelophile. [b] Relative rates in DMSO *vs.* MeOH. [c] Change in solvent activity coefficient of the SN2 transition state upon transfer from MeOH to DMSO. [d] Change in γ for the transition state of the $CH_3OTs + Nu^-$ reaction upon transfer from MeOH to dimethylformamide (ref 1).

Registry No.—*n*-Propyl tosylate, 599-91-7.

Acknowledgment.—This work was supported by the Robert A. Welch Foundation (Grant E-136).

(5) R. Fuchs, J. L. Bear, and R. F. Rodewald, *ibid.*, **91**, 5797 (1969).

Neighboring-Group Participation in Free-Radical Reactions of Halohydrins and Hydroxy Sulfides[1]

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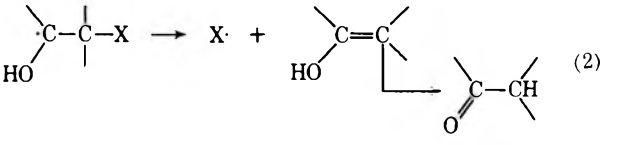
Peroxide-induced decomposition reactions of β-hydroxy sulfides (I) yielding mercaptans and ketones proceed by the free-radical chain sequence 1 and 2.[2]

(1)

I, X = RS
II, X = Cl
III, X = Br



(2)

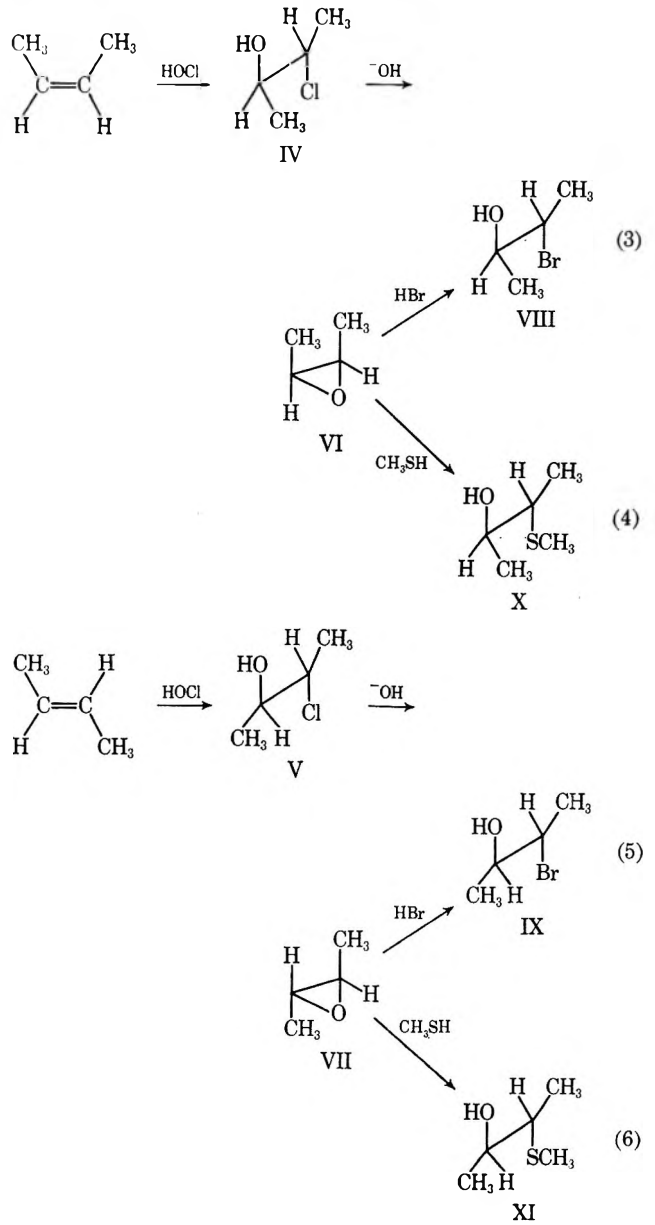
Bromohydrins (II) and chlorohydrins (III), as expected, decompose by a similar chain sequence (see Experimental Section) since halogen atoms are both good hydrogen atom abstractors and undergo β elimi-

(1) This work was supported by a grant (GP-8578) from the National Science Foundation.

(2) E. S. Huyser and R. M. Kellogg, *J. Org. Chem.*, **31**, 3366 (1966).

nation readily.[3] The stereochemical aspects of the hydrogen atom abstraction reaction in the chain sequence described here indicate participation of a bridged radical species in the transition state of the reaction.

The stereoisomeric *threo*- and *erythro*-3-chloro-2-butanols (IV and V, respectively) were prepared by addition of hypochlorous acid to *cis*- and *trans*-2-butene, respectively. *cis*- and *trans*-2,3-epoxybutanes (VI and VII) were obtained by reaction of IV and V, respectively, with base. Reaction of VI and VII with hydrobromic acid or sodium methyl sulfide in alcohol yielded the stereoisomeric bromohydrins VIII and IX and hydroxy sulfides X and XI.



Competition reactions of the stereoisomeric pairs serve to measure the relative rates at which the hydrogen abstraction reaction from the two isomers occurs. The results of these competition studies are given in Table I.

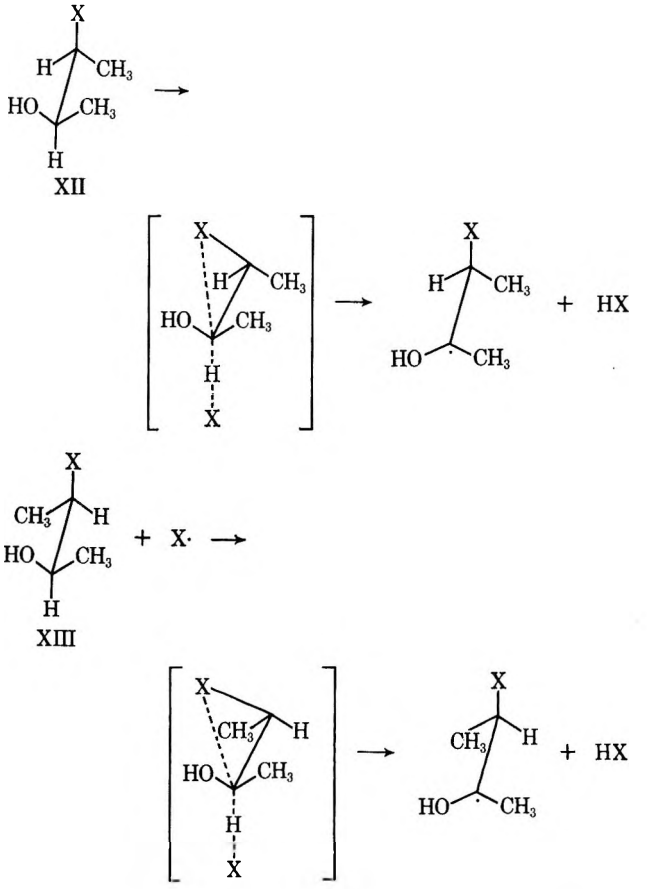
(3) L. P. Schmerling and J. P. West, *J. Amer. Chem. Soc.*, **71**, 2015 (1949); K. E. Wilzback, F. R. Mayo, and R. Van Meter, *ibid.*, **70**, 4069 (1948); D. H. R. Barton, *J. Chem. Soc.*, **148**, 155 (1949); N. V. Steinmetz and R. M. Noyes, *J. Amer. Chem. Soc.*, **74**, 4141 (1952); F. Wackhaltz, *Z. Phys. Chem. (Leipzig)*, **126**, 1, (1927).

TABLE I

COMPETITION REACTIONS OF STEREOISOMERIC 3-HALO- AND 3-METHYLTHIO-2-BUTANOLS

Compd	$k_{threo}/k_{erythro}$	No. of runs	Av dev
3-Chloro-2-butanols (IV and V)	1.02	2	0.01
3-Bromo-2-butanols (VIII and IX)	1.44	5	0.04
3-Methylthio-2-butanols (X and XI)	1.26	3	0.04

Although the isomeric chlorohydrins have essentially the same reactivity, the threo isomers of the bromohydrins and hydroxy sulfides are more reactive than the corresponding erythro isomers toward hydrogen abstraction. The greater reactivity of the threo isomers can be accounted for in terms of anchimeric assistance of the bromine and methanethio group in forming a bridged radical in the transition states of the hydrogen abstraction reaction. In order for the bridged radical to contribute to the transition state, its conformation must be such that the neighboring group is anti to the hydrogen being abstracted. The energy of the transition state of erythro isomers (XII) in this conformation is greater than that of the threo (XIII) owing to the gauche interaction of the two methyl groups in XII.



Bridging of a β bromine with the carbon from which a hydrogen is abstracted by a bromine atom has been suggested to account for the enhanced reactivities of β hydrogens in the brominations of bromoalkanes.[4]

(4) W. A. Thaler, *J. Amer. Chem. Soc.*, **85**, 2607 (1963); P. S. Skell and P. D. Readio, *ibid.*, **85**, 2849 (1963). For an alternative explanation, see D. D. Tanner, D. Darwish, M. W. Mosher, and N. J. Bunce, *ibid.*, **91**, 7398 (1969).

Such neighboring-group participation is a significant factor if the transition state of the reaction involves breaking of the carbon–hydrogen bond and consequently radical formation at the carbon atom allowing for the bridged radical to contribute to lowering the activation energy requirement. The effect is observed in the endothermic hydrogen abstraction by bromine atoms and might be expected in hydrogen atom abstraction by the thiyl radical which is also an endothermic reaction. Contribution of the bridged radical species to the hydrogen abstraction from the chlorohydrins IV and V by a chlorine atom is small. Little carbon–hydrogen bond breaking develops in the transition state of the reaction, and consequently the carbon has little radical character to allow for bridging with the β chlorine. This being the case, no advantage is obtained in the conformational requirement of positioning the chlorine anti to the abstracted hydrogen. The lack of a neighboring-group effect in the chlorohydrin reaction cannot be attributed to the inability of the chlorine, which is isoelectronic with bivalent sulfur, to form bridged radicals since such species have been reported in other systems.[5]

Experimental Section[6]

threo-**3-Chloro-2-butanol** (**IV**) was prepared from *cis*-2-butene and hypochlorous acid by the general method described by Coleman and Johnstone,[7] bp 24–26° (5 mm) [lit.[8] bp 36.5–40 (14 mm)]. The ir and nmr spectra of the material were consistent with the assigned structure.

erythro-**3-Chloro-2-butanol** (**V**) was prepared from *trans*-2-butene and hypochlorous acid,[7] bp 55–60° (80 mm) [lit.[8] bp 44–44.5° (16–20 mm)]. The ir and nmr spectra were consistent with the assigned structure.

cis-**2,3-Epoxybutane** (**VI**).—This material was prepared both by reaction of *cis*-2-butene with *m*-chloroperbenzoic acid following the procedure of Pasto and Cumbo[9] and by elimination of hydrogen chloride from *threo*-chloro-2-butanol with potassium hydroxide in aqueous solution as described by Wilson and Lucas,[10] bp 58–59° (lit.[10] bp 59.9–60.4°).

trans-**2,3-Epoxybutane** (**VII**).—This compound was prepared from *trans*-2-butene and *erythro*-3-chloro-2-butanol, respectively, by methods described in the previous experiment, bp 53.0–54.5° (lit.[10] bp 53.6–54.1°).

threo-**3-Bromo-2-butanol** (**VIII**).—*cis*-2,3-Epoxybutane was added dropwise with constant stirring to an excess of 48% hydrobromic acid cooled in an ice bath. The mixture was allowed to stir for 6 hr and then neutralized with sodium bicarbonate and extracted with ether. After the ether solution was dried over anhydrous magnesium sulfate, the solvent was removed leaving a residue which on distillation gave the desired product, bp 35–38° (5.8 mm) [lit.[11] bp 48–50° (12 mm)].

erythro-**3-Bromo-2-butanol** (**IX**).—*trans*-2,3-Epoxybutane gave IX when it was allowed to react with hydrobromic acid in the manner described in the previous experiments, bp 41–43° (6.2 mm) [lit.[11] bp 51–53° (12 mm)].

threo-**3-Methylthio-2-butanol** (**X**).—*cis*-2,3-Epoxybutane was added dropwise to an alcoholic solution of sodium methyl sulfide (prepared from methanethiol and sodium ethoxide in absolute ethanol) at 0–5°. After the solution was stirred at room temperature for 20 hr, the resulting mixture was taken up in ether and washed repeatedly with sodium bicarbonate and saturated sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and, after removal of the ether, distillation of the resulting residue gave the desired product (50% of theory), bp 38–39° (1.45–1.50 mm).

Anal. Calcd for $C_5H_{12}OS$: C, 50.00; H, 10.07; S, 26.70. Found: C, 50.12; H, 10.31; S, 26.12.

erythro-**3-Methylthiol-2-butanol** (**XI**) was prepared in about 50% yield from *trans*-2,3-epoxybutane by the same procedure, bp 48–51° (1.35–1.50 mm).

Anal. Calcd for $C_5H_{12}OS$: C, 50.00; H, 10.07; S, 26.70. Found: C, 50.34; H, 10.22; S, 26.29.

General Procedures for Competition Reaction.—Solutions consisting of a pair of epimeric alcohols, di-*tert*-butyl peroxide (5–10 mol %), an internal standard for the gas chromatographic analyses (chlorobenzene for the 3-chloro-2-butanols and bromobenzene for 3-bromo-2-butanols and 3-methylthio-2-butanols), and acid scavenger (propylene oxide or cyclohexene oxide) were divided into several Pyrex tubes, sealed, and placed in a constant temperature bath set at 125°. Tubes were removed after several hours, by which time 25–30% of the less reactive isomer had reacted, and then immediately cooled to 0°. The reaction mixtures were analyzed on a F & M Model 5750 gas chromatograph using a 8 ft × 1/8 in. column packed with 15% E600 on Chromosorb W. The peak areas of the epimeric alcohols and the internal standard were used to determine the amount of epimeric alcohols remaining in the sample. The relative reactivity ratios were calculated from the initial quantities and amounts remaining of each epimer using the equation

$$\frac{k_{\text{threo}}}{k_{\text{erythro}}} = \frac{\log (\text{threo})_i/(\text{threo})_f}{\log (\text{erythro})_i/(\text{erythro})_f}$$

where the subscripts i and f refer to the initial and final amounts, respectively.

Control Experiments.—When heated for several hours at 125° in the absence of *tert*-butyl peroxide, the isomeric halohydrins and hydroxy sulfides did not yield 2-butanone as a reaction product. All of the compounds did show some degree of thermal instability but decomposed at considerably slower rates than the *tert*-butyl peroxide induced reactions yielding 2-butanone. The thermal decomposition products were not identified.

Registry No.—IV, 10325-40-3; V, 10325-41-4; VIII, 19773-41-2; IX, 19773-40-1; X, 27022-36-2; XI, 27022-37-3.

(5) P. S. Skell, D. L. Tuleen, and P. D. Readio, *J. Amer. Chem. Soc.*, **85**, 2849 (1963).

(6) All boiling points are uncorrected. Elemental analyses performed by Wiler and Straus, Oxford, England.

(7) G. H. Coleman and F. J. Johnstone, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 158.

(8) E. R. Alexander and D. C. Dittmer, *J. Amer. Chem. Soc.*, **73**, 1665 (1951).

(9) D. J. Pasto and C. C. Cumbo, *J. Org. Chem.*, **30**, 1271 (1965).

(10) C. E. Wilson and H. J. Lucas, *J. Amer. Chem. Soc.*, **58**, 2399 (1936).

(11) J. K. Kochi and D. M. Singleton, *ibid.*, **90**, 1582 (1968).

On the Reality of Solvent Effects in the Decomposition of *tert*-Butyl Peroxide[1]

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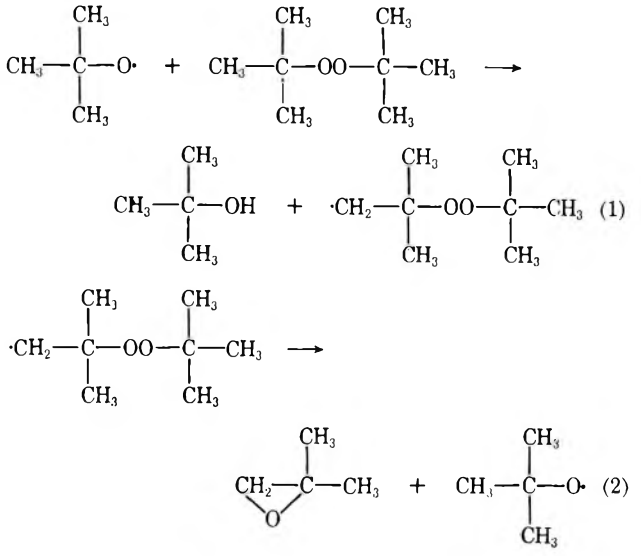
Although the rate of decomposition of *tert*-butyl peroxide was originally described as essentially the same in the gas phase and a variety of solvents,[2] appreciable variations have subsequently been reported. The decomposition rate of the pure liquid peroxide is increased severalfold by an induced decomposition[3]

(1) Partial support of the work by a grant from the Petroleum Research Fund of the American Chemical Society is gratefully acknowledged.

(2) J. H. Raley, F. F. Rust, and W. E. Vaughan, *J. Amer. Chem. Soc.*, **70**, 1336 (1948).

(3) E. R. Bell, F. F. Rust, and W. E. Vaughan, *ibid.*, **72**, 337 (1950).

via steps 1 and 2, and induced chains have also been observed in the presence of HCl[4] and SF_6[5] in the gas



phase and in the liquid phase in the presence of primary and secondary alcohols[6] or amines[7] and, *via* a more rapid electron transfer process, in the presence of alkoxide anions.[8] On the other hand, a reduction in decomposition rate is observed in viscous solvents,[9] due apparently to cage recombination of *tert*-butoxy radicals, and a similar viscosity dependence of quantum yield has been reported for the photochemical decomposition.[10]

Recently Huyser and Van Scoy[11] have reported a further effect of solvent polarity on the decomposition rate, and more particularly on heats and entropies of activation. Although their results lie in the order expected from data on solvent effects on the reactions of *tert*-butoxy radicals,[12] the magnitude of the effect is surprisingly large. Thus, for the extreme cases, cyclohexane and acetonitrile, $\Delta H^{\ddagger}$ is reported as 40.8 and 31.0 kcal/mol, respectively, and $\Delta S^{\ddagger}$ as +21.1 and −1.54 eu. Since their data were obtained at relatively high peroxide concentrations (5:1 solvent:peroxide mole ratios) and since those solvents in which decomposition was fast in general lacked reactive C–H bonds which could interrupt the chain sequence (1–2), it seemed to us that induced decomposition might account for their results, or, alternatively, they might be an artifact arising from the limited temperature range (15°) over which measurements were made.[13]

We have investigated the products of *tert*-butyl peroxide decomposition in several of Huyser's solvents at 125° and his concentrations, using isobutylene oxide yields as a measure of induced decomposition. In acetonitrile, the fastest solvent, it amounts to about 5% over the first half-life and is independent of conversion indicating that larger amounts are not being formed but then consumed in further reactions. Qualitatively similar yields are obtained in nitrobenzene and benzene, but they are lower in cyclohexane and negligible in cyclohexene, a good trap for both *tert*-butoxy and methyl radicals. At 100:1 acetonitrile:peroxide ratios, the isobutylene oxide yield is also negligible, although the decomposition rate is unchanged (see below). Accordingly we conclude that induced decomposition does not make a significant contribution to Huyser's rates.

Huyser's data indicate an isokinetic temperature for all his solvents at 164°, so that rates should diverge at lower temperatures. We have measured decomposition rates in acetonitrile and cyclohexene at 125 and 95° and cyclohexane at 95° (Table I). At the lower

TABLE I
RATE CONSTANTS FOR DECOMPOSITION OF *tert*-BUTYL PEROXIDE[a]

Solvent, mol ratio	Temp, °C	k, $sec^{-1} \times 10^7$
Acetonitrile, 5:1	125	377 ± 9
Acetonitrile, 101:1	125	389 ± 20
Acetonitrile, 5:1	125	347 ± 4[b]
Cyclohexene, 5:1	125	149 ± 3
Cyclohexene, 5:1	125	138 ± 2[b]
Acetonitrile, 104:1	95	9.53 ± 0.10
Acetonitrile, 104:1	95	9.24 ± 0.18[c]
Cyclohexane, 98:1	95	2.48 ± 0.11

[a] All by disappearance of peroxide unless indicated. Experimental errors are standard deviations. [b] Data of Huyser and Van Scoy. [c] By appearance of products.

temperature the ratio is considerably lower (3.84) than predicted by Huyser's parameters (7.16). Figure 1 is an Arrhenius plot combining both sets of data. Also included are the only other set of low-temperature data available: Offenbach and Tobolsky's measurements employing styrene polymerization as a measure of decomposition rate.[14] Table II lists heats and entropies

TABLE II
ACTIVATION PARAMETERS IN DECOMPOSITION OF *tert*-BUTYL PEROXIDE[a]

Solvent	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
Acetonitrile	34.2	6.5
Styrene[b]	34.8	6.7
Cyclohexane	38.4	15.2
Gas phase[c]	37.4	12.9

[a] Calculated by least square fit of data, Figure 1. [b] Styrene and benzene points combined. For styrene alone,[14] $\Delta H^{\ddagger}$ = 34.0 kcal/mol, $\Delta S^{\ddagger}$ = 4.6 eu. [c] Reference 15.

of activation calculated from the data shown in Figure 1. For styrene it was assumed that the decomposition rate at 120–135° was the same as reported by Huyser and Van Scoy in benzene, and also included are the results of Batt and Benson[15] for the reaction in the gas phase over an extended but higher temperature range.

(4) M. Flowers, L. Batt, and S. W. Benson, *J. Chem. Phys.*, **37**, 2662 (1962).
(5) L. Batt and F. R. Cruickshank, *J. Phys. Chem.*, **70**, 723 (1966).
(6) E. S. Huyser and C. J. Bredeweg, *J. Amer. Chem. Soc.*, **86**, 2401 (1964).
(7) E. S. Hyyser, C. J. Bredeweg, and R. M. Van Scoy, *ibid.*, 4148 (1964).
(8) W. V. Sherman, *ibid.*, **90**, 6773 (1968).
(9) C. Walling and H. P. Waits, *J. Phys. Chem.*, **71**, 2361 (1967).
(10) H. Kiefer and T. G. Traylor, *J. Amer. Chem. Soc.*, **89**, 6667 (1967).
(11) E. S. Huyser and R. M. Van Scoy, *J. Org. Chem.*, **33**, 3524 (1968).
(12) C. Walling and P. Wagner, *J. Amer. Chem. Soc.*, **86**, 3363 (1964).
(13) Although Huyser and Van Scoy assign experimental uncertainties to their parameters based on error analysis, these do not, of course, exclude the possibility of systematic errors of unforeseen nature. Over a 15° temperature range, a 5% uncertainty in k's (which is modest) corresponds to a 1.5 kcal uncertainty in $\Delta H^{\ddagger}$.
(14) J. A. Offenbach and A. V. Tobolsky, *J. Amer. Chem. Soc.*, **79**, 278 (1957).
(15) L. Batt and S. W. Benson, *J. Chem. Phys.*, **36**, 895 (1962).

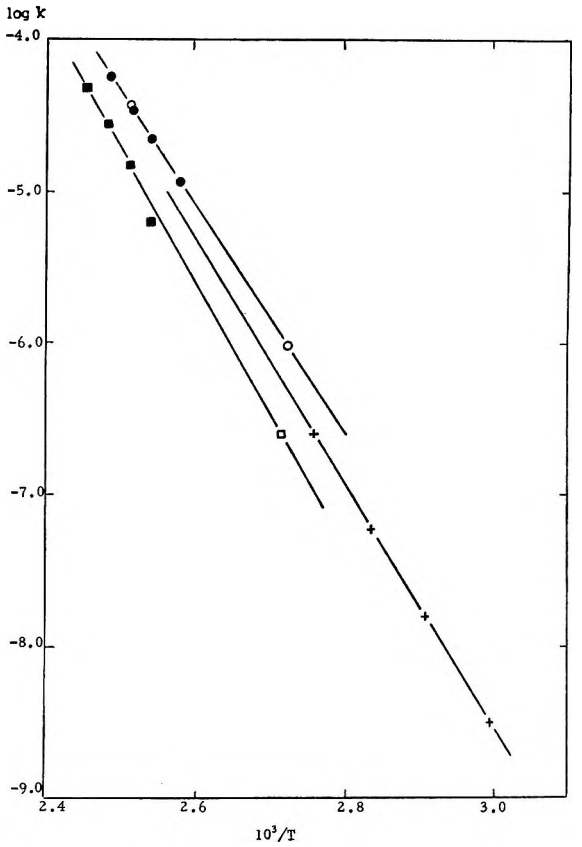


Figure 1.—Solvent effects on temperature dependence of *tert*-butyl peroxide decomposition: circles, acetonitrile; squares, cyclohexane; crosses, styrene; solid symbols, Huyser and Van Scoy; open symbols, this paper.

From Table II we conclude that, while the rate and activation parameters for the decomposition of *tert*-butyl peroxide do vary measurably with solvent, the magnitude of the effect is considerably less than reported by Huyser and Van Scoy. We also believe that our results point up the importance of determining activation parameters from data gathered over as wide a temperature range as possible. To place the matter in perspective, variations in rate of decomposition of *tert*-butyl peroixde with solvent and attributable to variations in reactant and transition-state solvation are comparable to or smaller than those previously observed with simple diacyl peroxides and peresters which decompose by single-bond scission and far smaller than the effects observed in those peroxides which decompose rapidly by concerted multibond scission.[16]

Experimental Section

Materials.—Peroxide and solvents were commercial materials, purified as necessary by conventional means and checked by gas–liquid chromatography (glc).

Decompositions.—Were carried out in sealed, degassed tubes in suitable thermostats, and products and decomposition rates were determined by glc analysis, using suitable internal standards added after reaction. Reaction rates were determined by monitoring either undercomposed peroxide or the appearance of products (*tert*-butyl alcohol plus acetone). Data on columns and conditions found effective for the different systems investigated appear in Table III.

Analysis of Data.—Rate constants were calculated from points from individual runs (usually 9), distributed in time over approximately 0.5–2 half-lives. Runs in both solvents at 95% were run concurrently to compensate for any drift in thermostat temperature over the 1–2 weeks required to achieve adequate reaction.

(16) For a recent discussion of such systems, *cf.* C. Walling, H. P. Waits, J. Milovanovic, and C. G. Pappiaonnov, *J. Amer. Chem. Soc.*, **92**, 4927 (1970).

Table III

Gas Chromatographic Data

Analytical column[a]	Column temp, °C[b]	Compounds analyzed[c]	Solvent
12 ft, 15% diisodecyl-phthalate	40	Acetone, isobutylene oxide, *tert*-butyl peroxide, 2-pentanone	Acetonitrile, cyclohexene, cyclohexane, *tert*-butyl alcohol, benzene, nitrobenzene
12 ft, 20% DEGS in tandem with 15 ft, 20% FFAP	68	*tert*-Butyl peroxide, acetone, *tert*-butyl alcohol, benzene[d]	Acetonitrile
12 ft, 10% silicone gum rubber UCC-W982	40	*tert*-Butyl alcohol, methylcyclohexane,[d] *tert*-butyl peroxide	Cyclohexane

[a] Stationary phase, 80–100 mesh VarAport 30. [b] Injector temp, 70–80°. [c] In order of elution. [d] Internal standard.

Registry No.—*tert*-Butyl peroxide, 110-05-4.

Diacetylation of Amines

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Received June 18, 1970

Several representative primary amines were acetylated under reflux conditions Table I shows the results of the treatment of these amines with boiling acetic anhydride Those primary amines of the type RCH_2NH_2 gave reasonably good yields of only *N,N*-diacetylamines, $RCH_2N(COCH_3)_2$. Primary amines of the type $RR'CHNH_2$ gave *N*-monoacetylamines, $RR'CHNHCOCH_3$, and *N,N*-diacetylamines depending on the nature of R and R'. $RR'R''CNH_2$ gave only *N*-monoacetylamine. Mono- or diacetylation is clearly a function of the steric requirements about the amino group. The reaction provides a useful route for obtaining *N,N*-diacetylamines in reasonably good yields, as shown in Table I.

The infrared spectra of the *N*-monoacetylamines show bands at 3225–3275 cm^{-1} due to the N–H stretch of amides of the type CH_3CONHR. In all compounds prepared, whether monoacetylamine or diacetylamine, the symmetrical N–H stretch of the methyl group in the acetyl function shows absorption at 1366–1374 cm^{-1}. The carbonyl group of the monoacetylamines show a strong band at *ca.* 1640 cm^{-1}. The carbonyl band of the diacetylamines show up at 1692 cm^{-1}. The difference in the frequency of absorption of the carbonyl group for monoacetylamines and diacetylamines was

(1) Taken from the Ph.D. Dissertation of K. H. Brown, Loyola University, 1970.

TABLE I

ACETYLATION OF AMINES

$$RNH_2 + Ac_2O \xrightarrow{\text{reflux}} RNHCOCH_3 + RN(COCH_3)_2$$

Starting amine	*N*-Acetylamine			*N*,*N*-Diacetylamine										
									% C		% H		% N	
	% yield	Mp or bp (mm), °C[a]	Registry no.	% yield	Bp, °C (mm)	Mp, °C	$n^{25}D$	$d^{27.5}$	Calcd	Found	Calcd	Found	Calcd	Found
Cyclopropylamine	0		27179-51-7	69	94.5 (10.0)		1.4686	1.11	59.57	59.76	7.80	7.82	9.93	9.79
Cyclobutylamine	0		27179-52-8	77	107 (10.5)		1.4712	1.06	61.94	61.94	8.39	8.43	9.03	8.96
Cyclopentylamine	74		27179-53-9	23	115–120 (11)			1.09						
Cyclohexylamine[b]	76	104–106		22	125 (10.0)			1.05						
Cycloheptylamine	66	55–56	27179-54-0	32	138 (9.0)									
Cyclooctylamine	66	45–46	27179-55-1	32	150 (9.0)		1.4765	1.01						
n-Propylamine	0		1563-84-4	65	85 (10.0)		1.4476	1.01	58.72	58.83	9.15	9.09	9.78	9.79
Isopropylamine	15	95 (10)	1563-85-5	30	95 (10.5)		1.4307	0.97	58.72	58.81	9.15	9.23	9.78	9.66
n-Butylamine	0		1563-86-6	90	63 (0.3)		1.4492	1.00	61.12	61.36	9.62	9.41	8.91	9.15
sec-Butylamine	35	101 (9)	19264-30-3	40	85 (9.0)		1.4361	0.96	61.12	61.19	9.62	9.64	8.91	9.07
Isobutylamine	0		1787-52-6	70	91 (10.0)		1.4467	0.99	61.12	60.97	9.62	9.72	8.91	8.90
tert-Butylamine	60	95–96		0										
Octadecylamine	0		27179-61-9	51		45–46			74.73	74.94	12.26	12.30	3.96	3.83
Ethylenediamine[e]	0		10543-57-4	25		149–150			52.62	52.77	7.07	6.99	12.28	12.25
Benzylamine[c]	0		3027-02-9	70	160 (30)									
Phenethylamine	0		27179-64-2	80	165 (11)		1.5254	1.16	70.22	70.20	7.37	7.23	6.83	6.86
2-Aminopyridine	0		3027-04-1	53	110 (0.3)									
3-Aminopyridine	0		27179-66-4	20		82–83			60.66	60.61	5.60	5.66	15.73	15.73
4-Aminopyridine	0		27179-67-5	25		150–151								
3-Picolylamine	0		27178-11-6	63	140 (0.4)		1.5370	1.21	62.48	62.64	6.30	6.38	14.58	14.54
4-Picolylamine	0		27178-12-7	51	150 (0.5)		1.5307		62.48	62.38	6.30	6.37	14.58	14.43
2-(2-Aminoethyl)-pyridine	0		27179-68-6	66	140 (0.4)		1.5238	1.21	63.57	63.30	6.84	6.85	13.58	13.50
Aniline[d]	0			50										

[a] The melting points of the *N*-alkylacetamides (*N*-acetylamines) prepared were verified with literature values. *N*-*tert*-Butylacetamide: B. Scholl, *Justus Liebigs Ann. Chem.*, **16**, 338 (1906). *N*-Isopropylacetamide, *N*-*sec*-butylacetamide, *N*-cyclopentylacetamide, *N*-cyclohexylacetamide, *N*-cycloheptylacetamide, and *N*-cyclooctylacetamide; M. Murakami, K. Akagi, and Y. Mori, *Bull. Chem. Soc.*, **35**, 11 (1962). [b] R. A. B. Bannard, *Can. J. Chem.*, **42**, 744 (1964). [c] C. K. Ingold and E. L. Holmes, *J. Chem. Soc.*, **127**, 1800 (1925). [d] P. P. Bedson and A. J. King, *ibid.*, **37**, 752 (1880). [e] Data given are for tetracetyl derivative.

used as an analytical probe in the identification of the products. Also, an estimate of the relative amounts of monoacetylamine and diacetylamine was made for those amines which gave both products. This estimate was made by comparison of the intensities of the two carbonyl bands.

The nuclear magnetic resonance data clearly show the difference between *N*-monoacetylamines and *N,N*-diacetylamines. The *N*-monoacetylamines show resonance at *ca.* τ 2.10 as a doublet due to the N–H proton, which is coupled with the C–H proton of the neighboring alkyl group. The methyl groups of the acetamido function provide a convenient method of estimating the relative amounts of monoacetylamine and diacetylamine in a given reaction. The methyl protons appear at τ 8.09 ± 0.03 for the *N*-monoacetylamines and at τ 7.70 ± 0.10 for the *N,N*-diacetylamines.

Experimental Section[2]

All melting points were obtained on a Fisher-Johns apparatus and are uncorrected. All boiling points were obtained using standard vacuum distillation techniques and are uncorrected. All nuclear magnetic resonance spectra were taken on a Varian A-60A instrument as 50% CCl_4 solutions, using 1% TMS as internal standard, except in those cases where solubility considerations required $CDCl_3$ as solvent. All infrared spectra were taken as neat smears (for liquids) or as KBr pellets (for solids) and were performed on a Beckman IR-5A spectrophotometer. All gas chromatography work was done with a 4-ft SE-30 column on an Aerograph gc instrument. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Acetylation of Amines.—The acetylation procedures were nearly the same for all the compounds studied. Therefore, the reactions of the amines examined are divided into two categories: those reactions which gave only a *N,N*-diacetylamine, and those reactions which gave a mixture of a *N*-monoacetylamine and a *N,N*-diacetylamine.

The Preparation and Isolation of a *N,N*-Diacetylamine.—(The acetylation of cyclopropylamine which is given below is typical.) Cyclopropylamine (4.80 g, 0.084 mol) was added dropwise to a mixture of acetic anhydride (125 ml) and anhydrous sodium acetate (0.5 g) contained in a 250-ml three-neck round-bottom flask equipped with reflux condenser, dropping funnel, thermometer, and magnetic stirring. The temperature was maintained at 25° by use of an ice bath since the exothermic reaction involved the addition of the volatile cyclopropylamine (bp 50°). The total time of addition was 10 min. The reaction mixture was then heated at reflux for 20 hr and cooled to room temperature. The reaction mixture, which was clear and yellow, was then rotary evaporated at approximately 70° and 10 mm for 2 hr, leaving a thick yellow sludge. Water (50 ml) was added, forming a yellow solution, which was then stirred at room temperature for 1 hr in order to hydrolyze any remaining acetic anhydride. This water solution was then extracted twice with ether (75 ml per extraction) and the combined ether layer was dried ($MgSO_4$), filtered, and concentrated on the rotary evaporator at reduced pressure, leaving 8.0 g (69%) of yellow *N,N*-diacetylcyclopropylamine. The yellow liquid was then distilled through a 6-in. Vigreux column at reduced pressure. After a small forerun (0.5 ml), the major fraction distilled at 94.5° (10.0 mm): $n^{25}D$ 1.4686; $d^{27.5}$ 1.11; ir (neat) 2980, 1692, 1368, 1250, 1035, and 970 cm^{-1}; nmr (CCl_4) τ 8.80–9.30 (m, 4), 7.78 (s, 6), and 7.40 (m, 1).

The Preparation, Isolation, and Separation of a Mixture of a *N*-Monoacetylamine and a *N,N*-Diacetylamine.—(The acetylation of *sec*-butylamine given below is typical.) *sec*-Butylamine (14.6 g, 20.0 ml, 0.20 mol) was added dropwise to a mixture of acetic anhydride (140 ml) and anhydrous sodium acetate (0.5 g). The procedure was identical with that of cyclopropylamine until the crude product was isolated. This crude product was submitted for infrared and nuclear magnetic resonance analysis. Comparison of the relative intensities of the carbonyl absorptions in the ir spectrum indicated a mixture of *N*-acetyl-*sec*-butylamine and *N,N*-diacetyl-*sec*-butylamine in the ratio of 7:8. Comparison of the relative areas under the singlet methyl peaks of the acetamido functions in the nmr spectrum corroborated the infrared findings. The crude liquid was then fractionally distilled through a 6-in. Vigreux column at reduced pressure. After a small forerun, 5 ml of clear colorless liquid was collected at 86–91° (8.75 mm). A small intermediate fraction was then distilled, and finally a 10-ml collection of clear colorless liquid was made at 101–101.5° (8.75 mm). The infrared spectral data clearly indicated that the 86–91° fraction was the *N,N*-diacetyl-*sec*-butylamine, and that the 101–101.5° fraction was the *N*-acetyl-*sec*-butylamine.[3] The identifications were made based on the conclusions set forth in the spectral discussion section of this paper: that the carbonyl absorption at 1692 cm^{-1} indicates diacetylamine, whereas the carbonyl absorption at 1640 cm^{-1} indicates monoacetylamine. The nmr spectra also clearly designate the high-boiling fraction to be pure monoacetylamine while the lower boiling fraction is seen to be nearly pure diacetylamine. The total yield, based on a 7:8 monoacetyl to diacetyl ratio, was 75%, or 35% *N*-acetyl-*sec*-butylamine and 40% *N,N*-diacetyl-*sec*-butylamine. The *N,N*-diacetyl-*sec*-butylamine was purified by preparative gc from an SE-30 column and analyzed: $n^{25}D$ 1.4361; $d^{27.5}$ 0.96; ir (neat) 2950, 1692, 1450, 1370, and 1240 cm^{-1}; nmr (CCl_4) τ 9.17 (m, 3), 8.67 (d, 3), 8.20 (m, 2), 6.18 (m, 1).

(2) The amines in this research were used as received without further purification. The following sources supplied the amines: Aldrich Chemicals, Milwaukee, Wis., Reilly Tar and Chemicals, Indianapolis, Ind., Eastman Kodak, Rochester, N. Y. Additionally, we thank Professor Harvey Posvic of our department for supplying us with generous samples from his amine collection.

(3) *N*-*sec*-Butylacetamide has a reported boiling point of 87° (3 mm). See Table I, footnote a.

Hydrogenolysis of Carbonyl Derivatives as a Route to Pure Aliphatic–Aromatic Hydrocarbons

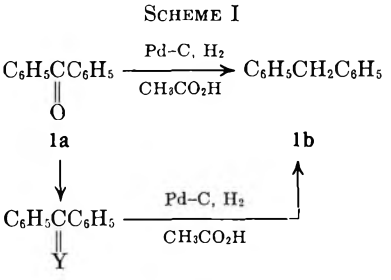
J. W. BURNHAM[1] AND E. J. EISENBRAUN*

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74074

Received July 6, 1970

Hydrogenolysis of ketones such as acetophenone, benzophenone (Scheme I), and 1-tetralone to the corresponding hydrocarbons is readily accomplished in good yield[2a–d] and has become an important synthesis route

SCHEME I



1c, Y = $NNHC_6H_3(NO_2)_2$
d, Y = $NNHCONH_2$
e, Y = $NNHC_6H_5$
f, Y = NOH

(1) (a) American Petroleum Institute Research Assistant (undergraduate, 1968–1969; graduate, 1969–present).

(2) (a) P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals," Academic Press, New York, N. Y., 1967. (b) Presented before the Southwest Regional Meeting of the American Chemical Society, Tulsa, Okla., Dec 4–6, 1969. (c) R. G. Melton, E. J. Eisenbraun, P. W. K. Flanagan, and M. C. Hamming, *Org. Prep. Proced.*, **2**, 37 (1970). (d) Aromatic aldehydes also may be hydrogenolyzed. (e) Correspondence regarding samples of hydrocarbons related to this and earlier[2c] work should be addressed to A. J. Streiff, American Petroleum Institute, Carnegie-Mellon University, Pittsburgh, Pa. 15213.

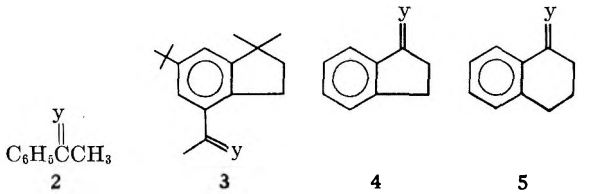
TABLE I
HYDROGENOLYSIS OF CARBONYL DERIVATIVES

Compd[a]	Reaction hr	% yield[b]
1a	1.5	95
1c	7	92[c]
1d	6	93[c]
1e	6	96[c]
1f	4	96[c]
2a	1.5	95
2c	6	81
2d	5	97
2e	5	94
2f	3	82
3a[d]	2.5	92
3c[d]	21	84
3d[e]	10	75
4a	1	87
4c	3	71
5a	1	94
5c[f]	4	95

[a] For preparation and melting points of these derivatives except as noted, see R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964, pp 147, 253, 289, 363, and 364. The melting points of these derivatives agreed with literature values. [b] Glc comparison with standards. [c] Gravimetrically determined as well. [d] Cl. Ferrero and R. Helg, *Helv. Chim. Acta*, 42, 2111 (1959). [e] M. G. J. Beets, H. Van Essen and W. Meerburg, *Recl. Trav. Chim. Pays-Bas*, 77, 854 (1958). [f] F. Ramirez and A. F. Kirby, *J. Amer. Chem. Soc.*, 74, 4331 (1952).

to pure hydrocarbons.[2e] However, in some cases, the available ketone and/or the resulting hydrocarbon could not be brought to the required purity, and it became necessary to resort to preparation of carbonyl derivatives for purification,[3] but, since the hydrocarbon was the desired product and the purified ketone was not required, we decided to investigate direct hydrogenolysis of carbonyl derivatives to hydrocarbons.

As applied to benzophenone (**1a**) or acetophenone (**2a**), which were used to screen for the most suitable derivative, the 2,4-dinitrophenylhydrazone appears to be the most effective derivative for hydrogenolysis to pure **1b** and **2b**. The results of hydrogenolysis experiments applied to several carbonyl derivatives are shown in Table I.



y = O	2a	3a	4a	5a
y = H_2	b	b	b	b
y = $NNHC_6H_3(NO_2)_2$	c	c	c	c
y = NNHCNH$_2$	d	d		
y = $NNHC_6H_5$	e			
y = NOH	f			

Gas–liquid chromatography (glc) studies were used to determine the extent of hydrogenolysis and hydrogenation. For example, acetophenone phenylhydrazone (**2e**) gave some phenethylamine as well as cyclohexylamine. Additional hydrogenolysis converted the former to ethylbenzene, and extraction with aqueous hydrochloric acid removed the latter. Glc studies were also used to identify the hydrocarbon hydrogenolysis products and to determine the yield of **1b**, **2b**, **3b**, **4b**, and **5b**. The nitrogenous hydrogenolysis–hydrogenation products of oximes, semicarbazones, and 2,4-dinitrophenylhydrazones were not investigated.

In general, the hydrogenolyses could be brought to completion in 3–7 hr. However, **3a** and its derivatives **3c** and **3d** were resistant to hydrogenolysis as compared to **1a** and **2a** and their derivatives. As a result of prolonged treatment, "overhydrogenation" was observed for **3a** and **3d** but surprisingly, the 2,4-dinitrophenylhydrazone **3c** cleanly hydrogenolyzed to the corresponding hydrocarbon **3b**.[4] Overhydrogenation may result from prolonged or severe treatment of **1a** or **2a** and their derivatives. This was absent in **4a** and **5a** and their 2,4-dinitrophenylhydrazones.

Experimental Section

General Hydrogenolysis Procedure.—The purified carbonyl derivative (0.03 mol) was introduced into a 300-ml stainless steel hydrogenation vessel containing 50 ml of acetic acid and 0.6 g of 10% Pd/C catalyst.[5a] The vessel was evacuated, hydrogen was introduced, and the vessel was shaken at 30–50 psi at 50–60° until the pressure drop ceased.[5b] Excess hydrogen was vented, and the vessel contents were filtered through Dicalite to remove the catalyst. The filtrate was diluted with 200 ml of water and extracted with ether (two 100-ml portions), and the extract was washed with 10% NaOH (two 100-ml portions), dried ($MgSO_4$), and concentrated by distillation or evaporation under reduced pressure. Other details are given in Table I.

Preparation of Carbonyl Derivatives.—The carbonyl derivatives used were prepared according to published procedures (Table I) and were purified by recrystallization from 95% ethanol except for **3c**, (2,4-DNP), which was best purified by successive recrystallization from nitroethane[6] and isopropyl alcohol.

Glc Studies of Hydrogenolysis Products.—A standard solution of the product hydrocarbon in ether (*ca.* 2%) was prepared, and the glc curve was obtained[7a] with duplicate or more injections (4 μl) onto a 0.25 in. × 11 ft column of 5% UC W-98[7b] coated on 80–100 mesh, acid-washed, DMCS-treated Chromosorb G heated at 190°. The peak areas of average injections were used to compare with peak areas obtained for each hydrogenolysis product. The yields (Table I) were derived from these data and also gravimetrically for benzophenone derivatives.

Acknowledgments.—We are grateful to the American Petroleum Institute for partial support of this work through Research Project 58A. We thank Dr. O. C. Dermer for having read the manuscript and the Research Foundation of Oklahoma State University for some assistance.

(3) H. R. Harrison and E. J. Eisenbraun, *J. Org. Chem.*, **31**, 1294 (1966).

(4) We are grateful to T. F. Wood, P. Porcaro, and A. Hochstetler of Givaudan Corp. for samples and analytical studies (nmr, mass spectrum, glc) which showed that hydrocarbons giving molecular ions at *m/e* 234 and 236 were present after hydrogenolysis of **3a**, *m/e* 244, to **3b**, *m/e* 230.

(5) (a) The 10% Pd/C catalyst was purchased as a stock item from Engelhard Industries. (b) A Parr Model 3920 hydrogenation apparatus was used.

(6) Nitroethane shows considerable promise as a recrystallizing solvent for otherwise insoluble 2,4-dinitrophenylhydrazones.

(7) (a) A Hewlett-Packard 5750B glc apparatus equipped with dual thermal conductivity filaments was used. (b) A Union Carbide Chemicals Co. methyl vinyl silicone purchased from Applied Science Laboratories, State College, Pa.

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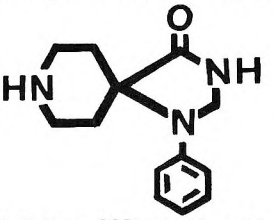

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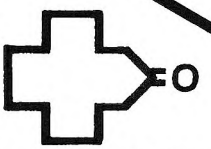
(1) Nature, 229, 149 (Jan. 15, 1971).
(2) A. Villeneuve et al, Curr. Therap. Res. 12, 819 (Dec. 1970).
(3) J. P. P. Heykants, Life Sci. 8, 1029 (1969).



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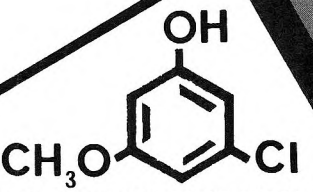

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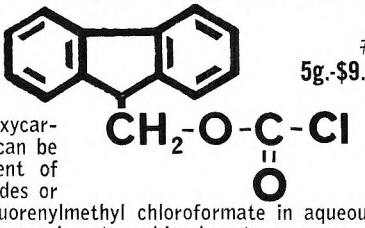

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(1) L.A. Carpino and G.Y. Han, J. Am. Chem. Soc., 92, 5748 (1970).

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