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THE JOURNAL OF Organic Chemistry®

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DECEMBER 3, 1971

Optically Active Amines. XII.[1] Synthesis and Spectral Properties of Some Optically Active α-Oximino Ketones and α-Amino Ketone Hydrochlorides. Dimerization of α-Amino Ketones[2]

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Received February 1, 1971

A number of α-oximino ketones, some with a steroidal carbon skeleton, were prepared. On the basis of their uv (isotropic absorption) spectra, they are assigned the anti oximino configuration. Their CD spectra in ethanol show a maximum near 340 nm associated with the carbonyl n → π* transition. This maximum is similar in sign and magnitude to that of a cisoid α,β-unsaturated ketone of the same chirality. A second maximum near 270 nm is tentatively assigned to the nitrogen n → π* transition. In 1 *N* ethanolic potassium hydroxide, CD maxima are observed for n → π* and π → π* transitions. The α-oximino ketones were reduced to the α-amino ketone hydrochlorides in ethanolic hydrogen chloride with hydrogen over a palladium catalyst. The CD spectra of the α-amino ketone hydrochlorides are interpreted on the basis of an antioctant contribution of the ammonium group. Treatment of the hydrochlorides of 3-amino-4-methyl-2-pentanone, 2-aminocyclopentanone, 2-aminocyclohexanone, 2α-amino-5α-androstan-17β-ol-3-one, (1*R*,3*S*)-3-amino-2-bornanone, and 16β-amino-5α-androstan-3α- and -3β-ol-17-one with bases causes the formation of the corresponding α-amino ketones. The latter condense to tautomeric mixtures of the dihydropyrazines. Only 16β-amino-5α-androstan-3α- and -3β-ol-17-one could be isolated free of the dihydropyrazines. Dihydropyrazines with alkyl or cyclohexano substituents are oxidized by air to the corresponding pyrazines. Attempts to oxidize the mixture of dihydropyrazines formed from 16β-amino-5α-androstan-3α-ol-17-one with hydrogen peroxide in aqueous potassium hydroxide gave only the *seco*-16,17-dioic acid. The dihydropyrazines formed by dimerization of (1*R*,3*S*)-3-amino-2-bornanone were oxidized in dioxane–water with sulfuric acid–sodium nitrite, and di[(1*R*)-bornano][2,3-*b*:2′,3′-*e*]pyrazine was isolated. Most of the steroidal α-oximino ketones and α-amino ketone hydrochlorides show no endocrine activity. 2α-Amino-5α-androstan-17β-ol-3-one hydrochloride has moderate antiuterotropic activity, but it is toxic.

In connection with our continuing interest in the stereochemistry and spectral properties of optically active amines,[1] we undertook the synthesis of a number of optically active primary α-amino ketones, for the most part those having a steroidal skeleton.

Although 16ξ-amino-5-androsten-3β-ol-17-one has been reported without characterization,[4] other steroidal primary α-amino ketones prepared earlier[5–7] have the amino group at a tertiary carbon atom in a sterically hindered environment.[5] The amino group is resistant toward futher reaction such as N substitution or dimerization to the corresponding dihydropyrazine.[8] Steroidal primary α-amino ketones with the amino group on a secondary carbon atom would be more reactive and might possess unusual biological properties. If the optically active α-amino ketones dimerize, oxidation of the resulting mixture of dihydropyrazines[8,9] would lead to a group of optically active pyrazines.

The successful reduction of α-oximino ketones in ethanolic hydrogen chloride with hydrogen over a palladium catalyst to α-amino ketone hydrochlorides[10] suggested the use of steroidal α-oximino ketones for the preparation of steroidal α-amino ketones having the amino group on a secondary carbon atom.

We now record the synthesis of a number of steroidal α-oximino ketones as well as a number of model compounds (Chart I) by way of the nitrosation of the corresponding ketones.[11] Most of these α-oximino ketones were reduced to the corresponding α-amino ketone hydrochlorides. On treatment with bases, the latter dimerize to a tautomeric mixture of the corresponding dihydropyrazines. Oxidation of some of the dihydropyrazines affords the respective pyrazines **11–15**.

(1) Paper XI: H. E. Smith and T. C. Willis, *J. Amer. Chem. Soc.*, **93**, 2282 (1971).

(2) Taken from the Ph.D. Dissertation of A. A. H., Vanderbilt University, Jan 1970. A preliminary report has appeared: H. E. Smith and A. A. Hicks, *Chem. Commun.*, 1112 (1970).

(3) NIH Predoctoral Fellow, 1967–1969.

(4) A. Hassner and A. W. Coulter, *Steroids*, **4**, 281 (1964).

(5) D. F. Morrow, M. E. Brokke, G. W. Moersch, M. E. Butler, C. F. Klein, W. A. Neuklis, and E. C. Y. Huang, *J. Org. Chem.*, **30**, 212 (1965).

(6) D. F. Morrow, M. E. Butler, and E. C. Y. Huang, *ibid.*, **30**, 579 (1965).

(7) G. Snatzke and A. Veithen, *Justus Liebigs Ann. Chem.*, **703**, 159 (1967).

(8) R. Zell, H. Brintzinger, B. Prijs, and H. Erlenmeyer, *Experientia*, **20**, 117 (1964).

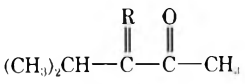
(9) H. E. Baumgarten and F. A. Bower, *J. Amer. Chem. Soc.*, **76**, 4561 (1954).

(10) W. H. Hartung, *ibid.*, **53**, 2248 (1931).

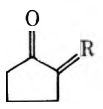
(11) O. Touster, *Org. React.*, **7**, 327 (1953).

In two cases, the α-amino ketones **7d** and **8d** were isolated.

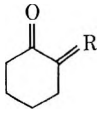
CHART I



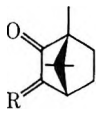
1a, R = H_2
b, R = *anti*-NOH
c, R = H and NH_3Cl



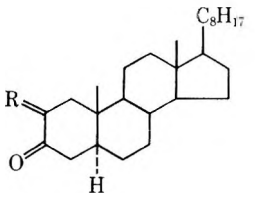
2a, R = H_2
b, R = NOH
c, R = H and NH_3Cl



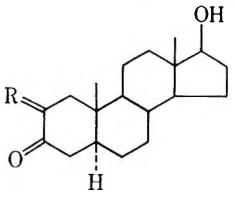
3a, R = H_2
b, R = NOH
c, R = H and NH_3Cl



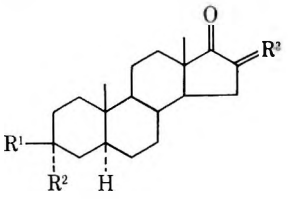
4a, R = H_2
b, R = *anti*-NOH
c, R = *exo*-H and *endo*-NH_3Cl



5a, R = H_2
b, R = *anti*-NOH

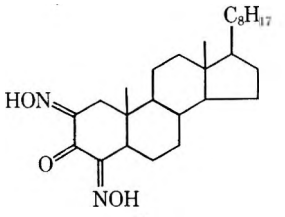


6a, R = H_2
b, R = *anti*-NOH
c, R = β-H and α-NH_3Cl



7a, R^1 = OH; R^2 = H; R^3 = H_2
b, R^1 = OH; R^2 = H; R^3 = *anti*-NOH
c, R^1 = OH; R^2 = H; R^3 = α-H and β-NH_3Cl
d, R^1 = OH; R^2 = H; R^3 = α-H and β-NH_2

8a, R^1 = H; R^2 = OH; R^3 = H_2
b, R^1 = H; R^2 = OH; R^3 = *anti*-NOH
c, R^1 = H; R^2 = OH; R^3 = α-H and β-NH_3Cl
d, R^1 = H; R^2 = OH; R^3 = α-H and β-NH_2



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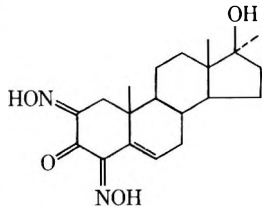

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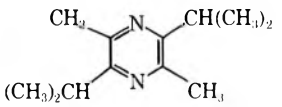

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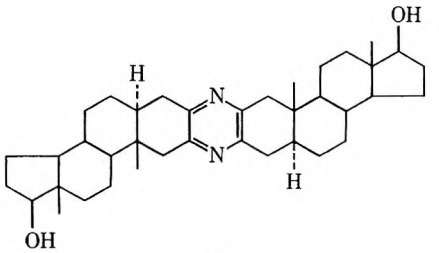

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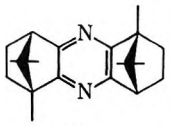

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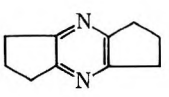

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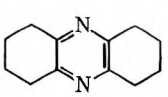

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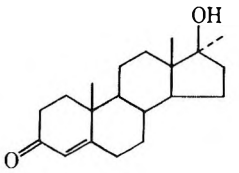
Results and Discussion

Synthesis of α-Oximino Ketones.—The successful nitrosation of several steroidal ketones,[12-14] including 5α-cholestan-3-one[12] (**5a**), 5α-androstan-17β-ol-3-one[13] (**6a**), and 5α-androstan-3β-ol-17-one[14] (**7a**) indicated that isoamyl nitrite or 2-octyl nitrite with potassium *tert*-butoxide in *tert*-butyl alcohol would be the most successful nitrosating agent. 2-Octyl nitrite was used to prepare 4-methyl-*anti*-3-oximino-2-pentanone[15] (**1b**), but the 2-oximino derivatives of cyclopentanone (**2a**) and cyclohexanone (**3a**) could not be prepared by nitrosation with 2-octyl nitrite in either a base-catalyzed or an acid-catalyzed reaction. Both 2-oximinocyclopentanone[16,17] (**2b**) and 2-oximinocyclohexanone[16,18] (**3b**) were prepared from the respective 2-ethoxycarbonyl cyclic ketones using sodium nitrite in sodium hydroxide.[17] As reported earlier,[18] **3b** was obtained only as a yellow oil. The latter was directly reduced to 2-aminocyclohexanone hydrochloride[19] (**3c**).

After (1*R*)-2-bornanone[20] (**4a**) [(+)-camphor] in *tert*-butyl alcohol was treated with 2-octyl nitrite in the presence of potassium *tert*-butoxide, none of the expected α-oximino ketone was isolated. Treatment of the sodium salt of **4a** in ether with 2-octyl nitrite gave (1*R*)-*anti*-3-oximino-2-bornanone[21] (**4b**).

The preparation of *anti*-2-oximino-5α-cholestan-3-one[12] (**5b**), *anti*-2-oximino-5α-androstan-17β-ol-3-one[13] (**6b**), *anti*-16-oximino-5α-androstan-3β-ol-17-one[14] (**7b**), and *anti*-16-oximino-5α-androstan-3α-ol-17-one (**8b**) was accomplished with a less than equivalent amount of 2-octyl nitrite in the presence of potassium *tert*-butoxide in *tert*-butyl alcohol. Treatment of 17α-methyl-4-androsten-17β-ol-3-one (**16**) with a less than equivalent amount of 2-octyl nitrite led to a mixture of monooximino and bisoximino ketones from which no pure



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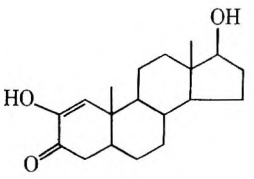
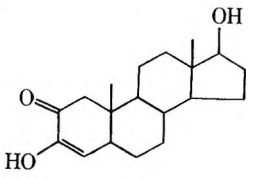


17a



17b

compound could be isolated. When a large excess of 2-octyl nitrite and potassium *tert*-butoxide is used with ketones with more than one site for nitrosation, the

(12) J. C. Sheehan and W. F. Erman, *J. Amer. Chem. Soc.*, **79**, 6050 (1957).
(13) G. Ohta, T. Takegoshi, K. Ueno, and M. Shimizu, *Chem. Pharm. Bull.*, **13**, 1445 (1965); *Chem. Abstr.*, **64**, 9785c (1966).
(14) J. L. Mateos, O. Chao, and H. Flores R, *Tetrahedron*, **19**, 1051 (1963).
(15) K. L. Hoy and W. H. Hartung, *J. Org. Chem.*, **23**, 967 (1958).
(16) The configuration(s) of the carbon to nitrogen double bond(s) is (are) unassigned.
(17) A. C. Cope, L. L. Estes, Jr., J. R. Emery, and A. C. Haven, Jr., *J. Amer. Chem. Soc.*, **73**, 1199 (1951).
(18) T. A. Geissman and M. J. Schlatter, *J. Org. Chem.*, **11**, 771 (1946).
(19) H. E. Baumgarten and J. M. Petersen, *J. Amer. Chem. Soc.*, **82**, 459 (1960).
(20) A. Fredga and J. K. Miettinen, *Acta Chem. Scand.*, **1**, 371 (1947).
(21) L. Claisen and O. Manasse, *Justus Liebigs Ann. Chem.*, **274**, 71 (1893).

TABLE I

SPECTRAL DATA FOR SOME α-OXIMINO KETONES

	Absolute ethanol		1 N ethanolic KOH	
	Uv	CD	Uv	CD
Compd	λ_{max}, nm (ϵ^a)	λ_{max}, nm ($[\theta]^b$)	λ_{max}, nm (ϵ^a)	λ_{max}, nm ($[\theta]^c$)
1b	315 (43),[d] 231 (10,000)		380 (59), 282 (15,000)	
2b	243 (8700)[e]		[f]	
4b	335 (39), 242 (9300)	335 (+1400), 243 (+24,000)	380 (70),[d] 290 (15,000)	385 (+1000), 336 (−5300), 290 (+36,000)
5b	[g]	[g]	400 (77), 299 (14,000)	420 (+330), 334 (−1400), 300 (+1500)
6b	340 (33),[d] 243 (7300)	342 (+2600), 277 (−2000)	410 (62), 300 (13,000)	425 (+1200), 332 (−4700), 305 (+4500)
7b	344 (58), 239 (10,000)	347 (+5300), 263 (−8400)	385 (93),[d] 292 (17,000)	420 (−560), 322 (+7600), 287 (−6400)
8b	345 (52), 238 (9900)	347 (+5800), 263 (−8600)	385 (73),[d] 290 (22,000)	420 (−410), 387 (−380), 365 (−460), 323 (+5500), 285 (−8400)

[a] Molar absorptivity. [b] Molecular ellipticity at 25–28° with c 0.0020–0.085 g/100 ml. [c] Molecular ellipticity at 25–28° with c 0.00078–0.14 g/100 ml. [d] Shoulder. [e] No absorption maximum or shoulder detected at a wavelength longer than 243 nm. [f] Decomposed in 1 N ethanolic KOH. [g] Too insoluble for measurement.

α,α′-bisoximino ketones are formed. In this way both 2,4-bisoximinocholestan-3-one[16,22,23] (**9**) and 2,4-bisoximino-17α-methyl-5-androsten-17β-ol-3-one[16] (**10**) were prepared, the latter from 17α-methyl-4-androsten-17β-ol-3-one (**16**).

Among the α-oximino ketones in Chart I, there are only four (**1b**, **5b**, **6b**, and **10**) whose parent ketones possess more than one distinct site for nitrosation.[11] The structure of **1b** is known[15] and is now confirmed by its nmr spectrum. For both **5b** and **6b**, the 2-oximino structure was assigned earlier.[12,13] The structure of **6b** is now verified by its conversion with sodium sulfite in acetic acid to androstan-17β-ol-2,3-dione[22,24,25] (**17**), which in deuteriochloroform is a mixture of the enol ketones **17a** and **17b**, the nmr spectrum showing, as expected,[26] two distinct vinylic proton signals. The structure of **10** is assigned in analogy to the nitrosation of 4-androsten-17β-ol-3-one with *n*-butyl nitrite and potassium *tert*-butoxide in *tert*-butyl alcohol which gives 2,4-bisoximino-5-androsten-17β-ol-3-one.[23]

For the α-oximino ketones **1b**, **4b**, and **6b**–**8b**, the anti configuration for the carbon–nitrogen double bond is assigned on the basis of their uv (isotropic absorption) spectra (Table I), a bathochromic shift of 50–60 nm for the absorption band near 240 nm occurring when the solvent is changed from ethanol to 1 N ethanolic potassium hydroxide. For the syn configuration a shift of this magnitude is not to be expected.[14,27,28] The low solubility of **5b** in ethanol is such that its uv spectrum in this solvent could not be measured. It is assigned the anti configuration on the basis of the similarity of its uv spectrum in 1 N ethanolic potassium hydroxide to that of **6b** in the same solvent. The configurations of the oximino groups in **2b**, which decomposes in 1 N ethanolic potassium hydroxide, in **3b**, which was obtained as an oil,[18] and in the α,α′-bisoximino ketones **9** and **10** are not assigned.[23]

Synthesis of α-Amino Ketone Hydrochlorides.—As reported earlier,[15] 4-methyl-*anti*-3-oximino-2-pentanone (**1b**) is smoothly reduced with hydrogen over 10% palladium on carbon in absolute ethanol containing 3 mol of hydrogen chloride per mole of ketone. The same reaction was used to prepare 2α-amino-5α-androstan-17β-ol-3-one hydrochloride (**6c**), 16β-amino-5α-androstan-3β-ol-17-one hydrochloride (**7c**), and 16β-amino-5α-androstan-3α-ol-17-one hydrochloride (**8c**) from the respective α-oximino ketones (**6b**–**8b**). The insolubility of *anti*-2-oximino-5α-cholestan-3-one (**5b**) in ethanolic hydrogen chloride precluded its reduction by this procedure. Application of this method to the reduction of (1*R*)-*anti*-3-oximino-2-bornanone (**4b**) gave (1*R*,3*S*)-3-amino-2-bornanone hydrochloride[21] (**4c**) in 7% yield, 54% of **4b** being recovered. A more complete conversion of **4b** to **4c** was accomplished by reduction of **4b** with zinc in aqueous sodium hydroxide and subsequent treatment of the resulting α-amino ketone with hydrogen chloride.[21]

No characterizable product was obtained from the catalytic reduction of 2-oximinocyclopentanone (**2b**) while the same procedure when applied to 2-oximinocyclohexanone (**3b**) gave 2-aminocyclohexanone hydrochloride[19] (**3c**) in only 7% yield. As described earlier,[19] both 2-aminocyclopentanone hydrochloride (**2c**) and **3c** were prepared in good yield by treatment of cyclopentylamine and cyclohexylamine, respectively, with *tert*-butyl hypochlorite.

With the exception of **2c**, the structures of the α-amino ketone hydrochlorides in Chart I follow from the

(22) There is no direct evidence concerning the configuration at C-5 in this compound.

(23) M. P. Cava, E. J. Glamkowski, and P. M. Weintraub, *J. Org. Chem.*, **31**, 2755 (1966).

(24) H. Dannenbery, D. D.-v. Dresler, and T. Köhler, *Chem. Ber.*, **93**, 1989 (1960).

(25) M. N. Huffman, *J. Biol. Chem.*, **167**, 273 (1947).

(26) C. R. Noller, A. Melera, M. Gut, J. N. Shoolery, and L. F. Johnson, *Tetrahedron Lett.*, No. 15, 15 (1960).

(27) D. H. R. Barton and J. M. Beaton, *J. Amer. Chem. Soc.*, **83**, 4083 (1961).

(28) M. P. Cava and B. R. Vogt, *J. Org. Chem.*, **30**, 3775 (1965).

structures of the α-oximino ketones from which they were prepared by reduction with hydrogen. The structure of **2c** was assigned earlier.[19]

The configuration of (1*R*,3*S*)-3-amino-2-bornanone hydrochloride (**4c**) follows from its nmr spectrum and the known absolute configuration of (1*R*)-2-bornanone (**4a**).[20] As has been shown with (1*R*,3*S*)-3-amino-2-bornanone,[29] the C-3 proton signal in the nmr spectrum of **4c** is a doublet with a coupling constant of 4.5 Hz as the result of the coupling of the C-3 proton with that at C-4. Application of the Karplus relationship[30] gives a value of approximately 40° for the dihedral angle between the C-3 and C-4 protons. Hence, the hydrogen atom at C-3 has the exo and the ammonium group has the endo configuration.

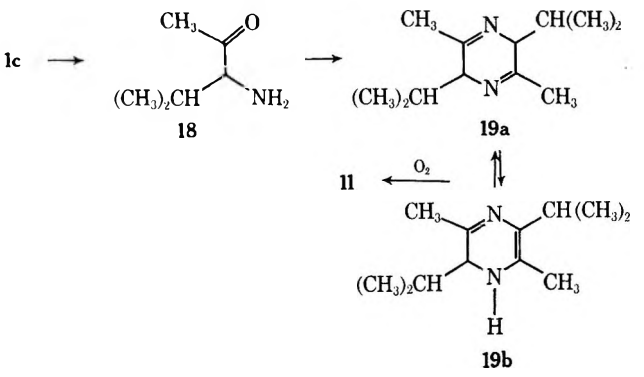
The configuration at C-2 in 2α-amino-5α-androstan-17β-ol-3-one hydrochloride (**6c**) is assigned on the assumption that the reduction of **6b** in strong acidic medium gives the more thermodynamically stable, equatorial epimer. This assignment is confirmed by CD studies of the α-amino ketone hydrochlorides discussed below.

The configuration at C-16 for 16β-amino-5α-androstan-3β- and -3α-ol-17-one hydrochloride (**7c** and **8c**) is assigned in analogy to the assignments made for 16-bromo-17-keto steroids.[31,32] The 16α and 16β bonds in the latter are bisectional,[31,32] each possessing the same degree of axial and equatorial character.[32] A substituent at either the 16α or 16β position will then have the same dihedral angle with the carbonyl bond. Equilibration studies of 16α- and 16β-bromo-5α-androstan-17-one[33] show that the 16β-bromo isomer is the more thermodynamically stable. Dipole–dipole interactions of the C-16 substituents with the carbonyl group must play only a minor role in this difference in stability. It is a good assumption that for the 16α- and 16β-amino hydrochloride derivatives of 17-keto steroids, it is the 16β-ammonium epimer which is the more thermodynamically stable. Also since the angular methyl group at C-13 shields the β face of a 16-oximino 17-keto steroid,[34] the kinetically controlled product of the catalytic reduction is the 16β-ammonium isomer.

Dimerization of α-Amino Ketones.—Treatment of 3-amino-4-methyl-2-pentanone hydrochloride[15] (**1c**) with 10% aqueous sodium hydroxide resulted in the dimerization of the resulting α-amino ketone **18** to a mixture of the dihydropyrazines **19** (Scheme I). This mixture is spontaneously oxidized by air to 2,5-diisopropyl-3,6-dimethylpyrazine (**11**). An ethereal extract of the reaction mixture was examined immediately, and its nmr spectrum showed signals only for the α-amino ketone **18** and the pyrazine **11**. When an aqueous solution of this material containing sodium hydroxide stood at room temperature, **11** precipitated. No dihydropyrazine was detected. Without direct evidence, it is assumed that the mixture of dihydropyrazines is composed of a number of substances, **19a**, **19b**, and other double bond isomers of **19a** and **19b**.

(29) O. E. Edwards and M. Lesage, *Can. J. Chem.*, **41**, 1592 (1963).
(30) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(31) J. Fishman and C. Djerassi, *Experientia*, **16**, 138 (1960).
(32) F. V. Brutcher, Jr., and W. Bauer, Jr., *J. Amer. Chem. Soc.*, **84**, 2236 (1962).
(33) J. Fajkos, *J. Chem. Soc.*, 3966 (1959).
(34) J. Fishman, *J. Org. Chem.*, **31**, 520 (1966).

SCHEME I

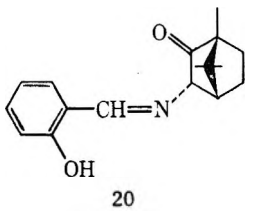


An aqueous solution of 2α-amino-5α-androstan-17β-ol-3-one hydrochloride (**6c**) was neutralized with aqueous sodium carbonate. The resulting yellow precipitate had an ir spectrum which showed weak carbonyl absorption at 1730 cm^{-1} and a stronger, broad band near 1670 cm^{-1}. The latter is attributed to the azomethine group of the dihydropyrazines. When the precipitate was dissolved in ethanol containing a trace of *p*-toluenesulfonic acid, the solution immediately became dark orange, and during 30 min di-(17β-hydroxy-5α-androstano)[2,3-*b*:2′,3′-*e*]pyrazine (**12**) precipitated as white needles.

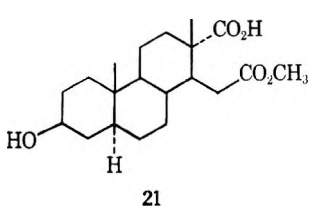
An aqueous solution of (1*R*,3*S*)-3-amino-2-bornanone hydrochloride (**4c**) was neutralized with 10% aqueous sodium hydroxide. A carbon tetrachloride extract of the reaction mixture was examined immediately. Its nmr spectrum showed signals for only the α-amino ketone. In subsequent spectra, these signals decreased in intensity and in 11.5 hr were replaced by other signals. The latter are assigned to a mixture of the dihydropyrazines. Preparative tlc on silica gel separated this mixture into three fractions. Removal of the main fraction and its reexamination with tlc separated the material into the same three fractions.

The pyrazine **13** was not detected in any of these experiments. Also, the α-amino ketone could not be isolated free of the dihydropyrazines. Treatment of an ethereal solution of the α-amino ketone with salicylaldehyde gave (1*R*,3*S*)-3-salicylidenimino-2-bornanone (**20**).

A methanolic solution of 16β-amino-5α-androstan-3β-ol-17-one hydrochloride (**7c**) was neutralized with 10% aqueous sodium hydroxide. The solution was stirred in air overnight. After dilution with water, no product was extracted from this solution with ether. Upon acidification of the solution, the 16-methyl ester of 16,17-*seco*-5α-androstan-3β-ol-16,17-dioic acid (**21**) was isolated.



20

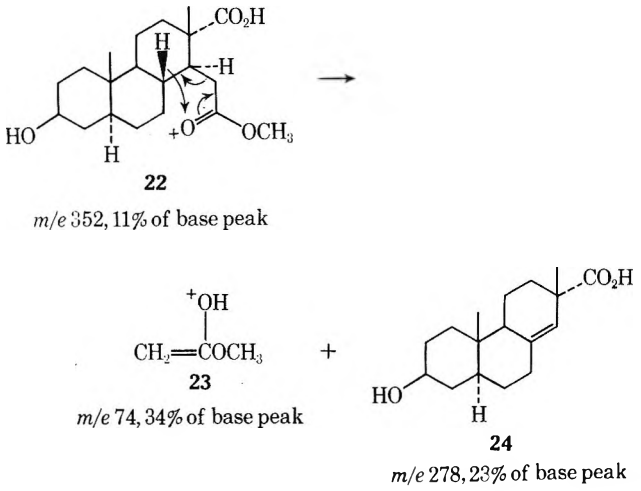


21

The ir and nmr spectra and other properties of this acid were compatible with **21** but also with the 17-methyl ester as an alternate. The mass spectrum of the compound has a parent ion (**22**) with *m/e* 352 and

two other significant ions with m/e 74 and 278. That with m/e 74 corresponds to a fragment (**23**) from a methyl ester possessing a γ-hydrogen atom capable of cleavage while undergoing a McLafferty rearrangement[35] (Scheme II). The ion with m/e 278 corresponds

SCHEME II



to the residual molecular fragment **24** after rearrangement. The 17-methyl ester molecular ion when rearranged would result in an ion of the same mass.

In another experiment, an aqueous solution of 16β-amino-5α-androstan-3β-ol-17-one hydrochloride (**7c**) was neutralized with aqueous sodium bicarbonate. A yellow precipitate of 16β-amino-5α-androstan-3β-ol-17-one (**7d**) formed. Although it was stable as the amorphous solid and as a solution in methanol under nitrogen, it could not be crystallized. Identification was made on the basis of its ir and mass spectra, but it was not characterized further. Heating of a benzene or of a chloroform solution of **7d** containing a trace of *p*-toluenesulfonic acid and then removal of the solvent gave an oil which on examination of its ir spectrum showed reduced carbonyl absorption at 1750 cm^{-1} and a very broad absorption at 1670–1730 cm^{-1}. The spectrum indicated that condensation to the dihydropyrazines had occurred. No pure compound could be isolated from this mixture.

Similarly, an aqueous solution of 16β-amino-5α-androstan-3α-ol-17-one hydrochloride (**8c**) was neutralized with aqueous sodium bicarbonate. The corresponding 16β-amino-5α-androstan-3α-ol-17-one (**8d**) was isolated. This α-amino ketone was also stable as the crystalline, yellow solid or as a methanolic solution under nitrogen. It was reprecipitated from ether on cooling. The original α-amino ketone hydrochloride **8c** and 16β-salicylidenimino-5α-androstan-3α-ol-17-one were readily prepared from the free base. The α-amino ketone apparently forms a mixture of dihydropyrazines when heated in chloroform containing a trace of *p*-toluenesulfonic acid. No pure compound could be isolated from this mixture.

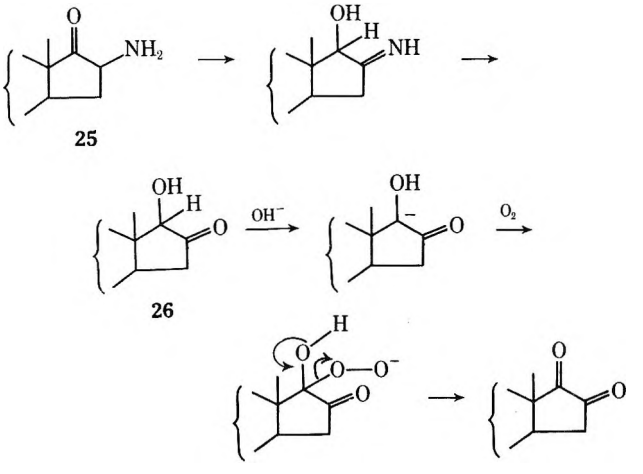
Oxidation of Dihydropyrazines.—A mixture of dihydropyrazines with alkyl or with cyclohexano substituents are spontaneously oxidized in air.[8,9] (1*R*,3*S*)-3-Amino-2-bornanone and the 16β-amino-5α-androstan-17-ones form dihydropyrazines which are stable in air. The reported[9] rapid oxidation with hydrogen peroxide in potassium hydroxide of the dihydropyrazines from dimerization of 2-aminocyclohexanone suggested the use of this reagent for the oxidation of the air stable dihydropyrazines.

Using this reagent, an attempt was made to oxidize the dihydropyrazine mixture formed from 16β-amino-5α-androstan-3α-ol-17-one hydrochloride (**8c**). No basic or neutral material was isolated from this reaction. The product was an acid which, although not completely characterized, is assumed to be the *seco*-16,17-dioic acid. This conclusion is based on the similarity of this peroxide oxidation to the air oxidation of 16β-amino-5α-androstan-3β-ol-17-one in methanolic sodium hydroxide and on the examination of the products formed on treatment of 2-aminocyclopentanone hydrochloride[19] (**2c**) and 2-aminocyclohexanone hydrochloride[9,19] (**3c**) with aqueous potassium hydroxide and then hydrogen peroxide.

With these reagents, **2c** gave dicyclopentano[*b*,*e*]pyrazine (**14**) in 47% yield. After acidification of the reaction mixture there was also obtained a small amount of glutaric acid. Also, **3c** was converted to dicyclohexano[*b*,*e*]pyrazine[9,36,37] (**15**) and adipic acid in 35 and 38% yield, respectively. No reference to adipic acid was made in the original report of the latter oxidation.[9]

A route for the formation of the *seco*-16,17-dioic acid from 16β-amino-5α-androstan-3α-ol-17-one (**8d**) as well as glutaric and adipic acid is shown in Scheme III.

SCHEME III



This same route will explain the formation of the 16-methyl ester of 16,17-*seco*-5α-androstan-3β-ol-16,17-dioic acid (**21**) on treatment of 16β-amino-5α-androstan-3β-ol-17-one hydrochloride (**7c**) in methanol with sodium hydroxide. As seen in Scheme III, an α-amino ketone **25** is converted to the α-hydroxy ketone **26**. A similar acid-catalyzed conversion was proposed to explain the conversion of 16ξ-amino-5-androsten-3β-ol-17-one to 5-androsten-3β,17β-diol-16-one.[4] A steroidal 2,3-dione was found to be oxidized to a *seco*-2,3-dioic acid with an aqueous mixture of potassium hydroxide and hydrogen peroxide.[38]

(35) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, pp 155–162 and 176–178.

(36) An alternate name for **15** is 1,2,3,4,6,7,8,9-octahydrophenazine.

(37) P. A. S. Smith, *J. Amer. Chem. Soc.*, **70**, 323 (1948).

(38) R. Hanna and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1945 (1961).

After the mixture of dihydropyrazines formed from (1*R*,3*S*)-3-amino-2-bornanone hydrochloride (**4c**) was heated with an aqueous mixture of potassium hydroxide and hydrogen peroxide, the mixture of dihydropyrazines was recovered unchanged. The mixture is readily oxidized in dioxane–water with sulfuric acid–sodium nitrite,[39] and di[(1*R*)-bornano][2,3-*b*:2′,3′-*e*]pyrazine[39] (**13**) was isolated.

Circular Dichroism Studies.—For the α-oximino ketones in absolute ethanol the weak uv absorption maximum at 315–345 nm (Table I) is assigned to the n → π* transition of the carbonyl group. Assuming that the α-oximino carbonyl chromophore is rotationally similar to a cisoid α,β-unsaturated ketone and that the preferred chirality of the chromophore fixes the sign of the Cotton effect associated with the carbonyl n → π* transition,[40,41] the observed positive Cotton effect (Table I) is predicted for this transition of *anti*-2-oximino-5α-androstan-17β-ol-3-one (**6b**).[42] In an octant projection,[41] the oximino π bond lies in the lower right or upper left far octant. The sign of this Cotton effect is the same but the molecular ellipticity at the maximum is about one-half that of the carbonyl n → π* transition Cotton effect of the parent ketone **6a** (Table II). Similarly, the observed positive Cotton effect is predicted for *anti*-16-oximino-5α-androstan-3β- and -3α-ol-17-one (**7b** and **8b**). Again, this Cotton effect is of the same sign but reduced in molecular ellipticity as compared with the carbonyl n → π* Cotton effect in the parent ketones. In **7b** and **8b**, the CD maxima are similar in sign and magnitude to that at 354 nm ([θ] +5700) shown by 16-methylene-19-nor-androst-4-en-17-one[43] (**27**). In the octant projections of **7b**, **8b**, and **27**, the carbon–nitrogen or the carbon–carbon π bond at C-16 lies in the lower right or upper left far octant.

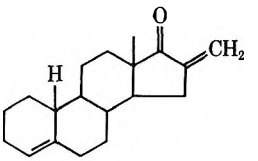
TABLE II

SPECTRAL DATA FOR SOME α-AMINO KETONE HYDROCHLORIDES IN ABSOLUTE ETHANOL

Compd	Uv λmax, nm (ε[a])	CD λmax, nm ([θ][b])
4a	290 (31)	295 (+5300)
4c	295 (27)[c]	318 (+1800),[c,d] 310 (+2200), 275 (−480)
6a	285 (22)	288 (+4400)
6c	284 (27)	286 (+5800)
7a	300 (40)	297 (+13,000)[e]
7c	300 (32)	309 (+8000)
8a	295 (43)	297 (+13,000)
8c	300 (36)	309 (+8100)

[a] Molar absorptivity. [b] Molecular ellipticity at 25–28° with *c* 0.010–0.10 g/100 ml. [c] Methanol was the solvent for this spectrum. [d] Shoulder.

In the CD spectra of **6b**, **7b**, and **8b** in absolute ethanol, there is also a negative maximum near 270 nm. This maximum is tentatively assigned to the nitrogen n → π* transition. The isotropic absorption band associated with this CD maximum is obscured by the strong π → π* absorption band centered near 240 nm. The latter absorption band is very intense and any CD associated with the transition could not be observed.



27

The oximino group and the carbonyl group in (1*R*)-*anti*-3-oximino-2-bornanone (**4b**) are coplanar. A positive CD maximum at 335 nm is observed for the carbonyl n → π* transition of **4b** in absolute ethanol. No dichroic absorption maximum in the 263–277-nm region was observed, but a strong positive maximum at 243 nm is associated with the π → π* transition. The absence of an oximino n → π* and the observation of a strong π → π* dichroic absorption band in the spectrum of **4b** is similar to observations made with optically active saturated oximes and testosterone oxime.[42] For these compounds only Cotton effects associated with a π → π* transition are observed.

When the α-oximino ketones are dissolved in 1 *N* ethanolic potassium hydroxide, the anionic form of the chromophore is produced. The uv bands due to the carbonyl n → π* and π → π* transitions are now at 380–410 and 280–300 nm, respectively. These transitions give rise to CD maxima. A CD maximum, tentatively assigned to the n → π* transition of the oximino group is also found near 330 nm. The uv absorption band for this latter transition is obscured by the π → π* absorption band at 280–300 nm. For **4b** and **6b** in 1 *N* ethanolic potassium hydroxide, the signs of the respective Cotton effects are the same as those in ethanol. There is probably a small distortion in the preferred conformations of the respective rings and now a negative CD maximum is observed for the oximino n → π* transition in **4b**. For **7b** and **8b**, the respective CD maxima have changed sign. This probably reflects a large change in the preferred conformation of the D ring.

As seen in Table II, introduction of an ammonium chloride group α to a carbonyl group has little effect on the carbonyl n → π* isotropic absorption maximum near 295 nm.

As has been noted with lycopodium alkaloids,[44] a positive charge on nitrogen makes an antioctant contribution[45] to the ORD. The negative Cotton effect displayed by 17aβ-methyl-17aα-methylamino-D-homoandrost-5-en-3β-ol-17-one hydrochloride and 17aα-amino-17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one hydrochloride near 300 nm has also been explained on this basis.[5] Also in β-amino adamantanones, a positive charge on nitrogen has been reported to give an antioctant contribution.[46] This conclusion is confirmed

(39) R. C. Cookson, J. Hudec, A. Szabo, and G. E. Usher. *Tetrahedron*, **24**, 4353 (1968).

(40) G. Snatzke, *Tetrahedron*, **21**, 413 (1965).

(41) G. Snatzke, *ibid.*, **21**, 439 (1965).

(42) A number of exceptions to this rule have been noted by P. Crabbé and L. Pinelo, *Chem. Ind. (London)*, 158 (1966).

(43) P. Crabbé, "Optical Rotary Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965, p 216.

(44) W. A. Ayer, J. A. Berezowsky, and D. A. Law, *Can. J. Chem.*, **41**, 649 (1963).

(45) If in an octant projection,[40] a group lying in an upper left or lower right far octant makes a negative contribution to the magnitude of the Cotton effect associated with the carbonyl n → π* transition, it is said to make an antioctant contribution to the ORD and CD or to display antioctant behavior.

(46) G. Snatzke and G. Eckhardt, *Tetrahedron*, **26**, 1143 (1970).

using the data in Table II. For (1*R*,3*S*)-3-amino-2-bornanone hydrochloride (**4c**), the ammonium group lies in an upper left or lower right far octant and the molecular ellipticity for the positive CD maximum, as compared to that of **4a** (Table II), is reduced. For **6c** the equatorial ammonium group causes a slight increase in the molecular ellipticity of the positive CD maximum near 287 nm. As expected with a 16β-ammonium group in **7c** and **8c**, the molecular ellipticity of the respective positive CD maxima is reduced.

The uv spectra of the pyrazines **11**, **14**, and **15** in methanol and in sulfuric acid were summarized and discussed in a preliminary report.[2] The uv and CD spectra of **12** in chloroform and **13** in methanol and in sulfuric acid were also shown and analyzed.[2] Details of these measurements as well as the ORD data for **12** and **13** are given in the Experimental Section.

Biological Activity.—The steroidal α-oximino ketones **5b**, **6b**, **7b**, **9**, and **10** were screened for general endocrine activity in rats.[47,48] All show essentially no activity. *anti*-16-Oximino-5α-androstan-3α-ol-17-one (**8b**) and the α-amino ketone hydrochlorides **7c** and **8c** were tested for androgenic activity.[48] In these tests, **8b** has a low androgenic activity but less than 5% of that of testosterone, whereas **7c** and **8c** are inactive. 2α-Amino-5α-androstan-17β-ol-3-one hydrochloride (**6c**) has no androgenic activity but shows moderate anti-uterotropic activity[49] at a high dose against estrone. It, however, is toxic as three of eight mice died in the test with the stimulator and five of eight mice died when **6c** was tested at a high dose by itself.

Experimental Section

Melting points were taken in capillary tubes and are corrected. Boiling points are not corrected. Optical rotations at the sodium D line were measured using a visual polarimeter and 1-dm sample tubes. Infrared absorption (ir) spectra were obtained with a Beckman Model IR-10 spectrophotometer.

Nuclear magnetic resonance (nmr) spectra were observed with a Varian Model A-60 spectrometer operating at 60 MHz. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane except when deuterium oxide (D_2O) was the solvent. As is indicated with these spectra, the chemical shifts are referenced to an internal standard of sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS). Coupling constants (J) are estimated to ± 0.5 Hz. In reporting the nmr spectra the following abbreviations are used: singlet, s; broad singlet, bs; doublet, d; triplet, t; septet, sept; multiplet, m.

Isotropic ultraviolet absorption (uv) spectra were obtained with a Cary Model 14 spectrophotometer using matched 1-cm cells and the normal variable slit.

Circular dichroism (CD) spectra and optical rotatory dispersion (ORD) curves were measured using a Cary Model 60 spectropolarimeter equipped with a CD Model 6001 accessory. The slit was programmed for a spectral band width of 1.5 nm, and a 1-cm cell was used. Cut-off was indicated when the dynode voltage reached 400 V for CD and 800 V for ORD measurements. In reporting these spectra the following abbreviations are used: maximum, max; minimum, min; peak, pk; trough, tr; inflection, infl; shoulder, sh; cut-off, c-off.

Mass spectra were obtained using a LKB Type 9000 mass spectrometer. The ionizing voltage was 70 eV. Only pertinent m/e values are reported. A molecular ion is indicated as M^+.

Elemental analyses and osmometric molecular weight determinations were done by Galbraith Laboratories, Knoxville, Tenn. The elemental composition of an α-oximino ketone is somewhat difficult to determine by combustion analysis. The general trend is for the percentage of nitrogen to be estimated correctly after combustion at the usual temperature. The estimated percentage of carbon, however, is consistently low and the estimated percentage of hydrogen is frequently incorrect. To overcome this difficulty, it is necessary to raise the combustion temperature higher than that normally used.

The purity of the compounds reported was verified by tlc which, in all cases, except as is discussed for **17**, indicated the presence of only one compound.

4-Methyl-*anti*-3-oximino-2-pentanone (**1b**) was prepared from 4-methyl-2-pentanone (**1a**) by an adaptation of an acid-catalyzed nitrosation technique[16] using 2-octyl nitrite.[50] Two recrystallizations of the crude product (78%) from petroleum ether (bp 40–60°) gave **1b** (29%) as long, white prisms: mp 76–78° (lit.[16] mp 76–77°); ir (KBr) 1670 (broad, C=N and C=O) and 3220 cm^{-1} (OH); nmr (CCl_4) δ 1.21 (d, 6, J = 7.0 Hz, C-4 CH_3 and C-5 H), 2.31 (s, 3, C-1 H), 3.36 (sept, 1, J = 7.0 Hz, C-4 H), and 9.05 ppm (bs, 1, OH).

3-Amino-4-methyl-2-pentanone Hydrochloride (**1c**).—At room temperature and atmospheric pressure, 1.47 g (11.4 mmol) of **1b** in 85 ml of absolute ethanol containing 1.29 g (35.4 mmol) of hydrogen chloride was reduced with hydrogen over 0.124 g of 10% palladium on carbon. After reduction, the catalyst was removed by filtration, and most of the solvent was evaporated at reduced pressure. Addition of ether caused the precipitation of crude **1c** (90%). Recrystallization from absolute ethanol–ether gave **1c** (51%) as fine, white prisms: mp 156–157° dec (lit. melting point one degree range between 150 and 160° with dec[16] and 153.5–154°[51]); ir (KBr) 1595 ($^+NH_3$) and 1730 cm^{-1} (C=O); nmr (D_2O–DSS) δ 0.90 (d, 3, J = 7.0 Hz, C-4 CH_3 or C-5 H), 1.14 (d, 3, J = 7.0 Hz, C-4 CH_3 or C-5 H), 2.35 (s, 3, C-1 H), 2.63 (m, 1, J = 4.0 and 7.0 Hz, C-4 H), 4.28 (d, 1, J = 4.0 Hz, C-3 H), and 6.29 ppm (s, 3, $^+NH_3$ exchanging).

2-Oximinocyclopentanone (**2b**).—2-Ethoxycarbonylcyclopentanone,[52] bp 100–104° (12 mm), was nitrosated with sodium nitrite in aqueous sodium hydroxide.[17] Recrystallization of the crude product (46%) from ether–petroleum ether (bp 40–60°) gave **2b** (21%): mp 68–70° [lit.[17] mp 65.5–67° (monohydrate) and 78.5–81° (hemihydrate)]; ir (KBr) 1645 (C=N), 1700 (C=O), 3580 cm^{-1} (OH).

2-Aminocyclopentanone Hydrochloride (**2c**).—Cyclopentanone was oxidized[19] with freshly distilled *tert*-butyl hypochlorite.[53] The crude product, a black tar, was triturated twice with isopropyl alcohol containing 1 ml of concentrated hydrochloric acid per 100 ml of alcohol. The combined alcoholic solutions were decolorized with Norite, diluted with an equal volume of ether, and refrigerated for 12 hr during which crude **2c** precipitated. Three recrystallizations of this solid from methanol–water gave **2c** (15%) as clusters of fine, white prisms: mp 142–144° dec (lit.[19] mp 146–147° dec); ir (KBr) 1615 ($^+NH_3$) and 1760 cm^{-1} (C=O); nmr (D_2O–DSS) δ 2.28 (m, 6, C-3 H, C-4 H, and C-5 H), 4.00 (m, 1, C-2 H), and 4.61 ppm (s, 3, $^+NH_3$ exchanging).

Anal. Calcd for $C_5H_{10}ClNO$: C, 44.29; H, 7.43; Cl, 26.15; N, 10.33; mol wt, 135.60. Found: C, 44.08; H, 8.00; Cl, 25.75; N, 10.18; mol wt (mass spectrum), 99 (M^+ – HCl = 99.13).

2-Oximinocyclohexanone (**3b**).—2-Ethoxycarbonylcyclohexanone was nitrosated with sodium nitrite in aqueous sodium hydroxide.[17] The resulting acidic aqueous solution of **3b** was extracted thoroughly with ether. The combined ether extracts were dried ($MgSO_4$) and the ether was evaporated at reduced pressure. Crude **3b** (56%) was thus obtained as a yellow oil (lit.[18] yellow oil).

2-Aminocyclohexanone Hydrochloride (**3c**).—As described for the preparation of **1c**, 9.11 g (71.7 mmol) of crude **3b** in ethanolic hydrogen chloride was reduced with hydrogen over 10% palladium on carbon. The 5.00 g (47%) of crude **3c** was re-

(47) All screenings for biological activity were provided for by the Endocrine Evaluation Branch, General Laboratories and Clinics, National Cancer Institute, National Institutes of Health, Bethesda, Md.

(48) A. G. Hilgar and D. J. Hummel, Ed., "Androgenic and Myogenic Endocrine Bioassay Data," Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Bethesda, Md., Aug 1964.

(49) A. G. Hilgar and L. C. Trench, Ed., "Uterotropic Endocrine Bioassay Data," General Laboratories and Clinics, National Cancer Institute, National Institutes of Health, Bethesda, Md., June 1968.

(50) Prepared by the method of M. Pezold and R. L. Shriner, *J. Amer. Chem. Soc.*, **54**, 4707 (1932), and had bp 71–75° (35 mm).

(51) F. E. Lehmann, A. Bretscher, H. Kühne, E. Sorkin, M. Erne, and H. Erlenmeyer, *Helv. Chim. Acta*, **33**, 1217 (1950).

(52) P. S. Pinkney, *Org. Syn.*, **17**, 30 (1937).

(53) Prepared by the method of H. M. Teeter and E. W. Bell, *ibid.*, **32**, 20 (1952), and had bp 73–79°.

crystallized twice from isopropyl alcohol–ether (Norit) followed by three recrystallizations from *n*-propyl alcohol–ether. Thus was obtained 0.764 g (7%) of **3c** as very fine, white prisms: mp 150–151° dec (lit.[19] mp 156° dec); ir (KBr) 1590 ($^+NH_3$) and 1730 cm^{-1} (C=O); nmr (D_2O-DSS) δ 1.85 (m, 6, C-3, C-4, and C-5 H), 2.52 (m, 2, C-6 H), 4.15 (m, 1, C-2 H), and 4.62 ppm (s, 3, $^+NH_3$ exchanging).

Cyclohexylamine was oxidized[19] with freshly distilled *tert*-butyl hypochlorite.[53] The crude product (55%) was recrystallized twice from isopropyl alcohol–ether (Norit). Thus was obtained **3c** (20%): mp 153–155° dec; ir identical with that of **3c** prepared by the reduction of 2-oximinocyclohexanone (**3b**).

(1*R*)-*anti*-3-Oximino-2-bornanone (4b).—As described previously,[21] (1*R*)-2-bornanone (**4a**), mp 173–175°, $[\alpha]^{25}D$ +46° (c 1.00, absolute C_2H_5OH) [lit. mp 176.3–176.5°,[54] $[\alpha]^{25}D$ +41.4 (*c* 0.7643, alcohol)[55]], was converted in ether to its sodium salt, and the latter was nitrosated with 2-octyl nitrite.[50] Pure **4b** (16%) was white prisms and had mp 150–154°; $[\alpha]^{24}D$ +198° (*c* 1.00, absolute C_2H_5OH) [lit. mp 153–154°;[21] $[\alpha]D$ +197.0° ($CHCl_3$)[56]]; ir (KBr) 1645 (C=N), 1745 (C=O), and 3400 cm^{-1} (broad, OH); nmr (CCl_4) δ 0.89 and 1.00 (two s, 3 and 6, respectively, C-8, C-9, and C-10 H), 1.67 (m, 4, C-5 and C-6 H), and 3.25 ppm (m, 1, C-4 H).

(1*R*,3*S*)-3-Amino-2-bornanone Hydrochloride (4c).—As described for the reduction of **1b** to **1c**, **4b** in ethanolic hydrogen chloride was reduced with hydrogen over 10% palladium on carbon. Recrystallization of the crude product from methanol–ether and then sublimation at 135° (2 mm) gave **4c** (7%): mp 207–212° dec; $[\alpha]^{24}D$ +26° (*c* 1.01, absolute C_2H_5OH) (lit. mp 223–225° dec[21] and 223–225°[57]).

The mother liquors from the recrystallization of **4c** were evaporated. Recrystallization of the residue from petroleum ether (bp 40–60°) gave crude **4b** (54%). Recrystallization from petroleum ether–ether (Norit) gave **4b** (38%), mp 152–154°.

Using the previously described procedure,[21] 3.17 g (17.5 mmol) of **4b** was reduced with zinc in aqueous sodium hydroxide. After the reduction was complete, the reaction mixture was thoroughly extracted with ether. The ethereal solution was dried (K_2CO_3), filtered, and then saturated with hydrogen chloride. Refrigeration of the solution for 12 hr resulted in the precipitation of 2.62 g (74%) of **4c** as white, microscopic prisms: mp 241–242° dec; $[\alpha]^{25}D$ +21° (*c* 1.28, CH_3OH); ir (KBr) 1600 ($^+NH_3$) and 1760 cm^{-1} (C=O); nmr (C_2D_5OD) δ 0.98 and 1.13 (two s, 6 and 3, respectively, C-8, C-9, and C-10 H), 1.82 (m, 4, C-5 and C-6 H), 2.62 (m, 1, C-4 H), 4.03 (d, 1, J = 4.5 Hz, C-3 H), and 5.57 ppm (s, 3, $^+NH_3$ exchanging).

***anti*-2-Oximino-5α-cholestan-3-one (5b).**—Under nitrogen, 0.421 g (0.0108 g-atom) of potassium was dissolved in 25 ml of dry *tert*-butyl alcohol. To this solution was added 0.752 g (1.94 mmol) of 5α-cholestan-3-one (**5a**), mp 129–131°, $[\alpha]^{25}D$ +40° (*c* 1.03, $CHCl_3$) [lit.[58] mp 129°, $[\alpha]D$ +41° ($CHCl_3$)], and then, by dropwise addition with stirring, 0.202 g (1.27 mmol) of 2-octyl nitrite[50] in 10 ml of dry *tert*-butyl alcohol. Stirring was continued for 2 hr. The reaction mixture was poured into 1 l. of ice water which was then acidified with dilute hydrochloric acid. The slightly acidic solution was refrigerated for 24 hr and the precipitate was collected by filtration. The solid was washed with water. Trituration with two 50-ml portions of acetone left 0.284 g (54%) of **5b** as white, microscopic cubes: mp 256–258° dec (lit.[12] mp 203–205°); $[\alpha]^{26}D$ +95° (*c* 1.00, 1 *N* ethanolic KOH); ir (KBr) 1620 (C=N), 1720 (C=O), and 3150 cm^{-1} (OH).

***anti*-2-Oximino-5α-androstan-17β-ol-3-one (6b).**—As described for the preparation of **5b**, 5α-androstan-17β-ol-3-one (**6a**), mp 170–175°, $[\alpha]^{26}D$ +33° (c 1.02, absolute C_2H_5OH) [lit.[59] mp 181°, $[\alpha]D$ +32° (alcohol)], was nitrosated in *tert*-butyl alcohol–potassium *tert*-butoxide using 2-octyl nitrite.[50] After dilution of the reaction mixture with water and acidification, the crude reaction product was too gelatinous for the usual isolation by filtration. Instead, the material was extracted into ether. The ethereal solvent was evaporated, and the residue thoroughly washed with water. After two recrystallizations from methanol, **6b** (12%) was white, microscopic plates: mp 265–268° dec; $[\alpha]^{26}D$ +67° (*c* 0.243, absolute C_2H_5OH) [lit.[13] mp 266–267°; $[\alpha]D$ +48.1° (*c* 0.77, pyridine)]; ir (KBr) 1620 (C=N), 1720 (C=O), 3150 (very broad, OH), 3480 (broad, OH), and 3620 cm^{-1} (OH).

Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.39. Found: C, 71.08; H, 9.45; N, 4.17.

2α-Amino-5α-androstan-17β-ol-3-one Hydrochloride (6c).—As described for the reduction of **1b** to **1c**, **6b** in ethanolic hydrogen chloride was reduced with hydrogen over 10% palladium on carbon. The crude hydrochloride (36%), mp >300° dec, was recrystallized from isopropyl alcohol–ether (Norit). Recrystallization then from methanol–ether gave **6c** (14%) as white, microscopic prisms: mp >300° dec; $[\alpha]^{25}D$ +40° (*c* 1.12, absolute C_2H_5OH); ir (KBr) 1720 (C=O), 3245 (broad, OH), and 3450 cm^{-1} (OH); nmr (CD_3OD) δ 0.77 (s, 3, C-18 or C-19 H), 1.20 (s, 3, C-18 or C-19 H), 4.18 (m, 1, C-2 H), and 4.78 ppm (s, 4, $^+NH_3$, and OH exchanging).

Anal. Calcd for $C_{19}H_{32}ClNO_2$: C, 66.75; H, 9.43; Cl, 10.37; N, 4.10. Found: C, 66.84; H, 9.50; Cl, 10.47; N, 4.09.

***anti*-16-Oximino-5α-androstan-3β-ol-17-one (7b).**—As described for the preparation of **5b**, 5α-androstan-3β-ol-17-one (**7a**), mp 173–175°, $[\alpha]^{25}D$ +90° (c 1.00, absolute C_2H_5OH) [lit.[59] mp 175°, $[\alpha]D$ +88° (alcohol)], was nitrosated in *tert*-butyl alcohol–potassium *tert*-butoxide using 2-octyl nitrite.[50] Recrystallization of the crude product from methanol gave **7b** (43%) as white needles: mp 236–241° dec (lit. mp 245–247°[14] and 218–219.5°[60] dec); $[\alpha]^{26}D$ −15° (*c* 1.00, absolute C_2H_5OH); ir (KBr) 1635 (C=N) and 1730 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.39. Found: C, 71.45; H, 9.17; N, 4.32.

16β-Amino-5α-androstan-3β-ol-17-one Hydrochloride (7c).—As described for the reduction of **1b** to **1c**, **7b** in ethanolic hydrogen chloride was reduced with hydrogen over 10% palladium on carbon. Recrystallization of the crude hydrochloride from ethanol–ether gave **7c** (41%) as white, microscopic prisms: mp >300° dec; $[\alpha]^{25}D$ +74° (*c* 1.06, absolute C_2H_5OH); ir (KBr) 1615 ($^+NH_3$), 1765 (C=O), and 3310 cm^{-1} (OH); nmr (CD_3OD) δ 0.89 (s, 3, C-18 or C-19 H), 0.98 (s, 3, C-18 or C-19 H), and 4.80 ppm (s, 4, $^+NH_3$ and OH exchanging).

Anal. Calcd for $C_{19}H_{32}ClNO_2$: C, 66.75; H, 9.43; Cl, 10.37; N, 4.10. Found: C, 66.50; H, 9.33; Cl, 10.44; N, 4.29.

***anti*-16-Oximino-5α-androstan-3α-ol-17-one (8b).**—As described for the preparation of **5b**, 5α-androstan-3α-ol-17-one (**8a**), mp 182–185°, $[\alpha]^{26}D$ +95° (*c* 1.03, absolute C_2H_5OH) [lit.[59] mp 183°, $[\alpha]D$ +94.5° (alcohol)], was nitrosated in *tert*-butyl alcohol–potassium *tert*-butoxide with 2-octyl nitrite.[50] Recrystallization of the crude product (100%) from methanol gave **8b** (70%) as white platelets: mp 217–219° dec; $[\alpha]^{27}D$ −20° (*c* 1.00, absolute C_2H_5OH); ir (KBr) 1635 (C=N), 1750 (C=O), 3150 (broad, OH), and 3520 cm^{-1} (sharp, OH).

Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.39. Found: C, 71.40; H, 9.13; N, 4.42.

16β-Amino-5α-androstan-3α-ol-17-one Hydrochloride (8c).—As described for the reduction of **1b** to **1c**, **8b** in ethanolic hydrogen chloride was reduced with hydrogen over 10% palladium on carbon. Recrystallization of the crude hydrochloride (84%) from absolute ethanol gave pure **8c** (32%) as very fine, white prisms: mp 255–259° dec; $[\alpha]^{26}D$ +81° (*c* 0.751, absolute C_2H_5OH); ir (KBr) 1640 ($^+NH_3$), 1765 (C=O), and 3360 cm^{-1} (OH); nmr (CD_3OD) δ 0.90 (s, 3, C-18 or C-19 H), 1.01 (s, 3, C-18 or C-19 H), and 4.80 ppm (s, 4, $^+NH_3$ and OH exchanging).

Anal. Calcd for $C_{19}H_{32}ClNO_2$: C, 66.75; H, 9.43; Cl, 10.37; N, 4.10. Found: C, 67.03; H, 9.53; Cl, 10.15; N, 4.04.

16β-Amino-5α-androstan-3α-ol-17-one (8d).—An aqueous solution of 0.541 g (1.58 mmol) of **8c** was filtered, neutralized with saturated aqueous sodium bicarbonate, and extracted with ether. The ethereal solution was dried (Na_2SO_4), and the ether was evaporated. The residue was recrystallized from ether, cooled in isopropyl alcohol–Dry Ice. There was obtained 0.082 g (17%) of **8d** as yellow needles: mp 178–180° dec; $[\alpha]^{24}D$ +46° (c 1.14, absolute C_2H_5OH); ir (KBr) 1620 (NH_2), 1730 (C=O), and 3500 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.82 (s, 3, C-18 or C-19 H), 0.90 (s, 3, C-18 or C-19 H), 1.88 (s, 2, NH_2), 3.15 (bs, 1, C-3 or C-16 H), and 4.05 (bs, 1, C-3 or C-16 H).

Anal. Calcd for $C_{19}H_{31}NO_2$: C, 74.71; H, 10.23; N, 4.59. Found: C, 74.61; H, 10.19; N, 4.35.

(54) F. Foerster, *Chem. Ber.*, **23**, 2981 (1890).
(55) D. H. Peacock, *J. Chem. Soc.*, **107**, 1547 (1915).
(56) M. O. Forster, *ibid.*, **103**, 662 (1913).
(57) P. Duden and W. Pritzkow, *Chem. Ber.*, **32**, 1538 (1899).
(58) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 28.
(59) Reference 58, p 519.
(60) M. N. Huffman and M. H. Lott, *J. Biol. Chem.*, **207**, 431 (1954).

16β-Salicylidenimino-5α-androstan-3α-ol-17-one.—To a solution of 0.507 g (5.07 mmol) of 16β-amino-5α-androstan-5α-ol-17-one (**8d**) in 10 ml of absolute ethanol was added 0.62 ml of absolute ethanol containing 5.08 mmol of salicylaldehyde and 5 mg of *p*-toluenesulfonic acid. After standing for 62 hr at room temperature, the solvent was evaporated and the residue was recrystallized from ethanol–water. There was obtained 0.087 g (42%) of the *N*-salicylidene derivative, mp 179–181°. Two additional recrystallizations of this substance from ethanol–water returned 0.034 g (16%) of yellow platelets: mp 182–184°; $[\alpha]^{24}D$ −70° (*c* 1.00, absolute C_2H_5OH); ir (KBr) 1625 (C=N), 1740 (C=O), and 3540 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.83 (s, 3, C-18 or C-19 H), 0.97 (s, 3, C-18 or C-19 H), 3.69 (m, 1, C-3 or C-16 H), 4.06 (bs, 1, C-3 or C-16 H), 7.12 (m, 4, aromatic H), and 8.42 ppm (s, 1, CH=N).

Anal. Calcd for $C_{26}H_{35}NO_3$: C, 76.24; H, 8.61; N, 3.42. Found: C, 75.79; H, 8.60; N, 3.23.

2,4-Bisoximino-5α-cholestan-3-one (9).—As described for the preparation of **5b**, except that a 16-fold excess of 2-octyl nitrite[50] was used, 5α-cholestan-3-one (**5a**) was nitrosated in *tert*-butyl alcohol–potassium *tert*-butoxide. The crude product was recrystallized twice from methanol. Recrystallization then from acetone gave **9** (47%) as yellow, microscopic plates: mp 222–223° dec (lit.[23] mp 234–235° dec); $[\alpha]^{25}D$ +138° (*c* 0.751, 1 *N* ethanolic KOH); ir (KBr) 1620 (C=N), 1730 (C=O), and 3200 cm^{-1} (broad, OH).

Anal. Calcd for $C_{27}H_{44}N_2O_3$: C, 72.93; H, 9.97; N, 6.30. Found: C, 72.99; H, 9.86; N, 6.04.

2,4-Bisoximino-17α-methyl-5-androsten-17β-ol-3-one (10).—As described for the preparation of **5b**, except that a fivefold excess of 2-octyl nitrite[50] was used, 17α-methyl-4-androsten-17β-ol-3-one (**16**), mp 164–167°, $[\alpha]^{26}D$ +76° (*c* 1.02, absolute C_2H_5OH) [lit.[59] mp 164°, $[\alpha]D$ +76° (alcohol)], was nitrosated in *tert*-butyl alcohol–potassium *tert*-butoxide. The crude product (17%) was collected by filtration and then was thoroughly washed with acetone. Recrystallization by evaporation of a methanol solution gave **10** (10%) as yellow, microscopic plates: mp >300° dec; $[\alpha]^{27}D$ −7° (*c* 0.502, absolute C_2H_5OH); ir (KBr) 1720 (C=O), 3150 (broad, OH), and 3500 cm^{-1} (OH).

Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.14; H, 7.64; N, 7.28.

2,5-Diisopropyl-3,6-dimethylpyrazine (11).—An aqueous solution of 5.93 g (39.1 mmol) of **1c** was neutralized with 10% aqueous sodium hydroxide. The solution was extracted with three portions of ether. The combined ethereal solutions were dried (Na_2SO_4). Evaporation of the ether gave 2.56 g of oil which was identified as a mixture of 3-amino-4-methyl-2-pentanone (**18**) and **11**: nmr of **18** (neat) δ 0.66 (d, 6, *J* = 7.0 Hz, C-4 CH_3 and C-5 H), 2.02 (s, 2, NH_2), and 2.17 ppm (s, 3, C-1 H). The oil was redissolved in aqueous sodium hydroxide, and **11** precipitated as white needles, mp 41–44°. Recrystallization of the solid from ethanol–water gave 0.872 g (23%) of **11** as white needles which was sublimed at 25° (0.05 mm): mp 44–46°; ir (KBr) 1430, 1465, and 1480 cm^{-1}; nmr (CCl_4) δ 1.23 [d, 6, *J* = 7.0 Hz, C-2 and C-5 $(CH_3)_2CH$], 2.47 (s, 3, C-3 and C-6 CH_3), and 3.12 ppm [sept, 1, *J* = 7.0 Hz, C-2 and C-5 $(CH_3)_2CH$].

Anal. Calcd for $C_{12}H_{20}N_2$: C, 74.95; H, 10.48; N, 14.57; mol wt, 192.30. Found: C, 74.85; H, 10.40; N, 14.57; mol wt (osmometric in $CHCl_3$), 189.

Di(17β-hydroxy-5α-androstano)[2,3-*b*:2′,3′-*e*]pyrazine (12).—An aqueous solution of 0.431 g (1.26 mmol) of **6c** was neutralized with saturated aqueous sodium carbonate. The solution was extracted with ether. The ethereal solution was dried (Na_2SO_4). Evaporation of the ether gave 0.338 g of residue: ir (KBr) 1670 (strong, C=N) and 1730 cm^{-1} (weak, C=O). The residue was dissolved in absolute ethanol and 0.027 g (0.16 mmol) of *p*-toluenesulfonic acid added. Immediately the solution became dark orange. After 5 min, precipitation of a solid began. It was complete after 0.5 hr. The precipitate was collected by filtration, washed with absolute ethanol, and dried. Thus was obtained 0.259 g (72%) of crude **12**. Recrystallization from chloroform–absolute ethanol gave 0.196 g (54%) of **12** as white needles: mp >300° dec; $[\alpha]^{25}D$ +79° (*c* 0.782, $CHCl_3$) ir (KBr) 1390–1400, 1445, and 3440–3460 cm^{-1} (broad, OH); nmr ($CDCl_3$) δ 0.78 (s, 3, C-18 or C-19 H) and 0.82 ppm (s, 3, C-18 or C-19 H); CD ($CHCl_3$) (*c* 0.00626) $[\theta]_{400}$ ±0, $[\theta]_{352}$ ±0, $[\theta]_{323}$ −1300 (max), $[\theta]_{316}$ ±0, $[\theta]_{313}$ +1100 (max), $[\theta]_{311}$ +970 (min), $[\theta]_{310}$ +1800 (max), $[\theta]_{307}$ +1100 (min), $[\theta]_{306}$ +1800 (max), $[\theta]_{303}$ +1300 (min), $[\theta]_{301}$ +1500 (max), $[\theta]_{297}$ +900 (min), $[\theta]_{296}$ +1200 (max), $[\theta]_{295}$ +990 (min), $[\theta]_{294}$ +1700 (sh), $[\theta]_{287}$ +5300 (max), $[\theta]_{263}$ ±0, $[\theta]_{246}$ +4600 (c-off); ORD ($CHCl_3$) (*c* 0.156) $[\phi]_{550}$ +620°, $[\phi]_{440}$ +1100° (c-off); (*c* 0.0156) $[\phi]_{440}$ +1200°, $[\phi]_{314}$ +5600° (pk), $[\phi]_{307}$ +4200° (tr), $[\phi]_{305}$ +4500° (pk), $[\phi]_{303}$ +3800° (tr), $[\phi]_{300}$ +5100° (pk), $[\phi]_{297}$ +4100° (tr), $[\phi]_{295}$ +6000° (pk), $[\phi]_{294}$ +4700° (tr), $[\phi]_{293}$ +6600° (pk), $[\phi]_{291}$ +4200° (tr), $[\phi]_{288}$ +7900° (pk), $[\phi]_{287}$ +5900° (tr), $[\phi]_{286}$ +6800° (pk), $[\phi]_{275}$ +2900° (tr), $[\phi]_{244}$ +16,000° (pk), $[\phi]_{240}$ +13,000° (c-off).

Anal. Calcd for $C_{38}H_{56}N_2O_2$: C, 79.67; H, 9.85; N, 4.89 mol wt, 572.84. Found: C, 79.50; H, 9.60; N, 4.60; mol wt (osmometric in $CHCl_3$), 547.

Di[(1*R*)-bornano][2,3-*b*:2′,3′-*e*]pyrazine (13).—A mixture of 0.560 g (2.75 mmol) of **4c**, water, and carbon tetrachloride was neutralized with 8 ml of 10% aqueous sodium hydroxide. The carbon tetrachloride solution was separated and reduced in volume to 1 ml, all within 25 min. The nmr of this solution showed signals for only (1*R*,3*S*)-3-amino-2-bornanone, δ 0.86 and 0.99 (two s, 6 and 3, respectively, C-8, C-9 and C-10 H), 3.21 (s, 2, NH_2, vanished on exchange with deuterium oxide), and 3.43 ppm (d, 1, *J* = 4.5 Hz, C-3 H). After 1 hr, the ratio of NH_2 protons to total methyl protons dropped from 2:9 to 1:6. After 11.5 hr, the ratio was 1:9. There was no evidence in any of the spectra for signals corresponding to **13**. Rather the final spectrum was that of a mixture of substances which is assumed to be the tautomeric dihydropyrazines. Complete removal of the solvent left a yellow oil. Preparative tlc on silica gel with elution with chloroform separated the mixture into three fractions. The major fraction was isolated and again preparative tlc as before separated it into three fractions with the same R_f values as before.

To a mixture of 2.95 g (9.88 mmol) of the dihydropyrazines formed from (1*R*,3*S*)-3-amino-2-bornanone as outlined above, 35 ml of dioxane, 8 ml of water, and 1.4 ml of concentrated sulfuric acid was slowly added a solution of 3.59 g (52.0 mmol) of sodium nitrite in 15 ml of 33% aqueous dioxane. After addition, the mixture was allowed to stand for 10 min. It was then neutralized with saturated aqueous sodium carbonate and extracted with methylene chloride. The methylene chloride solution was dried (Na_2SO_4), and the solvent removed. The residue was chromatographed on silica gel. Elution with chloroform gave 1.41 g (48%) of crude **13**, mp 154–160°. Recrystallization from ethanol–water returned 1.11 g (38%) of **13** as white needles, mp 159–161°. Sublimation of this solid at 120° (0.005 mm) gave 1.09 g (37%) of **13** as white, irregular, crystalline clusters: mp 159–160° (lit.[39] mp 159.5–160°); $[\alpha]^{24}D$ +66° (*c* 1.02, CH_3OH); ir (KBr) 1445 and 1485 cm^{-1}; nmr (CCl_4) δ 0.58, 0.99, and 1.28 (three s, 3, 3, and 3, respectively, C-8, C-9, and C-10 H), and 2.82 ppm (d, 1, *J* = 4.0 Hz, C-4 H); CD (CH_3OH) (*c* 0.00203) $[\theta]_{360}$ ±0, $[\theta]_{310}$ +5200 (max), $[\theta]_{300}$ +3800 (min), $[\theta]_{293}$ +4100 (max), $[\theta]_{258}$ ±0, $[\theta]_{243}$ ±0, $[\theta]_{225}$ −4400 (max), $[\theta]_{220}$ −2200 (c-off); CD (concentrated H_2SO_4) (*c* 0.00149) $[\theta]_{550}$ ±0, $[\theta]_{380}$ ±0, $[\theta]_{369}$ −8400 (max), $[\theta]_{357}$ ±0, $[\theta]_{337}$ +30,000 (max), $[\theta]_{319}$ +18,000 (min), $[\theta]_{277}$ +44,000 (max), $[\theta]_{247}$ ±0, $[\theta]_{234}$ −27,000 (max), $[\theta]_{210}$ ±0 (c-off); ORD (CH_3OH) (*c* 0.00406) $[\phi]_{400}$ +290°, $[\phi]_{325}$ +4100° (pk), $[\phi]_{310}$ +410° (infl), $[\phi]_{320}$ ±0°, $[\phi]_{287}$ −1800° (tr), $[\phi]_{245}$ ±0°, $[\phi]_{235}$ +180° (infl), $[\phi]_{215}$ +9300° (pk), $[\phi]_{210}$ +5400° (c-off).

Dicyclopentano[*b*,*e*]pyrazine (14).—To a solution of 7.01 g (51.6 mmol) of **2c** in 60 ml of 33% aqueous sodium hydroxide, heated on the steam plate, was added 12 ml of 31% aqueous hydrogen peroxide. Heating was continued until gas evolution ceased. The reaction mixture was cooled and 3.08 g (74%) of crude **14** was collected by filtration. Recrystallization from benzene (Norit) gave 1.96 g (47%) of impure **14** as long, white needles, mp 78–83°. Sublimation of this solid at 75° (0.005 mm) gave **14** as white prisms: mp 89–91°; ir (KBr) 1440 and 1470 cm^{-1}; nmr (CCl_4) δ 2.90 (unsymmetrical t, 2, C-1, C-3, C-5 and C-7 H) and 2.30 ppm (m, 1, C-2 and C-6 H). An analytical sample was prepared by sublimation and then protected from the air.

Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.96; H, 7.55; N, 17.49; mol wt, 160.21. Found: C, 74.85; H, 7.48; N, 17.51; mol wt (osmometric in benzene), 155.

The aqueous filtrate from above was thoroughly extracted with ether, acidified with concentrated hydrochloric acid, and again extracted with ether. These latter ether extracts were combined and dried ($MgSO_4$), and the ether was evaporated. Recrystallization of the residue from benzene (Norite) gave 0.112 g (1.6%) of glutaric acid: mp 91–94°; ir (KBr) identical with that of an authentic sample, mp 92–96°; mmp 95–97°.

Dicyclohexano[*b*,*e*]pyrazine[36] **(15).**—Using the procedure outlined above for the preparation of **14**, 2.02 g (13.5 mmol) of **3c** was converted to 0.443 g (35%) of crude **15**. Sublimation of the crude product at 55° (0.005 mm) gave 0.375 g (30%) of **15** as white, irregular, crystalline clusters: mp 107–108° (lit. mp 109.6–110.6[9] and 108–109°);[37] ir (KBr) 1390 and 1435 cm^{-1}; nmr (CCl_4) δ 1.85 (bs, 1, C-2, C-3, C-7, and C-8 H) and 2.78 ppm (bs, 1, C-1, C-4, C-6, and C-9 H).

As above, there was also isolated 0.748 g (38%) of crude acipic acid, mp 138–146°. Recrystallization from benzene gave 0.354 g (18%) of adipic acid: mp 149–153°; ir (KBr) identical with that of an authentic sample, mp 150–154°; mmp 149–156°.

Androstan-17β-ol-2,3-dione Monohydrate (17).—Using a procedure described earlier,[25] 0.285 g (0.892 mmol) of **6b** was treated with 3.5 g (0.028 mmol) of sodium sulfite in 15 ml of glacial acetic acid. Isolation of the product in the usual way[25] gave 0.076 g (26%) of crude **17**. Recrystallization from ethanol–water gave 0.027 g (9%) of **17** monohydrate: mp 161–164° dec (lit.[24] mp 232–234°, not hydrated, recrystallized from chloroform); uv max (absolute C_2H_5OH) 270 nm (ϵ 6400); nmr ($CDCl_3$) δ 0.77 (s, 3, C-18 or C-19 H), 1.05 (s, 3, C-18 or C-19 H), 5.71 (d, 0.2, J = 3.0 Hz, C-4 H of **17b**), and 6.39 ppm (s, 0.8, C-1 H of **17a**).

Anal. Calcd for $C_{19}H_{28}O_3 \cdot H_2O$: C, 70.77; H, 9.38; mol wt, 322.43. Found: C, 71.02; H, 9.33; mol wt (mass spectrum), 305 ($M^+ - H_2O + 1$ = 305.42), 304 ($M^+ - H_2O$).

(1*R*,3*S*)-3-Salicylidenimino-2-bornanone (20).—To a mixture of 25 ml of water, 25 ml of ether, and 0.498 g (2.44 mmol) of **4c** was added 8 ml of 10% aqueous sodium hydroxide. The layers were separated, and the aqueous layer was extracted with four 25-ml portions of ether. The combined ethereal solutions were washed with water, dried (K_2CO_3), and filtered. To this solution was added 3.5 ml of absolute ethanol containing 2.9 mmol of salicylaldehyde. The solvent was evaporated. The crystalline residue was recrystallized from methanol, and there was obtained 0.313 g (47%) of **20**, mp 103–105°. After sublimation at 90° (0.005 mm), there was obtained 0.285 g (43%) of **20** as yellow platelets: mp 107–108°; $[\alpha]^{25}D$ −170° (*c* 0.828, CH_3OH); ir (KBr) 1630 (C=N) and 1750 cm^{-1} (C=O); nmr (CCl_4) δ 0.91 and 1.01 (two s, 6 and 3, respectively, C-8, C-9, and C-10 H), 3.85 (d, 1, J = 4.5 Hz, C-3 H), 7.01 (m, 4, aromatic H), 8.50 (s, 1, CH=N), and 12.06 ppm (s, 1, OH).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.58; H, 7.82; N, 5.19.

Methyl 16,17-*seco*-5α-Androstan-3β-ol-16-oate-17-oic Acid (21).—A 10% excess of 10% aqueous sodium hydroxide was added to a solution of 0.303 g (0.886 mmol) of **7c** in 50 ml of methanol. The mixture was stirred overnight, diluted with water, and then thoroughly extracted with ether. Evaporation of the ether gave only a trace of residue. The aqueous solution was acidified with 2 *N* hydrochloric acid and again thoroughly extracted with ether. This ethereal solution was dried (Na_2SO_4), and evaporation of the ether gave 0.271 g of residue, mp 95–145°. Two recrystallizations of this solid from ethanol–water gave 0.082 g (26%) of **21** as very fine, white needles, mp 189–190°. Sublimation at 150° (0.005 mm) gave **21**: mp 183–184°; $[\alpha]^{22}D$ −90° (*c* 0.36, absolute C_2H_5OH); ir (KBr) 1715 (C=O), 2600 (CO_2H), and 3410 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.78 (s, 3, C-18 or C-19 H), 1.10 (s, 3, C-18 or C-19 H), 1.98 (s, 3, OCH_3), and 4.64 ppm (bs, 2, OH, disappeared on shaking with D_2O); mass spectrum *m/e* (% of base peak, assignment) 352 [11, **22** (M^+)], 278 (23, **24**), 74 (34, **23**).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15; mol wt, 352.46. Found: C, 68.38; H, 9.30; mol wt (mass spectrum), 352.

Registry No.—**1b**, 31571-12-7; **1c**, 5440-22-2; **2b**, 31579-37-0; **2c**, 5464-16-4; **3c**, 6946-05-0; **4a**, 464-49-3; **4b**, 31571-14-9; **4c**, 31638-54-7; **5b**, 31571-15-0; **6a**, 521-18-6; **6b**, 31571-17-2; **6c**, 20985-72-2; **7a**, 481-29-8; **7b**, 31615-29-9; **7c**, 31571-20-7; **8a**, 53-41-8; **8b**, 31571-22-9; **8c**, 31571-23-0; **8d**, 31571-24-1; **9**, 7768-89-0; **10**, 31571-26-3; **11**, 30590-92-2; **12**, 20985-93-7; **13**, 31571-28-5; **14**, 31579-41-6; **15**, 4006-50-2; **17a**, 31571-29-6; **17b**, 31571-30-9; **20**, 31571-31-0; **21**, 31615-30-2; 16β-salicylidenimino-5α-androstan-3α-ol-17-one, 31571-32-1.

Reactions of Amines. XVII. The Oxidation of α-Substituted α-Amino Ketones with Lead Tetraacetate[1,2]

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The oxidation of several α-substituted α-amino ketones with lead tetraacetate (or iodosobenzene diacetate) resulted in cleavage of the molecule between the carbonyl and carbinamine functions, yielding acid derivatives derived from the acyl moiety of the molecule and nitriles derived from the carbinamine moiety. In the presence of an alcohol moderate yields of ester and nitrile were obtained. In the absence of alcohol the yield of cleavage products was lower and acetylation of the amino ketone became a more competitive reaction. The oxidation of 2-amino-3,3-dimethyl-1-indanone (**11**) gave a moderate yield of 1,1-dimethylhomophthalic anhydride presumably derived from an intramolecular of an intermediate such as **12**.

This communication is the fifth[3] in a series directed toward the study of the oxidation of organic nitrogen compounds. Several of the next papers in this series will be concerned with the oxidation of nitrogen analogs of the 1,2-glycols[4] and α-hydroxy ketones[4] in which one or more carbon or oxygen atoms have been replaced by nitrogen. For purposes of later comparisons it is necessary to know first how simple analogs, such as the α-amino ketones, behave toward selected oxidants. In this paper the oxidation of *α-substituted* α-amino ketones with lead tetraacetate and iodosobenzene diacetate is discussed.

On the basis of the known, but imperfectly studied, cleavage of 1,2-amino alcohols to carbonyl compounds and imines (or nitriles) on oxidation with lead tetraacetate (eq 1)[4-6] and the known cleavage of α-hydroxy ketones to carbonyl compounds and acid derivatives with the same reagent (eq 2), it might be expected that

(1) Paper XVI: H. E. Baumgarten, R. D. Clark, L. S. Endres, and L. D. Hagemeier, *Tetrahedron Lett.*, 5033 (1967).

(2) This work was supported in part by Public Health Service Research Grant GM-13122 from the National Institute of General Medical Sciences and a National Aeronautics and Space Administration traineeship for H. W. T.

(3) (a) H. E. Baumgarten, P. L. Creger, and R. L. Zey, *J. Amer. Chem. Soc.*, **82**, 3977 (1960); (b) H. E. Baumgarten, A. Staklis, and E. Miller, *J. Org. Chem.*, **30**, 1203 (1965); (c) H. E. Baumgarten and A. Staklis, *J. Amer. Chem. Soc.*, **87**, 1141 (1965); (d) H. E. Baumgarten, W. F. Wittman, and G. J. Lehmann, *J. Heterocycl. Chem.*, **6**, 333 (1969).

(4) R. Criegee and C. A. Bunton in "Oxidations in Organic Chemistry," K. B. Wiberg, Ed., Part A, Academic Press, New York, N. Y., 1965, pp 277–366.

(5) J. Bollinger, Thesis, University of Marburg, Germany, 1937; cited in ref 4.

(6) H. J. Roth and A. Brandau, *Arch. Pharm. (Weinheim)*, **293**, 27 (1960).

$$RCHOHCHNH_2R' \xrightarrow{LTA} [RCHO + R'CH{=}NH] \xrightarrow{LTA} RCHO + R'CN \quad (1)$$

$$RCOCHOHR' \xrightarrow[R''OH]{LTA} RCO_2R'' + R'CHO \quad (2)$$

an α-substituted α-amino ketone would undergo a similar reaction to yield a nitrile (or imine) and an acid derivative (eq 3).

$$RCOCHNH_2R'' \xrightarrow[R''OH]{LTA} [RCO_2R'' + R'CH{=}NH] \xrightarrow{LTA} RCO_2R'' + R'CH \quad (3)$$

Furthermore, since Baer[7] has shown that oxidations of α-hydroxy ketones (eq 2) with lead tetraacetate are markedly accelerated by the addition of alcohols, it might be expected that oxidation of α-amino ketones would be similarly affected by added alcohol.

Although in some oxidations the principal difference between lead tetraacetate (LTA) and iodosobenzene diacetate (IBDA) as oxidants appears to be the greater oxidizing power of the former,[4] it will be shown later in this series that the two reagents can and frequently do lead to a substantially different array of products. For this reason, iodosobenzene diacetate has been included in the present study. Also, in some oxidations to be described in this series, particularly where more than 1 mol of lead tetraacetate appears to be required as oxidant, the optimum yield of a specific product may be obtained with substantially less than the theoretical amount of oxidant or may depend strongly on the order and rate of addition of reactants or on the temperature. Probably this is because of the greater or lesser effects of the competing side reactions (acetylation, acetoxylation, further oxidation, etc.) so common with lead tetraacetate. Examples of these effects will be further documented in various papers in this series. In the present study our interest has been in the course of the reactions and the nature of the products, and we have not tried to optimize either the ratios of reactants or the conditions. Instead, we have used either the theoretical or half the theoretical amount of oxidant and the mildest set of conditions leading to complete reaction of the *oxidant* in a reasonable length of time.

It has been observed also that the rate and course of lead tetraacetate oxidations in nonprotic solvents are affected by the presence of certain added acids and bases. For example, the initial rates of oxidation of amines[8] and of *N*-arylbenzohydroxamic acids[9] are depressed by addition of acetic acid. We have not studied the possible effects of added acids or bases, but it should be noted that our experiments were conducted with the hydrochloride of the amino ketone (because of the instability of the free amino ketone) and that varying amounts of acetic acid were formed during the course of these oxidations.

In substantial accord with the above expectations oxidation of α-aminovalerophenone (**1a**) hydrochloride with 1 or 2 mol of lead tetraacetate in methylene chloride containing some alcohol (methanol or ethanol) gave a mixture which contained 3–5% of benzoic acid (**8a**), 46–58% of alkyl benzoate (**3a**), 0–5% of acetic benzoic anyydride (**5a**), 40–54% of *n*-butyronitrile (**6a**), and 0–21% of *N*-acetyl-α-aminovalerophenone (**7a**) (Table I). Products **3a**, **5a**, **6a**, and **7a** may be rationalized by the mechanism shown in Scheme I, which may be regarded as derived from a contemporary version of the Baer mechanism for the oxidation of α-hydroxy ketones under similar conditions.[4,7] The principal difference between the mechanism shown here and that of Baer is that in the Baer mechanism the alcohol adds to the carbonyl group *before* attack by the oxidant. In some alcohol-assisted oxidations[10,11] the prior addition of alcohol appears unlikely. Furthermore, in contrast to the results of Baer, oxidation does take place in the absence of alcohol, although with lower yields of acid derivatives. These results suggest that prior addition of alcohol is not a requirement although such addition may provide an alternative path for oxidation.

It is also possible that the ester **3** could have formed in whole or in part by reaction of **5a** with methanol. The small amount of benzoic acid may have resulted from traces of water in the solvents reacting with **2a** prior to cleavage or with **5a** after cleavage. The amide **7a** could have resulted from the reaction of **1a** and **5a** although direct acetylation with lead tetraacetate, or some species derived therefrom, is a likely alternative because significant amounts of **7a** were obtained in only those oxidations in which a solution of **1a** in methylene chloride–methanol was added to solid lead tetraacetate (rather than to a solution of lead tetraacetate in methylene chloride).

To resolve some of these ambiguities, several oxidations of *p*-chloro- and *p*-methyl-α-aminopropiophenone hydrochlorides with lead tetraacetate were carried out in the presence and absence of added alcohol and the reaction mixtures were worked up in such a way as to convert any anhydride formed to acid. The results of these experiments are also given in Table I. In these experiments the yields of acid derivatives (**3** plus **8**) are much greater in the presence than in the absence of added alcohol. Furthermore, the yields of acetylated amino ketone **7** in the experiments without added alcohol are greater than the yields of acid **8**. These results suggest (1) that, in partial accord with the conclusions of Baer,[7] the ester formed on oxidation is derived largely from an intermediate such as **2** rather than entirely from the reaction of an anhydride (such as **5**) with the alcohol present and (2) that acetylation of the unreacted amino ketone must involve in part some species other than the mixed anhydride (such as **5**), probably some species derived from lead tetraacetate.

Oxidation of the hydrochloride of the cyclic α-amino ketone, α-aminocyclohexanone (**9**), with lead tetraacetate in methylene chloride containing ethanol gave a 50% yield of ethyl δ-cyanovalerate (**10**), but oxidation of the hydrochloride of 2-amino-3,3-dimethyl-1-indanone (**11**) under similar conditions gave a mixture of α-(*o*-carboethoxyphenyl)isobutyronitrile (**15**), 1,1-dimethylhomophthalic anhydride (**13**), and N-acetylated amino ketone **14** in the ratio (by nmr analysis)

(7) E. Baer, *J. Amer. Chem. Soc.*, **62**, 1597 (1940); **64**, 1416 (1942).
(8) A. Stojiljkovic, V. Andrejevic, and M. L. Mihailovic, *Tetrahedron*, **23**, 721 (1967).
(9) L. K. Dyall, J. O M. Evans, and J. E. Kemp, *Aust. J. Chem.*, **21**, 409 (1968).
(10) J. B. Aylward and R. O. C. Norman, *J. Chem. Soc. C*, 2399 (1969).
(11) H. E. Baumgarten, H. W. Taylor, C. D. Campbell, C. T. Watts, and D. J. Maitland, unpublished results.

TABLE I

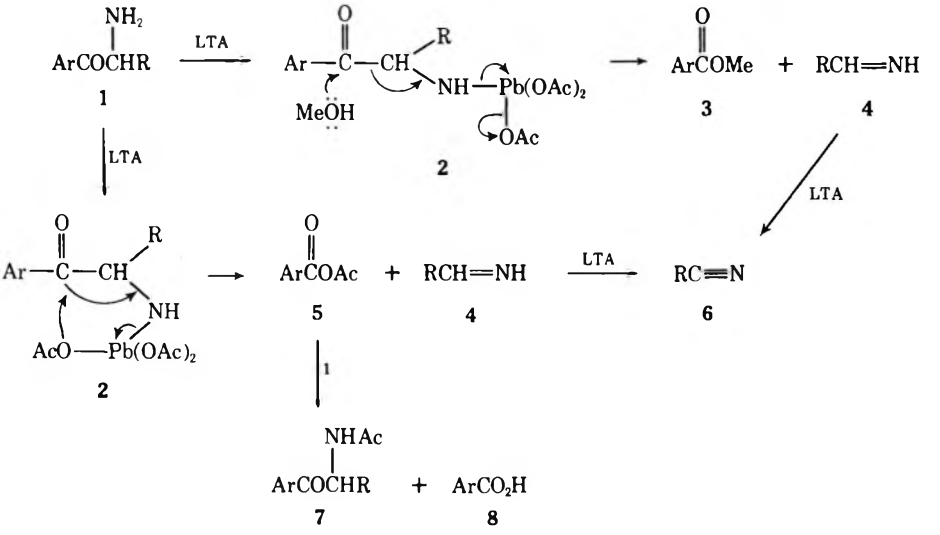
OXIDATIVE CLEAVAGE OF α-AMINO KETONES

$$\underset{1}{ArCOCH(NH_2)R} \xrightarrow[R'OH]{[O]} \underset{8}{ArCO_2H} + \underset{3}{ArCO_2R'} + \underset{6}{RCN} + \underset{7}{ArCOCHR}\ (NHAc)$$

Ar	R	Oxidant[a]	Solvent	% yield 8	3	6	7
C_6H_5	n-C_3H_7	1 LTA	CH_2Cl_2–EtOH	3.1	58	49	0
		1 LTA	CH_2Cl_2–MeOH		59	49	0
		2 LTA	CH_2Cl_2–EtOH	5.5	48	54	0
		2 LTA	CH_2Cl_2–MeOH	5	46	40	22
		2 IBDA	CH_2Cl_2–MeOH		17	19	40
		2 $NaIO_4$	MeOH	50	11	(62)[b]	
p-$CH_3C_6H_4$	CH_3	1 LTA	CH_2Cl_2	46	0		35
		1 LTA	$CHCl_3$–EtOH	19	43		10
		2 LTA	$CHCl_3$–EtOH	40	24	64	
		2 IBDA	$CHCl_3$–EtOH	29	15	94	0
p-ClC_6H_4	CH_3	1 LTA	CH_2Cl_2	28	0		41
		1 LTA	$CHCl_3$–EtOH	28	54		30

[a] LTA = lead tetraacetate; IBDA = iodosobenzene diacetate. Number indicates number of molar equivalents of oxidant per mole of α-amino ketone. [b] n-Butyric acid.

SCHEME I

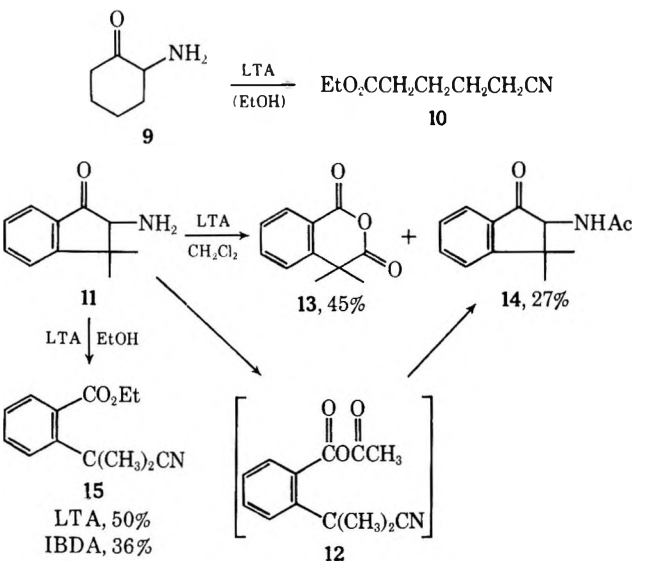


a, Ar = C_6H_5; R = n-C_3H_7
b, Ar = p-$CH_3C_6H_4$; R = CH_3
c, Ar = p-ClC_6H_4; R = CH_3

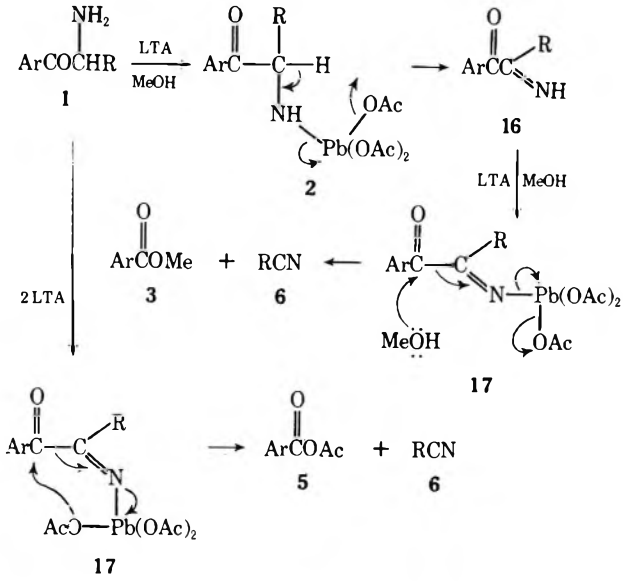
of 3:2:3. Oxidation of **11** in the absence of alcohol gave a 45% yield of **13** and 27% of **14**. These results are consistent with those from the acyclic ketones provided that it is assumed that the anhydride **13** arose from the intramolecular cyclization of an intermediate cyano ester **15** or, more probably, because of the high yield of **13** in alcohol-free methylene chloride, a cyano anhydride **12** (Scheme II).

All of the foregoing oxidation results are consistent with the simple overall picture of the reaction shown in Scheme I. However, these experiments do not distinguish between reasonable alternative mechanisms, those based solely on the analogy with α-hydroxy ketones (Scheme I) and those taking cognizance of the special properties of amines and imines (Scheme III). Although on the basis of the principle of conservation of mechanism the invocation of alternative mechanisms like that in Scheme III may appear unnecessary and perhaps undesirable, it will be shown in later papers in this series that oxidations proceeding by se-

SCHEME II



SCHEME III



quences related to that shown in Scheme III may be realized in the laboratory.

Oxidation of α-aminocyclohexyl phenyl ketone (**18**) hydrochloride, which cannot react by the route shown in Scheme III, with lead tetraacetate in chloroform solution containing some ethanol gave a 62% yield

	PhCO₂Et (6a)	PhCO₂H (8a)	(19)	(20)
LTA	44%	22%	62%	20%
IBDA	17%		30%	40%

of cyclohexanone (**19**), 44% of ethyl benzoate (**6a**), and 22% of benzoic acid (**8a**).[12] Thus, it appears that *α-substituted* α-amino ketones react with lead tetraacetate in a manner very much like that of α-hydroxy ketones.[7] In a later paper in this series this conclusion will be contrasted with quite different observations for other N analogs of the α-hydroxy ketones.

As noted above, most of the oxidations described here were carried out with both lead tetraacetate and iodosobenzene diacetate. In these experiments (but not necessarily those to be described in later papers) the principal observed differences between the two oxidants were lower yields of acid derivatives (and higher yields of N-acetylated amino ketone) and slower reactions with iodosobenzene diacetate. The yield differences are shown in the tables and equations. α-Aminovalerophenone hydrochloride was also oxidized with sodium periodate in methanol to yield 50% of benzoic acid, 11% of methyl benzoate, and 62% of *n*-butyric acid.

(12) Some N-acetylated α-amino ketone (**20**) was also present but the procedure used was not suitable for accurate determination of the yield of this product.

Experimental Section[13]

Oxidation of α-Aminovalerophenone.—The following procedure is typical of that employed in this study.

A solution of 0.500 g (0.00235 mol) of α-aminovalerophenone hydrochloride[10] in 10 ml of methylene chloride and 3 ml of dry ethanol was added dropwise over a period of 3 min to a solution of 2.08 g (0.00470 mol) of lead tetraacetate in 7 ml of dry methylene chloride at room temperature under nitrogen. The reaction mixture was accompanied with a slight yellow color change and the immediate deposition of lead salts. The solution was allowed to stir for 30 min after which time a negative starch iodide test was obtained. The reaction mixture was filtered through Celite (to remove lead salts) and a small aliquot of the filtrate was analyzed by glc using cyclohexanone as an internal standard and a 2-m column of OV-1 silicone oil at 55° (*n*-butyronitrile) and 90° (ethyl benzoate). The analysis indicated the following yields: *n*-butyronitrile, 0.087 g (54%);[14,15] ethyl benzoate, 0.169 g (48%).[4,15]

The remainder of the filtrate was extracted with saturated aqueous sodium bicarbonate. The aqueous layer was acidified with hydrochloric acid and extracted with three 25-ml portions of ether. Evaporation of the ether gave 0.015 g (5.5%)[14] of benzoic acid.

The Celite–lead salts mixture was extracted with 30% aqueous sodium hydroxide. Neutralization with hydrochloric acid, extraction with ether, and evaporation of the ether yielded a trace of benzoic acid, identified by comparison of its infrared spectrum with that of an authentic sample.

Evaporation of the dried organic layer from the bicarbonate extraction to approximately 1 ml followed by analysis by column chromatography (15 g of fluorosil) yielded no new identifiable products. A yellow residue (0.07–0.08 g) remained.

The above procedure was repeated using half the stated amount of lead tetraacetate (1.04 g, 0.00235 mol) in 7 ml of methylene chloride. The yields of products follow: *n*-butyronitrile, 0.080 g (49%);[15,16] ethyl benzoate, 0.206 g (58%);[15,16] benzoic acid, 0.009 g (3.1%);[16] residue 0.05–0.06 g.

No N-acetylated amino ketone could be found in the reaction mixtures from either of the above experiments.

A solution of 1.00 g (0.0047 mol) of α-aminovalerophenone hydrochloride[17] in 5 ml of methylene chloride and 5 ml of methanol was added in one portion with stirring to 4.4 g (0.01 mol) of dry lead tetraacetate. The solution, which became bright yellow for about 30 sec and then colorless, was stirred for 20 min and filtered. The filtrate was extracted with 25 ml of 10% aqueous sodium carbonate and then with 25 ml of 2 *N* hydrochloric acid. The solution was dried ($MgSO_4$) and evaporated. An aliquot of the pale yellow residual liquid was analyzed by glc using cyclohexanone as a standard and a column of 25% silicone oil on Chromosorb at 100°. The analysis indicated the following yields:[14,15] *n*-butyronitrile, 40%; methyl benzoate, 46%; and acetic benzoic anhydride, 5%. Dilution of the liquid residue with 100 ml of petroleum ether yielded 0.23 g (22%) of α-acetaminovalerophenone (7a), mp 59–59.5°.

Acidification of the basic extract yielded a trace of benzoic acid, mp 122°, the infrared spectrum identical with that of an authentic sample.

An authentic sample of 7a was prepared by adding 0.36 ml (0.005 mol) of acetyl chloride dropwise with stirring to a solution of 1.00 g (0.005 mol) of α-aminovalerophenone hydrochloride in 20 ml of pyridine. The mixture was stirred for 5 min, diluted with 30 ml of chloroform, extracted with two 50-ml portions of 2 *N* hydrochloric acid, dried ($MgSO_4$), and evaporated. The resulting oil was chromatographed on Florisil, the chloroform eluate yielding 0.80 g (83%) of α-acetaminovalerophenone: mp 59–59.5°; ir (CH_2Cl_2) 3450 (NH), 1704 (ketone C=O), and 1675 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 7.15–8.00 (m, 6, aromatic and NH protons), 5.55 (5, 1, J = 6 Hz, COCHN), 2.05 (s, 3, CH_3CO), and 0.70–1.70 (m, 7, aliphatic protons).

(13) Analyses by Micro-Tech Laboratories, Skokie, Ill.

(14) Based on amino ketone; expected maximum yield is 100%.

(15) Data from the calibration runs indicated that the glc analyses could be expected to have precision of ±1% for esters and ±3% for nitriles and accuracy of ±3% for esters and ±5% for nitriles.

(16) Based on amino ketone. Since only 1 equiv of oxidant was used, the expected maximum yield would be 50% *if both oxidative steps proceeded to completion.*

(17) H. E. Baumgarten, J. E. Petersen, and D. C. Wolf, *J. Org. Chem.*, **28**, 2369 (1963).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.19; H, 7.76; N, 6.15.

α-Aminovalerophenone hydrochloride (1.00 g, 0.0047 mol) was oxidized as described above using 2.22 g (0.005 mol) of lead tetraacetate. Work-up of the reaction and analysis by glc as described above gave the following yields:[15,16] *n*-butyronitrile, 49%; methyl benzoate, 59%.

To a solution of 3.32 g (0.01 mol) of iodosobenzene diacetate in 10 ml of dry methylene chloride was added a slurry of 1.00 g (0.0047 mol) of α-aminovalerophenone hydrochloride in 10 ml of dry methylene chloride and 5 ml of methanol. The solution was heated under reflux for 4 hr, cooled, extracted with 25 ml of 10% sodium carbonate solution and 25 ml of 2 *N* hydrochloric acid solution, dried ($MgSO_4$), and analyzed by glc as described above. The analysis indicated the following yields:[14,15] *n*-butyronitrile, 19%; methyl benzoate, 17%.

The solution was then evaporated yielding a brown oil. Petroleum ether (bp 30–60°) was added and the solution was evaporated again in order to remove most of the iodobenzene. This procedure was repeated twice and then petroleum ether was again added to the oil and the mixture was shaken for a few minutes. The petroleum ether solution was decanted and the resulting oil warmed (100°) in the rotary evaporator for 2 hr. The brown oil solid which crystallized on cooling was recrystallized from ether–petroleum ether, yielding 0.41 g (40%)[14] of *N*-acetyl-α-aminovalerophenone.

To a solution of 1.00 g (0.004 mol) of α-aminovalerophenone hydrochloride in 20 ml of methanol was added 1.72 g (0.008 mol) of sodium metaperiodate, and the solution was stirred overnight. The solution was filtered, diluted with water, and extracted with ether. The ether solution was extracted with 50 ml of 2 *N* hydrochloric acid and then with 50 ml of 10% sodium carbonate solution and dried ($MgSO_4$). Analysis by glc (60°) showed a trace of butyraldehyde to be present and 0.06 g (11%)[14,15] of methyl benzoate (methyl phenylacetate was added as a standard).

The basic extract was acidified and extracted with ether. The ether was evaporated and the resulting oily product was esterified[18] and analyzed by glc using cyclohexanone as a standard, indicating (at 100°) a 50% yield[14,15] of benzoic acid and (at 60°) a 62% yield[14,15] of butyric acid.

Oxidation of α-Amino-*p*-methylpropiophenone. A. Ethanol Present.—To a stirred solution of 2.25 g (0.005 mol) of lead tetraacetate in 20 ml of ethanol-stabilized chloroform was added a slurry of 1.00 g (0.005 mol) of α-amino-*p*-methylpropiophenone hydrochloride[19] in 20 ml of chloroform, and the solution was stirred for 5 min. The solution was diluted with 50 ml of ether, the lead salts were filtered off, and the filtrate was extracted with 50 ml of 10% aqueous sodium carbonate solution. The organic layer was dried ($MgSO_4$) and the solvent was evaporated leaving a brown oil. Chromatography of the oil on Florisil yielded, with ether, 0.35 g (43%)[16] of ethyl *p*-toluate (identified by glc, ir, and nmr), and with chloroform, 0.10 g (10%)[14] of α-acetamino-*p*-methylpropiophenone (**7b**), mp 65–66°.

The alkaline extract was acidified and filtered, yielding 0.13 g (19%)[16] of *p*-toluic acid, mp 179°, which was identified by comparison of its infrared spectrum with that of an authentic sample.

An authentic sample of **7b** was prepared as described above for α-acetaminovalerophenone: yield 77%; mp 66–66.5°; ir (CH_2Cl_2) 3450 (NH) and 1675 cm^{-1} (broad, amide + ketone C=O); ir (KBr) 1690 (ketone C=O) and 1670 cm^{-1} (amide C=O); nmr (CCl_4) δ 7.90 and 7.27 (d, 4, J = 8 Hz, aromatic protons), 5.45 (quartet, 1, J = 7 Hz, CH_2), 2.40 (s, 3, *p*-CH_3), 1.98 (s, 3, CH_3CO), and 1.23 (d, 3, J = 7 Hz, $CHCH_3$).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.24; H, 7.32; N, 6.54.

In another experiment a solution of 1.00 g (0.005 mol) of α-amino-*p*-methylpropiophenone hydrochloride in 20 ml of chloroform and 5 ml of absolute ethanol was added to 4.50 g (0.01 mol) of lead tetraacetate, and the resulting solution was stirred for 10 min, filtered, and extracted successively with 20 ml of 10% aqueous sodium carbonate, 20% sulfuric acid, and water. Analysis of the dried ($MgSO_4$) organic layer by glc at 75° (acetonitrile) and 125° (ethyl *p*-toluate) using cyclohexanone as an internal standard and a column of 20% silicone oil on Chromosorb R indicated that the mixture contained 0.13 g (64%)[14,15] of acetonitrile and 0.17 g (24%)[14,15] of ethyl *p*-toluate. Acidification of basic extract gave 0.27 g (40%)[14] of *p*-toluic acid. The infrared spectrum of the organic layer showed that a small amount of an anhydride was probably present.

B. Ethanol Absent.—To 2.25 g (0.005 mol) of lead tetraacetate was added a solution of 1.00 g (0.005 mol) of α-amino-*p*-methylpropiophenone hydrochloride in 30 ml of dry methylene chloride. The mixture was stirred for 1 hr and filtered. The filtrate was extracted with 50 ml of 10% aqueous sodium carbonate, dried ($MgSO_4$), and evaporated, yielding 0.36 g (35%)[14] of α-acetamino-*p*-methylpropiophenone, mp 66–66.5°. The aqueous layer was acidified and filtered, yielding 0.31 g (46%)[16] of *p*-toluic acid, mp 179°.

To 2.90 g (0.009 mol) of iodosobenzene diacetate was added a solution of α-amino-*p*-methylpropiophenone hydrochloride (1.00 g, 0.005 mol) in 20 ml of chloroform and 5 ml of absolute ethanol. The solution was stirred under reflux for 30 min, cooled, extracted successively with 50 ml of 10% sodium carbonate solution and 50 ml of 20% sulfuric acid solution, and dried ($MgSO_4$). To the solution was added cyclohexanone as an internal standard for glc analysis. The analysis for acetonitrile (75°) showed 0.17 g (92%)[14,15] to be present in the oxidation mixture. Analysis for ethyl *p*-toluate (125°) showed 0.10 g (15%)[14,15] to be present in the oxidation mixture. Acidification of the basic extracts yielded 0.21 g (29%))[14] of *p*-toluic acid.

Oxidation of α-Amino-*p*-chloropropiophenone. A. Ethanol Present.—To 2.22 g (0.005 mol) of lead tetraacetate was added a solution of 1.00 g (0.0045 mol) of α-amino-*p*-chloropropiophenone[20] hydrochloride in 35 ml of chloroform (ethanol stabilized). The solution was stirred for 10 min and filtered. The filtrate was extracted with 30 ml of 10% sodium carbonate solution, dried ($MgSO_4$), and evaporated, yielding 0.78 g of brown oil. The oil was taken up in carbon tetrachloride and analyzed by nmr. All of the observed peaks could be attributed to two compounds, ethyl *p*-chlorobenzoate [yield, 0.45 g (48%)][16] and α-acetamino-*p*-chloropropiophenone [yield, 0.30 g (25%)].[16]

A small portion of the mixture was chromatographed on Florisil, the ether eluate yielding pure ethyl *p*-chlorobenzoate (identified by its infrared spectrum) and the chloroform eluent yielding α-acetamino-*p*-chloropropiophenone: mp 106° (lit.[21] mp 106–107°); ir (neat) 3395 (NH), 1695 (ketone C=O), 1660 cm^{-1} (amide C=O); nmr (CCl_4) δ 7.96 and 7.40 (d, 4, J = 8 Hz, aromatic protons), 5.47 (q, 1, J = 7 Hz, CH_2), 1.96 (s, 3, CH_3CO), and 1.30 (t, 3, J = 7 Hz, *p*-CH_3).

Acidification of the basic extract yielded 0.20 g (28%) of *p*-chlorobenzoic acid, mp 241°, the ir spectrum identical with that of an authentic sample.

B. Alcohol Absent.—Oxidation of 1.00 g (0.0045 mol) of α-amino-*p*-chloropropiophenone hydrochloride with 2.22 g (0.005 mol) of lead tetraacetate using the procedure described for α-amino-*p*-methylpropiophenone hydrochloride yielded 0.20 g (28%)[16] of *p*-chlorobenzoic acid and 0.41 g (41%)[14] of α-acetamino-*p*-chloropropiophenone.

Oxidation of 1-Aminocyclohexyl Phenyl Ketone.—A slurry of 1.0 g (0.0042 mol) of 1-aminocyclohexyl phenyl ketone[22] hydrochloride in a solution of 20 ml of chloroform and 5 ml of absolute ethanol was added 2.25 g (0.0050 mol) of lead tetraacetate and the mixture was stirred for 15 min. The mixture was filtered, extracted successively with 25 ml of 10% aqueous sodium carbonate, 35 ml of 20% sulfuric acid, and water, dried ($MgSO_4$), and evaporated. The resulting 0.8 g of yellow liquid was analyzed by glc using iodobenzene as a standard and a column of 20% silicone oil on Chromosorb R at 120° and was found to contain a 59%[14,15] (0.24 g) yield of cyclohexanone and a 44%[14,15] (0.26 g) yield of ethyl benzoate.

Acidification of the alkaline extract yielded 0.10 g (20%)[14] of benzoic acid, mp 122°.

The infrared spectrum (peak at 3400 cm^{-1}, several peaks in C=O region) of the yellow liquid indicated the presence of an *N*-acetyl compound, but this compound could not be isolated in the pure state.

Oxidation of 3,3-Dimethyl-2-amino-1-indanone Hydrochloride. A. In the Absence of Alcohol.—A slurry of 3.0 g (0.014 mol) of

(18) R. O. Clinton and S. O. Laskowski, *J. Amer. Chem. Soc.*, **70**, 3135 (1948).

(19) Prepared in 65% yield by the method of ref 14, mp 223–224° dec. *Anal.* Calcd for $C_{16}H_{14}NOCl$: C, 60.15; H, 7.02; N, 7.02; Cl, 17.79. Found: C, 60.07; H, 7.15; N, 7.07; Cl, 17.93.

(20) Prepared in 33% yield by the method of ref 17, mp 226° dec. *Anal.* Calcd for $C_9H_{11}Cl_2NO$: C, 49.10; H, 5.02, N, 6.36; Cl, 31.96. Found: C, 48.76; H, 5.03; N, 6.59; Cl, 31.84.

(21) H. K. Müller, *Justus Liebigs Ann. Chem.*, **599**, 61 (1956).

(22) Prepared in 27% yield by the method of ref 17, sublimes above 220°. *Anal.* Calcd for $C_{13}H_{18}NOCl$: C, 65.13; H, 7.51; N, 5.84; Cl, 14.82. Found: C, 65.29; H, 7.62; N, 5.73; Cl, 14.85.

3,3-dimethyl-2-amino-1-indanone[23] hydrochloride in 50 ml of dry methylene chloride was added to 6.6 g (0.015 mol) of lead tetraacetate and the mixture was stirred for 30 min, filtered, extracted with 10% aqueous sodium carbonate solution, dried ($MgSO_4$), and evaporated. The resulting brown oil was dissolved in anhydrous ether and cooled overnight, yielding 0.7 g (25%)[14] of *N*-acetyl-3,3-dimethyl-2-amino-1-indanone: mp 116–117°; ir ($CHCl_3$) 3415 (NH), 1730 (ketone C=O), and 1690 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 1.12 (s, 3, CH_3 cis to amide), 1.62 (s, 3, CH_3 trans to amide), 2.13 (s, 3, CH_3CO), 4.75 (d, 1, J = 8 Hz, CH_2), and 7.80 (m, 5, aromatic and amide).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.84; H, 7.00; N, 6.24.

The ether solution was diluted with petroleum ether until the solution became cloudy and cooled overnight, yielding 1.2 g (45%)[15] of 1,1-dimethylhomophthalic anhydride: mp 79° (lit.[24] mp 81–82°); ir ($CHCl_3$) 1800 and 1750 cm^{-1}; nmr ($CDCl_3$) δ 1.76 (s, 6, CH_3) and 7.60 (m, 4, aromatic).

Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30; O, 25.24. Found: C, 69.77; H, 5.17.

A solution of 1.00 g (0.005 mol) of 2-amino-3,3-dimethyl-1-indanone hydrochloride (0.005 mol) of iodosobenzene diacetate and 30 ml of methylene chloride was heated under reflux for 4 hr. The yellow solution was extracted with 25 ml of 10% sodium carbonate solution, dried, and evaporated, yielding a brown oil. Petroleum ether was added to the oil and the mixture was evaporated to remove iodobenzene. This procedure was repeated several times until the iodobenzene odor no longer was apparent in the sample. The resulting oil (0.7 g) showed infrared absorption (neat) indicating the presence of anhydride (1820 and 1760 cm^{-1}) as well as amide (1690 and 3425 cm^{-1}). The oil was taken up in carbon tetrachloride and analyzed by nmr. The analysis indicated the oil contained 0.3 g (30%)[16] of 1,1-dimethylhomophthalic anhydride and 0.3 g (30%)[16] of 2-acetamino-3,3-dimethyl-1-indanone.

(23) Prepared in 48% yield by the method used by N. Levin, B. Graham, and H. Kolloff, *J. Org. Chem.*, **9**, 380 (1944), for the preparation of 2-aminoindanone, mp 213° dec *Anal.* Calcd for $C_{11}H_{14}ClNO$: C, 62.41; H, 6.62; N, 6.62; Cl, 16.78. Found: C, 62.14; H, 6.73; N, 6.65; Cl, 16.80.

(24) M. Anched and A. Blatt, *J. Amer. Chem. Soc.*, **63**, 1948 (1941).

B. In the Presence of Alcohol.—A slurry of 3,3-dimethyl-2-amino-1-indanone hydrochloride (2.0 g, 0.01 mol) in a solution of 25 ml of methylene chloride and 2.5 ml of ethanol was added to 4.4 g (0.01 mol) of lead tetraacetate. The mixture was stirred for 10 min, filtered, extracted with 10% aqueous sodium carbonate solution, dried ($MgSO_4$), and evaporated. The nmr spectrum of the resulting yellow oil (1.69 g) indicated a 3:3:2 ratio of α-(*o*-carboethoxyphenyl)isobutyronitrile–*N*-acetyl-3,3-dimethyl-2-amino-1-indanone–1,1-dimethylhomophthalic anhydride. The infrared spectrum (film) indicated the presence of nitrile (2240), amide (3425, 1690), ester (1730), and anhydride (1825, 1755 cm^{-1}). Separation of these compounds was not feasible.

Oxidation of α-Aminocyclohexanone Hydrochloride in the Presence of Alcohol.—A slurry of 2.0 g (0.013 mol) of α-aminocyclohexanone hydrochloride in a solution of 25 ml of methylene chloride and 2.5 ml of ethanol was added to 6.2 g (0.014 mol) of lead tetraacetate. The mixture was stirred for 30 min, filtered, extracted with 10% aqueous sodium carbonate solution, dried ($MgSO_4$), and evaporated yielding a brown oil. The oil was taken up in ether and petroleum ether was added until the solution became cloudy. The solution was refrigerated overnight yielding an impure oily solid, which was tentatively identified as α-acetaminocyclohexanone by its infrared and nmr spectra but which could not be completely purified. The remaining solution was evaporated, yielding a pale yellow liquid which was further purified by thin layer chromatography on silica (ether) yielding 0.5 g (25%)[16] of ethyl δ-cyanovalerate,[25] identified by its ir spectrum (neat) 2220 (C≡N) and 1720 cm^{-1} (C=O ester) (lit.[25] 2220, 1720 cm^{-1}), and refractive index $n^{25}D$ 1.436 (lit.[23] 1.44).

Registry No.—**1a**, 31952-46-2; **1b**, 31952-47-3; **1c**, 23933-82-6; **7a**, 31952-49-5; **7b**, 31952-50-8; **7c**, 31952-51-9; **9** HCl, 6946-05-0; **10**, 4450-39-9; **11** HCl, 31952-54-2; **13**, 31952-55-3; **14**, 31999-37-8; **15**, 31952-56-4; **18** HCl, 31952-57-5; lead tetraacetate, 546-67-8.

(25) O. Riobee, M. Lamant, and G. Lancher, *Bull. Soc. Chim. Fr.*, 1535 (1960).

Anodic Oxidations. IV.[1] Electrochemical Oxidation of 2,5-Dimethylthiophene

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Electrochemical oxidations of 2,5-dimethylthiophene in methanol resulted in three types of reactions, depending on the electrolytes used. (1) With ammonium bromide as electrolyte, the product was 3-bromo-2,5-dimethylthiophene exclusively. (2) With nonhalide electrolytes such as ammonium nitrate and sodium acetate, methoxide, and perchlorate, the formation of 2-methoxymethyl-5-methylthiophene was observed. (3) With sodium cyanide, the products were *cis*- and *trans*-2-cyano-5-methoxy-2,5-dimethyldihydrothiophenes (*cis*/*trans* = 2.3), together with comparable amounts of 3-cyano-2,5-dimethylthiophene and 2-methoxymethyl-5-methylthiophene. The bromination involves discharge of the bromide ion at the anode, whereas both the cyanation and methoxylation products are considered to have been derived from initial oxidation of 2,5-dimethylthiophene at the same electrode. Factors controlling the relative prevalence of the two pathways leading to the nuclear cyanation and the side-chain methoxylation are discussed, in reference to the case of 2,5-dimethylfuran studied previously.[1]

The electrochemical behavior of aromatic five-membered heterocycles other than furan still remains to be explored. Previous studies have only enlightened the electrolyses in methanol of thiophene and *N*-methylpyrrole in which methoxylation takes place.[2]

We reported, in a previous paper,[1] that the anodic oxidation of 2,5-dimethylfuran in a methanolic solution of sodium cyanide gave a 2:1 isomeric mixture of *cis*- and *trans*-2-cyano-5-methoxy-2,5-dimethyldihydrofurans. The overall reaction involved the initial oxidation of 2,5-dimethylfuran, and proceeded nonstereospecifically. It is known, on the other hand, that, when sodium acetate, sodium methoxide, and ammonium nitrate are used as electrolyte, 2,5-dimethoxy-2,5-dimethyldihydrofuran is produced.[3,4] These contrasting results demonstrate the importance of the electrolyte in electroorganic reactions. There are several other examples in the literature wherein the nature of the electrolytes may be product determining: the anodic methoxylation of furans bearing an electron-withdrawing group must be carried out with sulfuric acid as elec-

(1) Part III: K. Yoshida and T. Fueno, *J. Org. Chem.*, **36**, 1523 (1971).

(2) N. L. Weinberg and H. R. Weinberg, *Chem. Rev.*, **68**, 449 (1968).

(3) A. J. Baggaley and R. Brettle, *J. Chem. Soc. C*, 969 (1968).

(4) S. D. Ross, M. Finkelstein, and J. J. Uebel, *J. Org. Chem.*, **34**, 1018 (1969).

TABLE I

ANODIC OXIDATION OF 2,5-DIMETHYLTHIOPHENE IN METHANOL

Electrolyte anion	N^a	Decomposition[b] potential, V vs. sce	Anode potential, V vs. sce	Electricity, F	Product	Current efficiency, %	n, F/mol
ClO_4^-	0.00>	2.7[c]	1.20	0.030	II[h]	12[i]	1.6
NO_3^-	1.03	1.3, 1.1,[d] 1.5[e]	1.15	0.010	II	52[j]	1.7
AcO^-	2.72	1.7, 1.7[e]	1.50	0.008	II	53[k]	1.7
CH_3O^-		1.1	[g]	0.038	II	41	
Br^-	3.89	0.6, 0.7[f]	0.70	0.024	I	35	
CN^-	5.1	1.5	[g]	0.047	II	14	
					III_c	20	
					III_t	9	
					IV	7	

[a] Nucleophilicity constant.[10] [b] Data read from Figure 1, unless otherwise noted. [c] Taken from ref 11. Corrected for the Ag/Ag^+ potential *vs.* sce. [d] Value from ref 12. [e] Corrected value, ref 13. [f] Corrected value, ref 14. [g] Nonpotentiostatic oxidation at a terminal voltage of about 33 V. [h] Main product was undistillable residue. [i–k] Yield (based on 2,5-dimethylthiophene consumed): (*i*) 9%; (*j*) 44%; (*k*) 44%.

trolyte;[5] dimethylamides are alkoxylated in poor yield in the presence of sodium alkoxide, but in good yield with ammonium nitrate as electrolyte;[6] alkylaromatic compounds undergo nuclear acetoxylation in sodium acetate–acetic acid solution, but are subject to side-chain acetoxylation in acetic acid containing salts of other anions, such as perchlorate and tosylate.[7]

It is the purpose of the present report to investigate the influence of the electrolytes on the anodic oxidation of 2,5-dimethylthiophene in methanol and to compare the nature of the overall reaction with that previously observed for 2,5-dimethylfuran.[1] Since 2,5-dimethylthiophene will be oxidized at a relatively low anodic potential,[8] it is highly probable that the thiophene receives initial oxidation to a cationic species at the electrode as in the case of 2,5-dimethylfuran. Subsequent reactions of the cationic intermediate with nucleophiles may well differ in mode from those of a similar cation derived from 2,5-dimethylfuran.

Results

Reaction Products.—First of all, the ammonium bromide–methanol system was investigated, which has been the most thoroughly studied system for preparing dimethoxydihydrofurans since the pioneering work of Clauson-Kaas.[2] Controlled potential electrolysis of 2,5-dimethylthiophene at 0.7 V resulted in the formation of 3-bromo-2,5-dimethylthiophene (I).

When nonhalide electrolytes such as ammonium nitrate and sodium acetate, methoxide, and perchlorate were used, 2-methoxymethyl-5-methylthiophene (II) was formed. The product was identified as such from comparisons with the authentic samples prepared by other routes.

With methanolic sodium cyanide, products were *cis*- and *trans*-2-cyano-5-methoxy-2,5-dimethyldihydrothiophenes (III_c and III_t), and comparable amounts of 3-cyano-2,5-dimethylthiophene (IV) and 2-methoxymethyl-5-methylthiophene (II). The ratio of III_c to III_t as determined by the vpc and nmr methods was 2.3:1. Each product was isolated by fractional distillation and preparative vpc and identified by infrared and nmr spectroscopy. For the sake of comparison, the anodic oxidation of 2,5-dimethylthiophene in acetonitrile was performed with tetraethylammonium cyanide as the electrolyte. In this latter case, the formation of a small amount of IV was observed, together with a significant amount of tarry residue.

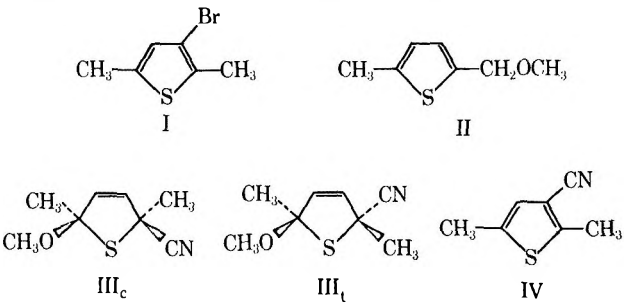


Table I[10–14] summarizes the results of electrolysis. The current efficiencies are based on the total charge passed; the formation of 1 mol of each product is assumed to require 2 *F*. It should be noted that only the cyanide ion, a considerably stronger nucleophile, was capable of producing 2,5-dihydrothiophene derivatives. The current efficiency for these reactions was 50% or so and the remainder of the current would be consumed with side reactions (presumably the formation of undistillable tarry residue). Side reactions must be electrochemically one-electron oxidation reactions. Then it can be rationally explained that coulometric *n* values are somewhat small, compared to theoretical two, and chemical yields are lower than current efficiencies.

Current–Potential Curves.—As a guide to mechanism, it is essential to clarify which chemical species is being oxidized at the anode, substrate or electrolyte anion. The most pertinent to this inquiry would be measurements of the current–potential curves, as has been stressed previously.[1] The results of such measurements for methanolic solutions of acetate, bromide, cyanide, methoxide, nitrate, and perchlorate salts,

(5) N. Clauson-Kaas and F. Limborg, *Acta Chem. Scand.*, **6**, 551 (1952).
(6) S. D. Ross, M. Finkelstein, and R. C. Petersen, *J. Amer. Chem. Soc.*, **88**, 4657 (1966).
(7) L. Eberson, *ibid.*, **89**, 4669 (1967).
(8) Although the oxidation potential of 2,5-dimethylthiophene is uncertain, it is probably 1.4 V or so, the half-wave potentials of 2,5-dimethylfuran, furan, and thiophene being 1.20, 1.70, and 1.91 V, respectively.[9]
(9) L. Eberson and K. Nyberg, *J. Amer. Chem. Soc.*, **88**, 1686 (1966).
(10) K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1963, p 424.
(11) J. P. Billon, *Bull. Soc. Chim. Fr.*, 863 (1962).
(12) N. L. Weinberg and T. B. Reddy, *J. Amer. Chem. Soc.*, **90**, 91 (1968).
(13) S. D. Ross, M. Finkelstein, and R. C. Petersen, *J. Org. Chem.*, **35**, 781 (1970).
(14) J. P. Millington, *J. Chem. Soc. B*, 982 (1969).

each with and without 2,5-dimethylthiophene, are shown in Figure 1.

Figure 1 shows that a methanolic solution of sodium perchlorate alone is not discharged unless the anode potential exceeds 1.3 V, whereas a solution containing 2,5-dimethylthiophene allows current to pass through it at 1.15 V. Clearly, 2,5-dimethylthiophene is oxidizable at a relatively low anode potential. An analogous situation was observed in the measurement with ammonium nitrate or sodium acetate as electrolyte.

By contrast, the ammonium bromide–methanol system was discharged at a potential as low as 0.7 V. The addition of 2,5-dimethylthiophene did not change the current–potential curve materially. These observations indicate that the species being oxidized at a potential around 0.7 V must be the bromide ion.

The sodium methoxide–methanol system is inbetween the above two cases, in that the electrolyte anion and the substrate are discharged at about the same potential. However, closer observation showed that the presence of 2,5-dimethylthiophene somewhat enhanced the current at lower potentials but tended to suppress it at higher potentials. Further, the current was observed to drift lower with time. Probably, a product of the electrolysis may be adsorbed to some extent on the anode, thus decreasing the area available for normal electrochemical reactions.

In the sodium cyanide–methanol system the situation was much the same as that for the sodium perchlorate system; 2,5-dimethylthiophene began to be oxidized at about 0.9 V, whereas the cyanide ion was discharged at about 1.5 V. In the presence of 2,5-dimethylthiophene, the current tended to diminish with time, perhaps because of increasing contamination of the anode surface by the electrolysis product. A similar phenomenon was observed in the tetraethylammonium cyanide–acetonitrile system.

Discussion

As has already been described, the anodic bromination of 2,5-dimethylthiophene involves the discharge of the bromide ion rather than the substrate at the first step. In view of the nature of the product, the brominating intermediate in this case would be molecular bromine rather than bromine atom. This possibility receives further support from the fact that 2,5-dimethyl-

$$2Br^- \xrightarrow{-2e} Br_2$$

thiophene readily reacts with bromine in methanol to form the same product, I, at a yield nearly equal to that gained by the electrochemical method. If bromine atom were an intermediate species, 2-bromomethyl-5-methylthiophene would be formed through hydrogen abstraction from the side chain followed by coupling with another bromine atom. No such product was observed in the electrolysis experiment.

On the contrary, with nonhalide electrolytes, the primary anodic process is the oxidation of 2,5-dimethylthiophene to a cationic species (most likely a cation radical) which subsequently reacts with nucleophiles.

With sodium cyanide as electrolyte, nuclear cyanation was brought about. In analogy with the results of potentiostatic anodic cyanation of 2,5-dimethylfuran,[1]

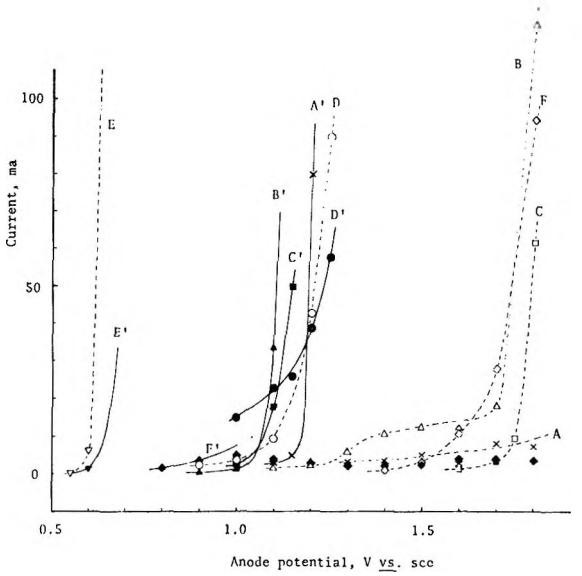
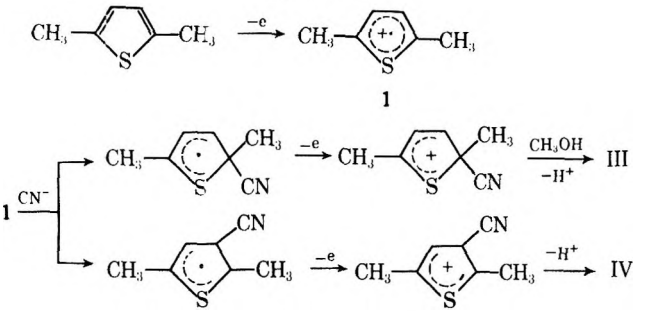


Figure 1.—Plots of current *vs.* anode potential at smooth platinum (8 cm²): (A) $NaClO_4$; (B) NH_4NO_3; (C) NaOAc; (D) NaOMe; (E) NH_4Br (F) NaCN. A prime represents the presence of 0.8 *M* 2,5-dimethylthiophene. The concentration of electrolytes was 0.8 *M* except for NH_4Br, where 0.7 *M* solution was used owing to its limited solubility.

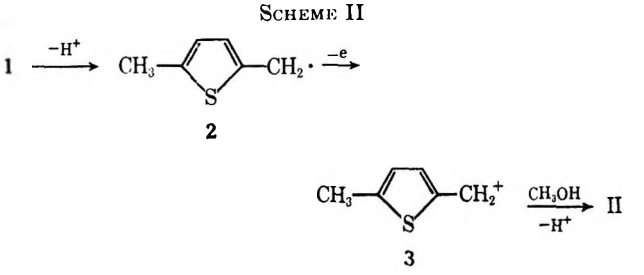
the following ionic mechanism would be reasonable (Scheme I).[15]

SCHEME I



With sodium acetate, sodium perchlorate, and ammonium nitrate as electrolyte, side-chain methoxylation was observed. A polar mechanism as in Scheme II is

SCHEME II



conceivable. The anodically generated cation radical **1** would lose a proton to produce the radical **2**, which

(15) There is another possibility that it is the cyanide ion that is discharged in the primary step. However, even when the cyanide ion is anodically oxidized the radical formed will not react with 2,5-dimethylthiophene; photochemically generated cyano radicals[16,17] are recognized not to attack 2,5-dimethylthiophene.

(16) C. A. Goy, D. H. Shaw, and H. O. Pritchard, *J. Phys. Chem.*, **69**, 1504 (1965).

(17) L. Eberson and S. Nilsson, *Discuss. Faraday Soc.*, No. 45, 242 (1968).

would subsequently undergo anodic oxidation to give a cation **3**, followed by nucleophilic attack by solvent.

When the anodic side-chain methoxylation is carried out in methanol containing sodium methoxide, the electrolyte anion as well as the substrate is oxidized in the primary anodic process. In this case, therefore, a mechanism in which the primary process is the discharge of the anion to form a methoxyl radical, which would then abstract hydrogen atom to form the radical **2**, cannot wholly be eliminated.

Comparisons of the present results with those gained previously[1,3,4] show a considerable difference in reactivity between 2,5-dimethylthiophene and 2,5-dimethylfuran. The anodic oxidation of 2,5-dimethylthiophene leads to nuclear cyanation or side-chain methoxylation, depending on the electrolytes used. By contrast, the electrochemical oxidation of 2,5-dimethylfuran occurs almost exclusively on the ring, giving dihydrofuran derivatives.[1,3,4] These are ascribed to the stabilities of initially generated cation radicals and their relative reactivities toward different nucleophiles.

It is to be expected that the facility of a loss of a proton from the cation radicals is related with the difference in total π-electronic energy E_π between the cation radicals **1** and the resultant radicals **2**; the cation radicals would the more readily eject a proton, the greater the gain in E_π on going from **1** to **2**. Table II summarizes

TABLE II

TOTAL π-ELECTRONIC ENERGY OF CATION RADICALS AND THEIR DEPROTONATED RADICALS[a]

	E_π, β	
	Cation radical **1**	Radical **2**
2,5-Dimethylthiophene	6.765	7.532
2,5-Dimethylfuran	9.180	9.173

[a] The parameters used were $h_S = 1.0$, $k_{C-S} = 0.5$, $h_O = 2.0$, $k_{C-O} = 0.8$, $h_C = -0.5$ (inductive model for the methyl group), $\delta = 0.1$, $\omega = 1.4$.

the values of E_π calculated for these intermediates by the ω technique as used in the HMO theory.[18] These data indicate that the cation radical **1** generated by the oxidation of the thiophene is stabilized by $-0.767\ \beta$ on forming the radical **2**, whereas the cation radical formed by the discharge of 2,5-dimethylfuran is more stable than its deprotonated radical by $-0.007\ \beta$. Therefore, the cation radical **1** formed from the thiophene would be liable to lose a proton prior to the solvent attack or else suffer nuclear attack of strong nucleophiles such as the cyanide ions. On the contrary, the cation radical derived from the furan would be reluctant to deprotonation, thus leading to the formation of nuclear addition products alone.

Finally, it should be noted that nuclear cyanation of the furan occurs preferentially at the 2 position, whereas in 2,5-dimethylthiophene both 2 and 3 positions are attacked. This might be attributed to the greater aromatic character of thiophene compared to furan.

In summary, anodic oxidation of 2,5-dimethylthiophene in methanol containing various nonhalide electrolytes such as ammonium nitrate and sodium acetate, methoxide, and perchlorate, produced the side-chain methoxylation product. Only sodium cyanide electrolyte was capable of forming dihydrothiophene derivatives. The difference in reaction mode between these systems may be ascribed to the greater nucleophilicity of the cyanide ion relative to other anions or the solvent. Evidence was presented in support of a mechanism in which the first step was discharge of the substrate to give a cationic species. Use of ammonium bromide as electrolyte resulted in the bromination at the 3 position, in which case the primary anodic process is the discharge of the bromide ion. The facility of a loss of a proton from the cation radicals of 2,5-dimethylthiophene is understandable from a large difference in total π-electronic energy between the cation radical and the resultant radical, in comparison with the case of 2,5-dimethylfuran.

Experimental Section

The electrolysis cell, electrodes, and their operation have been described previously.[1] All potentials are referred to a saturated calomel electrode. All experiments were performed under dry nitrogen. Nmr spectra were obtained with a JEOCO Model JNM-4H-100 spectrometer.

Materials.—2,5-Dimethylthiophene was prepared by the method of Farrar and Levine.[19] Analytical grade inorganic reagents were used with no purification other than drying. Tetraethylammonium cyanide was prepared according to the method given by Andreades and Zahnow.[20] Methanol was purified as previously described.[1] Acetonitrile was purified by distillation from phosphorus pentoxide and from potassium carbonate.

An authentic sample of 2,5-dimethyl-3-bromothiophene was prepared by treating 2-bromomethyl-5-methylthiophene with cuprous cyanide.[21] 2-Methoxymethyl-5-methylthiophene was obtained by treating 2-bromomethyl-5-methylthiophene with sodium methoxide in methanol, bp 86–88° (6 mm).

Controlled Potential Bromination of 2,5-Dimethylthiophene.—A methanolic solution (50 ml) of 2,5-dimethylthiophene (4.49 g, 0.04 mol) and ammonium bromide (3.43 g, 0.035 mol) was electrolyzed at 25° for 5 hr, using an anode potential of 0.70 V. The catholyte was methanol, 0.7 *M* in ammonium bromide. The total electricity used amounted to 0.024 *F*.

The electrolyzed mixture was poured into a large volume of water and extracted exhaustively with ether. The combined ether extract was washed successively with dilute sodium thiosulfate solution and dilute sodium bicarbonate solution. The solution was dried over anhydrous magnesium sulfate and filtered. The solvent and the thiophene remaining unchanged were evaporated off under reduced pressure. Vacuum distillation of the residual liquid yielded 0.8 g of colorless liquid boiling at 62–63° (4 mm). The fraction has retention time on vpc and ir and nmr spectra identical with those of a sample of authentic 3-bromo-2,5-dimethylthiophene; nmr spectrum (100 MHz, 10% in CCl_4) τ 3.55 (1 H singlet, vinyl proton), 7.65 (3 H singlet, methyl proton), and 7.72 (3 H singlet, methyl proton).

Anal. Calcd for C_6H_7BrS: C, 37.71; H, 3.69; Br, 41.82; S, 16.78. Found: C, 37.83; H, 3.64; Br, 42.05; S, 16.90.

The current efficiency is 35%.

Electrochemical Cyanation of 2,5-Dimethylthiophene.—A methanolic solution (50 ml) of 2,5-dimethylthiophene (4.49 g, 0.04 mol) and sodium cyanide (1.96 g, 0.04 mol) was electrolyzed at 3–6°, with a current of 0.1 A at 33 V for 12 hr, until 0.047 *F* of charge was passed through the solution. The catholyte was a methanolic solution of sodium cyanide (0.8 *M*). The electrolysate was treated as usual.[1] Vacuum distillation gave the following fractions: (1) bp 63° (4 mm), 0.20 g; (2) bp 74–76° (4 mm), 0.50 g; (3) bp 82–84° (4 mm), 1.20 g.

Fraction 1 was redistilled: ir spectrum 3000 (=CH), 2820 (OCH_3), 1160, 1090, and 1045 cm^{-1} (COC); nmr spectrum τ 3.36 (1 H doublet, vinyl proton, J = 3.5 cps), 3.50 (1 H doublet,

(18) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, pp 115, 135.

(19) M. W. Farrar and R. Levine, *J. Amer. Chem. Soc.*, **72**, 4433 (1950).

(20) S. Andreades and E. W. Zahnow, *ibid.*, **91**, 4181 (1969).

(21) J. Lecocq, *Ann. Chim. (Paris)*, **3**, 62 (1948); *Chem. Abstr.*, **42**, 7281 (1948).

vinyl proton, J = 3.5 cps), 5.58 (2 H singlet, methylene proton), 6.76 (3 H singlet, methoxy proton), and 7.55 (3 H singlet, methyl proton).

Anal. Calcd for $C_7H_{10}OS$: C, 59.12; H, 7.09; S, 22.54. Found: C, 59.23; H, 7.22; S, 22.10.

The ir and nmr spectra of this material were identical with an authentic sample of 2-methoxymethyl-5-methylthiophene (II).

The vpc analysis of fraction 3 showed three peaks with a small amount of 2-methoxymethyl-5-methylthiophene. Each component was then separated in pure form by preparative vpc, the column packing being PEG 6000.

The first substance was liquid: ir spectrum 2240 cm^{-1} (CN); nmr spectrum τ 3.30 (1 H singlet), 7.43 (3 H singlet, methyl proton), and 7.58 (3 H singlet, methyl proton).

Anal. Calcd for C_7H_7NS: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.28; H, 5.15; N, 10.01.

These results suggest that this product material is 3-cyano-2,5-dimethylthiophene (IV).[22]

The second substance was also liquid: ir spectrum 3000 (=CH) 2830 (OCH_3), 2240 (CN), 1645 (C=C), 1125, 1110, 1080, 1050, and 1045 cm^{-1} (COC); nmr spectrum τ 4.16 (1 H doublet, vinyl proton, J = 6.0 cps), 4.38 (1 H doublet, vinyl proton, J = 6.0 cps), 6.76 (3 H singlet, methoxy proton), 8.24 (3 H singlet, methyl proton), and 8.26 (3 H singlet, methyl proton).

Anal. Calcd for $C_8H_{11}NOS$: C, 56.78; H, 6.55; N, 8.28; S, 18.94. Found: C, 56.86; H, 6.53; N, 8.25; S, 18.88.

The third substance had mp 48–48.5°; ir spectrum 3000 (=CH), 2830 (OCH_3), 2240 (CN), 1645 (C=C), 1130, 1105, 1080, and 1045 cm^{-1} (COC); nmr spectrum τ 4.18 (1 H doublet, J = 6.0 cps), 4.30 (1 H doublet, J = 6.0 cps), 6.83 (3 H singlet), and 8.15 (6 H singlet).

Anal. Calcd for $C_8H_{11}NOS$: C, 56.78; H, 6.55; N, 8.28; S, 18.94. Found: C, 56.43; H, 6.49; N, 7.93; S, 18.81.

These data suggest that the latter two substances are geometrical isomers of 2-cyano-5-methoxy-2,5-dimethyldihydrothiophene (III_c and III_t). The structural assignments for the two isomers, III_c and III_t, were based on their nmr spectra. The methoxy protons of III_c (τ 6.76) resonated at a magnetic field a little lower than did those of III_t (τ 6.83). It is apparent from molecular models that the methoxy protons in the cis isomer are located closer to the cyano group than those in the trans isomer, indicative of the lower-field shift of the methoxy protons in the former compound.[1] This implies that the product III_c is assignable cis configuration. The individual isomers were unchanged both at room temperature and on vpc, but on warming in carbon tetrachloride there was a significant interconversion accompanied by some decomposition. A trace of sulfuric acid also exerted the same agency.

Fraction 2 was a mixture of 2-methoxymethyl-5-methylthiophene (II), 3-cyano-2,5-dimethylthiophene (IV), and 2-cyano-5-methoxy-2,5-dimethyldihydrothiophene (III_c and III_t).

(22) R. Justoni, *Gazz. Chim. Ital.*, **71**, 375 (1941).

The current efficiencies of the products were as follows: 2-methoxymethyl-5-methylthiophene (II), 0.54 g (14%, based on 2e process); 3-cyano-2,5-dimethylthiophene (IV), 0.28 g (7%); *cis*-2-cyano-5-methoxy-2,5-dimethyldihydrothiophene (III_c), 0.72 g (20%); *trans*-2-cyano-5-methoxy-2,5-dimethyldihydrothiophene (III_t), 0.32 g (9%).

Electrochemical Cyanation of 2,5-Dimethylthiophene in Acetonitrile.—An acetonitrile solution (50 ml) of 2,5-dimethylthiophene (4.49 g, 0.04 mol) and tetraethylammonium cyanide (6.25 g, 0.04 mol) was electrolyzed at 3–6°, with a current of 0.1 A at 33 V for 7 hr, until 0.027 F of charge was passed through the solution. The catholyte was a acetonitrile solution of tetraethylammonium cyanide (0.8 M). The electrolyzed mixture was treated with a large volume of water and the organic material was extracted with ether. The combined ether extract was washed thoroughly with water, dried over anhydrous magnesium sulfate, and filtered. Vpc analysis (internal standard, anisole) showed that 1.18 g of 2,5-dimethylthiophene had been consumed, corresponding to 2.5 electrons lost per 2,5-dimethylthiophene molecule. The thiophene remaining unchanged as well as ether was then evaporated off under reduced pressure. Vacuum distillation of the residual liquid yielded 0.1 g of liquid boiling at 70–75° (1 mm) and a tarry residue. The vpc analysis showed that this fraction contained a small amount of 3-cyano-2,5-dimethylthiophene. No attempt was made to identify other components.

Electrochemical Methoxylation of 2,5-Dimethylthiophene.—In a typical experiment a methanolic solution (50 ml) of sodium methoxide (sodium, 0.92 g, 0.04 g-atom) and 2,5-dimethylthiophene (4.49 g, 0.04 mol) was electrolyzed at 4–6°, with a current of 0.08 A at 33 V for 12 hr, until 0.038 F of charge had passed through the solution. The catholyte was a methanolic solution of sodium methoxide (0.8 M). The electrolysate was treated as usual. Vacuum distillation yielded 1.1 g of liquid boiling at 52–52.5° (4 mm). The vpc analysis and ir and nmr data showed that this material was 2-methoxymethyl-5-methylthiophene. The current efficiency is 41%.

In experiments with sodium perchlorate as the electrolyte, a methanolic solution (50 ml) of 2,5-dimethylthiophene (4.49 g, 0.04 mol) and sodium perchlorate (4.90 g, 0.04 mol) was electrolyzed at 25° for 3.5 hr, using an anode potential of 1.20 V. The catholyte was a methanolic solution of sodium perchlorate (0.8 M). The electricity was 0.030 F. The electrolyzed mixture was treated as usual and the ethereal solution was concentrated to 50 ml at 0°. Vpc analysis showed that 2.17 g of 2,5-dimethylthiophene had been consumed (corresponding to 1.6 F per mole of substrate) and 0.26 g of 2-methoxymethyl-5-methylthiophene had been produced.

Registry No.—I, 31819-37-1; II, 31819-38-2; III_c, 31819-39-3; III_t, 31819-40-6; IV, 31883-38-2; 2,5-dimethylthiophene, 638-02-8.

Aryl Hydrodisulfides

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Phenyl hydrodisulfide and its para-substituted derivatives, as well as β-naphthyl hydrodisulfide, were synthesized, and their ir and nmr spectra were measured. Sulfhydryl proton chemical shifts of para-substituted phenyl hydrodisulfides were best correlated with Taft's σ_R, $\Delta\nu_{SSH} = 15.8\sigma_R - 200.8$ (r = 0.993).

An attempt to synthesize phenyl hydrodisulfide (2e) has been reported by Böhme and Zinner[1] in connection with alkyl hydrodisulfides and related derivatives. However, they obtained an oily substance which unfortunately was not identified as phenyl hydrodisulfide. Special interest was generated in this oily substance during our studies on aralkyl hydrodisulfide.[2] If aryl hydrodisulfides were successfully synthesized, we would be able to compare and correlate their nmr spectra with those of the corresponding arenethiols. Several years ago, Marcus and Miller[3] found that nmr frequencies of sulfhydryl groups in meta- and para-substituted benzenethiols correlate with Hammett's σ (ρ = −21.8). Later, Marcus, *et al.*,[4] pointed out that insertion of such

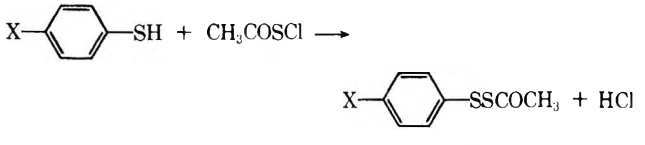
(1) H. Böhme and G. Zinner, *Justus Liebigs Ann. Chem.*, **585**, 142 (1954).
(2) J. Tsurugi, Y. Abe, T. Nakabayashi, S. Kawamura, T. Kitao, and M. Niwa *J. Org. Chem.*, **35**, 3263 (1970).
(3) S. H. Marcus and S. I. Miller, *J. Phys. Chem.*, **68**, 331 (1964).
(4) S. H. Marcus, W. F. Reynolds, and S. I. Miller, *J. Org. Chem.*, **31**, 1872 (1966).

an atom as tetrahedral carbon or divalent sulfur diminishes the substituent effects between one-half to one-third of the original value. These papers predict that insertion of an additional sulfur atom into the sulfur–hydrogen bond of an arenethiol may give ρ values of *ca.* -5.7 to -8.5. The present paper reports the synthesis and ir and nmr spectra of para-substituted phenyl and β-naphthyl hydrodisulfides.

Results and Discussion

Preparation and Identification of Aryl Hydrodisulfides.—Acetyl aryl disulfides (**1a–h**), the precursors of the respective hydrodisulfides (**2a–h**), and acetyl β-naphthyl disulfide (**1i**)[5] were synthesized as shown in Scheme I (for yields, see Table IV). An attempt to prepare acetyl *p*-nitrophenyl disulfide was unsuccessful.

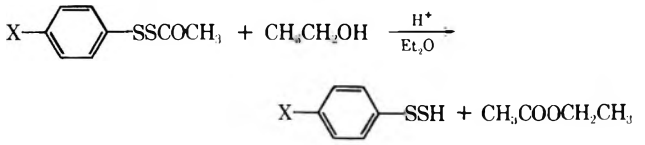
SCHEME I



1a, X = C_2H_5O
b, X = CH_3O
c, X = *tert*-C_4H_9
d, X = CH_3
e, X = H[5]
f, X = F
g, X = Br
h, X = Cl

In our previous paper[6] it was shown that acetyl aralkyl disulfides are solvolyzed in ethanol containing hydrogen chloride for 4 hr to produce the hydrodisulfides in over 99% purity. In the present work nmr analyses indicate that ethanolyses of the acetyl disulfides, **1d**, **1e**, and **1i**, gave only 70, 60, and 15% of **2d**, **2e**, and **2i**, respectively, and that the remaining starting material gave the corresponding thiols. When the reaction mixture in ethanolic hydrogen chloride was diluted with ether and the reaction time was prolonged to 16–20 hr, the yields of the aryl hydrodisulfides **2** were improved (Scheme II, **2d**, **2e**, and **2i** in 95, 95, and 70%

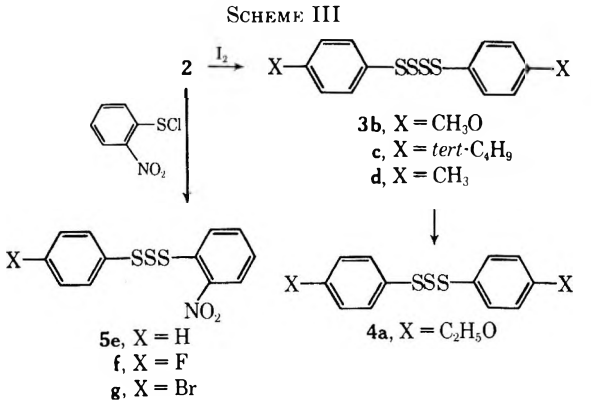
SCHEME II



2a, X = C_2H_5O
b, X = CH_3O
c, X = *tert*-C_4H_9
d, X = CH_3
e, X = H
f, X = F
g, X = Br

yield, respectively). In the case of **1a–c** the yields of **2a–c** were 100% on the basis of the nmr spectra. Of these hydrodisulfides **2c** was most stable and elemental analysis could be carried out before decomposition occurred. Compounds **2f** and **2g** could not be produced efficiently. In general, aryl hydrodisulfides presented here were slightly yellow viscous oils that gradually decomposed at room temperature to give hydrogen sulfide, thiol, and so on. They were comparably stable, however, in carbon tetrachloride, chloroform, cyclohexane, and carbon disulfide solutions, and could be stored as such for several days at room temperature. Distillation of the hydrodisulfides did not always improve their purity. An additional proof for the formation of **2a–g** was their conversion to polysulfidic compounds *via* the route shown in Scheme III. The

SCHEME III



3b, X = CH_3O
c, X = *tert*-C_4H_9
d, X = CH_3

5e, X = H
f, X = F
g, X = Br

4a, X = C_2H_5O

oxidation product of **2a** was the corresponding trisulfide (**4a**), which seemed to form by the desulfurization of the tetrasulfide. β-Naphthyl hydrodisulfide (**2i**) was also oxidized to its tetrasulfide (**3i**). Ethanolysis of **1h** gave only decomposition products, thiol, di- and trisulfide, sulfur, hydrogen sulfide, and *ethyl acetate*. This suggests that *p*-chlorophenyl hydrodisulfide is highly unstable and that it decomposes soon after formation. All the above results seem to elucidate the reason why Böhme, *et al.*,[1] could not obtain phenyl hydrodisulfide.

Infrared Spectra.—The infrared spectra of para-substituted phenyl and β-naphthyl hydrodisulfides indicate weak absorptions at 2515–2540 cm^{-1} (Table I)

TABLE I
IR S–H STRETCHING ABSORPTION OF ARYL HYDRODISULFIDES AND ARENETHIOLS

	cm^{-1}			cm^{-1}	
Ar	SSH	SH	Ar	SSH	SH
p-$C_2H_5OC_6H_4$	2520	2575	C_6H_5	2515	2580
p-$CH_3OC_6H_4$	2525	2575	*p*-FC_6H_4	2525	2580
p-*tert*-$C_4H_9C_6H_4$	2520	2575	*p*-BrC_6H_4	2540	2600
p-$CH_3C_6H_4$	2520	2575	β-$C_{10}H_7$	2530	2600

that are assigned to the S–H stretching. The S–H stretching absorption bands of the corresponding arenethiols[7] appear at 2575–2600 cm^{-1}, that is, about 50–70 cm^{-1} higher than in the former. This tendency is similar to that observed in alkyl hydrodisulfides and alkanethiols.[8]

(5) H. Böhme and M. Clement, *Justus Liebigs Ann. Chem.*, **576**, 61 (1952).

(6) T. Nakabayashi and J. Tsurugi, *J. Org. Chem.*, **28**, 813 (1963).

(7) According to L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, Methuen, London, 1958, the S–H bond in thiols absorbs at 2550–2600 cm^{-1}.

(8) (a) J. Tsurugi, Y. Abe, and S. Kawamura, *Bull. Chem. Soc. Jap.*, **43**, 1890 (1970). (b) Sulfur–hydrogen stretching absorptions of benzyl and benzhydryl hydrodisulfide were at 2515 and 2510 cm^{-1}, respectively, while the corresponding thiols absorb at 2570 cm^{-1}.

Nmr Spectra.—It is known that the sulfhydryl proton magnetic resonance of monosubstituted benzenethiols is correlated with Hammett's σ value ($\Delta\nu_{SH} = -21.8\sigma - 195.1$, $r = 0.952$),[3] while the absence of such a correlation can be noted for para-substituted phenyl hydrodisulfides (Tables II and III). However, when

TABLE II

CHEMICAL SHIFTS OF SULFHYDRYL PROTONS IN PARA-SUBSTITUTED PHENYL HYDRODISULFIDES AND THIOLS (HERTZ)

X	In p-XC_6H_4SSH	In p-XC_6H_4SH
C_2H_5O	−208.3	−187.9
CH_3O	−208.6	−188.3
tert-C_4H_9	−202.3	−190.8[a]
CH_3	−202.6	−191.0[a]
H	−201.3	−195.4[a]
F	−208.1	−195.4[a]
Br	−203.9	−197.2[a]

[a] Reference 3.

TABLE III

CHEMICAL SHIFTS OF SULFHYDRYL PROTONS IN PARA-SUBSTITUTED PHENYL HYDROSULFIDES p-XC_6H_4SSH DISSOLVED IN A FEW SOLVENTS (7%)

	Hz			
X	Cyclohexane	CCl_4	CS_2	$CDCl_3$
C_2H_5O	−205.0	−209.5	−211.2	−219.5
CH_3O	−205.5	−210.3	−211.3	−219.6
H	−193.9	−199.7	−203.6	−209.0
F		−208.2	−211.8	−217.4

the nmr data are related to values which incorporate resonance effects, excellent correlations are obtained. For example, a relationship between $\Delta\nu_{SSH}$ and σ_R° values[9] is given by $\Delta\nu_{SSH} = 18.2\ \sigma_R^\circ - 200.7$ ($r = 0.972$). A correlation of $\Delta\nu_{SSH}$ to σ_R values is more satisfactory, $\Delta\nu_{SSH} = 15.8\sigma_R - 200.8$ ($r = 0.993$) (Figure 1). When a set of $\sigma_I - \sigma_R$ is used, $\Delta\nu_{SSH} = -0.381\ \sigma_I + 15.5\sigma_R - 200.8$ ($r = 0.993$) is obtained. A fit of the resonance values into the Yukawa–Tsuno equation[10] gives a correlation, $\Delta\nu_{SSH} = -7.81\ \sigma_i + 22.2\sigma_\pi - 201.3$ ($r = 0.963$). It is noteworthy that in these correlations the proton magnetic resonance of sulfhydryl protons in para-substituted phenyl hydrodisulfides appears to be governed largely by the resonance term, and that ρ values have opposite signs as compared with those of the Hammett relation with thiols. If the present observation were to result from an electronic effect, then a chemical shift to higher fields would result from introduction of an electron-donating group in the benzene nucleus and this would lead to a negative ρ value. The above observation, therefore, indicates that large electron-releasing resonance in the benzene nucleus gives a minus anisotropic effect to the terminal sulfhydryl proton which, in turn, causes a shift to the lower field.[11]

(9) R. T. C. Brownlee, R. E. J. Hutchinson, A. R. Katritzky, T. T. Tidwell, and R. D. Topson, *J. Amer. Chem. Soc.*, **90**, 1757 (1968).

(10) Y. Tsuno, Symposium on the Hammett Relationship Abstr., Kyoto, Japan, Oct 12, 1967, p 1.

(11) p-Trimethylsilylphenyl hydrodisulfide is an interesting compound, because, in contrast to the compounds in Table II which have minus σ_R substituents, it has an opposite σ_R sign. In spite of all our efforts, acetyl p-trimethylsilylphenyl disulfide was not obtained in a relatively pure state. However, a product of ethanolysis of this slightly impure disulfide was satisfactory (*ca.* 98%) for nmr measurements. The chemical shift, −199.5 Hz (the corresponding thiol, −194.9 Hz), was fitted to the above correlations, *e.g.*, $\Delta\nu_{SSH} = -0.395\sigma_I + 15.0\sigma_R - 200.9$ ($r = 0.994$).

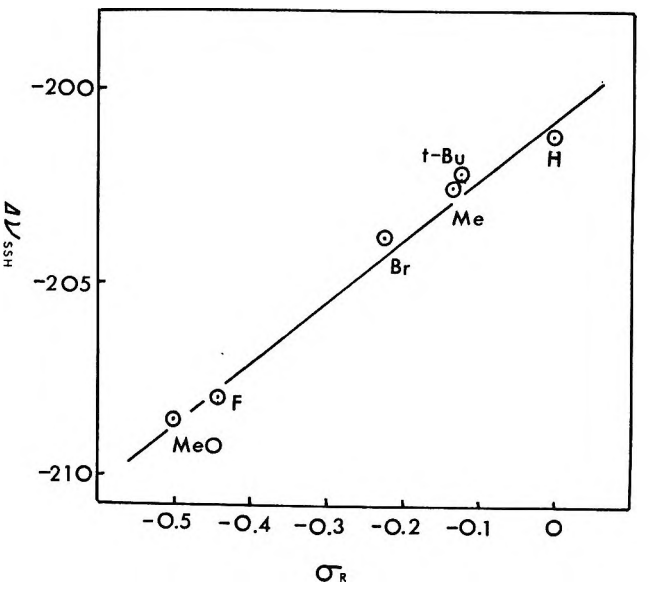
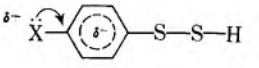


Figure 1.—A plot of Taft's σ_R *vs.* values of $\Delta\nu_{SSH}$ from Table II, for para substituents in CCl_4.

It is apparent that the sulfur–sulfur bond in the hydrodisulfide molecule does not transmit conjugation and permits only very little I effect, at least in its ground state.



Experimental Section

All melting points were determined on a Shimazu micro melting point apparatus and are uncorrected. Infrared spectra were taken with a JASCO IR-S spectrometer on neat samples. Proton magnetic resonance spectra were produced by means of a JNM 3H-60 spectrometer with tetramethylsilane as an internal standard. All chemical shifts were determined by the side-band technique. Chemical shifts reported in Table II were obtained by taking the average of three values at each of three concentrations in the dilute range,[3] below *ca.* 1 M, and extrapolating to zero concentration. The three-parameter equations ($\Delta\nu_{SSH}$, σ_I, σ_R: $\Delta\nu_{SSH}$, σ_i, σ_π) are results of computer-programmed computations.

p-Methoxy-[12], p-ethoxy-[12], and p-fluorobenzenethiols[13] acetyl sulfenyl chloride,[14] and o-nitrobenzenesulfenyl chloride[15] were prepared by the known procedures. Other thiols were commercial samples of pure grade and were used without purification. Acetyl phenyl disulfide (1e), bp 93–95° (0.05 mm) [lit. bp 146–148° (11 mm)], and acetyl β-naphthyl disulfide (1i), mp 56–57° (lit. mp 58–59°), were prepared by the method of Böhme and Clement.[5]

Acetyl Para-Substituted Phenyl Disulfides (1a–d, 1f–h).—Acetyl p-ethoxyphenyl disulfide (1a) was prepared as follows. To a stirred solution of p-ethoxybenzenethiol (1.95 mmol) in 20 ml of anhydrous ether was added acetyl sulfenyl chloride (2.15 mmol) in 10 ml anhydrous ether under nitrogen atmosphere with stirring for 15 min at −10°. Stirring was stopped after additional 30 min, the solution was kept overnight, and volatiles were removed at 7 mm. The highly viscous yellow oil was purified by distillation under vacuum.

Other disulfides (1b–d, 1f–h) were prepared similarly, and are characterized in Table IV.

(12) M. Protiva, M. Rajsner, E. Adlerova, V. Seidlova, and Z. J. Vejdelek, *Collect. Czech. Chem. Commun.*, **29**, 2161 (1964); *Chem. Abstr.*, **62**, 524 (1965).

(13) M. Rajsner, V. Seidlova, and M. Protiva, *Cesk. Farm.*, **11**, 451 (1962); *Chem. Abstr.*, **49**, 2773 (1963).

(14) J. Tsurugi and T. Nakabayashi, *J. Org. Chem.*, **24**, 807 (1959).

(15) M. H. Hubacher in "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 455.

TABLE IV

Compd	Bp, °C (mm)	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % S or others	Found, % C	Found, % H	Found, % S or others
1a	113–115 (0.1)	72	$C_{10}H_{12}O_2S_2$	52.61	5.30	28.08	52.57	5.40	28.18
1b	112–115 (0.1)	71	$C_9H_{10}O_2S_2$	50.44	4.70	29.92	50.21	4.64	30.08
1c	123–127 (0.05)	>80	$C_{12}H_{16}OS_2$	59.96	6.71	26.67	59.91	6.87	26.79
1d	95–103 (0.05)	>80	$C_9H_{10}OS_2$	54.51	5.08	32.33	54.41	5.13	32.37
1f	74–75 (0.15), mp 26°	84	$C_8H_7OFS_2$	47.51	3.49	F, 9.39	47.69	3.74	F, 9.24
1g	113–118 (0.01)	84	$C_8H_7OBrS_2$	36.51	2.68		36.59	2.97	
1h	84 (0.05)	>80	$C_8H_7OClS_2$	43.98	3.23		43.93	3.45	

Ethanolyses of Acetyl Para-Substituted Phenyl Disulfides (1a–g) and Acetyl β-Naphthyl Disulfide (1i)—To a solution of acetyl para-substituted phenyl disulfide (2 g, 7.6–10.8 mmol) or acetyl β-naphthyl disulfide (2 g, 8.5 mmol) in anhydrous ether (20 ml) was added 5 *N* alcoholic hydrogen chloride (8 ml) at room temperature. After 16–20 hr, volatiles were removed and the residual high viscous yellow oil was subjected to nmr analysis. Nmr spectra showed that some para-substituted phenyl hydrodisulfides were pure. Distillation did not always improve the purities of the hydrodisulfides (Table V).

TABLE V

Compd	Bp, °C (mm)	Purity in nmr, % Before distn	Purity in nmr, % After distn
2a	71–72.5 (0.05)	100	99
2b	53–56.5 (0.05)	100	99
2c		100	
2d	95–100 (0.06)	95	
2e	60 (0.05)	95	
2f	29–32 (0.05)	92	91
2g		70	
2i		80	

***p*-*tert*-Butylphenyl Hydrodisulfide (2c)**.—The highly viscous oil described above was subjected to elemental analysis without further purification.

Anal. Calcd for $C_{10}H_{14}S_2$: C, 60.56; H, 7.12; S, 32.33. Found: C, 60.50; H, 7.07; S, 32.12.

Bis(*p*-methoxyphenyl) Tetrasulfide (3b).—To *p*-methoxyphenyl hydrodisulfide (2b, 0.27 mmol) was added an excess of 1 *N* alcoholic iodine solution. To this was added benzene (*ca.* 20 ml). The solution obtained was washed with 1 *N* aqueous sodium thiosulfate solution followed by water, and dried over magnesium sulfate. Benzene was replaced by a small amount of alcohol and the mixture was chilled with liquid nitrogen. The yellow crystals obtained were recrystallized once from alcohol–benzene, then twice from ether–hexane, mp 56.5–58.5° (0.035 mmol, 24%). For elemental analysis, additional recrystallization was performed from ether–hexane, mp 58–58.5° (0.0096 mmol, 7%).

Anal. Calcd for $C_{14}H_{14}O_2S_4$: C, 49.10; H, 4.12; S, 37.44. Found: C, 49.07; H, 4.03; S, 37.50.

Bis(*p*-*tert*-butylphenyl) Tetrasulfide (3c).—Under conditions similar to those mentioned above a yellow oil was obtained from *p*-*tert*-butylphenyl hydrodisulfide (2c). The oil was crystallized from petroleum ether (bp 30–40°) at −20°. The crystals, after removal of the insoluble portion in petroleum ether (bp 30–40°), were recrystallized from ethanol–petroleum ether, mp 66–68°.

Anal. Calcd for $C_{20}H_{26}S_4$: C, 60.87; H, 6.64; S, 32.49. Found: C, 60.58; H, 6.43; S, 32.64.

***p*-Tolyl Tetrasulfide (3d)**.—Under conditions similar to those mentioned above, a white solid was obtained from *p*-tolyl hydrodisulfide (2d). The solid was recrystallized from ethanol, mp 67–68°. The crystals were recrystallized from ether–petroleum ether, mp 71–72° (lit. mp 75°).[16]

Anal. Calcd for $C_{14}H_{14}S_4$: C, 54.15; H, 4.54; S, 41.30. Found: C, 54.20; H, 4.26; S, 41.39.

β-Naphthyl Tetrasulfide (3i).—Under conditions similar to those mentioned above, a white solid was obtained from β-naphthyl hydrodisulfide (2i). The solid was recrystallized from ethanol–benzene three times, mp 102–103° (lit. 101°).[16]

Anal. Calcd for $C_{20}H_{14}S_4$: C, 62.79; H, 3.69; S, 33.52. Found: C, 63.02; H, 3.57; S, 33.35.

Bis(*p*-ethoxyphenyl) Trisulfide (4a).—By means of a procedure similar to that described for the *p*-methoxy derivative, a low-melting solid was obtained from *p*-ethoxyphenyl hydrodisulfide (2a, 0.27 mmol). The solid was crystallized from ether–hexane to give pale yellow crystals, which were recrystallized from the same solvent, mp 61–64.5° (0.024 mmol, 22%). For elemental analysis, the crystals were carefully recrystallized again from the same solvent, mp 64.5–65.5° (0.0053 mmol, 5%).

Anal. Calcd for $C_{16}H_{18}O_2S_3$: C, 56.77; H, 5.46; S, 28.41. Found: C, 56.72; H, 5.51; S, 28.55.

***p*-Bromophenyl *o*-Nitrophenyl Trisulfide (5g)**.—To a stirred solution of *p*-bromophenyl hydrodisulfide (2g, 2.26 mmol) in 20 ml of anhydrous ether was added *o*-nitrobenzenesulfenyl chloride (2.3 mmol) in 40 ml of anhydrous ether under a nitrogen stream at 0°. The oil obtained after evaporation of the solvent was crystallized in ether–hexane, mp 102–104° (1.1 mmol, 48%). The crude product was recrystallized twice from ether–ethyl acetate, mp 110.5–111.5°.

Anal. Calcd for $C_{12}H_8O_2BrNS_3$: C, 38.51; H, 2.15; N, 3.74. Found: C, 38.52; H, 2.03; N, 3.46.

***p*-Fluorophenyl *o*-Nitrophenyl Trisulfide (5f)**.—Under conditions similar to those mentioned above, a yellow oil was obtained from *p*-fluorophenyl hydrodisulfide (2f). A solution of the oil in hot hexane (40°), after removal of the insoluble portion by filtration, was chilled to give crystals. The crystals were recrystallized twice from the same solvent, mp 46–47°.

Anal. Calcd for $C_{12}H_8O_2FNS_3$: C, 45.99; H, 2.57; N, 4.47; S, 30.69. Found: C, 46.03; H, 2.48; N, 4.44; S, 30.31.

***o*-Nitrophenyl Phenyl Trisulfide (5e)**.—Under conditions similar to those mentioned above, a yellow oil was obtained from phenyl hydrodisulfide (2e). The oil was crystallized in ether–hexane at −20°. The crude product (mp 86.5–88.5°) was recrystallized from hexane–benzene three times, mp 93.5–94.5°.

Anal. Calcd for $C_{12}H_9O_2NS_3$: C, 48.79; H, 3.07; N, 4.74; S, 32.57. Found: C, 48.98; H, 3.05; N, 4.64; S, 32.75.

Registry No.—**1a**, 31818-97-0; **1b**, 31570-54-4; **1c**, 31818-99-2; **1d**, 14227-19-1; **1f**, 31819-01-9; **1g**, 31819-02-0; **1h**, 14193-03-4; **2a**, 31883-35-9; **2b**, 31819-04-2; **2c**, 31819-05-3; **2d**, 31819-06-4; **2e**, 31819-07-5; **2f**, 31819-08-6; **2g**, 31819-09-7; **3b**, 31819-10-0; **3c**, 31819-11-1; **3d**, 25769-92-0; **3i**, 31819-17-7; **4a**, 31121-14-9; **5e**, 31819-14-4; **5f**, 31819-15-5; **5g**, 31819-16-6.

(16) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. III, Chemical Publishing Co., Inc., New York, N. Y., 1960, p 413.

The Action of Hydrogen Sulfide on Aminoalkanethiosulfuric Acids (Bunte Salts) to Give Di-, Tri-, and Tetrasulfides

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The reaction of hydrogen sulfide with several alkanethiosulfuric acids bearing amino functions has been studied. When primary and secondary aminoalkanethiosulfuric acids were treated with hydrogen sulfide, the product isolated in each case was the bis(aminoalkyl) disulfide thiosulfuric acid salt. 2-Aminoethaneselenosulfuric acid gave the corresponding diselenide XIV. Of the five *tert*-amino compounds treated with hydrogen sulfide, only 2-(dimethylamino)ethanethiosulfuric acid gave the expected disulfide. 2-Morpholinoethanethiosulfuric acid (III) gave the corresponding sulfenyl thiosulfate IV and trisulfide V. The other *tert*-aminoalkanethiosulfuric acids produced tetrasulfides. Of these, di-*n*-heptylaminoethanethiosulfuric acid gave a tetrasulfide which formed an unusually stable complex VII with six molecules of hydrogen sulfide. The synthesis of two unsaturated Bunte salts, 4-amino-2-butene-1-thiosulfuric acid (XVI) and 4-amino-2-butyne-1-thiosulfuric acid (XVII), has been achieved in a novel manner.

The reaction of sulfide ion with organic thiosulfates (Bunte salts) is fascinating in that the type of product obtained varies with the nature of the Bunte salt. For example, Bernthsen[1] and Levkoev, *et al.*,[2] prepared thiophenols from aromatic thiosulfates by treating them with inorganic sulfides. When the reaction was performed with sodium *o*-nitrophenylthiosulfate[3] or aliphatic Bunte salts, such as *N*-cyclohexylcarbamoylmethylthiosulfate,[3] sodium phenoxycarbonylmethylthiosulfate,[3] sodium 2-amino-2-carboxyethylthiosulfate (sodium *S*-sulfocysteine),[3] sodium *S*-2-oxocyclohexylthiosulfate,[4] or potassium 2-ureidoethylthiosulfate,[5] the corresponding disulfides were obtained. However, under essentially identical conditions, sulfide treatment of Bunte salts such as ethyl-,[3,6] allyl-,[3,6] benzyl-,[3] and *p*-tolylthiosulfates[3] gave trisulfides. Disodium trimethylenedithiosulfate[7] and disodium *o*-phenylenedithiosulfate[7] gave cyclic trisulfides, while sodium benzamidoethylthiosulfate[5] gave a mixture of the corresponding di- and trisulfides. By modifying the reaction mixture so that it contained formaldehyde to trap the sulfite formed, the tetrasulfide was obtained in addition to the di- and trisulfides when sodium methylthiosulfate was the starting Bunte salt.[6] Gutmann[8] claimed that the reaction of sodium ethylthiosulfate with potassium sulfide in ethanol gave a yellow solution of ethyl hydrodisulfide. Further information pertaining to this reaction may be found in a recent review.[9]

The apparent lack of predictability of the reaction of sulfide ion with organic thiosulfates has led us to investigate several aspects of it. Since sodium 2-amino-2-carboxyethylthiosulfate was the only amino-Bunte salt studied previously,[3] a number of aminoalkanethiosulfuric acids were treated with hydrogen sulfide to determine what effect, if any, the amino group had on the nature of the final product.

When hydrogen sulfide was bubbled into an essentially neutral aqueous solution of 2-aminoethanethiosulfuric acid (I), a zwitterionic Bunte salt, the precipitation of elemental sulfur occurred within several minutes. Hydrogen sulfide was added until the reaction was complete and after removal of the sulfur from the mixture, bis(2-aminoethyl) disulfide (cystamine) was obtained in good yield as its thiosulfuric acid salt II (eq 1). The latter was identified by elemental analysis

$$\underset{\text{I}}{2H_2NCH_2CH_2SSO_3H} + 3H_2S \longrightarrow \underset{\text{II}}{(H_2NCH_2CH_2S-)_2\cdot H_2S_2O_3} + 3S + 3H_2O \quad (1)$$

and its ir spectrum which showed intense peaks in the region of 9.09, 10.0, and 15.05 μ, typical of a thiosulfuric acid salt.[10] An authentic sample of II was prepared by treating cystamine dihydrochloride with 1 equiv of sodium thiosulfate (eq 2). The stoichiometry

$$(H_2NCH_2CH_2S-)_2\cdot 2HCl + Na_2S_2O_3 \longrightarrow \text{II} + 2NaCl \quad (2)$$

of eq 1 was verified by obtaining >95% of the calculated quantity of sulfur in several runs and was found to apply to reactions of water-soluble Bunte salts bearing primary and secondary amino groups (*cf.* Table I).

The reaction is visualized as taking place by a stepwise mechanism, in which hydrosulfide ion attacks the sulfenyl sulfur atom of I to form the aminoethylhydrodisulfide anion and sulfurous acid (eq 3). The hydrodisulfide anion then reacts with unreacted I to generate cystamine and thiosulfuric acid (eq 4). In a somewhat analogous reaction, Kawamura, *et al.*,[11] proposed that sodium benzylthiosulfate combines with benzylhydrodisulfide to account for the formation of dibenzyl di-

$$\text{I} + HS^- \longrightarrow [H_2NCH_2CH_2SS^-] + H_2SO_3 \quad (3)$$

$$[H_2NCH_2CH_2SS^-] + \text{I} \longrightarrow (H_2NCH_2CH_2S-)_2 + H^+ + S_2O_3^{-2} \quad (4)$$

$$H_2SO_3 + 2H_2S \longrightarrow 3S + 3H_2O \quad (5)$$

(1) A. Bernthsen, *Justus Liebigs Ann. Chem.*, **251**, 1 (1889).
(2) I. I. Levkoev, N. N. Svoshnikov, I. N. Gorbacheva, N. S. Barvyn, and T. V. Krasnova, *Zh. Obshch. Khim.*, **24**, 280 (1954) [English translation: *J. Gen. Chem. USSR*, **24**, 283 (1954)].
(3) B. Milligan, B. Saville, and J. M. Swan, *J. Chem. Soc.*, 4850 (1961).
(4) B. Milligan and J. M. Swan, *ibid.*, 5552 (1961).
(5) K. Schimmelschmidt, H. Hofmann, E. Mundlos, G. Laber, and M. Schorr, *Chem. Ber.*, **96**, 33 (1963).
(6) B. Milligan, B. Saville, and J. M. Swan, *J. Chem. Soc.*, 3608 (1963).
(7) B. Milligan and J. M. Swan, *ibid.*, 2901 (1965).
(8) A. Gutmann, *Ber.*, **48**, 1162 (1915).
(9) D. L. Klayman and R. J. Shine, *Quart. Rep. Sulfur Chem.*, **3** [3], 189 (1968).
(10) F. A. Miller and C. H. Wilkins, *Anal. Chem.*, **24**, 1253 (1952); M. G. Voronkov and A. Ya. Legzdin, *Zh. Org. Khim.*, **3**, 465 (1967).
(11) S. Kawamura, Y. Otsuji, T. Nakabayashi, T. Kitao, and J. Tsurugi, *J. Org. Chem.*, **30**, 2711 (1965).

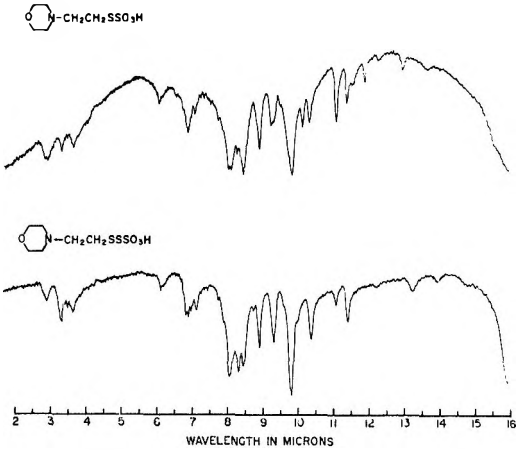


Figure 1.—Ir spectrum of III and IV.

sulfide and thiosulfate ion. In eq 5 the sulfurous acid is reduced by hydrogen sulfide.[12]

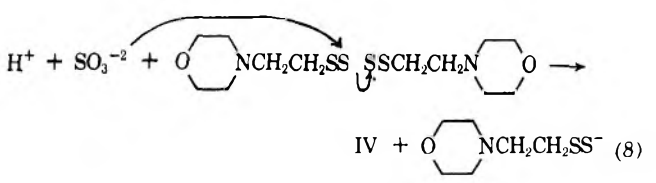
No sulfur precipitated when the sodium salt of I reacted with hydrogen sulfide in aqueous solution (eq 6). In addition to II, sodium thiosulfate was isolated

$$2H_2NCH_2CH_2SSO_3Na + H_2S \longrightarrow II + Na_2SO_3 \quad (6)$$

which formed according to eq 7.[13] Those aminoalkanethiosulfuric acids which were water insoluble were solubilized by conversion to their sodium salts in an aqueous–methanolic solution prior to treatment with hydrogen sulfide.

$$4Na_2SO_3 + 2H_2S \longrightarrow 3Na_2S_2O_3 + 2NaOH + H_2O \quad (7)$$

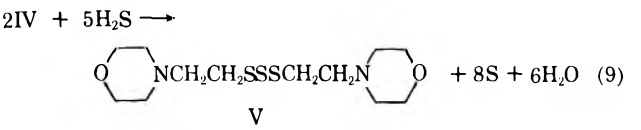
While 2-(dimethylamino)ethanethiosulfuric acid gave the expected product, two anomalous reactions were found to occur with other alkylthiosulfuric acids possessing a tertiary amino group. The most unusual reaction was that of 2-morpholinoethanethiosulfuric acid (III) with hydrogen sulfide which gave a low yield of 2-morpholinoethanesulfenylthiosulfate (IV) and bis(2-morpholinoethyl) trisulfide (V). The sulfenylthiosulfate IV was identified by elemental analysis and by its ir spectrum (Figure 1), which, while similar to that of III, differs from it in that there is a new peak at 8.30 μ, one missing at 10.10 μ, and an intensified absorption at 10.35 μ. Compound IV is less soluble in water than its parent Bunte salt III and tends to lose sulfur if its aqueous solution is heated excessively. Although the mechanism for its formation is not known with certainty, it is not unlikely that it involves the sulfite cleavage of bis(2-morpholinoethyl) tetrasulfide (eq 8),



(8)

the latter having originated by oxidation of the corresponding hydrodisulfide (*cf.* eq 3). The hydrodisulfide anion, a by-product in eq 8, is probably recycled to the tetrasulfide by a similar oxidative process.

On treating the sulfenylthiosulfate IV in aqueous solution with additional hydrogen sulfide, sulfur and the trisulfide V were isolated in a ratio close to that indicated by eq 9. The trisulfide V is difficult to obtain



(9)

in a very pure state due to its tendency to extrude elemental sulfur and leave the disulfide. While the di- and trisulfides have identical ir spectra, their behavior on tlc and their nmr spectra are dissimilar. The yield of the sulfenylthiosulfate could be improved by limiting the quantity of hydrogen sulfide reacting with III. Further investigation would be desirable to ascertain the influence of the morpholino moiety on the course of the above-described reaction.

Only recently has a sulfenylthiosulfate, obtained by a different route, been isolated[14] although another such compound was described earlier as an intermediate.[15]

The reaction of hydrogen sulfide with other Bunte salts bearing a tertiary amino group, *i.e.*, di-*n*-heptyl- and dibenzylaminoethanethiosulfuric acids, was also examined. Both gave difficultly purifiable heavy oils which analyzed as tetrasulfides and whose formation can be rationalized as having occurred through the oxidation of the intermediate hydrodisulfides (Table II).

The initial product obtained from the reaction of di-*n*-heptylaminoethanethiosulfuric acid is a low-melting, bright yellow crystalline solid which is stable at room temperature if kept in a closed container. The compound loses hydrogen sulfide slowly if left open to the atmosphere, at a moderate rate when heated gently *in vacuo*, and very rapidly when dissolved in various solvents, especially chloroform. The resultant chloroform solution, which loses its yellow color as the H_2S is dispelled, on evaporation leaves bis(diheptylaminoethyl) tetrasulfide and, sometimes, elemental sulfur. The yellow complex analyzed for the association of six molecules of hydrogen sulfide with each of the tetrasulfide and could be regenerated from a suspension of the tetrasulfide in methanol by bubbling hydrogen sulfide into it.

Another example of hydrogen sulfide complexation with a tertiary amine was reported by McDaniel and Evans[16] who prepared the hydrosulfide salt of triethylamine in methanol solution at 0°. The hydrosulfide salt reversibly absorbed 2 mol of hydrogen sulfide at −78.5°; however, the complex was not stable at room temperature. Hydrogen bonding of the additional 2 mol of H_2S with the hydrosulfide ion was held responsible for their uptake by the amine salt.

We propose, in our case, that the tetrasulfide which is formed at one of the initial stages of the reaction is converted into its dihydrosulfide salt VI which, in the pres-

(12) R. C. Brasted, "Comprehensive Inorganic Chemistry," Vol. VIII, Van Nostrand, Princeton, N. J., 1961, p 43.

(13) L. C. Schroeter, "Sulfur Dioxide," Pergamon Press, London, 1966, p 92.

(14) S. J. Brois, J. F. Pilot, and H. W. Barnum, *J. Amer. Chem. Soc.*, **92**, 7629 (1970).

(15) O. Foss, *Acta Chem. Scand.*, **1**, 307 (1947).

(16) D. H. McDaniel and W. G. Evans, *Inorg. Chem.*, **5**, 2180 (1966).

Table I

Bis(aminoalkyl) Disulfide Thiosulfuric Acid Salts, $(RS-)_2 \cdot H_2S_2O_3$

	R	Registry no.	Mp, °C	% yield	Recrystn solvent	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Found, % C	Found, % H	Found, % N	Found, % S
1[a]	$H_2NCH_2CH_2-$		175–182 dec	91	H_2O	$C_4H_{14}N_2O_3S_4$	18.03	5.30	10.51	48.14	18.10	4.97	10.63	47.94
2[b]	$H_2N(CH_2)_6-$	31645-69-9	185–187	90	H_2O	$C_{12}H_{30}N_2O_3S_4$	38.07	7.99	7.40	33.87	38.09	7.96	7.47	33.77
3	$H_2NCH_2CH{=}CHCH_2-$	31645-70-2	143 dec	90	H_2O–EtOH	$C_8H_{18}N_2O_3S_4$	30.16	5.70	8.80	40.27	29.99	5.58	8.69	40.08
4[c]	$H_2NC(=NH)NHCH_2CH_2-$	31645-71-3	190–191 dec	55	H_2O	$C_6H_{18}N_6O_3S_4$	20.56	5.18	23.98	36.59	20.86	5.15	23.99	36.27
5[d]	n-$C_4H_9NHCH_2CH_2-$	31645-72-4	109–112	86	H_2O–EtOH	$C_{12}H_{30}N_2O_3S_4$	38.07	7.99	7.40	33.87	38.14	7.95	7.41	33.82
6[d]	n-$C_{10}H_{21}NHCH_2CH_2-$	31645-73-5	120–122	93[e]	MeOH	$C_{24}H_{54}N_2O_3S_4$	52.70	9.95	5.12	23.45	53.16	10.25	5.09	23.25
7[d]	$C_6H_5(CH_2)_4NHCH_2CH_2-$	31645-74-6	115–120	59[e]	MeOH	$C_{24}H_{38}N_2O_3S_4$	54.30	7.22	5.28	24.16	54.42	7.16	5.19	24.17
8	$(CH_3)_2N^+CH_2CH_2-$	31645-75-7	103–104	70	H_2O–EtOH	$C_6H_{22}N_2O_3S_4$	29.79	6.88	8.69	39.77	29.62	6.78	8.75	39.55
9[d]	$(CH^3)_3N^+CH_2CH_2-$	31645-76-8	154–154.5	96	H_2O–EtOH	$C_{10}H_{26}N_2O_3S_4$	34.26	7.48	7.99	36.58	34.35	7.95	7.97	36.11
10[d]	$C_6H_5CH_2NHCH_2CH_2-$	31645-77-9	111–113	65	H_2O–EtOH	$C_{18}H_{26}N_2O_3S_4$	48.40	5.87	6.27	28.71	48.32	5.90	6.29	28.44

[a] Bunte salt reported by H. Bretschneider, *Monatsh. Chem.*, **81**, 372 (1950); D. L. Klayman, W. F. Gilmore, and T. R. Sweeney, *Chem. Ind. (London)*, 1632 (1965). [b] Bunte salt reported in ref 19. [c] Bunte salt reported by A. Kaluszyner, *Bull. Res. Counc. Isr., Sect. A*, **9**, 35 (1960); D. L. Klayman, M. M. Grenan, and D. P. Jacobus, *J. Med. Chem.*, **12**, 723 (1969). [d] Bunte salt reported by D. L. Klayman and W. F. Gilmore, *ibid.*, **7**, 823 (1964). [e] Reaction performed on the sodium salt of the aminoalkanethiosulfuric acid.

Table II

Bis(alkylaminoethyl) Tetrasulfides

$$\begin{matrix} R \\ R' \end{matrix}\!>\!NCH_2CH_2SSSSCH_2CH_2N\!<\!\begin{matrix} R \\ R' \end{matrix}$$

R	R′	Registry no.	% yield	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Found, % C	Found, % H	Found, % N	Found, % S
n-C_7H_{15}	n-C_7H_{15}		39	$C_{32}H_{68}N_2S_4$	63.10	11.25	4.60	21.05	63.03	11.07	4.55	21.40
$C_6H_5CH_2$	$C_6H_5CH_2$	31645-78-0	68	$C_{32}H_{36}N_2S_4$	66.62	6.29	4.86	22.23	66.92	6.17	4.78	22.01
CH_3	$C_6H_5CH_2$	31645-79-1	47	$C_{20}H_{28}N_2S_4$[a]	56.56	6.65	6.60	30.20	55.03	6.60	6.22	32.52

[a] The analytical data suggests the formula, $C_{20}H_{28}N_2S_{4.4}$. If correction is made for $S_{0.4}$, then the analytical data conforms more closely with theory, *i.e.*, C, 56.68; H, 6.79; N, 6.41; S, 31.57.

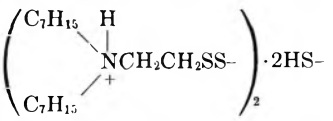
Table III

Aminoethanethiosulfuric Acids

$$RCH_2CH_2X \cdot HX + Na_2S_2O_3 \longrightarrow RCH_2CH_2S_2O_3H$$

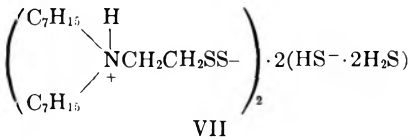
R	Registry no.	Mp, °C	% yield	Recrystn solvent	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Found, % C	Found, % H	Found, % N	Found, % S
$(CH_3)_2N-$	14013-30-0	187.5	66	MeOH	$C_4H_{11}NO_3S_2$	25.93	5.98	7.56	34.61	25.93	5.97	7.52	34.47
$(C_6H_5CH_2)(CH_3)N-$	31645-81-5	132–135	68	EtOH	$C_{10}H_{15}NO_3S_2$	45.96	5.78	5.36	24.53	45.79	5.71	5.26	24.80
$(C_6H_5CH_2)_2N-$	31645-82-6	168–169	67	MeCN	$C_{16}H_{19}NO_3S_2$	56.94	5.67	4.15	19.00	57.14	5.89	4.20	19.14
		177.5–179.5	76	H_2O–MeOH	$C_6H_{13}NO_4S_2$	31.70	5.76	6.16	28.21	31.95	6.14	6.03	28.04
$(n$-$C_7H_{15})_2N-$	31645-83-7	138.5	52[a]	EtOH	$C_{16}H_{35}NO_3S_2$	54.35	9.98	3.96	18.14	54.05	10.03	3.83	18.07

[a] Prepared by alkylation of 2-aminoethanethanethiosulfuric acid; *cf.* D. L. Klayman and W. F. Gilmore, *J. Med. Chem.*, **7**, 823 (1964).



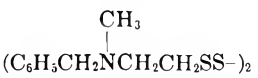
VI

ence of excess hydrogen sulfide, absorbs an additional 2 mol of H_2S per amine moiety present, *i.e.*, 4 mol, to give the observed product VII. An attempt is being made to determine the lattice structure of VII by X-ray crystallography.



VII

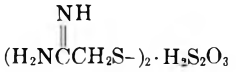
Inasmuch as 2-benzyl- and the water-soluble 2-dimethylaminoethanethiosulfuric acid each give the corresponding disulfides on reaction with hydrogen sulfide, it was of interest to see what would be obtained with *N*-benzyl-*N*-methylaminoethanethiosulfuric acid. In this case, the tetrasulfide VIII was afforded which, like the other tetrasulfides and the trisulfide obtained in this study, was difficult to obtain analytically pure. Reid[17] has reviewed the problems associated with the



VIII

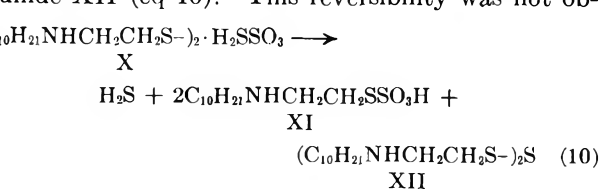
characterization and purification of organic polysulfides.

If one excludes the anomalous results obtained with the morpholino derivative and the water-insoluble *tert*-aminoalkylthiosulfates, the method described here for the conversion of Bunte salts possessing primary and secondary amino groups to disulfides is valuable in that it is very mild and, thus, can be performed in the presence of labile functional groups. It has been reported to us that amidinomethylthiosulfuric acid, for example, was smoothly converted to the disulfide IX by the hydrogen sulfide method.[18]



IX

The evolution of hydrogen sulfide was detected in the course of recrystallizing bis(2-decylaminoethyl) disulfide thiosulfuric acid salt (X) from methanol. When a methanol solution of the disulfide was intentionally boiled for 24 hr, the solution rapidly turned yellow and from it was isolated the parent Bunte salt, 2-decylaminoethanethiosulfuric acid (XI), and the corresponding trisulfide XII (eq 10). This reversibility was not observed, however, with II which was recovered essentially unchanged after boiling in methanol for 5 days.

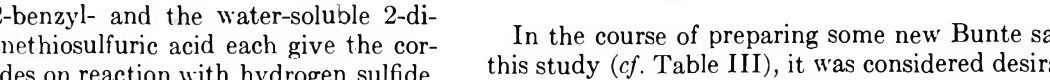


(10)

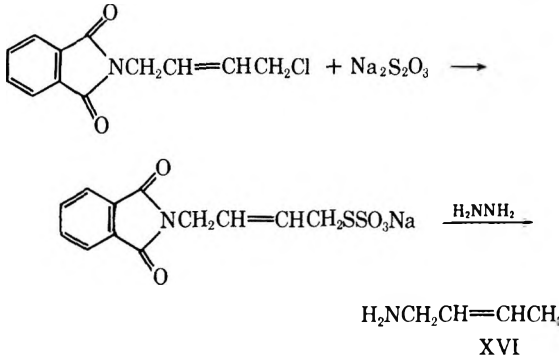
This is a further example of how N substitution influences, in some way, the reactivity of the sulfur functionality.

The selenium analog of I, 2-aminoethaneselenosulfuric acid (XIII), reacted with hydrogen sulfide in aqueous solution to give, in addition to sulfur, bis(2-aminoethyl) diselenide thiosulfuric acid salt (XIV) (eq 11). 2-Aminoethylphosphorothioate sodium salt (XV) was unaffected by hydrogen sulfide.

(11)



In the course of preparing some new Bunte salts for this study (*cf.* Table III), it was considered desirable to make two unsaturated examples, *i.e.*, 4-amino-2-butene-1-thiosulfuric acid (XVI) and 4-amino-2-butyne-1-thiosulfuric acid (XVII). Attempts to prepare these Bunte salts by the reaction[19] of sodium thiosulfate with the requisite amino halides derived from phthalimidobutenyl- or -butynyl chlorides gave products for which satisfactory microanalytical data could not be obtained. Successful syntheses were achieved, however, by forming the sodium phthalimidothiosulfates from the above-mentioned phthalimidohalides, followed by hydrazinolysis to generate the amine function. This atypical approach of introducing the thiosulfate before the amine moiety into the molecule is illustrated for XVI in scheme (eq 12). This is also the first report of the hydrolysis of a phthalimido group while maintaining the integrity of a thiosulfate moiety, a functional group known for its lability in base. While XVI gave the anticipated disulfide on hydrogen sulfide treatment, XVII gave only polymeric material.



(12)

XVI

Experimental Section[20]

Reaction of H_2S. A. With Water-Soluble Primary and Secondary Aminoalkanethiosulfuric Acids.—Hydrogen sulfide was slowly bubbled for 1–2 hr into an ice-cooled, stirred solution of 0.03 mol of an aminoalkanethiosulfuric acid in 100 ml of H_2O. Elemental sulfur which precipitated in the course of the reaction was removed by filtration, and the filtrate was treated again with H_2S to ensure that the reaction had gone to completion. The

(17) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. III, Chemical Rubber Publishing Co., New York, N. Y., 1960, p 387.

(18) R. D. Westland, Parke, Davis and Co., personal communication, 1970.

(19) D. L. Klayman, M. M. Grenan, and D. P. Jacobus, *J. Med. Chem.*, **12**, 510 (1969).

(20) Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Microanalyses were performed by Mr. Joseph F. Alicino, New Hope, Pa. 18938. Infrared spectra were determined as KBr pellets on a Beckman IR-5 spectrophotometer. Nmr spectra were taken on a Varian A-60 using TMS as an internal standard.

solution was evaporated to dryness under reduced pressure and the residual bis(aminoalkyl) disulfide thiosulfuric acid salt was recrystallized from the appropriate solvent.

B. Water-Insoluble Primary and Secondary Aminoalkanethiosulfuric Acids.—In a solution of 0.01 mol of sodium hydroxide in 5 ml of water and 30 ml of methanol was dissolved 0.01 mol of a water-insoluble aminoalkanethiosulfuric acid. An additional 10–20 ml of water was added and hydrogen sulfide was bubbled slowly into the solution for *ca.* 0.5 hr. In contrast to the above procedure, the product, rather than elemental sulfur, precipitated from solution.

C. 2-Aminoethaneselenosulfuric Acid (XIII).—Into a solution of 1.5 g (7.35 mmol) of 2-aminoethaneselenosulfuric acid (XIII)[21] in 15 ml of water was bubbled H_2S for 0.5 hr. The elemental sulfur which formed was filtered off and the filtrate evaporated to dryness under reduced pressure to give 1.22 g (92%) of bis(2-aminoethyl) diselenide thiosulfuric acid salt (XIV). Recrystallization from water gave small white needles, mp 172–175° dec, whose ir spectrum was almost identical with that of II: 9.05 (s), 10.22 (s), 15.05 μ (SSO_3^{-2}).

The sodium salt of XIII, on treatment with H_2S, gave an 87% yield of XIV.

Anal. Calcd for $C_4H_{14}N_2O_3S_2Se_2$: C, 13.38; H, 3.92; N, 7.78; S, 17.80; Se, 43.84. Found: C, 13.11; H, 4.22; N, 7.82; S, 17.74; Se, 43.81.

D. 2-Morpholinoethanethiosulfuric Acid (III).—Into a solution of 4.54 g (0.02 mol) of 2-morpholinoethylthiosulfuric acid in 70 ml of water was bubbled H_2S for 15 min. The S (0.65 g, 0.02 mol) which precipitated in the course of the reaction was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was stirred with several portions of $CHCl_3$ and the solvent removed from the combined extracts leaving bis(2-morpholinoethyl) trisulfide (V) as a pale yellow oil: nmr (CCl_4) δ 3.83–3.58 and 2.60–2.36 (symmetric A_2X_2 triplets centered at 3.70 and 2.48, magnetically nonequivalent morpholino methylene protons, 8 H) and 3.32–2.28 (symmetric A_2X_2 multiplet centered at 2.80, magnetically equivalent ethyl methylene protons, 4 H).

Anal. Calcd for $C_{12}H_{24}N_2O_2S_3$: N, 8.63; S, 29.64. Found: N, 8.21; S, 29.94.

The $CHCl_3$-insoluble material was triturated with methanol to give 1.79 g of 2-morpholinoethylsulfenylthiosulfuric acid (IV) contaminated with a small amount of starting material. Recrystallization of the solid from water gave 1.0 g of IV, mp 184–185° dec; for ir *cf.* Figure 1.

Anal. Calcd for $C_6H_{13}NO_4S_3$: C, 27.78; H, 5.05; N, 5.40; S, 37.09. Found: C, 27.77; H, 4.76; N, 5.45; S, 36.88.

E. 2-Morpholinoethanesulfenylthiosulfuric Acid (IV).—Hydrogen sulfide was bubbled for 15 min into a solution of 100 mg (0.384 mmol) of IV in 10 ml of water. The solvent was removed *in vacuo* and the residue was first extracted with hot hexane to remove the sulfur (20.8 mg, 0.65 mmol) and then with $CHCl_3$. The $CHCl_3$ sol on evaporation gave 24.5 mg (0.076 mmol) of the trisulfide, V, whose nmr spectrum was identical with that described above. Some unreacted IV (46.7 mg, 0.18 mmol) was recovered.

Anal. Calcd for $C_{12}H_{24}N_2O_2S_3$: S, 29.64. Found: S, 29.19.

F. Di-*n*-heptylaminoethanethiosulfuric Acid.—The title compound (1.76 g, 0.005 mol) was dissolved in a solution of 0.2 g (0.005 mol) of sodium hydroxide in 3 ml of water and 25 ml of methanol. Hydrogen sulfide was bubbled into the solution for 0.5 hr which turned orange and from which separated very fine brilliant yellow crystals. After cooling the mixture, the yellow solid was collected (1.0 g) and washed with methanol. H_2S was bubbled into the filtrate which was cooled for *ca.* 16 hr to give an additional 0.3 g of the yellow compound.

The material could not be recrystallized without its losing H_2S. Most of it melted at 65–67° dec while some small particles melted at 111° (sulfur). The solid is remarkably stable in a closed vial but slowly degenerates into an oil (tetrasulfide) after several weeks when exposed to the atmosphere. Upon dissolving the yellow solid in common organic solvents and especially in $CHCl_3$, hydrogen sulfide evolution occurred, a process which could be accelerated by the application of heat. The solvent was evaporated and the oil was separated from any sulfur by extraction with hexane to give the tetrasulfide (*cf.* Table II).

When heated at 50–100° under reduced pressure to constant weight, the yellow complex VII lost 6 equiv of H_2S (25.0% of its weight; theory, 25.1%). The H_2S could also be titrated with I_2 if $CHCl_3$ was added (found 24.6%).

Anal.[22] Calcd for ($C_{32}H_{68}N_2S_4 \cdot 6H_2S$) ($C_{32}H_{80}N_2S_{10}$): C, 47.23; H, 9.91; N, 3.44; S, 39.41; neut equiv, 407. Found: C, 47.14; H, 9.33; N, 3.38; S, 39.39; neut equiv, 406.

Compound VII could be purified by regeneration from the tetrasulfide by bubbling H_2S into a suspension of the latter in methanol. The oil was solubilized to give a yellow solution and then the yellow solid precipitated from solution.

G. Dibenzylaminoethanethiosulfuric acid was dissolved in a methanol–H_2O solution containing 1 equiv of sodium hydroxide. Hydrogen sulfide was passed into the solution causing the separation of a heavy oil. After the mixture was permitted to stand for several hours, the supernatant liquid was decanted. The residual oil was dissolved in $CHCl_3$, the solution was dried, and the solvent was removed under reduced pressure leaving the bis(dibenzylaminoethyl) tetrasulfide.

H. *N*-Methyl-*N*-benzylaminoethanethiosulfuric acid was treated as above except that 2-days standing was required before the tetrasulfide separated from solution.

Bis(2-aminoethyl) Disulfide Thiosulfuric Acid Salt (II, Alternative Synthesis).—To a soluion of 7.44 g (0.03 mol) of sodium thiosulfate pentahydrate in 50 ml of water was added 6.75 g (0.03 mol) of cystamine dihydrochloride. Complete solution was effected by gentle heating and the product II was collected after cooling and was recrystallized from water (2.84 g, 36%),[23] mp 176–180° dec. Its ir spectrum was identical with that of II prepared by the hydrogen sulfide route.

Anal. Calcd for $C_4H_{14}N_2O_3S_4$: C, 18.03; H, 5.30; N, 10.51; S, 48.14. Found: C, 18.18; H, 5.30; N, 10.48; S, 48.09.

***N*-(4-Chloro-2-butenyl)phthalimide.**—The title compound (mp 104–105°, from 2-propanol) was prepared from 1,4-dichloro-2-butene in 82% yield by the method described earlier.[19]

Anal. Calcd for $C_{12}H_{10}ClNO_2$: C, 61.15; H, 4.28; N, 5.94; Cl, 15.05. Found: C, 61.13; H, 4.17; N, 5.95; Cl, 14.91.

***N*-(4-Chloro-2-butynyl)phthalimide.**—This phthalimide was synthesized from 1,4-dichloro-2-butyne as indicated above. The product, mp 120–121° (from MeOH), was obtained in 81% yield.

Anal. Calcd for $C_{12}H_8ClNO_2$: C, 61.68; H, 3.45; N, 6.00; Cl, 15.18. Found: C, 61.98; H, 3.64; N, 6.00; Cl, 15.12.

Sodium 4-Phthalimido-2-butenylthiosulfate.—*N*-(4-Chloro-2-butenyl)phthalimide (4.70 g, 0.02 mol) was added to a solution of 4.96 g (0.02 mol) of $Na_2S_2O_3 \cdot 5H_2O$ in 40 ml of water and 60 ml of methanol. The solution was heated on a steam bath until the test for inorganic thiosulfate was negative. The solution was evaporated to dryness *in vacuo* and the residue was extracted with a large volume of hot EtOH to give the desired product in 82% yield, mp 186–188° dec (from MeOH).

Anal. Calcd for $C_{12}H_{10}NS_2O_5Na \cdot 0.8H_2O$: C, 41.20; H, 3.34; N, 4.01; S, 18.33. Found: C, 41.41; H, 3.24; N, 4.07; S, 18.21.

Sodium 4-Phthalimido-2-butynylthiosulfate.—*N*-(4-Chloro-2-butynyl)phthalimide (11.7 g, 0.05 mol) was added to a solution of 12.4 g (0.05 mol) of $Na_2S_2O_3 \cdot 5H_2O$ in 100 ml of water and 50 ml of MeOH. After heating the solution on a steam bath until the thiosulfate test was negative, it was treated as indicated above. The product, which was obtained in 53% yield, melted at 180–183° dec (from MeOH).

Anal. Calcd for $C_{12}H_8NO_5S_2Na \cdot 3H_2O$: C, 37.21; H, 3.64; N, 3.62; S, 16.56. Found: C, 37.47; H, 3.80; N, 3.66; S, 16.87.

4-Amino-2-butene-1-thiosulfuric Acid (XVI).—To 3.03 g (9 mmol) of sodium 4-phthalimido-2-butenylthiosulfate a solution of 0.5 ml (10 mmol) of 100% hydrazine hydrate (64% hydrazine in water) in 25 ml of EtOH was added. Stirring and heating caused rapid solution of the thiosulfate. After *ca.* 0.5 hr solid material separated from solution and the mixture was heated and stirred for an additional 1–3 hr until no further precipitation occurred. A solution of 5 ml of glacial HOAc in 25 ml of EtOH was then added to the stirred reaction mixture which was refluxed for an additional 10 min. The mixture was evaporated to dryness *in vacuo* and the residue was triturated with *ca.* 25 ml of water. The 1.32 g (90%) of phthalhydrazide, mp 338–343° (lit.

(21) D. L. Klayman, *J. Org. Chem.*, **30**, 2454 (1965); W. H. H. Günther and H. G. Mautner, *J. Med. Chem.*, **7**, 229 (1964).

(22) Analysis was performed on a twice regenerated sample which was dried at room temperature for 2 hr *in vacuo*.

(23) No attempt was made to maximize the yield.

mp 341–344°[24]), collected by filtration, was washed again with water. The combined filtrate and washings were decolorized with charcoal, if necessary, and evaporated to dryness *in vacuo*. 4-Amino-2-butene-1-thiosulfuric acid (1.49 g, 90%) was recrystallized from H_2O–EtOH and obtained as shiny white flakes, mp 168–169° dec.

Anal. Calcd for $C_4H_9NO_3S$: C, 26.22; H, 4.95; N, 7.64; S, 34.99. Found: C, 26.32; H, 5.03; N, 7.69; S, 34.78.

4-Amino-2-butyne-1-thiosulfuric Acid (XVII).—To 43.5 g (0.112 mol) of sodium 4-phthalimido-2-butynylthiosulfate was added a solution of 7.19 g (0.144 mol) of 100% hydrazine hydrate (64% hydrazine in water) in 350 ml of MeOH. The yellow solution was stirred and gently refluxed for 1.5 hr. (A solid began to precipitate after *ca.* 15 min of heating.) A solution of 70 ml of glacial HOAc in 350 ml of MeOH was then added to the stirred reaction mixture which was then heated for an additional 20 min. The orange mixture was cooled and filtered. The filtrate was evaporated under reduced pressure at 40°, and the combined solid residues were extracted with three 250-ml portions of water. The insoluble phthalhydrazide (16.8 g, 93%) was collected by filtration and washed with 75 ml of water. The combined filtrate and washings were decolorized with charcoal and evaporated to dryness under reduced pressure at 50°. 4-Amino-2-butyne-1-thiosulfuric acid (11.7 g, 58%), after washing with EtOH, was recrystallized from water, giving the product as shiny off-white flakes, mp >170° dec.

Anal. Calcd for $C_4H_7NO_3S_2$: C, 26.51; H, 3.89; N, 7.73; S, 35.38. Found: C, 26.51; H, 3.94; N, 7.66; S, 35.22.

(24) H. D. K. Drew and H. H. Hatt, *J. Chem. Soc.*, 16 (1937).

Disproportionation of Bis(decylaminoethyl) Disulfide Thiosulfuric Acid Salt (X).—A solution of 2.73 g (0.005 mol) of X in 80 ml of MeOH was heated under reflux for 24 hr during which time H_2S was evolved. The solution was evaporated to dryness under reduced pressure and the residue was triturated with *ca.* 30 ml of hexane and cooled. The insoluble Bunte salt XI, 1.44 g (96%), was collected by filtration. The hexane filtrate was taken to dryness to give 1.07 g (92%) of the trisulfide XII, a tan-colored oil.

Anal. Calcd for $C_{24}H_{52}N_2S_3$: C, 62.00; H, 11.27; N, 6.03; S, 20.69. Found: C, 61.02; H, 11.09; N, 6.58; S, 21.75.

Registry No.—II, 31645-59-7; III, 31645-60-0; IV, 31645-61-1; V, 31645-62-2; VII, 31645-63-3; XII, 31645-64-4; XIII, 2697-60-1; XIV, 31645-66-6; XVI, 31645-67-7; XVII, 31645-68-8; *N*-(4-chloro-2-butenyl)phthalimide, 31645-84-8; *N*-(4-chloro-2-butynyl)phthalimide, 4819-69-6; sodium 4-phthalimido-2-butenylthiosulfate, 31645-86-0; sodium 4-phthalimido-2-butynylthiosulfate, 31645-87-1; hydrogen sulfide, 7783-06-4.

Acknowledgment.—We thank Dr. Thomas E. Fink, Arless E. Murray, Jr., and David Bower for their technical assistance and Dr. Thomas R. Sweeney for his interest in this investigation.

Carbodiimide–Sulfoxide Reactions. XII.[1] Reactions of Sulfonamides

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The reactions of aryl- and alkylsulfonamides with DMSO and DCC in the presence of anhydrous orthophosphoric acid has been shown to give *S,S*-dimethyl-*N*-sulfonylsulfilimines in high yields. *N*-Alkylsulfonamides cannot form sulfilimines but rather react slowly with DMSO and DCC to form *N*-alkyl-*N*-(1,3-dicyclohexyl-1-ureidomethyl)sulfonamides. A similar reaction of *N*-benzyl-*p*-toluenesulfonamide with DMSO and phosphorus pentoxide gave *N,N'*-methylenebis(*N*-benzyl-*p*-toluenesulfonamide) as the major product. *N*-Arylsulfonamides such as *p*-toluenesulfonanilide react with DMSO and DCC so as to introduce methylthiomethyl groups in either or both of the unsubstituted ortho positions. Several sulfonanilides containing methyl, nitro, and cyano substituents in the ortho positions of the aniline ring gave products in which methylthiomethyl groups were introduced on nitrogen or at an available ortho position. The very acidic sulfonamide saccharin did not react in a similar way but rather gave a 1:1 adduct with DCC in high yield.

In the preceding paper in this series[1] the previously described mild acid-catalyzed reactions of alcohols,[3] phenols,[4] enols,[5] and oximes[6] with dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC) were extended to carboxylic acids, hydroxamic acids, and carboxylic acid amides. Simple primary amides of carboxylic acids were found to be readily converted into *N*-acyl-*S,S*-dimethylsulfilimines, while compounds such as benzanilide were completely inert and imides of various sorts reacted slowly to give either *N*-(methylthiomethyl) or *N*-(1,3-dicyclohexyl-1-ureidomethyl) derivatives. In the present paper we extend these studies to the reactions of several types of sulfonamides.

p-Toluenesulfonamide (**1**) reacted quite readily with DMSO and DCC in the presence of 0.5 equiv of anhydrous orthophosphoric acid to form *S,S*-dimethyl-*N*-*p*-toluenesulfonylsulfilimine (**4**), which was isolated in crystalline form in 77% yield without necessity of chromatography. Sulfonylsulfilimines[7] of this type are fairly well-known compounds that have been prepared by the reactions of sulfonylnitrenes[8] with dialkyl sulfides. The nitrenes can be generated *via* either α elimination of chloride ion from salts of *N*-chlorosulfonamides (*e.g.*, chloramine-T)[9] or by photolysis of sulfonylazides.[10] Alternatively, sulfonylsulfilimines have been prepared by the reactions of sulfonamides with DMSO in the presence of either phosphorus pentoxide or acetic anhydride[11] and by the reaction of sulfonyl iso-

(1) For part XI, see U. Lerch and J. G. Moffatt, *J. Org. Chem.*, **36**, 3391 (1971).

(2) Syntex postdoctoral Fellow, 1966–1968.

(3) (a) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661, 5670 (1965); (b) for a review, see J. G. Moffatt in "Techniques and Applications in Organic Synthesis: Oxidation," Vol. 2, R. Augustine and D. J. Trecker, Ed., Marcel Dekker, New York, N. Y., 1971.

(4) (a) M. G. Burdon and J. G. Moffatt, *J. Amer. Chem. Soc.*, **88**, 5855 (1966); (b) *ibid.*, **89**, 4725 (1967).

(5) A. F. Cook and J. G. Moffatt, *ibid.*, **90**, 740 (1968).

(6) A. H. Fenselau, E. H. Hamamura, and J. G. Moffatt, *J. Org. Chem.*, **35**, 3546 (1970).

(7) For a review on sulfilimines, see F. Challanger in "Organic Sulfur Compounds," Vol. 2, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, p 339.

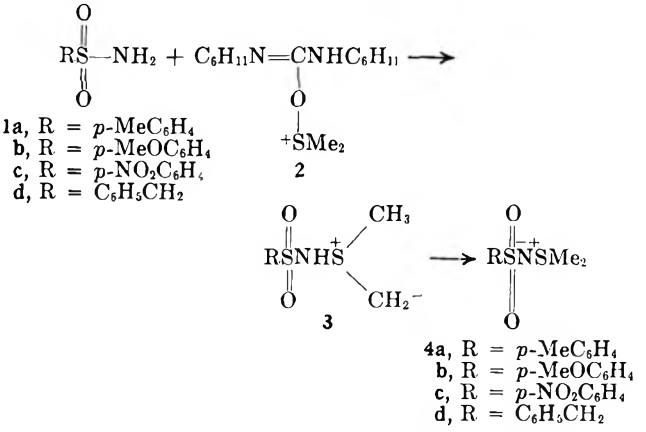
(8) D. S. Breslow in "Nitrenes," W. Lwowski, Ed., Interscience Publishers, New York, N. Y., 1970, p 245.

(9) F. G. Mann and W. J. Pope, *J. Chem. Soc.*, 1052 (1922).

(10) (a) L. Horner and A. Christmann, *Chem. Ber.*, **96**, 388 (1963); (b) L. Horner, G. Bauer, and J. Dourges, *ibid.*, **98**, 2631 (1965).

(11) D. S. Tarbell and C. Weaver, *J. Amer. Chem. Soc.*, **63**, 2939 (1941).

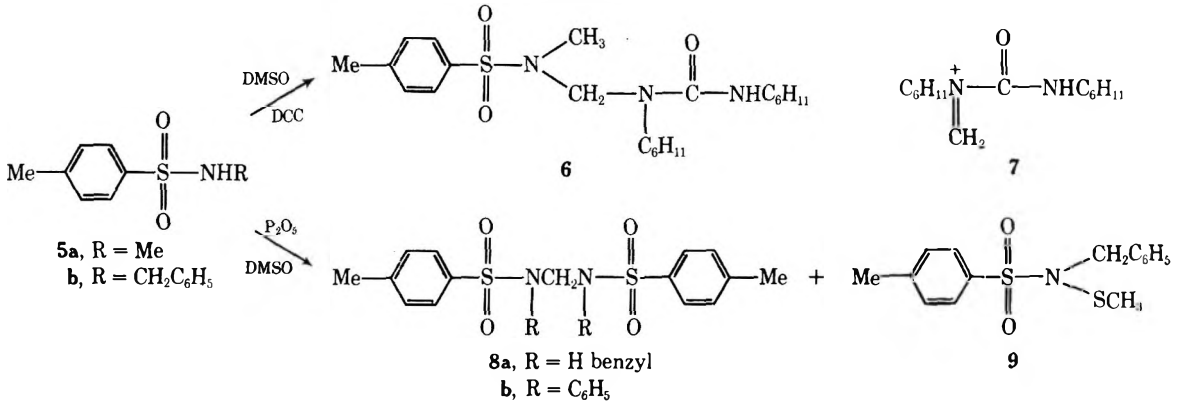
cyanates with sulfoxides.[12] In the present case, the formation of **4** doubtless involves direct attack of the amide nitrogen of **1** upon the DMSO–DCC adduct (**2**) to give the sulfonium ylide (**3**) which then undergoes a prototropic shift to form the more stable sulfilimine (**4**).



In this sequence we assume that the ylide **3** is the direct product of the condensation of **1** and **2** by an intramolecular proton abstraction mechanism similar to that we have proposed for the oxidation of alcohols.[13] If indeed this does not apply, then the direct product from reaction of **1** and **2** would be protonated form of **4**. which could then readily lose a proton to form the sulfilimine. Similar reactions between *p*-methoxybenzenesulfonamide (**1b**) and *p*-nitrobenzenesulfonamide (**1c**) and DMSO–DCC led to the formation of the corresponding sulfilimines (**4b** and **4c**)[10] in yields of 66 and 90%. The case of **1c** provides a clear example of a reaction in which DCC is not the preferred carbodiimide. The sulfilimine (**4c**) is extremely insoluble and crystallizes from the reaction mixture with dicyclohexylurea when DCC is used. By using diisopropylcarbodiimide the resulting diisopropylurea is quite soluble in many organic solvents and pure **4c** can be isolated in 90% yield by direct crystallization from methanol. On the other hand, the ylides **4a** and **4b** are soluble in water but can be conveniently recovered from the aqueous extracts during the usual reaction work-up by extraction into chloroform. In all three cases, the yields of sulfilimines are much higher than those obtained by photolysis of the sulfonylazides in dimethyl sulfide.[10] The sulfilimines **4a** and **4c** have also been obtained in yields of 17 and 44% by the mechanistically related acid-catalyzed reaction of the corresponding sulfonamides with DMSO and phenyl cyanate at 100°.[14] As an example of an aliphatic sulfonamide, the reaction of toluene-α-sulfonamide (**1d**) gave the corresponding sulfilimine (**4d**) in 70% yield.

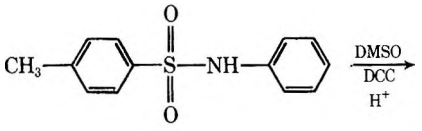
Photolysis of the related *N*-benzoylsulfilimines in methanol was previously shown to proceed *via* formation of the *N*-acylnitrene which reacted with the solvent or rearranged to an isocyanate.[1] Similar irradiation of a methanolic solution of **4a**, however, gave 26% ammonium *p*-toluenesulfonate, 17% *p*-toluenesulfonamide, and at least five other minor products that have not been identified.

Simple aliphatic substitution of the sulfonamide nitrogen as in *N*-methyl-*p*-toluenesulfonamide (**5a**) of course blocks the formation of sulfilimines. A very slow reaction does occur between **5a**, DMSO, and DCC, but even after 10 days 57% of unreacted **5a** was recovered. The only isolable new product was shown to be *N*-methyl-*N*-(1,3-dicyclohexyl-1-ureidomethyl)-*p*-toluenesulfonamide (**6**), which presumably arises from reaction of the amide with a species such as **7** as proposed previously for other slow reactions.[1] On the other hand, *N*-benzyl-*p*-toluenesulfonamide (**5b**) reacted fairly readily with DMSO in the presence of phosphorus pentoxide at room temperature, giving *N*,*N*′-methylenebis(*N*-benzyl-*p*-toluenesulfonamide) (**8a**) in 58% yield. The formation of methylene bisamides has previously been reported by Sekera and Rumpf[15] during reactions of N-substituted sulfonamides with DMSO and phosphorus pentoxide at 150°. These authors have proposed a mechanism for this reaction involving an *N*-alkyl derivative of the ylide (**3**) as an intermediate but this has been questioned by Martin, *et al.*[16] An alternative possibility is the direct condensation of the sulfonamide with formaldehyde generated by decomposition of DMSO.[1] We have previously described the formation of methylene bisamides upon reaction at room temperature of carboxylic acid amides with DMSO and phosphorus pentoxide while the corresponding reactions using DCC gave *N*-acylsulfilimines.[1] A second crystalline product was also isolated in 7% yield from the reaction of **5b** with DMSO and phosphorus pentoxide and shown by elemental analysis and nmr spectroscopy to be *N*-benzyl-*N*-methylthio-*p*-toluenesulfonamide (**9**). This compound presumably arises by nucleophilic demethylation of an intermediate *N*-dimethylsulfonium derivative by reaction with phosphate anion or perhaps even DMSO.

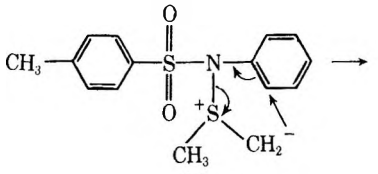


(12) C. King, *J. Org. Chem.*, **25**, 352 (1960).
(13) J. G. Moffatt, *ibid.*, **36**, 1909 (1971).
(14) D. Martin and H.-J. Niclas, *Chem. Ber.*, **102**, 31 (1969).
(15) A. Sekera and P. Rumpf, *C. R. Acad. Sci.*, **260**, 2252 (1965).
(16) D. Martin, H.-J. Niclas, and A. Weise, *Chem. Ber.*, **102**, 23 (1969).

The presence of an aromatic substituent on the sulfonamide nitrogen led to different results. Thus, the reaction of *p*-toluenesulfonanilide (**10**) under the usual



10



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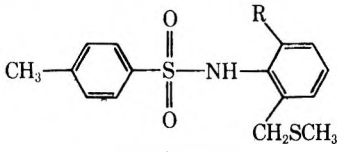
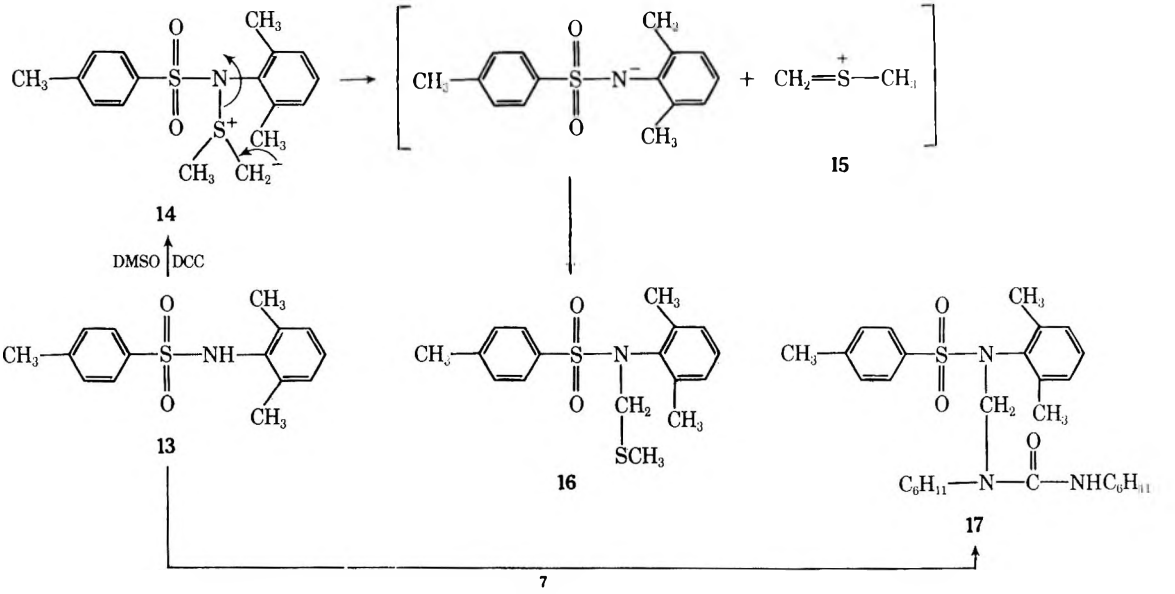


12a, R = H
b, R = CH_2SCH_3

conditions led to the isolation of two compounds **12a** (24%) and **12b** (27%) in which methylthiomethyl groups were introduced in one or both of the available ortho positions of the aromatic ring. This result is very reminiscent of what was previously described for the reactions of phenols with DMSO and DCC[4] *via* an intramolecular ortho alkylation reaction originating from the initially formed sulfonium ylide (**11**). The dialkylated product (**12b**) is, of course, the result of a second reaction of **12a** with DMSO and DCC in the same way. The structures of **12a** and **12b** were unequivocally confirmed by their ready desulfurization with nickel to the known *p*-toluenesulfono-*o*-toluidide[17] and *p*-toluenesulfono-2′,6′-xylidide.[18]

As was found in other cases, the reaction of **10** with DMSO and phosphorus pentoxide took a different course and gave *N*,*N*′-methylenebis-*p*-toluenesulfonanilide (**8b**) in 66% yield. The latter compound was readily identified by its elemental analysis and its nmr spectrum which showed the methylene bridge as a 2-proton singlet at 5.58 ppm.

It was previously shown that the reactions of 2,6-disubstituted phenols, such as 2,6-dimethylphenol, with DMSO and DCC led to the formation of 6-methylthiomethylcyclohexa-2,4-dien-1-ones. The latter compounds were shown to readily rearrange to the corresponding 4-methylthiomethylphenols under acidic conditions, the reaction proceeding by dissociation of the dienone into the methylmethylenesulfonium ion which then alkylated the para position of the released phenol.[4b] In order to see whether a similar reaction would occur in the sulfonanilide series, *p*-toluenesulfono-2′,6′-xylidide (**13**)[18] was treated with DMSO and DCC. A slow reaction occurred from which it was possible to isolate two crystalline products in yields of 21 and 25% in addition to 49% of unreacted **13**. These proved to be the N-substituted derivatives *N*-methylthiomethyl-*N*-*p*-toluenesulfonyl-2,6-xylidine (**16**) and *N*-(1,3-dicyclohexyl-1-ureidomethyl)-*N*-*p*-toluenesulfonyl-2,6-xylidine (**17**), the structures being readily apparent from their nmr spectra. It thus appears that the initial sulfonium ylide (**14**) show little, if any, tendency toward intramolecular alkylation of the xylidine moiety but rather dissociates into the anion of the starting material (**13**) and the methyl methylenesulfonium ion (**15**). Recombination of the latter species then gives the *N*-methylthiomethyl derivative (**16**). The urea derivative (**17**) once again is probably derived from a species such as **7**.

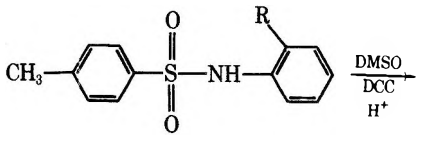


14 **15** **13** **16** **17** **7**

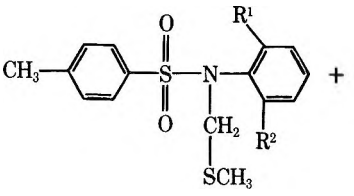
An attempt to prepare *N*-*p*-toluenesulfonyl-2,6-dichloroaniline failed, since the reaction of 2,6-dichloroaniline with a slight excess of *p*-toluenesulfonyl chloride led instead to *N*,*N*-di-*p*-toluenesulfonyl-2,6-dichloroaniline, which was isolated in 67% yield.

In those cases where there is still a single, unsubstituted ortho position on the aniline ring, both nitrogen alkylation and aromatic substitution take place. Thus, the reaction of *N*-(2-cyanophenyl)-*p*-toluenesulfonamide (**18a**) with DMSO and DCC gave as its major product the *N*-methylthiomethyl derivative (**19a**, 47%) in addition to smaller amounts of aromatic ortho alkylation product (**20**, 9%) and the bismethylthiomethyl compound **19b** (22%). In a similar way the reaction

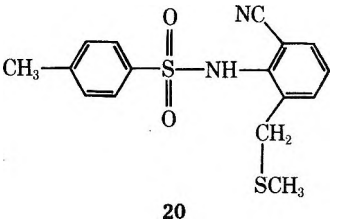
(17) F. D. Chattaway, *J. Chem. Soc.*, **85**, 1186 (1901).
(18) B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **73**, 809 (1954).



18a, R = CN
b, R = NO_2



19a, R^1 = CN; R^2 = H
b, R^1 = CN; R^2 = CH_2SCH_3
c, R^1 = NO_2; R^2 = H
d, R^1 = NO_2; R^2 = CH_2SCH_3

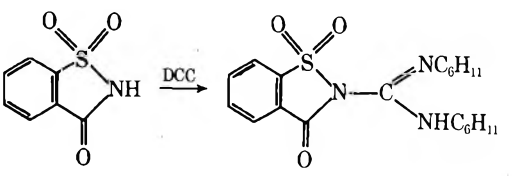


20

of *N*-(2-nitrophenyl)-*p*-toluenesulfonamide (**18b**) gave 54% of *N*-(methylthiomethyl)-*N*-(2-nitrophenyl)-*p*-toluenesulfonamide (**19c**) and 8% of the product (**19d**) alkylated on both nitrogen and the aromatic ring. In the case of the compound **19d** it is clear from the nmr spectrum that the methylthiomethyl group on the aromatic ring is indeed situated ortho to the amide function. Thus one aromatic proton, almost certainly that adjacent to the nitro group, is located at distinctly lower field than the others and appears as a quartet (J_{ortho} = 7 Hz, J_{meta} = 2 Hz) at 7.99 ppm. No orientation of the methylthiomethyl group other than that in **19e** permits this proton to have both ortho and meta neighbors. A similar orientation for **19b** and **19d** is expected on mechanistic grounds (*cf.* **12a**, **12b**, **19d**) but has not been rigorously proved. The nmr spectra of the doubly alkylated compounds (**19b** and **19d**) are also interesting in that the NCH_2S protons are nonequivalent and appear as AB quartets (J_{gem} = 14 Hz) centered at 4.91 and 4.95 ppm, respectively. This is undoubtedly a consequence of restricted rotation and is not observed in less substituted molecules where these protons appear as singlets. In the case of the nitro compound (**19d**), but not the nitrile (**19b**), the $ArCH_2$ group is also nonequivalent and appears as an AB quartet.

Finally, it might be mentioned that attempts to react saccharin (**21**) with DMSO and DCC failed to proceed in the desired way. Rather than reacting with the DMSO–DCC adduct (**2**), this very acidic sulfonamide added directly to DCC, giving, in essentially quantitative yield, a 1:1 adduct considered to be the guanidine (**22**). This same product was obtained in 93% yield by reaction of **21** and DCC in ethyl acetate. It is presumably the same material briefly described by Micheel and Lorenz,[19] although the melting point reported by these authors is 10° lower than that found by us.

(19) F. Micheel and M. Lorenz, *Justus Liebigs Ann. Chem.*, **698**, 242 (1966).



21 **22**

Subsequent papers in this series will describe the reactions of further types of nitrogenous functional groups with the DMSO–DCC reagent.[20]

Experimental Section

General experimental methods are as previously described.[1]

***S*,*S*-Dimethyl-*N*-*p*-toluenesulfonylsulfilimine (4a).**—A solution of anhydrous orthophosphoric acid in DMSO (1.6 ml of 3 *M*, 5 mmol) was added to a solution of *p*-toluenesulfonamide (1.71 g, 10 mmol) and DCC (6.18 g, 30 mmol) in DMSO (10 ml) and benzene (5 ml). After 2 days at 23° the mixture was diluted with ethyl acetate, dicyclohexylurea was removed by filtration, and the filtrate was extracted four times with water. The combined aqueous extracts were then repeatedly extracted (five times) with chloroform until tlc (chloroform–methanol, 9:1) showed complete removal of **4a**. The chloroform extracts were dried ($MgSO_4$) and evaporated, leaving a crystalline residue that was recrystallized from ethanol, giving 1.78 g (77%) of **4a** as long needles: mp 158–159° (lit.[10a] mp 158–159°); λ_{max}^{MeOH} 230 mμ (ε 11,330); ν_{max} (KBr) 1635 and 1580 cm^{-1}; nmr (DMSO-d_6) 2.37 (s, 3, $ArCH_3$), 2.69 (s, 6, SMe_2), 7.38 and 7.74 ppm (d, 2, *J* = 8 Hz, Ar); mass spectrum (70 eV) *m/e* 231 (M^+), 216 (M − CH_3) 167 (M − SO_2), 155 (M − Me_2SN), 152, 124 (Me_2SNSO).

Anal. Calcd for $C_9H_{13}NO_2S_2$: C, 46.75; H, 5.67; N, 6.06; S, 27.27. Found: C, 46.78; H, 6.14; N, 6.10; S, 27.57.

***S*,*S*-Dimethyl-*N*-*p*-methoxybenzenesulfonylsulfilimine (4b).**—A reaction between *p*-methoxybenzenesulfonamide (1.87 g, 10 mmol), DCC (6.18 g, 30 mmol), and anhydrous phosphoric acid (5 mmol) in DMSO (10 ml) and benzene (5 ml) was carried out exactly as above except that several further extractions with chloroform were necessary to remove the product from the aqueous phase. Crystallization of the final residue from ethanol (15 ml) gave 1.62 g (66%) of **4b**: mp 138.5–139.5°; λ_{max}^{MeOH} 239 mμ (ε 17,000); ν_{max} (KBr) 1600, 1580, 1495 cm^{-1}; nmr ($CDCl_3$) 2.67 (s, 6, SMe_2), 3.85 (s, 3, OMe), 6.93 and 7.84 ppm (d, 2, *J* = 9 Hz, Ar); mass spectrum (70 eV) *m/e* 247 (M^+), 232 (M − CH_3), 183 (M − SO_2), 171 ($MeOC_6H_4SO_2$), 168, 124 (Me_2SNSO).

Anal. Calcd for $C_9H_{13}NO_3S_2$: C, 43.73; H, 5.30; N, 5.67. Found: C, 43.78; H, 5.25; N, 5.46.

***S*,*S*-Dimethyl-*N*-*p*-nitrobenzenesulfonylsulfilimine (4c).**—Anhydrous phosphoric acid (5 mmol) was added to a solution of *p*-nitrobenzenesulfonamide (2.02 g, 10 mmol) and diisopropylcarbodiimide (3.78 g, 30 mmol) in DMSO (10 ml) and benzene (5 ml). After 16 hr the mixture was diluted with ethyl acetate and filtered. The resulting crystals were washed with ethyl acetate, dried (3.5 g), and crystallized from ethanol giving 2.36 g (90%) of pure **4c**: mp 186–187° (lit.[10a] mp 184°); λ_{max}^{MeOH} 271 mμ (ε 10,400); ν_{max} (KBr) 1610, 1530, 1355, 1285 cm^{-1}; nmr (DMSO-d_6) 2.73 (s, 6, SMe_2), 7.98 and 8.38 ppm (d, 2, *J* = 8 Hz, Ar); mass spectrum *m/e* 262 (M^+), 247 (M − CH_3), 198 (M − SO_2), 183 (*m/e* 198 − CH_3), 122 ($C_6H_4NO_2$), 76 (Me_2SN), 62 (Me_2S).

Anal. Calcd for $C_8H_{10}N_2O_4S_2$: C, 36.65; H, 3.84; N, 10.69. Found: C, 36.40; H, 3.74; N, 10.62.

***S*,*S*-Dimethyl-*N*-α-toluenesulfonylsulfilimine (4d).**—A solution of α-toluenesulfonamide (1.71 g, 10 mmol), DCC (6.18 g, 30 mmol), and anhydrous phosphoric acid (5 mmol) in DMSO (10 ml) and benzene (5 ml) was kept at 23° for 3 days. The mixture was then diluted with ethyl acetate and worked up as for **4a**. Crystallization of the chloroform-soluble product from ethanol gave 1.61 g (70%) of **4d** as needles: mp 147–148°; λ_{max}^{MeOH} 210 mμ (ε 9400), 215 (9100), 359 (200); ν_{max} (KBr) 1490, 1270 cm^{-1}; nmr ($CDCl_3$) 2.40 (s, 6, SMe_2), 4.25 (s, 2, $ArCH_2SO_2$), 7.45 (s, 5, Ar); mass spectrum (70 eV) *m/e* 231 (M^+), 167 (M − SO_2), 140 (Me_2SNSO_2), 91 ($C_6H_5CH_2$).

(20) U. Lerch and J. G. Moffatt, *J. Org. Chem.* in press.

Anal. Calcd for $C_9H_{13}NO_2S_2$: C, 46.75; H, 5.67; N, 6.06. Found: C, 46.63; H, 5.70; N, 5.85.

Photolysis of *S,S*-Dimethyl-*N*-*p*-toluenesulfonylsulfilimine (4a).—A solution of **4a** (1.16 g, 5 mmol) in methanol (90 ml) was irradiated for 19 hr in a quartz tube under argon using a 15W General Electric G 15T8 germicidal lamp. Some insoluble material was removed and the filtrate was evaporated and crystallized from chloroform–methanol giving 247 mg (26%) of ammonium *p*-toluenesulfonate which melted with decomposition at 250–280°: λ_{max}^{MeOH} 222 mμ (ε 11,400); nmr (DMSO-d_6), 2.29 (s, 3, $ArCH_3$), 7.17 and 7.60 (d, 2, J = 8 Hz, Ar), 7.2 ppm (br s, 4, NH_4).

Anal. Calcd for $C_7H_{11}NO_3S$: C, 44.41; H, 5.86; N, 7.40. Found: C, 44.21; H, 6.38; N, 7.35.

Preparative tlc (ethyl acetate–methanol, 5:1) of the mother liquors gave 41 mg (4%) of unreacted **4a**, 141 mg (17%) of *p*-toluenesulfonamide, and at least five other unidentified, minor products.

Reaction of *N*-Methyl-*p*-toluenesulfonamide (5a).—A solution of **5a** (1.85 g, 10 mmol), DCC (5.8 g, 28 mmol), and anhydrous phosphoric acid (5 mmol) in DMSO (5 ml) and benzene (5 ml) was allowed to react for 10 days. Following the usual work-up with ethyl acetate the product was purified by preparative tlc using CCl_4–acetone (85:15) giving 1.05 g (57%) of unreacted **5a** and 670 mg (16%) of *N*-methyl-*N*-(1,3-dicyclohexyl-1-ureidomethyl)-*p*-toluenesulfonamide (**6**): mp 134–136° from ether; λ_{max}^{MeOH} 230 mμ (ε 13,700); ν_{max} (KBr) 1645 and 1530 cm^{-1}; nmr ($CDCl_3$) 0.8–2.1 (m, 20, cyclohexyl), 2.45 (s, 3, $ArCH_3$), 2.69 (s, 3, NCH_3), 3.7 (m, 2, >CHN), 4.54 (s, 2, NCH_2N), 5.25 (m, 1, NH), 7.36 (d, 2, J = 8 Hz, Ar), 7.70 ppm (d, 2, J = 8 Hz, Ar).

Anal. Calcd for $C_{22}H_{35}N_3O_3S$: C, 62.67; H, 8.37; N, 9.97; S, 7.61. Found: C, 62.74; H, 8.19; N, 9.92; S, 7.81.

Reaction of *N*-Benzyl-*p*-toluenesulfonamide (5b) with DMSO–Phosphorus Pentoxide.—After addition of **5b** (2.6 g, 10 mmol) to a premixed solution of P_2O_5 (1.7 g) in DMSO (15 ml) the mixture was kept for 48 hr at 23°, and the crystalline product was removed by filtration and washed with ether, giving 1.55 g (58%) of *N*,*N*′-methylenebis(*N*-benzyl-*p*-toluenesulfonamide) (**8a**): mp 196–197° (unchanged upon recrystallization from benzene); $\lambda_{max}^{dioxane}$ 2.30 mμ (ε 22,100); nmr ($CDCl_3$) 2.37 (s, 6, $ArCH_3$), 4.43 (s, 4, $ArCH_2N$), 4.87 (s, 2, NCH_2N), 7.2 ppm (m, 18, Ar).

Anal. Calcd for $C_{29}H_{30}N_2O_4S_2$: C, 65.14; H, 5.66; N, 5.24; S, 11.99. Found: C, 65.32; H, 6.12; N, 5.07; S, 11.87.

The mother liquors were worked up as usual and purified by preparative tlc using CCl_4–acetone (9:1), giving 465 mg (18%) of unreacted **5b** and 221 mg (7.2%) of *N*-benzyl-*N*-methylthio-*p*-toluenesulfonamide (**9**): mp 77–86° (from hexane, unchanged by repeated crystallization); λ_{max}^{MeOH} 230 mμ (ε 14,600); ν_{max} (KBr) 1600 and 1500 cm^{-1}; nmr ($CDCl_3$) 2.10 (s, 3, SMe), 2.35 (s, 3, $ArCH_3$), 4.55 (s, 2, $ArCH_2N$), 7.1–7.9 ppm (m, 9, Ar); mass spectrum (70 eV) *m/e* 307 (M^+), 259 (M − CH_3SH), 155 ($CH_3C_6H_4SO_2$), 150, 105, 91.

Anal. Calcd for $C_{15}H_{17}NO_2S_2$: C, 58.60; H, 5.57; N, 4.56; S, 20.86. Found: C, 58.77; H, 5.62; N, 4.39; S, 20.63.

Reaction with *p*-Toluenesulfonanilide (10). A. With DMSO–DCC.—A solution of **10** (2.45 g, 10 mmol), DCC (6.18 g, 30 mmol), and anhydrous phosphoric acid (5 mmol) in DMSO (10 ml) and benzene (5 ml) was allowed to react for 3 days at 23° and then worked up with ethyl acetate. Preparative tlc on three plates using two developments with CCl_4–acetone (9:1) gave 720 mg (29%) of unreacted **10** and two faster bands. The faster band gave only 240 mg of an oil that decomposed upon attempted distillation. Rechromatography of the slower band separated two compounds, the slower of which was crystallized from hexane giving 740 mg (24%) of 2-methylthiomethyl-*N*-*p*-toluenesulfonylaniline (**12a**): mp 93–95°; λ_{max}^{MeOH} 220 mμ (sh, ε 17,900); ν_{max} (KBr) 3300, 1610, 1500 cm^{-1}; nmr ($CDCl_3$) 1.81 (s, 3, SMe), 2.32 (s, 3, $ArCH_3$), 3.37 (s, 2, $ArCH_2S$), 7.4 ppm (m, 9, Ar and NH); mass spectrum (70 eV) *m/e* 307 (M^+), 196, 181, 152 (M − $MeC_6H_4SO_2$), 136 (M − $MeC_6H_4SO_2NH_2$).

Anal. Calcd for $C_{15}H_{17}NO_2S_2$: C, 58.60; H, 5.57; N, 4.56; S, 20.86. Found: C, 58.84; H, 5.55; N, 4.48; S, 21.06.

The faster portion was crystallized from hexane giving 990 mg (27%) of 2,6-di(methylthiomethyl)-*N*-*p*-toluenesulfonylaniline (**12b**): mp 89.5–91°; λ_{max}^{MeOH} only end absorption; ν_{max} (KBr) 3280, 1600, 1460, 1435 cm^{-1}; nmr ($CDCl_3$) 1.85 (s, 6, SMe), 2.41 (s, 3, $ArCH_3$), 3.49 (s, 4, $ArCH_2S$), 7.3 ppm (m, 8, Ar and NH).

Anal. Calcd for $C_{17}H_{21}NO_2S_3$: C, 55.55; H, 5.76; N, 3.81; S, 26.17. Found: C, 55.68; H, 5.54; N, 3.85; S, 26.29.

B. With DMSO–Phosphorus Pentoxide.—Phosphorus pentoxide (2.5 g) was added gradually to DMSO (20 ml) and cooled to room temperature. *p*-Toluenesulfonanilide (3.61 g, 15 mmol) was then added and the mixture was stirred at 23° for 20 hr. Since much unreacted **10** was still present, the mixture was heated to 70° for 4 hr. Upon cooling, crystalline *N*,*N*′-methylenebis-*p*-toluenesulfonanilide (**8b**, 945 mg) separated: mp 212–214°; λ_{max}^{MeOH} 233 mμ (ε 2800); ν_{max} 1600, and 1495 cm^{-1}; nmr ($CDCl_3$) 2.36 (s, 6, $ArCH_3$), 5.58 (s, 2, NCH_2N), 7.2 ppm (m, 18, Ar); mass spectrum (70 eV) *m/e* 260 (M − TsNAr), 247 (TsNAr), 155 ($MeC_6H_4SO_2$).

Anal. Calcd for $C_{27}H_{26}N_2O_4S_2$: C, 63.75; H, 5.55; N, 5.51; S, 12.61. Found: C, 63.91; H, 5.26; N, 5.69; S, 12.75.

The mother liquors were extracted three times with water, dried, and purified by preparative tlc using benzene–ethyl acetate (19:1) giving only 653 mg (18%) of unreacted **10** and 1.59 g (total yield 2.52 g, 66%) of **8b**.

Desulfurization of 12a and 12b.—A solution of **12b** (175 mg) in methanol (5 ml) was stirred for 3 hr with about 2 g of Davidson sponge nickel.[21] The mixture was then filtered and evaporated, leaving 111 mg (84%) of crystalline *p*-toluenesulfono-2′,6′-xylidide, mp 135–137° from benzene–hexane (lit.[18] mp 136.5–137.5°). This material was identical with an authentic sample by infrared spectra, tlc, and mixture melting point.

Identical treatment of **12a** (105 mg) for 45 min gave 84 mg (97%) of *p*-toluenesulfono-*o*-toluidide, mp 108–109°, that was identical with an authentic sample.[17]

Reaction of *p*-Toluenesulfono-2′,6′-xylidide (13).—A solution of **13** (2.75 g, 10 mmol),[18] DCC (5.8 g), and anhydrous phosphoric acid (5 mmol) in DMSO (5 ml) and benzene (5 ml) was kept at 23° while the reaction was followed by tlc using CCl_4–acetone (9:1). After 8 days it was worked up using ethyl acetate and separated on four preparative tlc plates (9:1 CCl_4–acetone), giving two major bands. Elution of the fastest band gave 712 mg (21%) of crystalline *N*-methylthiomethyl-*N*-*p*-toluenesulfonyl-2,6-xylidine (**16**): mp 128–130° from hexane; λ_{max}^{MeOH} 234 mμ (sh, ε 11,000), 276 (1300); ν_{max} (KBr) 1600, 1470, 1340 cm^{-1}; nmr ($CDCl_3$) 2.11 (s, 6, $ArMe_2$), 2.18 (s, 3, SMe), 2.45 (s, 3, $ArCH_3$), 4.79 (s, 2, NCH_2S), 7.2–7.8 ppm (m, 7, Ar).

Anal. Calcd for $C_{17}H_{21}NO_2S_2$: C, 60.86; H, 6.31; N, 4.18; S, 19.11. Found: C, 60.89; H, 6.27; N, 4.34; S, 19.37.

Rechromatography of the slower band using CCl_4–acetone (87:13) separated it into two bands, the slower of which contained 1.34 g (49%) of unreacted **13**. Crystallization of the faster band from methanol gave 1.28 g (25%) of *N*-(1,3-dicyclohexyl-1-ureidomethyl)-*N*-*p*-toluenesulfonyl-2,6-xylidine (**17**): mp 158–195°; λ_{max}^{MeOH} 233 mμ (ε 12,800), 264 (1800), 276 (ε 1100); ν_{max} (KBr) 3400, 1660, 1535 cm^{-1}; nmr ($CDCl_3$), 1–2.2 (m, 20, cyclohexyl), 2.85 (s, 6, $ArMe_2$), 2.42 (s, 3, ArMe), 3.50 (m, 2, CHN), 5.00 (s, 2, NCH_2N), 6.56 (d, 1, J = 8 Hz, NH), 7.1–7.7 ppm (m, 7, Ar).

Anal. Calcd for $C_{29}H_{41}N_3O_3S$: C, 68.07; H, 8.08; N, 8.21; S, 6.27. Found: C, 68.04; H, 8.20; N, 8.11; S, 6.40.

***N*-(2-Cyanophenyl)-*p*-toluenesulfonamide (18a).**—Anthranilonitrile and *p*-toluenesulfonyl chloride (1.1 equiv) were allowed to react in pyridine at 100° for 5 hr. The mixture was then poured into water and the precipitate was crystallized from methanol, giving **18a** in 87% yield: mp 138–139°; λ_{max}^{MeOH} 209 mμ (ε 31,400), 220 (sh, 22,800); nmr ($CDCl_3$) 2.37 (s, 3, ArMe), 7.5 ppm (m, 9, Ar and NH).

Anal. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.74; H, 4.44; N, 10.29; S, 11.78. Found: C, 61.75; H, 4.44; N, 10.16; S, 11.89.

Reaction of *N*-(2-Cyanophenyl)-*p*-toluenesulfonamide (18a).—A solution of **18a** (2.72 g, 10 mmol), DCC (5.8 g), and anhydrous phosphoric acid (5 mmol) in DMSO (5 ml) and benzene (5 ml) was kept for 2 days and worked up with ethyl acetate. The extracted organic phase was chromatographed on four plates using CCl_4–acetone (85:15), giving three bands. Elution of the fastest band gave 878 mg (22%) of *N*-(2-cyano-6-methylthiomethylphenyl)-*N*-methylthiomethyl-*p*-toluenesulfonamide (**19b**): mp 101–102° from ether–hexane; λ_{max}^{MeOH} 222 mμ (sh, ε 23,700), 289 (sh, 1900); ν_{max} (KBr) 2240, 1610, 1585 cm^{-1}; nmr ($CDCl_3$) 2.03 (s, 3, SMe), 2.22 (s, 3, SMe), 2.42 (s, 3, ArMe), 3.82 (s, 2, $ArCH_2S$), 4.76 and 5.05 (d, 1, J_{gem} = 14 Hz, NCH_2S), 7.5 ppm (m, 7, Ar).

(21) Davidson Chemical Division of W. R. Grace & Co., Cincinnati, Ohio.

Anal. Calcd for $C_{18}H_{20}N_2O_2S_3$: C, 55.07; H, 5.14; N, 7.14; S, 24.50. Found: C, 54.64; H, 5.12; N, 6.87; S, 24.18.

Elution of the middle band and crystallization from ether gave 1.575 g (47%) of *N*-(2-cyanophenyl)-*N*-methylthiomethyl-*p*-toluenesulfonamide (**19a**): mp 97–98°; λ_{max}^{MeOH} 220 mμ (sh, ε 21,600), 276 (sh, 1700); ν_{max} (KBr) 2250, 1600, 1495 cm^{-1}; nmr ($CDCl_3$) 2.22 (s, 3, SMe), 2.37 (s, 3, ArMe), 4.70 (s, 2, NCH_2S), 7.4 ppm (m, 8, Ar); mass spectrum (70 eV) *m/e* 332 (M^+), 285 (M − SMe), 177 (M − $ArSO_2$), 155 ($MeC_6H_4SO_2$), 130 (*m/e* 177 − SMe).

Anal. Calcd for $C_{16}H_{16}N_2O_2S_2$: C, 57.81; H, 4.85; N, 8.43; S, 19.29. Found: C, 57.47; H, 5.22; N, 8.25; S, 19.32.

Rechromatography of the slowest band using five developments with CCl_4–acetone (82:18) separated 464 mg (17%) of unreacted **18a** from 293 mg (9%) of *N*-(2-cyano-6-methylthiomethylphenyl)-*p*-toluenesulfonamide (**20**): mp 125–128° from ether; λ_{max}^{MeOH} 222 mμ (sh, ε 28,200), 285 (sh, 1700); ν_{max} (KBr) 3300, 2240, 1635, 1600, 1585 cm^{-1}; nmr ($CDCl_3$) 1.89 (s, 3, SMe), 2.42 (s, 3, ArMe), 3.55 (s, 2, $ArCH_2S$), 7.5 ppm (m, 8, Ar and NH); mass spectrum (70 eV) *m/e* 332 (M^+), 177 (M − $MeC_6H_4SO_2$), 155 ($MeC_6H_4SO_2$), 131 (*m/e* 177 − SMe).

Anal. Calcd for $C_{16}H_{16}N_2O_2S_2$: C, 57.81; H, 4.85; N, 8.43; S, 19.29. Found: C, 57.83; H, 5.02; N, 8.25; S, 19.20.

Reaction of *N*-(2-Nitrophenyl)-*p*-toluenesulfonamide (18b).—A solution of **18b** (2.92 g, 10 mmol), DCC (6.18 g, 30 mmol), and anhydrous phosphoric acid (5 mmol) in DMSO (10 ml) and benzene (5 ml) was kept for 3 days at room temperature. After dilution with ether, filtration, and three extractions with water, the solution was extracted four times with 1 *N* sodium hydroxide. Acidification of the extracts and extraction with chloroform gave 0.79 g of relatively pure unreacted **18b**. Preparative tlc of the alkali insoluble fraction using three developments with hexane–ether (3:2) gave two products. Elution of the major, slower band gave 1.90 g (54%) of *N*-(2-nitrophenyl)-*N*-methylthiomethyl-*p*-toluenesulfonamide (**19c**) as a very viscous yellow syrup. An analytical sample could be distilled in a Kugelrohr apparatus[22] at 150° (10^{-3} mm): λ_{max}^{MeOH} 227 mμ (ε 17,400); ν_{max} (KBr) 1605, 1550, 1175 cm^{-1}; nmr ($CDCl_3$) 2.20 (s, 3, SMe), 2.41 (s, 3, ArMe), 4.87 (s, 2, NCH_2S), 7.1–7.9 ppm (m, 8, Ar).

Anal. Calcd for $C_{15}H_{16}N_2O_4S_2$: C, 51.14; H, 4.58; N, 7.95. Found: C, 51.47; H, 4.72; N, 7.71.

Elution of the faster and gave 355 mg (8%) of *N*-(methylthiomethyl)-*N*-(2-methylthiomethyl-6-nitrophenyl)-*p*-toluenesulfonamide (**19d**) as a viscous syrup: λ_{max}^{MeOH} 225 mμ (sh, ε 18,500); ν_{max} (KBr) 1600, 1535 cm^{-1}; nmr ($CDCl_3$) 2.12 (s, 3, SMe), 2.20 (s, 3, SMe), 2.42 (s, 3, ArMe), 3.77 and 4.15 (d, 1, J_{gem} = 14 Hz, $ArCH_2S$), 4.74 and 5.17 (d, 1, J_{gem} = 14 Hz, NCH_2S), 7.1–8 ppm (m, 7, Ar).

Anal. Calcd for $C_{17}H_{20}N_2O_4S_3$: C, 49.51; H, 4.89; N, 6.79. Found: C, 49.86; H, 4.97; N, 6.61.

***N*,*N*-Di-*p*-Toluenesulfonyl-2,6-dichloroaniline.**—A solution of 2,6-dichloroaniline (8.1 g, 50 mmol) and *p*-toluenesulfonyl chloride (10.0 g, 53 mmol) in pyridine (30 ml) was heated under reflux for 2 days. After evaporation of the solvent the residue was triturated with aqueous methanol (1:1) giving 7.8 g (67%) of *N*,*N*-di-*p*-toluenesulfonyl-2,6-dichloroaniline: mp 252–255° (raised to 256–258° upon recrystallization from chloroform–methanol); ν_{max} (KBr) 1600, 1570, 1495, 1440 cm^{-1}; nmr ($CDCl_3$) 2.46 (s, 6, ArMe), 7.32 (m, 7, Ar), 7.95 (d, 4, *J* = 8 Hz, Ar).

Anal. Calcd for $C_{20}H_{17}NO_4S_2Cl_2$: C, 51.07; H, 3.64; N, 2.98; S, 13.63. Found: C, 50.95; H, 3.67; N, 3.04; S, 13.64.

***N*-(1,3-Dicyclohexylformamidin-2-yl)saccharin (22).**—Saccharin (1.83 g, 10 mmol) and DCC (2.26 g, 11 mmol) were dissolved in ethyl acetate (5 ml) with gentle warming. After a few minutes crystals began to separate and after 16 hr the mixture was diluted with hexane and filtered. The crystals were washed with hexane and dried, leaving 4.0 g of **22** contaminated with only a trace of dicyclohexylurea. Recrystallization from methanol gave 3.62 g (93%) of pure **22**: mp 200–201°; λ_{max}^{MeOH} 225 mμ (ε 21,700); ν_{max} (KBr) 3310, 1665, 1570 cm^{-1}; nmr ($CDCl_3$) 0.9–2.5 (m, 20, cyclohexyl), 3.8 and 4.5 (m, 1, >CHN), 5.38 (d, 1, $J_{H,NH}$ = 7 NH), 7.5–8.0 ppm (m, 4, Ar); mass spectrum (70 eV) *m/e* 389 (M^+), 308 (M − C_6H_9), 226 (M − $2C_6H_9$), 206 (DCC^+), 183 (M − HDCC).

Anal. Calcd for $C_{20}H_{27}N_3O_3S$: C, 61.68; H, 6.99; N, 10.79. Found: C, 61.48; H, 7.05; N, 10.53.

Registry No.—**2**, 29494-72-2; **4a**, 31657-44-7; **4b**, 31657-42-8; **4c**, 31657-43-9; **4d**, 31657-44-0; **5a**, 640-61-9; **5b**, 1576-37-0; **6**, 31657-47-3; **8a**, 31657-48-4; **8b**, 1109-54-2; **9**, 31657-50-8; **10**, 68-34-8; **12a**, 31657-51-9; **12b**, 31657-52-0; **13**, 4703-15-5; **16**, 31657-54-2; **17**, 31657-55-3; **18a**, 31659-28-6; **18b**, 6380-13-8; **19a**, 31659-30-0; **19b**, 31659-31-1; **19c**, 31659-32-2; **19d**, 31659-33-3; **20**, 31659-34-4; **22**, 31659-33-5; ammonium *p*-toluenesulfonate, 4124-42-9; *N*,*N*-di-*p*-toluenesulfonyl-2,6-dichloroaniline, 31659-37-7; DMSO, 67-68-5.

(22) R. Graeve and G. H. Wahl, *J. Chem. Educ.*, **41**, 279 (1964).

Addition of Sulfonyl Chlorides to Acetylenes. I. Stereoselective Syntheses of β-Chlorovinyl Sulfones[1]

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The copper-catalyzed addition of sulfonyl chlorides to acetylenes makes possible the one-step syntheses of β-chlorovinyl sulfones in high yields. The stereoselective 1:1 addition apparently takes place by a free-radical chain reaction in which the copper catalyst functions as a chlorine atom transfer agent. The stereochemical course of the addition and configurational assignments of the isomeric adducts are discussed. Addition products of aryl-, methane-, and chloromethanesulfonyl chlorides and phenylacetylene, terminal alkynes (1-hexyne and 1-octyne), nonterminal alkyne (3-hexyne), and diphenylacetylene are described.

This paper presents examples of 1:1 additions of sulfonyl chlorides across the triple bond yielding β-chlorovinyl sulfones in high yields; these examples describe the addition of an arylsulfonyl chloride (R = C_6H_5) and alkylsulfonyl chlorides (R = CH_3, $ClCH_2$) to phenylacetylene, 1-hexyne, 1-octyne, and 3-hexyne, as well as the addition of *p*-toluenesulfonyl chloride to diphenylacetylene.[2]

$$RSO_2Cl + R'C{\equiv}CR'' \longrightarrow RSO_2CR'{=}CClR''$$

R = C_6H_5, *p*-$CH_3C_6H_4$, CH_3, ClCH

R′ = H, C_2H_5;

R″ = C_6H_5, C_2H_5, *n*-C_4H_9, *n*-C_6H_{13}

The known synthetic routes leading to β-chlorovinyl sulfones are usually based on at least two steps. Typically, step 1 involves (a) nucleophilic addition of a

(1) Presented before the Second Organic Sulphur Symposium, Groningen, The Netherlands, May 1966; Y. Amiel, *Tetrahedron Lett.*, 661 (1971).

(2) After this paper was submitted for publication, W. E. Truce, C. T. Goralski, L. W. Christensen, and R. H. Bavry, *J. Org. Chem.*, **35**, 4217 (1970), described the addition of benzenesulfonyl chloride to phenylacetylene, giving a monoadduct of an unknown configuration, whereas treatment of benzenesulfonyl chloride with diphenylacetylene resulted only in recovered diphenylacetylene.

thiol[3] or a thiophenol[4] to a chloroacetylene and

$$RSH + R'C{\equiv}CCl \longrightarrow \underset{\mathbf{1a}}{RSCR'{=}CHCl}$$

(b) addition of a sulfenyl chloride to an acetylene.[5]

$$RSCl + HC{\equiv}CR' \longrightarrow \underset{\mathbf{1b}}{RSCH{=}CClR'}$$

In step 2, the β-chlorovinyl sulfide (**1a** or **1b**) is subsequently oxidized to the corresponding sulfone.[6] Many of these thiols or sulfenyl chlorides are produced from the corresponding sulfonyl chlorides *via* reduction.[7] Therefore, the synthesis of β-chlorovinyl sulfones by a direct one-step addition reaction represents a distinct advance over previous syntheses.

Results and Discussion

The addition of sulfonyl chloride to the acetylenic bond takes place, in substantially homogenous solutions, by catalysis of copper(I) or copper(II) salts, under similar conditions as described for the free-radical addition of sulfonyl chlorides to olefins.[8] In the absence of catalyst no adduct formation was observed.[9] The reaction may be conducted with equimolar amounts of the reactants,[10] at reflux temperatures or preferably in a sealed tube, where rates of reaction could be conveniently followed by dilatometry. The reaction in a sealed tube proved to be much cleaner and faster, particularly when degassing removed atmospheric oxygen which resulted in decreased induction periods. The fact that the addition of the RSO_2 moiety occurred at the terminal carbon atom of terminal acetylenes, as in the case of terminal olefins,[8,11] strongly indicated the free-radical nature of the addition to acetylenes.

$$RSO_2Cl \longrightarrow RSO_2\cdot \quad (1)$$

$$RSO_2\cdot + HC{\equiv}CR' \longrightarrow RSO_2CH{=}\dot{C}R' \quad (2)$$

$$RSO_2CH{=}\dot{C}R' + RSO_2Cl \longrightarrow RSO_2CH{=}CClR' + RSO_2\cdot \quad (3)$$

Analogously when benzenesulfonyl chlorides and phenylacetylene were made to react in the presence of benzoyl peroxide, only telomeric sulfones were obtained, even in the presence of a large excess of sulfonyl chloride. However, the use of copper catalyst prevented telomerization and only 1:1 adducts were obtained.

In the copper chloride catalyzed addition of sulfonyl chlorides to vinylic monomers and other olefins, Asscher and Vofsi[8] suggested a redox-transfer mechanism; they proposed that the catalyst participated in every single cycle of the chain propagation as a chlorine atom transfer agent. In its oxidized form the copper catalyst is a much more reactive chlorine donor than the covalently bound chlorine of sulfonyl chloride. According to that mechanism the relatively slow transfer step, which is observed in a conventional process, is completely superseded in the presence of this catalyst by very fast reduction–oxidation steps. Likewise, it is suggested that a redox-transfer mechanism operates under similar conditions for the addition of sulfonyl radicals to acetylenes. Hence, step 3 is to be replaced by the two following successive steps, 4 and 5. Cupric

$$RSO_2CH{=}\dot{C}R' + CuCl_2 \longrightarrow RSO_2CH{=}CClR' + CuCl \quad (4)$$

$$CuCl + RSO_2Cl \rightleftharpoons CuCl_2 + RSO_2\cdot \quad (5)$$

chloride is known to be an efficient radical scavenger.[12] Step 4 represents an example of a well-studied ligand-transfer reaction[13] taking place on a vinyl radical. Few copper and iron salts catalyzed addition reactions to acetylenes are described to proceed in the ligand shell of the metal ion.[14] In step 5 other copper salts were found to generate sulfonyl radicals.[15] In cases where cupric ion catalysts were applied, a minute quantity of Cu(II) is reduced to Cu(I) while phenylacetylene is chlorinated.

It is interesting to note that, in these redox catalysis reactions conducted in the presence of ammonium, cuprous, and cupric chlorides, no oxidative coupling products of terminal acetylenes were formed. Moreover, an attempted oxidative coupling of phenylacetylene itself under these conditions did not take place. It seems that the described conditions favor a ligand-transfer process whereas a one-electron transfer is unfavorable for an oxidative coupling reaction.[16]

The stereochemical course of this addition reaction was investigated and was based mainly on the configurational proof of the carefully isolated adducts. Preliminary experiments of the copper-catalyzed reaction of benzenesulfonyl chloride with phenylacetylene in acetonitrile, in the presence of triethylammonium chloride,[17] gave high yields of a crystalline 1:1 addition product. Chromatographic separations revealed the presence of another compound; that this was an isomer of the main product was shown by elemental analysis, and catalytic reduction which gave the same known 2-phenylethyl phenyl sulfone.[18] The yield of adduct, mp 80°, was 72% and of the isomer, mp 84°, was 12%. Comparison of molecular models of these stereoisomers shows quite distinct differences. The cis addition product can accommodate a coplanar configuration, as shown in structure **3**, while the trans addition product (**2**) cannot attain coplanarity due to steric hindrance. In this configuration the *C*-phenyl group is apparently forced out of coplanarity and free rotation of this benzene ring is inhibited by the bulky sulfone group as

(3) L. I. Zakharkin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 437 (1959).

(4) W. E. Truce, M. M. Boudakian, R. F. Heine, and R. J. McManimie, *J. Amer. Chem. Soc.*, **78**, 2743 (1956); L. Maioli and G. Modena, *Bull. Sci. Fac. Chim. Ind. Bologna*, **16**, 86 (1958).

(5) F. Montanari, *Gazz. Chim. Ital.*, **86**, 406, 735 (1956); N. Kharasch and C. N. Yiannios, *J. Org. Chem.*, **29**, 1190 (1964), and preceding papers; N. Kharasch, Z. S. Ariyan, and A. J. Havlik, *Quart. Rep. Sulfur Chem.*, **1**, 93 (1966); V. Caló, G. Scorrano, and G. Modena, *J. Org. Chem.*, **34**, 2020 (1969), and preceding papers.

(6) A. Schöberl and A. Wagner, "Methoden der Organischen Chemie," Vol. IX, 4th ed, Houben-Weyl, Ed., Georg Thieme, Stuttgart, 1955, p 227.

(7) R. Adams and C. S. Marvel, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 504.

(8) A. Oroehov, M. Asscher, and D. Vofsi, *J. Chem. Soc. B*, 255 (1969); M. Asscher and D. Vofsi, *ibid.*, 947 (1968), and preceding papers.

(9) The only reported example of addition of a sulfonyl halide to an acetylene involved *p*-toluenesulfonyl iodide and phenylacetylene; see W. E. Truce and G. C. Wolf, *Chem. Commun.*, 150 (1969).

(10) Usually a slight excess of phenylacetylene was used; a minute amount, as discussed later, was chlorinated.

(11) M. S. Kharasch and R. A. Mosher, *J. Org. Chem.*, **17**, 453 (1952); F. W. Stacey and J. F. Harris, Jr., *Org. React.*, **13**, 200 (1963).

(12) J. K. Kochi and D. M. Mog, *J. Amer. Chem. Soc.*, **87**, 522 (1965).

(13) D. C. Nonhebel and W. A. Waters, *Proc. Roy. Soc., Ser. A*, **242**, 16 (1957); J. K. Kochi, *Science*, **155**, 415 (1967).

(14) A. V. Dombrovski, *Zh. Obshch. Khim.*, **27**, 3050 (1957); F. Minisci and R. Galli, *Tetrahedron Lett.*, 1679 (1965).

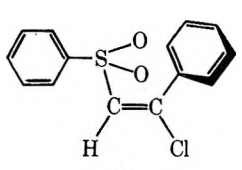
(15) To be published in a forthcoming paper.

(16) W. Eglinton and W. McCrea, *Advan. Org. Chem.*, **4**, 225 (1963).

(17) A quaternary ammonium chloride was used in these reactions for various reasons,[8] such as an aid to solubilize the copper salts through complex formation. This phenomenon is investigated further in a forthcoming publication.

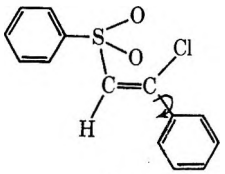
(18) T. Posner, *Ber.*, **38**, 651 (1905).

shown in structure 2 and interference in resonance stabilization would be anticipated. The ultraviolet spectrum of the described main product, melting at 80°, had an absorption in the styryl band region at 262 mμ (ε 10,000) while the absorption of the minor isomeric adduct was observed at 275 mμ (ε 20,000). It is obvious by these data that the adduct **3** has a higher degree of conjugation resulting from planarity in the styryl moiety. The configurational assignment of **2** and **3** to the main and minor addition products, respectively was based upon the ultraviolet spectra.



2

trans addition
(main) product



3

cis addition
(minor) product

Further evidence supporting the above-stated configurational assignments was based on dehydrochlorination reactions of **2** and **3**. Adduct **2** was recovered unchanged and in almost quantitative yield despite prolonged heating with a tertiary amine. However, **3** was so readily dehydrochlorinated that the known phenylethynyl phenyl sulfone[19] was obtained by merely eluting the dissolved adduct on a basic chromatographic column. It is known that β-elimination reactions of halo olefins to form acetylenes proceed best when the elements to be eliminated are located trans to each other.[20]

The reactions described in this paper represent a stereoselective addition reaction affording, in high yields, probably the kinetic-preferred, trans addition product as a result of a trans addition process. Trans additions to acetylenes are more frequently observed,[21,22] although cis additions have been occasionally mentioned, particularly in a few ionic,[23] photochemical,[24] and heterogeneous phase[25] addition reactions. The "trans addition rule" proposed by Truce and Simms[21] for the nucleophilic addition of thiols to phenylacetylene has been well accepted; the same stereochemical course of addition was described to take place by a free-radical chain mechanism to give the less stable cis vinylic sulfides, which were readily isomerized by an excess of thiyl radicals.[26] The ionic and radical addition of sulfenyl chloride to acetylenes also occurs, in general, in a trans fashion.[5,27]

(19) W. E. Truce, H. E. Hill, and M. M. Boudakian, *J. Amer. Chem. Soc.*, **78**, 2760 (1956).

(20) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 348.

(21) W. E. Truce and J. A. Simms, *J. Amer. Chem. Soc.*, **78**, 2756 (1956).

(22) S. I. Miller, *ibid.*, **78**, 6091 (1956).

(23) E. Winterfeldt in "Chemistry of Acetylenes," H. G. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, pp 275, 280, 294, 302, 313, 321.

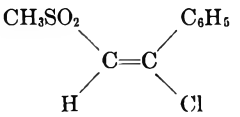
(24) L. D. Bergel'son, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1235 (1960).

(25) R. A. Benkeser and R. A. Hickner, *J. Amer. Chem. Soc.*, **80**, 5298 (1958).

(26) N. Kharasch, S. J. Potempa, and H. L. Wehrmeister, *Chem. Rev.*, **39**, 269 (1946); A. A. Oswald, K. Griesbaum, B. E. Hudson, Jr., and J. M. Bregman, *J. Amer. Chem. Soc.*, **86**, 2877 (1964); A. A. Oswald and K. Griesbaum in "The Chemistry of Organic Sulfur Compounds," Vol. 2, N. Kharasch and C. Y. Meyers, Ed., Pergamon Press, Elmsford, N. Y., 1966, p 233; K. Griesbaum, *Angew. Chem., Int. Ed. Engl.*, **9**, 273 (1970).

(27) V. Caló, G. Modena, and G. Scorrano, *J. Chem. Soc. C*, 1339, 1344 (1968).

The addition of methanesulfonyl chloride to phenylacetylene, under described conditions, gave the trans addition product **4** in 65% yield. This alkylsulfonyl chloride was less reactive than benzenesulfonyl chloride and longer induction periods and reaction times were required. The isomeric adduct, **5**, was obtained in 10% yield by subjecting the reaction mixture to column chromatography.



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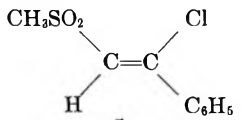


5

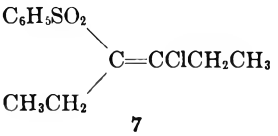
Configurational assignments were based on the same criteria as for the previously described adducts. Additions of sulfonyl chlorides were also carried out with terminal and nonterminal alkynes, leading to the previously unknown β-chlorovinyl alkyl sulfones. Under the described conditions, addition products of benzenesulfonyl chloride with 1-hexyne and 1-octyne were synthesized.

$$C_6H_5SO_2Cl + HC{\equiv}CR \longrightarrow \underset{\mathbf{6}}{C_6H_5SO_2CH{=}CClR}$$

R = *n*-butyl, *n*-hexyl

Benzenesulfonyl chloride was added to a nonterminal alkyne, *e.g.*, 3-hexyne, under the same conditions.

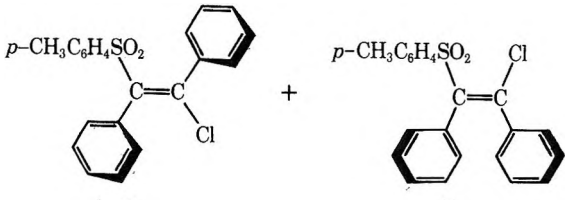
$$C_6H_5SO_2Cl + CH_3CH_2C{\equiv}CCH_2CH_3 \longrightarrow$$



7

Benzenesulfonyl chloride was also added to diphenylacetylene. After heating equimolar amounts of *p*-toluenesulfonyl chloride and diphenylacetylene, in the presence of cupric chloride and triethylammonium chloride in acetonitrile at 139° for 24 hr, 80% conversion (calculated on *p*-toluenesulfonyl chloride consumed) was obtained, whereas 15% of unreacted starting materials was recovered. The two isomeric adducts were separated by column chromatography giving a distribution of 53% of **8** and 47% of **9**. Compound **8** was pre-

$$p\text{-}CH_3C_6H_4SO_2Cl + C_6H_5C{\equiv}CC_6H_5 \longrightarrow$$



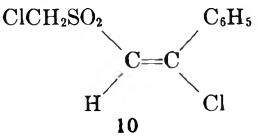
8 **9**

viously obtained by oxidation of the corresponding sulfide for which a trans configuration was postulated.[28] Structural assignments of **8** and **9** were based on spectral comparisons. Nmr spectra of the two isomeric adducts revealed that the methyl group in **9** was slightly deshielded as compared to **8**. A similar effect was observed in the nmr spectra of the two isomeric addition products of *p*-toluenesulfonyl chloride and phenyl-

(28) L. Di Nunno, G. Melloni, G. Modena, and G. Scorrano, *Tetrahedron Lett.*, 4405 (1965).

acetylene.[15] This resemblance supports the configurational assignment for both isomers. Neither **8** nor **9** can accommodate a coplanar configuration. The slight bathochromic shift shown by **9** suggested a somewhat better conjugation; molecular models tend to substantiate this.

To get some comparison of reactivity of sulfonyl radicals toward acetylenes and olefins, the additon of chloromethanesulfonyl chloride to phenylacetylene and 1-octyne was investigated. It has been reported previously[29] that this sulfonyl chloride decomposes with elimination of sulfur dioxide, and subsequent addition of chloromethyl radical to the olefin. Chloromethanesulfonyl chloride gave with phenylacetylene a 20% yield of the expected adduct (**10**), whereas, in the case of styrene, the corresponding addition product was obtained in 60% yield.[30]



10

Kharasch, *et al.*,[31] described phenylacetylene as being less reactive than styrene. On the other hand, it seems that sulfonyl radicals attack alkynes more readily than corresponding olefins. While the attempted copper-catalyzed addition of chloromethanesulfonyl chloride to 1-octene gave no adduct,[30] 1-octyne did lead to the expected adduct (**11**) in 6% yield.

$$ClCH_2SO_2Cl + HC{\equiv}C(CH_2)_5CH_3 \longrightarrow ClCH_2SO_2CH{=}CCl(CH_2)_5CH_3$$

11

Addition of benzenesulfonyl chloride to 1-hexyne and 1-hexene, under the same conditions, again indicated that the alkyne is a much more reactive substrate than the corresponding olefin. Thus, adduct formation (based on isolated product, yields calculated on total benzenesulfonyl chloride) after 2, 4, 8, 12, and 24 hr for 1-hexyne and 1-hexene were 30 *vs.* 6%, 44 *vs.* 14%, 60 *vs.* 28%, 67 *vs.* 36%, and 71 *vs.* 55%, respectively.

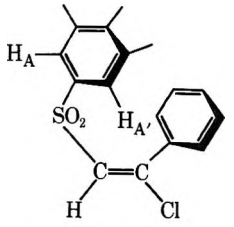
The simultaneous catalytic hydrogenation and hydrogenolysis of the alkynic adduct, as well as the catalytic hydrogenolysis of the alkenic adduct, gave the identical saturated sulfone. Similarly, **4**, **5**, and **10** gave the known 2-phenylethyl methyl sulfone.[21]

The alkynic addition products (**6**, **7**, and **11**), which were liquids, were purified by fractional distillation under reduced pressure; spectral data indicated a trans addition configuration, although presence of some cis addition products in the distillates could not be excluded.

In addition to very significant differences between the trans and cis addition products in the ultraviolet, the infrared spectra proved to be very useful in the identification of the isomeric adducts, particularly in the chromatographic separations. It was possible to characterize the structural isomers on the basis of sharp and strong -CH= out-of-plane bending vibrations at 11.05 and 10.76 μ of the trans addition products and at 10.72 and 10.92 μ of the cis addition products. Additional distinctions were also found in the C=C stretching frequencies region: at 6.19 μ for trans addition products and at 6.36 μ for corresponding isomers, apparently due to higher conjugation of the latter.

An nmr comparison of the stereoisomers showed that the vinylic proton of the cis addition products was more deshielded (**3**, δ 7.16; **5**, δ 7.15) than in the trans addition products (**2**, δ 6.98; **4**, 6.92; **10**, δ 6.87). This effect is evidently due to the location of the vinylic proton in **3** and **5** in the deshielding zone of the neighboring cis phenyl ring.[32]

Two phenyl protons of **2** and **3** were found to be more deshielded than the remaining eight aromatic protons present in the two phenyl rings. These protons, ortho to the carbon atom attached to the electronegative sulfone group, appeared in each case as a doublet, being more deshielded in **3** (δ 8.08, J = 8 Hz) than in **2** (δ 7.54, J = 5 Hz); this indicated a shielding effect in the latter due to the proximity in space of the two phenyl rings, in a displaced face-to-face conformation[33] (see **12**). A similar shielding effect of the phenyl ring on the methyl protons was noted in **4** (δ 2.73), as compared to **5** (δ 3.20). Such an effect was observed (*vide supra*) in **8** and **9**, to a much lesser extent, for the protons of the para-substituted methyl groups.



12

Experimental Section[34]

Materials.—Phenylacetylene and methanesulfonyl and benzenesulfonyl chlorides obtained from Fluka (puriss) were distilled before use; chloromethanesulfonyl chloride was prepared from trithiane by chlorinolysis in water;[35] 1-hexyne, bp 71–72°, was synthesized from *n*-butyl bromide and sodium acetylide in liquid ammonia;[36] 1-octyne, bp 76–77° (150 mm), was synthesized in a similar way; 3-hexyne was obtained from Colombia Organic Chemicals Co.; diphenylacetylene was prepared according to the literature;[37] anhydrous cuprous chloride (pract) was obtained from Fluka; anhydrous cupric chloride was obtained from the dihydrate (B. D. H., reagent grade) by dehydration at 110° to constant weight; triethylammonium chloride (B. D. H., reagent grade) was crystallized from isopropyl alcohol and dried at 100°; acetonitrile from Fluka (puriss) was dried over P_2O_5; benzoyl peroxide was obtained from Fisher, Florisil, 100–200 mesh, was obtained from Floridin Co.; and silica gel (Kieselgel H) was obtained from Merck.

(29) M. Gibson, H. Goldwhite, and C. Harris, *Chem. Ind.* (*London*), 1721 (1962); *Tetrahedron*, **20**, 1613 (1964).

(30) M. Asscher and D. Vofsi, *J. Chem. Soc.*, 4962 (1964).

(31) M. S. Kharasch, J. J. Jerome, and W. H. Urry, *J. Org. Chem.*, **15**, 966 (1950).

(32) D. R. Davis and J. D. Roberts, *J. Amer. Chem. Soc.*, **84**, 2252 (1962); NMR Spectra Catalog, Varian Associates, Palo Alto, Calif., 1962, No. 232; Gurudata, J. B. Stothers, and J. D. Talman, *Can. J. Chem.*, **45**, 731 (1967).

(33) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1960, pp 66–68.

(34) All melting points and boiling points are uncorrected. Ir spectra were determined in $CHCl_3$ on a Perkin-Elmer Infracord Model 237B spectrophotometer; uv spectra were obtained in aqueous C_2H_5OH on a Cary Model 14M spectrophotometer; nmr spectra were measured in $CDCl_3$ on a Varian A-60 instrument with TMS as internal standard and chemical shifts are reported in δ (ppm) units. Microanalyses were performed in our microanalytical section directed by Mr. R. Heller.

(35) I. B. Douglass, V. G. Simpson, and A. K. Sawyer, *J. Org. Chem.*, **14**, 273 (1949).

(36) K. N. Campbell and B. K. Campbell, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 117.

(37) L. I. Smith and M. M. Falkof, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 350.

(*E,Z*)-**2-Benzenesulfonyl-1-chlorostyrene (2 and 3).**—A mixture of 8.8 g (50 mmol) of benzenesulfonyl chloride, 5.36 g (52.5 mmol) of phenylacetylene, 134 mg (1 mmol) of anhydrous cupric chloride, and 413 mg (3 mmol) of triethylammonium chloride in 3 g of acetonitrile was introduced into a Carius tube, cooled in liquid air, degassed (three times) at 0.1 mm, sealed, and heated for 3 hr at 100°. After a 10-min induction period the reaction began as indicated by the onset of contraction. Nearly 90% of reaction took place after 1.5 hr. After contraction stopped the tube was cooled in liquid air and then opened. The semisolid reaction mixture was dissolved in methylene chloride, transferred to a separatory funnel, and washed with water and an aqueous solution of disodium ethylenediaminetetraacetate until free from copper, and the organic layer was dried (Na_2SO_4). Evaporation of solvent gave 12.3 g of crude material which was subsequently crystallized from methanol to give 9.7 g (77% yield) of **2**: mp 80°; uv λ_{max} 212 mμ (ε 16,000) and 262 (10,000); ir 6.19, 6.27, 6.72, 6.92, 7.58, 7.65, 7.76, 8.62, 8.72, 9.25, 9.77, 10.02, 10.76, 11.05, and 12.3 μ; nmr δ 6.98 (s, 1 H, vinylic), 7.35–7.47 (m, 8 H, aromatic), 7.54 (d, 2 H, aromatic, J = 5 Hz).

Anal. Calcd for $C_{14}H_{11}ClO_2S$: C, 60.32; H, 3.97; S, 11.51; Cl, 12.72. Found: C, 60.49; H, 3.86; S, 11.53; Cl, 12.7.

A crude reaction mixture was chromatographed over 120 g of Florisil; elution with ether–*n*-hexane (1:3) gave 12 mg of the known diphenyl disulfide,[38] mp 61°.

Anal. Calcd. for $C_{12}H_{10}S_2$: C, 65.89; H, 4.72; S, 28.73. Found: C, 65.92; H, 4.70; S, 28.81.

The subsequent elution afforded 10 g (72%) of the above-described adduct, **2**. A further elution with ether–*n*-hexane (1:1) gave 1.67 g (12%) of **3**: mp 84° (methanol); uv λ_{max} 212 mμ (ε 15,500), 219 (15,500), and 275 (20,000); ir 6.28, 6.36, 6.72, 6.92, 7.22, 7.58, 7.65, 7.7, 8.1, 8.23, 8.5, 8.72, 9.22, 9.77, 10.01, 10.72, 10.92, and 12.2 μ; nmr δ 7.16 (s, 1 H, vinylic), 7.25–7.35 (m, 8 H, aromatic), and 8.08 (d, 2 H, aromatic, J = 8 Hz).

Anal. Calcd for $C_{14}H_{11}ClO_2S$: C, 60.32; H, 3.97; S, 11.51; Cl, 12.72. Found: C, 60.53; H, 3.86; S, 11.79; Cl, 12.88.

Before Florisil was applied, Al_2O_3 (Woelm activity II) was tried. On this adsorbent phenylethynyl phenyl sulfone,[19] mp 74.5° (methanol), was formed in small amounts and was eluted with ether–*n*-hexane (1:5): ir 4.62 (–C≡C–), 7.63 and 8.58 μ ($-SO_2-$).

Anal. Calcd for $C_{14}H_{10}O_2S$: C, 69.17; H, 4.03; S, 13.48. Found: C, 69.42; H, 4.16; S, 13.21.

An addition reaction was performed with the same reagent mixture under reflux conditions in a nitrogen atmosphere; the temperature of the reaction mixture was 96°. After 6 hr the reaction was worked up as described before. Benzenesulfonyl chloride (4.85 g) and phenylacetylene (3.2 g) were recovered and the crude material (4.8 g, 35% conversion) was chromatographed over Florisil, affording 4.0 g (60%) of **2** and 0.6 g (10%) of **3** (yields are based on reacted benzenesulfonyl chloride).

Catalytic Reduction of 2, 3, and Phenylethynyl Phenyl Sulfone.—Adducts **2**, **3**, and phenylethynyl phenyl sulfone were reduced with H_2 over 5% Pd/C in methanol at 25° and atmospheric pressure; in each of three reductions 2-phenylethyl phenyl sulfone,[18] mp 58–59° (ethanol), was obtained quantitatively. An attempted preferential hydrogenolysis did not work; hydrogenation of the double bond took place simultaneously.

Sodium Borohydride Reduction of 2 and 3.—Adducts **2** and **3** were reduced in diglyme at 25°; the same saturated 2-phenylethyl phenyl sulfone was obtained.

Addition Reaction of Benzenesulfonyl Chloride to Phenylacetylene in the Presence of Benzoyl Peroxide.—A mixture of 17.6 g (100 mmol) of benzenesulfonyl chloride, 2.04 g (20 mmol) of phenylacetylene, and 0.48 g (2 mmol) of benzoyl peroxide in 5 ml of methylene chloride was introduced into a Carius tube, cooled in liquid air, evacuated to 0.1 mm, degassed (three times), sealed, and heated for 2 hr at 100°. After a 25-min induction period the reaction began as indicated by volume contraction and color darkening. After 2 hr the tube was cooled in liquid air and then opened. Volatile fractions were distilled off under reduced pressure. Most of the reactants were recovered unchanged, leaving a viscous telomeric residue (0.98 g). Chromatographic separation over Florisil did not lead to any solid product. The ir of the various fractions showed typical sulfone absorptions (7.6 and 8.7 μ).

Attempted Oxidative Coupling of Phenylacetylene.—To determine if phenylacetylene would undergo an oxidative coupling reaction under the above-described redox conditions, a mixture of 1.02 g (10 mmol) of phenylacetylene, 0.3 g (3 mmol) of anhydrous cuprous chloride, 0.7 g (5 mmol) of anhydrous cupric chloride, and 1.38 g (10 mmol) of triethylammonium chloride in 3 g of acetonitrile was heated in a sealed tube, after prior degassing (three times), for 17 hr at 100°. After usual work-up, removal of unreacted phenylacetylene and volatile chlorinated products (having a density greater than water and giving a positive Beilstein test) under reduced pressure, a semisolid residue weighing 58 mg was obtained. From this, only 15 mg of diphenyl-α-diacetylene, mp 87.5°, was isolated; this was probably formed during the work-up process, which was done in the presence of air. A mixture melting point of 87.5° was obtained with an authentic sample prepared by oxidative coupling in the presence of air.

Attempted Dehydrochlorination of 2.—A solution of 1.39 g (5 mmol) of **2** and 1.11 g (6 mmol) of triethylamine in 3 ml of benzene was heated in a sealed tube for 20 hr at 100°. Only traces of triethylammonium chloride precipitating out in the solution were found. As a result of a chromatographic separation, 1.2 g (92%) of the starting material (**2**) was recovered.

(*E,Z*)-**2-Methanesulfonyl-1-chlorostyrene (4 and 5).**—The addition reaction and the work-up procedure were carried out as described for benzenesulfonyl chloride using 7.4 g (50 mmol) of methanesulfonyl chloride. After a 45-min induction period, 10 hr of reaction time was required. The crude material (7.9 g) was obtained by distillation, bp 128–133° (0.2 mm), as an oily material ($n^{22}D$ 1.588) which slowly solidified at room temperature and subsequently chromatographed over Florisil. Elution with ether–*n*-hexane (1:3) gave 6.5 g (65% yield) of **4**: mp 59–60° (methanol); uv λ_{max} 213 mμ (ε 8000) and 253 (8000); ir 6.18, 6.27, 6.72, 6.92, 7.1, 7.58, 7.65, 8.75, 10.35, 10.74, 11.02, and 12.2 μ; nmr δ 2.73 (s, 3 H, CH_3), 6.92 (s, 1 H, vinylic), and 7.45–7.65 (m, 5 H, aromatic).

Anal. Calcd for $C_9H_9ClO_2S$: C, 49.88; H, 4.17; S, 14.8; Cl, 16.36. Found: C, 49.94; H, 4.19; S, 14.72; Cl, 16.43.

Further elution with ether–*n*-hexane (1:1) of the same chromatogram afforded 2.15 g (10% yield) of **5**: mp 53.5–54° (methanol); uv λ_{max} 212 mμ (ε 8000) and 264 (16,000); ir 6.26, 6.36, 6.72, 6.92, 7.1, 7.58, 7.7, 8.75, 10.27, 10.72, 10.92, and 12.2 μ; nmr δ 3.20 (s, 3 H, CH_3), 7.15 (s, 1 H, vinylic), and 7.45–7.75 (m, 5 H, aromatic).

Anal. Calcd. for $C_9H_9ClO_2S$: C, 49.88; H, 4.17; S, 14.8; Cl, 16.36. Found: C, 49.85; H, 4.13; S, 14.91; Cl, 16.52.

1-Benzenesulfonyl-2-chloro-1-hexene (6, R = *n*-Butyl).—A mixture of 8.8 g (50 mmol) of benzenesulfonyl chloride, 4.52 g (55 mmol) of 1-hexyne, 134 mg (1 mmol) of cupric chloride, 413 mg (3 mmol) of triethylammonium chloride, and 3 g of acetonitrile was introduced into a Carius tube, cooled in liquid air, degassed three times at 0.1 mm, sealed, and heated at 100°. The reaction began after a 20-min induction period, as indicated by the onset of contraction, measured by dilatometry. After 16 hr, when contraction stopped, the tube was cooled in liquid air and then opened. The reaction mixture was transferred to a separatory funnel and washed with water and an aqueous solution of disodium ethylenediaminetetraacetate until free from copper, and the organic layer was dried (Na_2SO_4). Evaporation of solvent gave, after fractional distillation, 9.7 g (75%) of a colorless oil: bp 123–124° (0.17 mm); $n^{22}D$ 1.5452; mp 13–14° (methanol); ir (neat) 6.18, 6.25, 6.72, 6.82, 6.92, 7.22, 7.53, 7.63, 7.66, 7.82, 8.12–8.28, 8.47, 8.66, 8.88, 9.21, 9.77, 9.82, 10.0, 10.1, 10.25, 11.03, 11.5, 12.2, 13.3, 13.95, and 14.63 μ; nmr δ 0.95 (t, 3 H, CH_2CH_3), 1.48 (m, 4 H, $CH_2CH_2CH_2CH_2$), 2.97 (m, 2 H, $CClCH_2$), 6.55 (s, 1 H, vinylic), 7.5–8.07 (m, 5 H, aromatic).

Anal. Calcd for $C_{12}H_{15}ClO_2S$: C, 55.70; H, 12.39; Cl, 13.70; S, 12.39. Found: C, 56.00; H, 12.50; Cl, 13.78; S, 12.50.

By varying reaction time, under some conditions, the following yields of isolated addition product (calculated on total benzenesulfonyl chloride) were obtained: 30% (2 hr), 44% (4 hr), 60% (8 hr), 67% (12 hr), and 71% (24 hr).

Addition of Benzenesulfonyl Chloride to 1-Hexene.—The reaction was carried out in the same way as described above, using 1-hexene (4.52 g) instead of 1-hexyne. The reaction was followed by dilatometry. After 24 hr, contraction stopped, and

(38) This compound was also found in other reactions in which benzenesulfonyl radicals were involved; see J. L. Kice and N. E. Pawlowsky, *J. Amer. Chem. Soc.*, **86**, 4898 (1964); J. L. Kice and N. A. Favstritsky, *J. Org. Chem.*, **35**, 114 (1970); P. Koch, E. Ciuffarin, and A. Fava, *J. Amer. Chem. Soc.*, **92**, 5971 (1970).

the reaction mixture was worked up by the usual procedure to give 7.15 g (55%) of phenyl (2-chloro-*n*-hexyl) sulfone as a colorless oil by fractional distillation, bp 135–138° (0.2 mm), $n^{26}D$ 1.5265. This oil solidified at room temperature and was recrystallized from methanol: mp 33–34°; ir (neat) 6.29, 6.85, 6.92, 7.25, 7.53, 7.65, 7.82, 8.12, 8.68, 8.88, 9.22, 9.35, 9.78, 10.02, 10.27, 10.65, 11.2, 11.45, 11.8, 12.88, 13.5, and 14.63 μ.

Anal. Calcd for $C_{12}H_{17}ClO_2S$: C, 55.27; H, 6.57; Cl, 13.60; S, 12.30. Found: C, 55.38; H, 6.62; Cl, 13.30; S, 12.25.

By varying reaction time, under the same conditions, the following yields of isolated addition product (calculated on total benzenesulfonyl chloride) were obtained: 6% (2 hr), 14% (4 hr), 28% (8 hr), and 36% (12 hr).

1-Benzenesulfonyl-2-chloro-1-octene (6, R = *n*-Hexyl).—The reaction was carried out and worked up exactly as described in the above experiments, using 6.06 g (55 mmole) of 1-octyne instead of 1-hexyne, and 9.3 g (65%) of the adduct, in the form of a colorless oil, was obtained by fractional distillation: bp 144–148° (0.15 mm); $n^{22}D$ 1.5350; ir (neat) 6.18, 6.24, 6.72, 6.82, 6.92, 7.22, 7.52, 7.63, 8.06–8.26, 8.47, 8.66, 8.85, 9.21, 9.62, 10.0, 10.68, 11.15, 12.2, 13.3, 13.95, and 14.63 μ; nmr δ 0.87 (t, 3 H, CH_3), 1.35 [m, 8 H, $(CH_2)_4$], 2.95 (m, 2 H, $ClCH_2$), 6.57 (s, 1 H, vinylic), and 7.53–8.05 (m, 5 H, aromatic).

Anal. Calcd for $C_{14}H_{19}ClO_2S$: C, 58.62; H, 6.68; Cl, 12.36; S, 11.13. Found: C, 58.92; H, 6.73; Cl, 12.35; S, 11.56.

3-Benzenesulfonyl-4-chloro-3-hexene (7).—The reaction was carried out in the same way as described in the above experiments, using 3-hexyne instead of 1-hexyne, to give 7.75 g (60%) of the adduct, in the form of a colorless oil, as obtained by fractional distillation: bp 122–128° (0.2 mm); $n^{25}D$ 1.5628; ir (neat) 6.18, 6.78, 6.88, 6.92, 7.28, 7.55, 7.67, 8.65, 8.78, 9.25, 9.95, 10.6, 10.9, 12.15, 13.2, 13.6, and 14.6 μ; nmr δ 1.09 [t, 3 H, $C(Cl)CH_2$-$\mathbf{CH_3}$, J = 5 Hz],[33] 1.12 [t, 3 H, $C(SO_2C_6H_6)CH_2\mathbf{CH_3}$, J = 5 Hz], 2.56 [q, 2 H, $C(Cl)\mathbf{CH_2}CH_3$, J = 7 Hz],[33] 3.04 [q, 2 H, $C(SO_2C_6H_5)\mathbf{CH_2}CH_3$, J = 7 Hz], and 7.5–8.0 (m, 5 H, aromatic).

Anal. Calcd for $C_{12}H_{15}ClO_2S$: C, 55.70; H, 5.84; Cl, 13.70; S, 12.39. Found: C, 55.31; H, 5.61; Cl, 13.36; S, 12.62.

Adducts of *p*-Toluenesulfonyl Chloride and Diphenylacetylene (8 and 9).—A mixture of 4.775 g (25 mmol) of *p*-toluenesulfonyl chloride, 4.456 g (25 mmol) of diphenylacetylene, 201 mg (1.5 mmol) of anhydrous cupric chloride, and 344 mg (2.5 mmol) of triethylammonium chloride in 4 g of acetonitrile was introduced into a Carius tube, cooled in liquid air, degassed (three times) at 0.1 mm, sealed, and heated for 20 hr at 139°. After the usual work-up, the residue (7.85 g) was subjected to column chromatography using silica gel (Kieselgel H, Merck), to which 5% of silver nitrate was impregnated and finally 2% of water was added. Elution with *n*-pentane afforded 0.625 mg (15%) of unreacted *p*-toluenesulfonyl chloride and 0.534 mg (12%) of unreacted diphenylacetylene; the solvent eluted *ca.* 40 mg of *trans*-dichlorostilbene, mp 143°, which had correct analysis and was compared with an authentic sample synthesized according to the literature.[39] Further elution gave the trans addition product (8), which was recrystallized from methanol, giving 3.33 g (53% of the adduct mixture): mp 142–143° (lit.[28] mp 140°); ir (KBr) 6.14, 6.26, 6.67, 6.93, 7.53, 7.63, 7.70, 7.73, 7.76, 7.82, 8.06, 8.37, 8.41, 8.43, 8.65, 8.92, 9.18, 9.28, 9.65, 9.78, 10.35, 10.90, 11.65, 12.26, 13.25, 13.5, 14.37, 14.5, 14.54, 14.8, and 15.53 μ; nmr δ 2.34 (s, 3 H, CH_3) and 7.1–7.95 (m, 14 H, aromatic).

Anal. Calcd for $C_{21}H_{17}ClO_2S$: C, 68.37; H, 4.65; Cl, 9.61; S, 8.69. Found: C, 68.62; H, 4.48; Cl, 9.48; S, 8.67.

(39) C. Davidson, *J. Amer. Chem. Soc.*, **40**, 397 (1918).

It was rather difficult to separate the mixture of the two adducts, and fractions containing mixtures were rechromatographed. Continued elutions afforded 2.95 g (47% of the adduct mixture) of the stereoisomeric adduct (9), obtained after crystallization from *n*-hexane in the form of plates: mp 153.5–154.5°; ir (KBr) 6.24, 6.27, 6.31, 6.35, 6.68, 6.92, 7.12, 7.22, 7.53, 7.63, 7.73, 7.95, 8.12, 8.38, 8.41, 8.58, 8.65, 9.18, 9.67, 9.77, 9.96, 10.25, 10.8, 11.75, 12.4, 13.1, 13.5, 14.4, and 14.7 μ; nmr δ 2.43 (s, 3 H, CH_3), 7.1–7.24 (m, 10 H, aromatic), 7.30 [d, 2 H, aromatic (meta to CSO_2),[15] J = 8.5 Hz], and 7.80 [d, 2 H, aromatic (ortho to CSO_2), J = 8.5 Hz].

Anal. Calcd. for $C_{21}H_{17}ClO_2S$: C, 68.37; H, 4.65; Cl, 9.61; S, 8.69. Found: C, 68.54; H, 4.66; Cl, 9.68; S, 8.64.

(*E*)-2-Chloromethanesulfonyl-1-chlorostyrene (10).—This addition reaction and work-up procedure was carried out as described for benzenesulfonyl chloride using 7.4 g (50 mmol) of chloromethanesulfonyl chloride. After 2.5 hr heating at 100° the tube was cooled in liquid air and then opened. Volatile material, including a relatively high volume of sulfur dioxide, was removed; no unreacted sulfonyl chloride remained. Distillation gave 0.45 g of a chlorinated olefinic liquid, probably 2-chloromethane-1-chlorostyrene, bp 95° (0.5 mm), and 2.5 g (20% yield) of 6, bp 138° (0.15 mm), which solidified and was crystallized from methanol: mp 51–52°; ir 6.18, 6.27, 6.72, 6.92, 7.22, 7.58, 7.72, 8.73, 10.73, 11.02, and 12.2 μ; nmr δ 4.21 (s, 2 H, CH_2), 6.87 (s, 1 H, vinylic), and 7.42–7.62 (m, 5 H, aromatic).

Anal. Calcd for $C_9H_8Cl_2O_2S$: C, 43.04; H, 3.21. Found: C, 42.86; H, 3.35.

Catalytic Reduction of 4, 5, and 10.—Adducts 4, 5, and 10 were reduced with H_2 over 5% Pd/C in methanol at 25° and atmospheric pressure; in each of the three reductions the known 2-phenylethyl methyl sulfone[21] was obtained quantitatively.

1-Chloromethanesulfonyl-2-chloro-1-octene (11).—The reaction was carried out in the same way as described in the first experiment, using 7.4 g (50 mmol) of chloromethanesulfonyl chloride and 6.06 g (55 mmole) of 1-octyne. After 2.5 hr the tube was cooled in liquid air and then opened. A relatively large amount of sulfur dioxide was found to be present in the reaction mixture, while no unreacted sulfonyl chloride remained. After removing the chlorinated olefinic liquid by distillation, there was obtained what is believed to be 1-chloromethyl-2-chloro-1-octene, bp 82–90° (0.2 mm). The desired adduct (11), 0.78 g (6%), was obtained as a colorless oil, at 132–136° (0.2 mm): ir ($CHCl_3$) 6.19, 6.57, 6.82, 6.97, 7.12, 7.22, 7.45, 7.87, 8.1, 8.7, 8.92, 9.52, 10.7, 11.4, 11.75, and 12.4 μ.

Anal. Calcd. for $C_9H_{16}Cl_2O_2S$: C, 41.70; H, 6.22. Found: C, 41.52; H, 6.38.

Catalytic Reduction of 6 (R = *n*-Butyl) and Phenyl (2-Chloro-*n*-hexyl) Sulfone (Addition Product of Benzenesulfonyl Chloride and 1-Hexene).—Simultaneous hydrogenation and hydrogenolysis of 6 (R = *n*-butyl) and hydrogenolysis of phenyl (2-chloro-*n*-hexyl) sulfone with H_2 over Pd/C in methanol at 25° and atmospheric pressure gave in each case the oily saturated sulfone; these two reduction products were compared by infrared (neat) giving identical spectra.

Registry No.—2, 31598-92-2; 3, 31598-93-3; 4, 20101-30-8; 5, 31598-95-5; 6 (R = *n*-butyl), 31598-96-6; 6 (R = *n*-hexyl), 31598-97-7; 7, 31598-98-8; 8, 31598-99-9; 9, 31599-00-5; 10, 31599-01-6; 11, 31599-02-7; benzenesulfonyl chloride, 98-09-9; phenylacetylene, 536-74-3; 1-hexene, 592-41-6; phenyl (2-chloro-*n*-hexyl) sulfone, 31662-29-0.

Addition of Sulfonyl Chlorides to Acetylenes. II.[1] Stereoselective Control in the Syntheses of β-Chlorovinyl Sulfones

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The stereoselective, free-radical, copper-catalyzed addition of benzenesulfonyl chloride to phenylacetylene could be controlled by polar factors to give preferentially either trans or cis addition products. Excess chloride ions, or highly polar solvents, promoted formation of trans addition products, while cis addition predominated in low polarity solvents (*e.g.*, carbon disulfide). Acetonitrile had an exceptional behavior. The kinetically controlled trans addition product was isomerized with difficulty to the thermodynamically more stable stereoisomer. The photochemical isomerization of both isomers and suggested mechanisms for the addition reaction are discussed. Stereoselective addition of para-substituted benzenesulfonyl chlorides to phenylacetylene and characterization of these adducts are described.

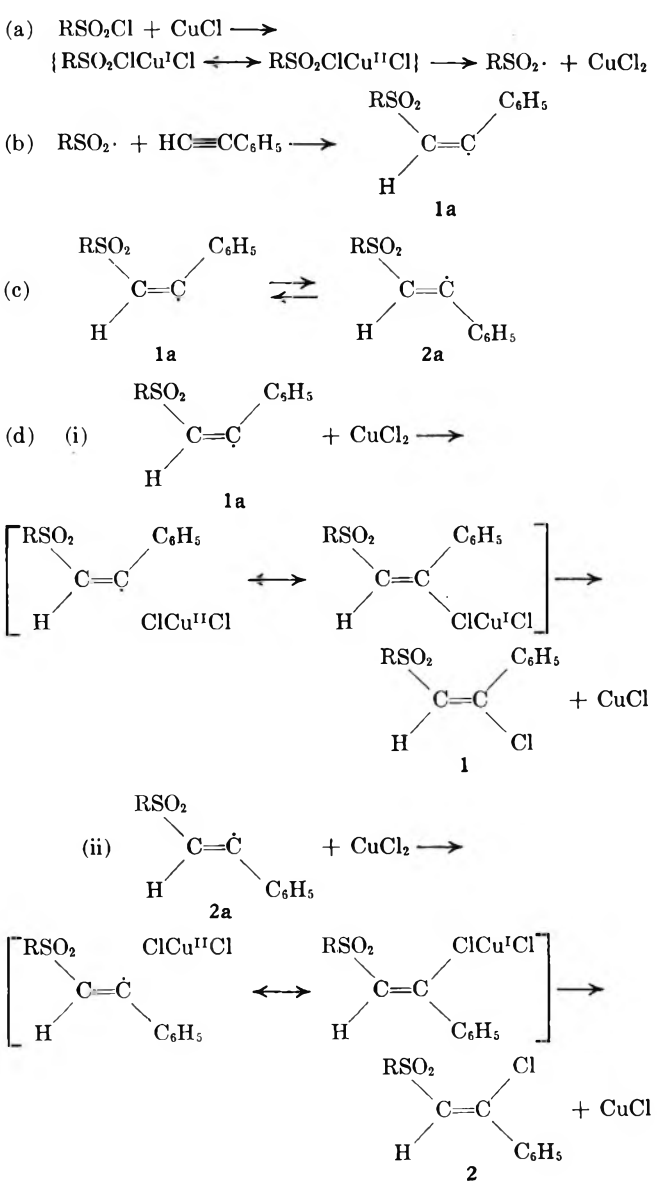
The stereoselective, copper-catalyzed addition of sulfonyl chlorides to phenylacetylene by a free-radical, redox-transfer chain mechanism was reported in the preceding paper. Since the addition was stereoselective, it was of interest to find conditions to alter the ratio of cis–trans adducts.

The overall reaction can be visualized by a frequently encountered mechanism for radical additions to acetylenes[2,3] assuming a trans addition.[4] This consists of four essential steps: (a) formation of sulfonyl radicals by cuprous chloride *via* a chlorine atom abstraction;[5] (b) attack by sulfonyl radicals on the terminal carbon of phenylacetylene with consequent formation of a resonance-stabilized cis intermediate radical (**1a**); (c) partial inversion of the trigonal carbon radical (**1a**) into a trans intermediate radical (**2a**) by equilibration to favor under specific reaction conditions, a more stable configuration; (d) in the product-forming step, scavenging of both isomeric radicals by cupric chloride, by a ligand-transfer process,[6] probably, in competition with each other due to polar and steric factors[7] (see Scheme I).

Several investigations dealing with the cis–trans isomerization of vinyl and styryl radicals have been reported[8] and values of the barrier of inversion for some of these radicals have been estimated.[3,7]

Considering the above stereoselectivity controlling factors, attempts were made to examine if the cis–trans distribution could be changed by varying experimental parameters. Also, it was desired to get more of the

SCHEME I



cis addition products which were obtained as minor by-products. There are no general synthetic routes to the corresponding *trans*-β-chlorovinyl sufides, which have been previously used as precoursers of these compounds. The only reported cis addition product, *p*-$CH_3C_6H_4SO_2CH{=}CClC_6H_5$, was obtained by oxidation of β-chlorovinyl sulfide, which was formed in minor

(1) Part I: Y. Amiel, *J. Org. Chem.*, **36**, 3691 (1971).

(2) R. A. Benkeser and R. A. Hickner, *J. Amer. Chem. Soc.*, **80**, 5298 (1958); R. A. Benkeser, M. L. Burrous, L. E. Nelson, and J. W. Swisher, *ibid.*, **83**, 4385 (1961); A. A. Oswald, K. Griesbaum, B. E. Hudson, Jr., and J. M. Bregman, *ibid.*, **86**, 2877 (1964); A. A. Oswald and K. Griesbaum in "The Chemistry of Organic Sulfur Compounds," Vol. 2, N. Kharasch and C. Y. Meyers, Ed., Pergamon Press, Elmsford, N. Y., 1966, p 233; K. Griesbaum, *Angew. Chem., Int. Ed. Engl.*, **9**, 273 (1970).

(3) P. S. Skell and R. G. Allen, *J. Amer. Chem. Soc.*, **86**, 1559 (1964).

(4) W. E. Truce and J. A. Simms, *ibid.*, **78**, 2756 (1956); S. I. Miller, *ibid.*, **78**, 6091 (1956).

(5) A. Orochov, M. Asscher, and D. Vofsi, *J. Chem. Soc. B*, 255 (1969); M. Asscher and D. Vofsi, *ibid.*, 947 (1968), and preceding papers.

(6) D. C. Nonhebel and W. A. Waters, *Proc. Roy. Soc., Ser. A*, **242**, 16 (1957); C. H. Bamford, A. D. Jenkins, and R. Johnston, *Trans. Faraday Soc.*, **55**, 418 (1959); F. Minisci and R. Galli, *Tetrahedron Lett.*, 533 (1962); J. K. Kochi, *Tetrahedron*, **18**, 483 (1962); *J. Amer. Chem. Soc.*, **84**, 2785 (1962); *Science*, **155**, 415 (1967).

(7) L. A. Singer and N. P. Kong, *J. Amer. Chem. Soc.*, **88**, 5213 (1966); *Tetrahedron Lett.*, 2089 (1966); *ibid.*, 4849 (1969); R. M. Kopchik and J. A. Kampmeier, *J. Amer. Chem. Soc.*, **90**, 6733 (1968).

(8) G. D. Sargent and M. W. Browne, *ibid.*, **89**, 2788 (1967); W. G. Bentrude, *Annu. Rev. Phys. Chem.*, **18**, 300 (1967); O. Simamura, *Top. Stereochem.*, **4**, 21 (1969); M. Julia in "Chemistry of Acetylenes," H. G. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, p 345; L. A. Singer, *Intra-Sci. Chem. Rep.*, **4**, 139 (1970).

TABLE I

REACTIONS OF SULFONYL CHLORIDES (10 MMOL) WITH PHENYLACETYLENE (11 MMOL) IN THE PRESENCE OF CUPRIC CHLORIDE (0.2 MMOL) AND CHLORIDE SALT[a] (0.3 MMOL) IN ACETONITRILE (3 G) AT 100°

No.	RSO_2Cl	Chloride	Time, hr	Conversion,[b] %	Adduct distribution, % 1 (R = C_6H_5)	2 (R = C_6H_5)
1	C_6H_5	NEt_3HCl	4	84	92	8
2	C_6H_5	LiCl	4	78	90	10
3	C_6H_5		6	85	17	83
4	CH_3	NEt_3HCl	16	73	96	4
5	CH_3		16	75	7	93

[a] If indicated. [b] Calculated on sulfonyl chloride consumed.

Essentially the same effect was obtained when lithium chloride was used instead of the ammonium chloride.

A dramatic change was noted when experiments were conducted with copper(I or II) chloride catalyst in the absence of triethylammonium (or lithium) chloride; almost a complete reversal of cis–trans distributions was obtained (see Table I).

Solvent Effects.—It was found that solvent polarity also had a remarkable influence on the adduct distribution. Surprisingly, trans addition product (1, R = C_6H_5) was predominantly obtained, even in the absence of added chlorides, when the reactions were run in solvents with a high dielectric constant; the cis addition product (2, R = C_6H_5) was predominantly formed in solvents with a low dielectric constant. A striking

TABLE II

REACTIONS OF BENZENESULFONYL CHLORIDE (10 MMOL) WITH PHENYLACETYLENE (11 MMOL) IN THE PRESENCE OF COPPER CATALYST AND TRIETHYLAMMONIUM CHLORIDE[a] (1, 5 MMOL) IN VARIOUS SOLVENTS AT 100°

No.	$CuCl_2$, mmol	Solvent (g)	Additive (g)	Time, hr	Conversion, %[b]	Adduct distribution, % 1 (R = C_6H_5)	2 (R = C_6H_5)
1	0.25	Nitrobenzene (4)		12	69	94	6
2	0.25	Nitrobenzene (1)	Acetonitrile (1)	5	59	36	64
3	0.25	*N*-Hexamethylphosphoric triamide (1)		12	61	95	5
4	0.25	*N*-Hexamethylphosphoric triamide (1)	Acetonitrile (1)	5	63	44	56
5	0.25	Tetramethylene sulfone (1)		5	66	93	7
6	0.25	Tetramethylene sulfone (1)	Acetonitrile (1)	5	70	26	74
7	0.25	Pyridine (3)		5	34	88	12
8	0.5	Diglyme (3)		4	75	16	84
9	0.5	Carbon disulfide (5)		16	81	16	84
10	0.5	Carbon disulfide (5)	NEt_3HCl (1.5 mmol)	16	88	82	18

[a] If indicated. [b] Calculated on sulfonyl chloride consumed.

quantities as a by-product.[9] These adducts are also interesting because, unlike the trans addition products, they easily undergo β-trans-dehydrochlorination to give the corresponding α-ethynyl sulfones.[1]

Results

The following experiments describe modifications which turned out to be of major importance in controlling the stereochemical course of this addition reaction. To favor formation of cis addition isomers (2), an attempt was made to reduce the efficiency of step d, thus altering competition with step c.

Effect of Added Chloride Ions.—As described previously,[1] triethylammonium chloride was used in addition to the cupric chloride catalyst. By adding chloride ions, chlorocuprates are formed; these complexes are more soluble in acetonitrile and are known to be very efficient radical scavengers,[10] thus making step d faster.

(9) V. Caló, G. Modena, and G. Scorrano, *J. Chem. Soc. C*, 1339, 1344 (1968). The addition of sulfenyl chlorides to a triple bond [F. Montanari, *Gazzetta*, **86**, 735 (1956); W. E. Truce and M. M. Boudakian, *J. Amer. Chem. Soc.*, **78**, 2748 (1956); L. Benati, M. Tiecco, and A. Tundo, *Boll. Sci. Fac. Chim. Ind. Bologna*, **21**, 177 (1963); A. Dondoni, G. Modena, and G. Scorrano, *ibid.*, **22**, 26 (1964)], as well as to a double bond [D. J. Cram, *J. Amer. Chem. Soc.*, **71**, 3883 (1949); A. J. Havlik and N. Kharasch, *ibid.*, **78**, 1207 (1956); G. H. Schmid and V. M. Csizmadia, *Can. J. Chem.*, **44**, 1338 (1966)] is known to occur in trans fashion.

(10) J. K. Kochi and D. M. Mog, *J. Amer. Chem. Soc.*, **87**, 522 (1965).

reversal was again observed when a chloride salt was added to solvents of the latter kind, *e.g.*, carbon disulfide (see Table II, no. 9 and 10).

Acetonitrile as Solvent.—Acetonitrile exhibited an unusual behavior, different from the other dipolar, aprotic solvents (see Table II, no. 1, 3, and 5); unexpectedly, 2 was predominantly formed (see Table I, no. 3). The distribution was shifted in favor of cis addition product when acetonitrile was added in a 1:1 ratio to other dipolar, aprotic solvents (see Table II, no. 1–6). The extent of formation appeared to be dependent on the amount of acetonitrile (see Table III, no. 2 and 3).

Cuprous Chloride, Instead of Cupric Chloride, as the Catalyst.—Table III shows that cuprous chloride behaves essentially like cupric chloride, perhaps favoring somewhat the formation of 2. The same result was obtained with equimolar amounts of cuprous chloride and sulfonyl chloride in the presence of copper metal (see Table III, no. 4), in order to keep the concentration of cupric chloride as low as possible, thus expecting a decrease in rate of step d. It is clear, though, that no special effect is observed.

Stereoselective Syntheses of Para-Substituted Benzenesulfonyl Chlorides to Phenylacetylene.—Stereoselective syntheses of the following cis and trans addi-

TABLE III

REACTIONS OF BENZENESULFONYL CHLORIDE (10 MMOL) WITH PHENYLACETYLENE (11 MMOL) IN THE PRESENCE OF COPPER CHLORIDE CATALYST AND TRIETHYLAMMONIUM CHLORIDE[a] IN ACETONITRILE, 6 HR AT 100°

No.	Copper catalyst (mmol)	NEt_3HCl, mmol	Acetonitrile, g	Conversion, %[b]	Adduct distribution, % 1 (R = C_6H_5)	2 (R = C_6H_5)
1	CuCl (0.6)	1.8	3	78	94	6
2	CuCl (0.6)		1	82	12	88
3	CuCl (0.6)		7	87	44	56
4	CuCl (10) Cu powder (0.04[c])		7	92	43	57
5	CuCl (0.01)		2	18[d]	20	80
6	CuCN (0.2)		3	71	24	76
7	CuCN (0.01)		2	12[d]	22	78
8	$Cu(OAc)_2 \cdot H_2O$ (0.1)		2	14	85	15

[a] If indicated. [b] Calculated on sulfonyl chloride consumed. [c] Gram-atoms. [d] In these experiments small amounts (*ca.* 50 mg) of 1,3,5-triphenylbenzene, mp 170°, were isolated.

TABLE IV

REACTIONS OF *p*-TOLUENESULFONYL CHLORIDE (20 MMOL) WITH PHENYLACETYLENE (21 MMOL) IN THE PRESENCE OF A COPPER CATALYST AND TRIETHYLAMMONIUM CHLORIDE[a] AT 100° IN THE FOLLOWING SOLVENTS

No.	Copper catalyst (mmol)	NEt_3HCl, mmol	Solvent (g)	Time, hr	Conversion, %[b]	Adduct distribution, % 3 (R = CH_3)	4 (R = CH_3)
1	$CuCl_2$ (0.2)	0.4	Acetonitrile (7)	16	88	92	8
2	$CuCl_2$ (0.2)		Tetramethylene sulfone (2)	16	74	94	6
3	$CuCl_2$ (0.2)		Acetonitrile (7)	8	80	48	52
4	CuCl (0.2)		Acetonitrile (1)	12	72	25	75
5	CuCl (0.2)		Acetonitrile (3)	12	78	29	71
6	CuCl (0.2)		Acetonitrile (7)	12	85	35	65
7	CuCN (0.1)		Acetonitrile (2)	8	75[c]	30	70
8	CuCl (0.1)		Diglyme (5)	12	70	38	62
9	CuCl (0.3)		Carbon disulfide (5)	16	74	26	74

[a] If indicated. [b] Calculated on sulfonyl chloride consumed. [c] See footnote *d*, Table III.

TABLE V

REACTIONS OF *p*-CHLOROBENZENESULFONYL CHLORIDE (20 MMOL) WITH PHENYLACETYLENE (21 MMOL) IN THE PRESENCE OF COPPER(I OR II) CHLORIDE AND TRIETHYLAMMONIUM CHLORIDE[a] AT 100° IN THE FOLLOWING SOLVENTS

No.	Copper chloride (mmol)	NEt_3HCl mmol	Solvent (g)	Time, hr	Conversion, %[b]	Adduct distribution, % 3 (R = Cl)	4 (R = Cl)
1	$CuCl_2$ (0.2)	0.4	Acetonitrile (3)	3	96	93	7
2	$CuCl_2$ (0.2)		Acetonitrile (3)	3	90	34	66
3	CuCl (0.2)		Acetonitrile (3)	3	92	31	69
4	CuCl (0.2)		Carbon disulfide (5)	6	88	27	73

[a] If indicated. [b] Calculated on sulfonyl chloride consumed.

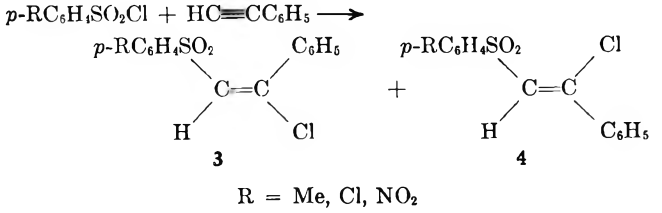
TABLE VI

REACTIONS OF *p*-NITROBENZENESULFONYL CHLORIDE (20 MMOL) WITH PHENYLACETYLENE (21 MMOL), IN THE PRESENCE OF COPPER(I OR II) CHLORIDE AND TRIETHYLAMMONIUM CHLORIDE[a] AT 100° IN THE FOLLOWING SOLVENTS

No.	Copper chloride (mmol)	NEt_3HCl, mmol	Solvent (g)	Time, hr	Conversion, %[b]	Adduct distribution, % 3 (R = NO_2)	4 (R = NO_2)
1	$CuCl_2$ (0.2)	0.4	Acetonitrile (2)	3.5	94	93	7
2	$CuCl_2$ (0.2)		Acetonitrile (10)	4.5	82	72	28
3	$CuCl_2$ (0.2)		Acetonitr le (2)	4.5	88	46	54
4	CuCl (0.2)		Acetonitrile (2)	4.5	92	42	58
5	CuCl (0.2)		Carbon disulfide (5)	12	72	45	55

[a] If indicated. [b] Calculated on sulfonyl chloride consumed.

tion products under various conditions are shown in Tables IV–VI.



R = Me, Cl, NO_2

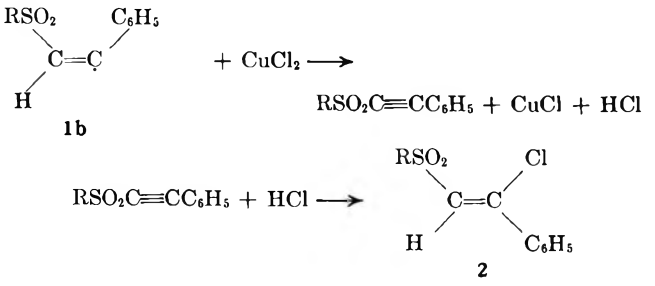
Discussion

These experiments indicate that the addition reactions are strongly dependent on the polarity of the medium. Polar factors may have a pronounced role in homolytic reactions, particularly when polarizable species are involved. This appears to be so when highly electrophilic sulfonyl radicals attack a polar substrate and, moreover, when adduct formation takes place by a reduction–oxidation process involving copper-co-

ordination compounds. Solvation and coordination of participants may operate on the transition states, thus directing the course of adduct formation by stereoelectronic factors. Complex formation between sulfonyl radicals and solvent molecules with a π-electron system of an alkene has been reported.[11] Complex formation with nucleophilic solvents was shown to make radicals more selective; the reactivity of radicals toward abstractions is known to be considerably modified by the solvent.[12] The fact that trans addition product (**1**) is predominantly formed in high dielectric constant solvents could be attributed to the preferred solvent interactions with the less hindered radical[7] **1a**. Hence, a shift in the fast, configurational equilibration of the trigonal radicals (step c) in favor of **1a** would lead to the formation of the kinetically controlled trans addition product (**1**). Redox potentials and bond dissociation energies, which affect step d, are also solvent dependent. It would be difficult to differentiate between the solvent effects on the equilibration process (step c), or on the transition states in step d, which affects the bond dissociation required for the chlorine transfer.

The exceptional behavior of acetonitrile is presently unclear, but this may reflect weaker complexing power toward the compound radical **1a**, compared with the other aprotic, dipolar solvents, enabling more equilibration (step c) to take place. It might be also that in this solvent the product-forming, ligand transfer, step d is less efficient. It is known that Cu(II) and chloride ions are weakly solvated in acetonitrile[13] and cuprous species are more stabilized in this solvent.[14] Cuprous species are stronger chloride ion acceptors than Cu(II) ions; consequently, retardation in chlorine-atom transfer would be anticipated. However, when additional chloride ions are added, a mass-action effect shifts the equilibria and higher chlorocupric complexes are formed and, indeed, the complexes were shown to be very efficient radical scavengers.[10,15]

Although the proposed mechanism for the formation of cis addition product *via* a trans addition process followed by isomerization of the intermediate radical is plausible, more experimental evidence would be desired. There exists also the possibility of a concurrent cis addition as a result of a concerted reaction mechanism. Another route leading to cis addition products could be described by the following elimination–addition process.



1b **2**

In this oxidative elimination, electron-transfer step,[6] α-ethynyl sulfone is presumably formed; in the subsequent step trans addition of HCl would take place. Such an elimination–addition process would be particularly inconceivable in the case of a nonterminal acetylene, such as diphenylacetylene.[1]

Several experiments were carried out to attempt the isomerization of the kinetically formed trans addition product, *via* addition–elimination of sulfonyl radicals, into the thermodynamically more stable planar adduct. The trans addition product (**1**, R = C_6H_5) was heated with a sulfonyl chloride, in the presence of copper chloride, under conditions which favored formation of **2** (R = C_6H_5). After 22 hr at 100°, only 10% of the adduct was converted into the corresponding isomer (**2**, R = C_6H_5), whereas the rest was recovered unchanged. The cis addition product (**2**) did not isomerize under these conditions, and in both cases no diaddition product was found. This strongly suggests that sulfonyl radicals, which are generated in the same way as in the original addition reaction, are very inefficient in attacking the double bond; this is probably due to either steric reasons or because of the strong inductive effect of the electron-withdrawing sulfonyl group, which diminishes the reactivity of the olefinic bond toward radicals of an electrophilic nature.

The photochemical isomerization of 2-benzenesulfonyl-1-chlorostyrenes worked very well, because both the cis (**1**, R = C_6H_5) and the trans (**2**, R = C_6H_5) isomers gave the same photostationary state cis (85%)–trans (15%) mixture.

The reactivity of para-substituted benzenesulfonyl chlorides was, as expected, shown to be dependent on the inductive effects of the para substituents. Generation of sulfonyl radicals was much faster with electron-withdrawing substituents,[16] while *p*-toluenesulfonyl chloride was much less reactive, due to the opposite inductive effect of the methyl group. The copper-catalyzed, redox-transfer, chain additions of substituted aromatic sulfonyl chlorides, as demonstrated in the case of styrene,[5] were shown to follow Hammett's rule; the observed small substituent effects also indicated that atom transfers rather than electron transfers operate in such reactions.

Structural proof and configurational assignment were based on the same criteria as previously described.[1] The known trans addition products (**3**, R = CH_3, NO_2)[9] were obtained previously by oxidation of the corresponding β-chlorovinyl sulfides.

Reductions of the cis and trans addition products gave, in each case, the same saturated sulfone. The configuration of the stereoisomers was based on spectral evidence, as discussed earlier.[1] Products having the trans addition structure have ultraviolet absorptions at shorter wavelengths; the isomeric adducts showed bathochromic shifts of the styryl band and had much stronger intensities (see Table VII). Infrared spectra proved to be valuable, particularly in identifying chromatography as shown previously.[1]

In the nmr spectra, the vinylic protons were shown to be more deshielded in the coplanar configurations (**4**) than in the corresponding noncoplanar adducts (**3**) as mentioned earlier.[1] Additional splitting of four

(11) E. S. Huyser and L. Kim, *J. Org. Chem.*, **32**, 618 (1967).
(12) G. A. Russell, *J. Amer. Chem. Soc.*, **80**, 4987 (1958); C. Walling and M. F. Mayahi, *ibid.*, **81**, 1485 (1959).
(13) I. V. Nelson, R. C. Larson, and R. T. Iwamoto, *J. Inorg. Nucl. Chem.*, **22**, 279 (1961).
(14) R. C. Larson and R. T. Iwamoto, *J. Amer. Chem. Soc.*, **82**, 3239 (1960).
(15) M. Talât-Erben and N. Önal, *Can. J. Chem.*, **38**, 1154 (1960).
(16) E. C. Ladd, U. S. Patent 2,573,580 (1952); *Chem. Abstr.*, **46**, 7588 (1952).

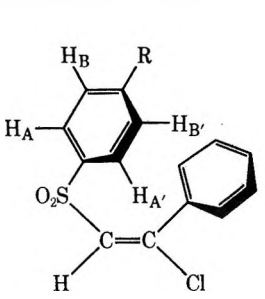
TABLE VII

ULTRAVIOLET SPECTRA

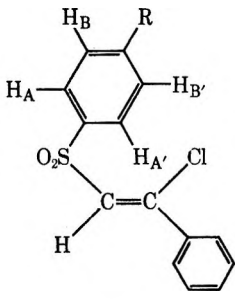
	3				4			
	Phenyl bands		Styryl bands		Phenyl bands		Styryl bands	
R	λ_{max}	ϵ	λ_{max}	ϵ	λ_{max}	ϵ	λ_{max}	ϵ
H	212	16,000	262	10,000	212, 219	15,500	275	20,000
CH_3	209	18,500	246	12,500	212, 219	14,000	276	20,000
Cl	213	15,000	241	14,500	212, 219	15,500	276	20,500
NO_2	213	18,000	256	15,500	212	17,000	286	20,000

TABLE VIII

NMR DATA[a] OF *p*-BENZENESULFONYL ADDITION PRODUCTS



3



4

R	Vinyl protons (s)	Methyl protons (s)	Phenyl protons AA' (d)	BB' (d)	Remaining (m)	Vinyl protons (s)	Methyl protons (s)	Phenyl protons AA' (d)	BB' (d)	Remaining (m)
CH_3	6.93[a]	2.35 (3 H)	7.51	7.15	7.36 (5 H)	7.16	2.45 (3 H)	7.97	7.36	7.26–7.75 (5 H)
			J = 8.5					J = 8.5		
Cl	6.93		7.40[b]		7.26–7.36 (7 H)	7.17		8.00	7.44	7.20–7.36 (5 H)
			J = 4					J = 8.5		
NO_2	7.02		7.77	8.23	7.25–7.59 (5 H)	7.22		8.27	8.50	7.45–7.79 (5 H)
			J = 9					J = 9		

[a] Measured in $CDCl_3$ on a Varian A-60 with TMS as internal standard; chemical shifts reported in δ (ppm) and apparent spin couplings (J) in Hz units; s = singlet, d = doublet, m = multiplet. [b] Partial overlap.

deshielded protons of the para-substituted benzene ring were also quite characteristic. These four protons appeared as a typical AA'BB' pattern for a para-disubstituted phenyl ring. Spectral comparisons (see Table VIII) indicated that the protons ortho to the electronegative sulfone group (H_A and $H_{A'}$) were more deshielded than those in the meta positions (H_B and $H_{B'}$) in *p*-methyl- (**3** and **4**, R = CH_3) and in *p*-chlorobenzenesulfonyl adducts (**3** and **4**, R = Cl); however, a reversed order is suggested for the *p*-nitro adducts (**3** and **4**, R = NO_2), in which the deshielding effect of the nitro group is much stronger than that of the sulfone group. These protons were more shielded in the trans addition products than in the cis addition isomers (see Table VIII), due to the proximity in space of the two phenyl rings (see **3**).[1] A similar, small shielding effect of the phenyl ring on the protons of the *p*-methyl group was noted in **3** (R = CH_3) as compared to **4** (R = CH_3) (see Table VIII).

Experimental Section[17]

Materials.—Phenylacetylene and methanesulfonyl and benzenesulfonyl chlorides, from Fluka (puriss), were distilled before use; para-substituted benzenesulfonyl chlorides (Eastman Kodak, White Label) were dissolved in methylene chloride, washed with ice–water, dried ($CaCl_2$), and after evaporation of solvent recrystallized from 2-propanol; *p*-toluenesulfonyl chloride and *p*-chlorobenzenesulfonyl chloride were distilled before recrystallization; anhydrous cupric chloride was obtained from the dihydrate (B. D. H., reagent grade) by dehydration at 110° to constant weight; triethylammonium chloride (B. D. H., reagent grade) was crystallized from 2-propanol and dried at 100°; acetonitrile (Fluka, puriss) was distilled over P_2O_5; nitrobenzene (puriss), *N*-hexamethylphosphoric triamide (pract), tetramethylene sulfone (purum), and pyridine (purum) were refluxed over KOH pellets and then distilled; diglyme (pract), carbon disulfide (purum), cuprous chloride (purum), lithium chloride (purum), and benzophenone (purum) were obtained from Fluka; and Florisil (100–200 mesh) was obtained from Floridin Co.

(*E,Z*)-2-Benzenesulfonyl(or 2-Methanesulfonyl)-1-chlorostyrenes (1 and 2, R = C_6H_5, CH_3).—These addition reactions were carried out in Carius tubes which were sealed at 0.1 mm after degassing (three times) according to the amounts and conditions described in Tables I–III. Rates of reactions were followed by dilatometry. After contraction stopped, the tube was cooled in ice–water and opened. The reaction mixtures were usually dissolved in methylene chloride and transferred to a separatory funnel, washed with water and with an aqueous solution of disodium ethylenediaminetetraacetate until free from copper; the organic layer was dried (Na_2SO_4) and the crude material, which was obtained after evaporation of the solvent, was subjected to column chromatography, using Florisil. Elutions with *n*-hexane afforded unreacted sulfonyl chloride and phenylacetylene (if indicated), and small amounts (*ca.* 50 mg) of 1,3,5-triphenylbenzene, mp 170° (see Table III, no. 5 and 7), which had the correct analysis and was compared with an authentic sample. Elutions with ether–*n*-hexane (1:3) gave the trans addition products (**1**, R = C_6H_5, CH_3), while cis addition isomers (**2**, R = C_6H_5, CH_3) were eluted with ether–*n*-hexane (1:1). The characterization of these adducts was described in the preceding paper.

(*E,Z*)-2-(Para-substituted benzenesulfonyl)-1-chlorostyrenes (3 and 4).—These addition reactions were carried out in Carius tubes which were sealed at 0.1 mm after degassing (three times) according to the amounts and conditions described in Tables IV–VI. Rates of reactions were followed by dilatometry. After contraction stopped, the tube was cooled in ice–water and opened. The reaction mixtures were usually dissolved in methy-

(17) All melting points are uncorrected. Ir spectra were determined on a Perkin-Elmer Model 125 or 237B spectrophotometer; uv spectra were obtained in aqueous C_2H_5OH on a Cary Model 14M spectrophotometer. Irradiation was conducted using Hanau Q81 high-pressure mercury vapor lamps. Microanalyses were performed in our microanalytical section directed by Mr. R. Heller.

lene chloride and transferred to a separatory funnel, washed with water and with an aqueous solution of disodium ethylenediaminetetraacetate until free from copper; the organic layer was dried (Na_2SO_4) and the crude material, which was obtained after evaporation of the solvent, was subjected to column chromatography, using Florisil. The first elutions, with ether–*n*-hexane (1:9), afforded some unreacted sulfonyl chloride and phenylacetylene (if indicated); trans addition products were eluted with ether–*n*-hexane (1:4), and the isomeric adducts with ether–*n*-hexane (1:1).

(*E,Z*)-2-*p*-**Toluenesulfonyl-1-chlorostyrenes (3 and 4, R = CH_3).**—These adducts were obtained using the above-described general procedure, and conditions given in Table IV. An induction period of 35 min was observed. 1,3,5-Triphenylbenzene (28 mg) was isolated from the earlier chromatographic fractions of experiment no. 7 (see Table IV). Recrystallizations from ethanol gave colorless needles of trans addition product (**3**, R = CH_3): mp 102.5–103.5° (lit.[9] mp 102–103°); ir ($CHCl_3$) 6.19, 6.22, 6.27, 6.92, 7.12, 7.22, 7.58, 7.65, 7.72, 8.1–8.2, 8.75, 9.25, 9.8, 10.76, 11.05, and 12.2 μ.

Anal. Calcd for $C_{15}H_{13}ClO_2S$: C, 61.71; H, 4.48; Cl, 12.11; S, 10.95. Found: C, 61.48; H, 4.41; Cl, 12.07; S, 10.98.

Recrystallizations from methanol gave colorless prisms of cis addition product (**4**, R = CH_3): mp 124.5–125.5° (lit.[9] mp 123–124°); ir ($CHCl_3$) 6.28, 6.30, 6.36, 6.72, 6.92, 7.12, 7.22, 7.58, 7.65, 7.65, 7.77, 8.15–8.25, 8.75, 9.27, 9.8, 9.22, 9.98, 10.72, 10.92, and 12.2 μ.

Anal. Calcd for $C_{15}H_{13}ClO_2S$: C, 61.71; H, 4.48; Cl, 12.11; S, 10.95. Found: C, 61.67; H, 4.46; Cl, 12.17; S, 11.05.

Catalytic Reductions of 3 and 4 (R = CH_3).—Reductions of 2-(*p*-toluenesulfonyl)-1-chlorostyrenes with H_2 over 5% Pd/C, in methanol at 25° and atmospheric pressure, gave in each case 2-phenylethyl *p*-tolyl sulfone.[18]

(*E,Z*)-2-(*p*-**Chlorobenzenesulfonyl**)-1-**chlorostyrenes (3 and 4, R = Cl).**—These adducts were obtained using the above-described general procedure, and conditions given in Table V. Recrystallizations from methanol gave colorless needles of trans addition product (**3**, R = Cl): mp 114.5–115.5°; ir ($CHCl_3$) 6.19, 6.27, 6.73, 6.92, 7.17, 7.58, 7.72, 7.82, 8.6, 8.68, 8.75, 9.77, 9.87, 10.75, 11.05, and 12.3 μ.

Anal. Calcd for $C_{14}H_{10}Cl_2O_2S$: C, 53.68; H, 3.22; Cl, 22.64; S, 10.24. Found: C, 53.13; H, 3.40; Cl, 23.05; S, 10.95.

Recrystallizations from acetone–2-propanol gave colorless plates of cis addition product (**4**, R = Cl): mp 111.5–112.5°; ir ($CHCl_3$) 6.26, 6.36, 6.72, 6.92, 7.17, 7.58, 7.72, 7.83, 8.2, 8.75, 9.17, 9.22, 9.87, 10.72, 10.92, and 12.3 μ.

Anal. Calcd for $C_{14}H_{10}Cl_2O_2S$: C, 53.68; H, 3.22; Cl, 22.64; S, 10.24. Found: C, 53.88; H, 3.19; Cl, 22.89; S, 10.41.

(*E,Z*)-2-(*p*-**Nitrobenzenesulfonyl**)-1-**chlorostyrenes (3 and 4, R = NO_2).**—These adducts were obtained using the above-described general procedure, and conditions given in Table VI. Recrystallizations from methanol gave colorless plates of trans addition product (**3**, R = NO_2): mp 127–128° (lit.[9] mp 123–125°); a transition point at 114° was noted, at which the compound melted and immediately solidified until the final melting point; ir ($CHCl_3$) 6.19, 6.27, 6.36, 6.53, 6.78, 6.92, 7.12, 7.25, 7.38, 7.58, 7.72, 7.8, 8.6, 8.73, 9.27, 9.8, 10.75, 10.05, 11.65, and 12.3 μ.

Anal. Calcd for $C_{14}H_{10}ClNO_4S$: C, 51.95; H, 3.11; Cl, 10.95; N, 4.33; S, 9.91. Found: C, 51.92; H, 3.02; Cl, 11.03; N, 4.24; S, 10.02.

Recrystallization from methanol–ethyl acetate gave colorless plates of cis addition product (**4**, R = NO_2): mp 157–158°; ir ($CHCl_3$) 6.36, 6.4, 6.55, 6.72, 6.92, 7.12, 7.38, 7.52, 7.60, 8.08, 8.20, 8.74, 8.92, 9.22, 9.85, 10.73, 10.85, 11.6, and 12.3 μ.

Anal. Calcd for $C_{14}H_{10}ClNO_4S$: C, 51.95; H, 3.11; Cl, 10.95; N, 4.33; S, 9.91. Found: C, 52.06; H, 2.97; Cl, 10.87; N, 4.27; S, 10.05.

Isomerization of 1 (R = C_6H_5) into 2 (R = C_6H_5).—A mixture of 139 mg (0.5 mmol) of adduct 1 (R = C_6H_5), 88 mg (0.5 mmol) of benzenesulfonyl chloride, and 6.9 mg (0.05 mmol) of cupric chloride in 0.25 g of acetonitrile was heated at 100° for 22 hr. The solvent and the unreacted benzenesulfonyl chloride were distilled off. The remaining solid residue, including catalyst, was chromatographed over 25 g of Florisil. Elution with ether–*n*-hexane (1:3) gave 120 mg of unchanged adduct 1 (R = C_6H_5) and further elution with ether–*n*-hexane (1:1) gave 14 mg (10% conversion) of the cis addition isomer (**2**, R = C_6H_5).

Photochemical Isomerization.—A solution of 1.39 g (5 mmol) either of trans addition product (1, R = C_6H_5) or cis addition isomer (**2**, R = C_6H_5) in 100 ml of benzene, in the presence of 1.5 g of benzophenone, as a photosensitizer, was irradiated for 2 hr by a Hanau Q81 high-pressure mercury vapor lamp fitted into Pyrex tubes. The lamp was immersed in the reaction mixture, which was cooled externally with running water, and oxygen-free nitrogen was passed through the mixture throughout the irradiation. The internal temperature was kept at 30–32°. The same photostationary mixture of the two addition products, 1 (R = C_6H_5) (85%) and **2** (R = C_6H_5) (15%) was isolated, after removal of solvent and benzophenone by high vacuum distillation, following adduct separation by column chromatography as previously reported. The adducts were identified by melting point and ir spectra as earlier described.

Registry No.—**3** (R = H), 31598-92-2; **3** (R = CH_3), 19738-00-2; **3** (R = Cl), 31599-05-0; **3** (R = NO_2), 31599-06-1; **4** (R = H), 31598-93-3; **4** (R = CH_3), 19738-01-3; **4** (R = Cl), 31599-09-4; **4** (R = NO_2), 31599-10-7; methanesulfonyl chloride, 124-63-0; benzenesulfonyl chloride, 98-09-9; *p*-toluenesulfonyl chloride, 98-59-9; *p*-chlorobenzenesulfonyl chloride, 98-60-2; *p*-nitrobenzenesulfonyl chloride, 98-74-8; phenylacetylene, 536-74-3; cupric chloride, 7447-39-4; cuprous chloride, 7758-89-6; triethylammonium chloride, 554-68-7; 1,3,5-triphenylbenzene, 612-71-5.

(18) E. P. Kohler and H. Potter, *J. Amer. Chem. Soc.*, **57**, 1316 (1935).

Nuclear Magnetic Resonance Characteristics of Thiomethylene Groups in a Stereoisomeric Pair of Model Quinolizidines and Some Related Thiospirane *Nuphar* Alkaloids[1]

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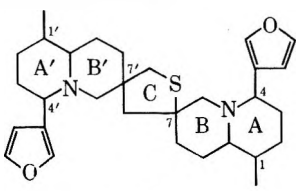
3(e)-Methyl-3(a)-methylthiomethylquinolizidine (1a) and 3(a)-methyl-3(e)-methylthiomethylquinolizidine (1b) were prepared and their nmr spectra were determined. The chemical shift of the axial thiomethylene in 1a is found at lower field than the equatorial thiomethylene of 1b. On the basis of this relationship and reported nmr properties of neothiobinupharidine and thionuphlutine-A and -B, the presence of an equatorial thiomethylene group in each of the latter two alkaloids is proposed.

Axial and equatorial methyl groups attached to *trans*-quinolizidines can be distinguished by nuclear magnetic resonance chemical shift differences.[2] Thus for an axial–equatorial pair of 3-methylquinolizidines, the axial methyl is found at lower field than its equatorial counterpart. A similar relation might be expected for methylene groups as well as methyl groups.

We have prepared the various methylene derivatives **1**–**4** (Table I) and have studied their nuclear magnetic resonance spectra. The prime objective of this work was to provide experimental evidence which would substantiate an expected relation between chemical shift and the stereochemistry of thiomethylene groups when attached to C-3 of a trans-fused quinolizidine system. Such a demonstrated relation could prove useful in making stereochemical assignments of similarily placed thiomethylene groups in neothiobinupharidine,[3] and thionuphlutine-A and -B;[4] all of these are stereoisomeric *Nuphar* alkaloids which belong to the structural type represented by **5**.



5

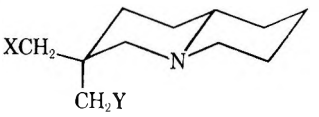
Synthesis and Nmr of Model Compounds.—A mixture containing the stereoisomeric alcohols **2a** and **2b** as well as a number of other partially reduced intermediates had been obtained in the course of following a well-known procedure for the preparation of 3-alkylquinolizidines[5,6] through the reduction of 1-(2-pyridyl)-3,3-dicarbethoxybutane over copper chromite. The two alcohols could be separated by various chromatographic procedures described in the Experimental Section. The mixture of alcohols was converted to a mixture of acetates, **3a** and **3b**, which could be separated by glc. Both acetate isomers absorbed in the ir at 5.75 μ and showed strong Bohlmann bands[2,7,8] in the region of 3.60 μ.

A mixture of liquid tosylates, **4a** and **4b**, was obtained from the mixture of alcohols. Treating the tosylate mixture in 2-methoxyethanol solution with lithium methyl mercaptide gave a mixture of the 3-methyl-3-methylthiomethylquinolizidines, **1a** and **1b**. This sulfide mixture was separated into the pure stereoisomeric sulfides by glc.

A sample of 3(e)-methyl-3(a)-methylthiomethylquinolizidine (**1a**) was prepared from the corresponding pure alcohol **2a** by employing nearly the same scheme as was used in converting the mixture of alcohols to the mixture of sulfides. The only departure was that the tosylate **4a** in methylene chloride solution was treated with methyl mercaptan in place of lithium methyl mercaptide. Resulting was a single sulfide, **1a**, which was identical with one of the two sulfides separated by

TABLE I

NMR CHARACTERISTICS[a,b] FOR AXIAL AND EQUATORIAL 3-CH_3,3-CH_2–X QUINOLIZIDINES



Axial series			Equatorial series		
X = H, Y =	δ, CH_2Y	δ, CH_3[c]	Y = H, X =	δ, CH_2X	δ, CH_3[c]
SCH_3, **1a**	2.80 (s)	0.90	SCH_3, **1b**	2.40 (s)	1.14
OH, **2a**	3.68 (s)	0.74	OH, **2b**	3.32 (s)	1.08
OAc, **3a**	4.22 (AB q, 9 Hz)	0.86	OAc, **3b**	3.80 (s)	1.10
OTs, **4a**	4.14 (AB q, 8 Hz)	0.84	OTs, **4b**	3.68 (s)	1.06

[a] Measured in deuteriochloroform solution relative to tetramethylsilane. [b] s = singlet; q = quartet. [c] All methyl groups were observed as singlets.

(1) This work was supported by the McIntire–Stennis Cooperative Forestry Research Program of the U. S. D. A. and the National Institute of Allergy and Infectious Diseases, Grant AI 10188, National Institutes of Helath, U. S. Public Health Service.

(2) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962).

(3) (a) G. I. Birnbaum, *Tetrahedron Lett.*, 4149 (1965); (b) D. Achmatowicz and J. T. Wróbel, *ibid.*, 129 (1964); (c) O. Achmatowicz, H. Banazek, G. Spiteller, and J. T. Wróbel, *ibid.*, 927 (1964).

(4) R. T. LaLonde, C. F. Wong, and W. P. Cullen, *ibid.*, 4477 (1970).

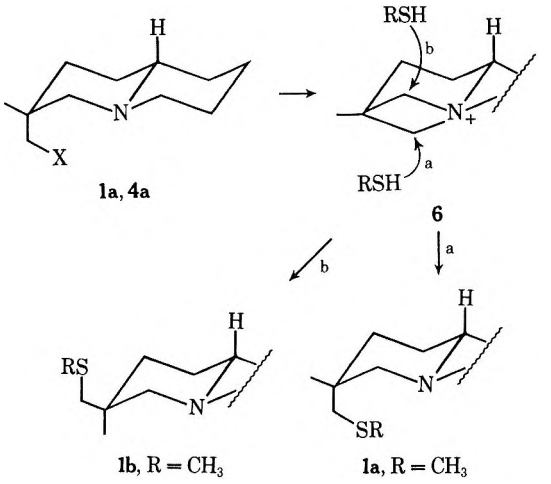
(5) V. Boekelheide and S. Rothchild, *J. Amer. Chem. Soc.*, **71**, 879 (1949).

(6) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *ibid.*, **77**, 439 (1955).

(7) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

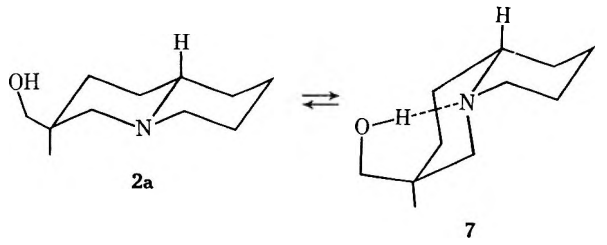
(8) M. W. Wiewiorowski and J. Skolick, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **10**, 1 (1962).

glc from the mixture of sulfides. That the resulting sulfide **1a** possessed the same steric disposition of groups substituted at C-3 as did its alcohol precursor **2a** was demonstrated by the consistency of methyl and thiomethylene chemical shifts with similar data for alcohol, acetate, and tosylate. These data are summarized in Table I. In each case, the methyl groups of the series **1a–4a** were found upfield relative to the methyls of the series **1b–4b**. Had the conversion of tosylate to sulfide taken place by way of an azetidinium ion **5**, possibly the precursor alcohol **2a** would have afforded the equatorial sulfide **1b**. The intermediacy of a structurally



similar azetidinium ion resulting from lupinine derivatives has been observed.[9] However, should such an intermediate intervene and should it have been responsible for the incorporation of an equatorial rather than an axial thiomethylene, then the concomitantly formed axial methyl group should have been observed at low field rather than at high field as was in fact observed.

The stereochemistry of precursor alcohols **2a** and **2b** was established in the following manner. First, the Bohlmann bands displayed by the alcohols (**2a** and **2b**), acetates, and sulfides were of equal intensity. Therefore, the isomer possessing the axial hydroxymethyl group must be a trans-fused quinolizidine and cannot be represented by a cis-fused, hydrogen-bonded structure such as **7** since the latter is expected to display no Bohlmann ir bands or, at best, bands which are less intense than those of the corresponding *trans*-quinolizidine.[8]



Second, the isomeric alcohol **2a** displayed a strong, broad, intramolecular hydrogen-bonded hydroxyl band at 3260 cm^{-1} which is a frequency lower than the range (3530–3480 cm^{-1}) characteristic of five-membered-ring, hydrogen-bonded hydroxyquinolizidines[10] but within the region (~3300 cm^{-1}) where six-membered-ring, hydrogen-bonded hydroxymethylquinolizidines absorb.[11] A second much weaker free hydroxyl band at 3640 cm^{-1} was also observed. Lowering the concentration 50-fold to 0.01 *M* did not change the relative intensity of the 3260- and 3640-cm^{-1} bands. In contrast, the second isomeric alcohol **2b** showed a sharp band at 3620 cm^{-1} and a broad, intermolecular hydrogen-bonded band in the region of 3100–3500 cm^{-1}. The latter diminished in intensity as the concentration decreased and at a concentration of 0.01 *M* disappeared completely. Therefore the axial hydroxymethyl group was assigned to the isomer **2a** displaying the ir properties of an intramolecular, hydrogen-bonded hydroxyl group. Confirming this stereochemical assignment is the greater mobility of **2a** on both adsorption and gas–liquid columns.

The stereochemistry of thiomethylene groups in **1a** and **1b** follows from the stereochemistry assigned to the precursor alcohols and the conservation of that stereochemistry in the tosylation and nucleophilic displacement steps leading to the respective sulfides. As the data of Table I show, the axial thiomethylene is found at a lower field than is its equatorial counterpart.

Nmr of Thiospirane *Nuphar* Alkaloids.—The chemical shift data for the quinolizidine model sulfides **1a** and **1b** are reproduced in Table II and compared with similar

Table II
Chemical Shift Values for Axial and Equatorial CH_2S and SCH_3

Sulfide	CH_2S δ	CH_2S Assignment	SCH_3 δ
$CH_3SCH_2CH_3$	2.53[a]		2.10
$CH_3S(CH_2)_4CH_3$	2.50[a]		2.08
1a	2.80	Axial	2.14
1b	2.40	Equatorial	2.13
NTBN,[b] **5**	2.69[c]	Axial[d]	
TN-A,[b] **5**	2.32	Equatorial	
TN-B,[b] **5**	2.33	Equatorial	

[a] N. S. Bhacca, L. F. Johnson, and J. N. Schoolery, "NMR Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962. [b] NTBN = neothiobinupharidine; TN-A = thionuphlutine-A; TN-B = thionuphlutine-B. [c] Reference 3b. [d] Reference 3a.

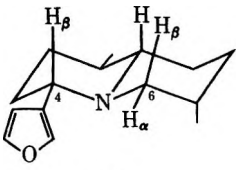
data for simple sulfides and the three known stereoisomeric thiospirane, *Nuphar* alkaloids, **5**. The thiomethylene attached to the A′B′ quinolizidine system of neothiobinupharidine is axial. This assignment of relative stereochemistry follows from an X-ray study of this alkaloid.[3a] In an earlier interpretation[3b] of the nmr of neothiobinupharidine, the resonance reported at δ 3.04, 2.94, 2.83, and 2.69 was attributed to the six protons α to nitrogen. The next higher field resonance band was observed in the region of δ 1.77–1.48. Judging from the chemical shifts of the model sulfides given in Table II, an axial thiomethylene also might come into resonance in the δ 3.04–2.69 region. Reasonably, the reported six-proton resonance in the δ 3.04–2.69 region represents not six protons α to nitrogen but rather two thiomethylene protons plus four protons α to nitrogen. The latter

(9) O. E. Edwards, G. Fodor, and L. Marion, *Can. J. Chem.*, **44**, 13 (1966), and references cited therein.

(10) T. A. Crabb, R. F. Newton, and D. Jackson, *Chem. Rev.*, **71**, 109 (1971).

(11) (a) F. Bohlmann, E. Winterfeldt, H. Laurent, and W. Ude, *Tetrahedron*, **19**, 195 (1963); (b) F. Bohlmann, E. Winterfeldt, P. Studt, H. Laurent, G. Boroschewski, and K.-M. Kleine, *Chem. Ber.*, **94**, 3151 (1961).

four would be the two protons α to both nitrogen and the furan ring plus the two equatorial protons attached to C_6 and $C_{6'}$. This reinterpretation of the reported nmr of neothiobinupharidine is based in part on the nmr of deoxynupharidine,[12] **8**, which displays the $C_{4\beta}$



8

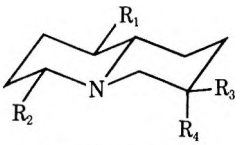
(axial) proton at δ 2.88, the $C_{6\alpha}$ (equatorial) proton at δ 2.70, but the $C_{6\beta}$ (axial) proton at a much higher field—δ 1.88. The C_{10} (axial) proton also is in the region δ 1.7–1.9. Therefore, either one of the resonances at δ 2.69 or 2.83 reported for neothiobinupharidine would appear to be plausible chemical shift values for the thiomethylene protons of this alkaloid. However, the δ 2.69 band was reported[3b] as strong, integrated for two hydrogens, and was assigned to CH_2N. No integration was given for the resonance band at δ 2.83, but on the grounds that the C_4 proton of deoxynupharidine comes into resonance at δ 2.88 it seems that the reported δ 2.83 could also be attributed to C_4 and $C_{4'}$ protons of neothiobinupharidine. Consequently, the best choice for the thiomethylene resonance would be the δ 2.69 band.

In contrast to the δ 2.69 thiomethylene resonance of neothiobinupharidine, the same group in the stereoisomeric thionuphlutines-A and -B is observed[4] at somewhat higher field—2.32 and 2.33, respectively. On the basis of the low field–high field relation of pairs of equatorial and axial thiomethylene groups, the higher field resonance for the thionuphlutines relative to neothiobinupharidine must mean that the former two alkaloids have an equatorial thiomethylene attached to the A′B′ quinolizidine system. That these equatorial thiomethylene groups are attached to trans-fused quinolizidine systems follows from the following observation. Solutions of thionuphlutine-A and -B and deoxynupharidine which are of equal normality all exhibit Bohlmann bands of equal intensity.

One other point relevant to the use of **1a** and **1b** as models for the thiospirane *Nuphar* alkaloids should be discussed. Conceivably the suitability of **1a** and **1b** might be questioned on the basis that **1a** and **1b** contain no 3-furyl group as do the various stereoisomeric alkaloids **5**. Consequently, the axial and equatorial thiomethylene groups in **5** might be subject to anisotropic effects which the same groups in **1a** and **1b** are not. However, as can be seen from the data given in Chart I, the effect of the 3-furyl group is shielding to nearly the same extent for both axial and equatorial methyl groups and reasonably will be shielding for thiomethylene groups as well. In fact, the magnitude of this effect is observed to be the same for equatorial thiomethylene groups when the model compound **1b** is compared to thionuphlutine-A (-B) (Chart I). The anisotropic effect of the 3-furyl group on an axial thiomethylene awaits an nmr investigation of neothiobinupharidine and a definite assignment of the thiomethylene resonance for this alkaloid. Unfortunately, we have not detected the presence of neothiobinupharidine in any of the species of North American *Nuphar* which have been investigated in our laboratories.

CHART I

THE ANISOTROPIC EFFECT OF THE 3-FURYL GROUP ON AXIAL AND EQUATORIAL CH_3 AND CH_2S GROUPS



	CH_3, δ[a]
$R_1 = R_2 = R_3 = H$; $R_4 = CH_3$	1.08
$R_1 = R_4 = CH_3$; $R_2 =$ 3-furyl; $R_3 = H$	1.00
$\Delta^{(ax)}_{CH_3} = \delta$ 0.08	
$R_1 = R_2 = R_4 = H$; $R_3 = CH_3$	0.82
$R_1 = R_3 = CH_3$; $R_2 =$ 3-furyl; $R_4 = H$	0.73
$\Delta^{(eq)}_{CH_3} = \delta$ 0.09	

$\Delta^{(eq)}_{CH_2S} = \delta^{1b}_{CH_2S,\,eq} - \delta_{TN\text{-}A(-B)^b} = 2.40^a - 2.32^a = \delta$ 0.08

[a] Measured in deuteriochloroform solution relative to tetramethylsilane. [b] TN-A (-B) = thionuphlutine-A (-B).

In conclusion, **1a** and **1b** are appropriate models for ascertaining chemical shift differences of axial and equatorial thiomethylene groups. Using these models in conjunction with a reinterpretation of the earlier published nmr data for neothiobinupharidine, the thiomethylene groups of thionuphlutine-A and -B are believed to be equatorial.

Experimental Section

Spectra were obtained as follows: nmr in $CDCl_3$ solution, 2% TMS (δ 0.0), Varian A-60A, symbols s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively; ir in solution as indicated, Perkin-Elmer 137 and 621; mass spectrum at 70 eV and 160–165° with an all-glass heated inlet except where indicated otherwise. Melting points were determined on a Köfler micro hot stage and are uncorrected. Glc conditions were 0.25-in. 5% Carbowax, 195°, He (75% of maximum flow), Varian-Aerograph 200, unless indicated otherwise. The elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

3-Methyl-3-hydroxymethylquinolizidines.—According to the literature procedure,[13] vinylpyridine was treated with the sodium enolate of ethyl methylmalonate to obtain 1-(2-pyridyl)-3,3-dicarbethoxybutane. The last named (200 g, 0.72 mol) in 300 ml of dioxane was heated at 230° under 130 atm of hydrogen with 30 g of copper chromite catalyst. Distillation of the product gave 90 g of 3-methylquinolizindine, bp 90–91° (18.5 mm), $n^{20}D$ 1.4740, and 35 g (26.8%), bp 90–93° (2 mm), of a mixture of hydroxymethylquinolizidines and quinolizidones, ir 6.1–6.2 μ.

A 2-g sample of the higher boiling fraction in CH_2Cl_2 solution was washed with dilute aqueous HCl. The aqueous solution was basified (pH 14) with sodium hydroxide and then extracted repeatedly with CH_2Cl_2. The extract was dried (Na_2SO_4) and the solvent was evaporated to give 1.27 g of residue showing no lactam band at 6.1–6.2 μ. The residue was eluted first with benzene from a column of 38 g of neutral alumina (activity II). Fraction number, weight in milligrams, and volume of eluent in milliliters are as follows: 1, 423, 200; 2, 231, 200; 3, 54, 50; 4, 200 ml. Continued elution with 200 ml of 25% methanol–benzene gave fraction 5, which with fraction 4 amounted to 618 mg. Fractions 2 and 3 consisted of pure 3(e)-methyl-3(a)-

(12) C. F. Wong, E. Auer, and R. T. LaLonde, *J. Org. Chem.*, **35**, 517 (1970).

(13) F. Bohlmann, E. Winterfeldt, G. Boroschewski, R. Meyer-Mader, and B. Gatscheff, *Chem. Ber.*, **96**, 1792 (1963).

hydroxymethylquinolizidine (2a): mp 48–50°; glc 6 min. mass spectrum *m/e* (rel intensity) 183 (37), 182 (84), 168 (44), 152 (96), 151 (5), 124 (31), 98 (67), 97 (100), 84 (82), 83 (75), 57 (63), 55 (82); ir (CH_2Cl_2) 3640 (weak), 3260 cm^{-1} (broad and strong), 3.58, 3.62 μ; ir 0.50, 0.25, 0.17, 0.13, 0.12, 0.06, 0.01 *M* in CCl_4 (3-mm cell); observed an invariable intensity of 3260- and 3640-cm^{-1} bands relative to CH bands and a linear plot of concentration *vs.* intensity of the 3260-cm^{-1} band; nmr δ 5.0 (br s, 1 H, OH), 3.68 (s, 2 H, CH_2OH), 2.8 (m, 2 H, NCH eq), 1.0–2.1 (m, 13 H), 0.74 (s, CCH_3 eq). Fractions 4 and 5 contained a mixture of the stereoisomeric 3-methyl-3-hydroxymethylquinolizidines, glc 6 and 7.4 min, bp 50° (0.05 mm).

Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.56; N, 7.64. Found: C, 72.24; H, 11.70; N, 7.53.

By preparative glc was obtained pure liquid 3(a)-methyl-3(e)-hydroxymethylquinolizidine (2b): glc 7.4 min; mass spectrum *m/e* (rel intensity) 183 (39), 182 (84), 168 (14), 152 (92), 151 (53), 124 (30), 98 (59), 97 (100), 84 (78), 83 (74), 57 (58), 55 (95); ir (CH_2Cl_2) 3620 (s) and 3100–3500 cm^{-1}; ir (CCl_4) 0.53–0.01 *M*, 3100–3500-cm^{-1} band absent at 0.01 *M*; nmr 3.32 (s, 2 H, CH_2OH), 1.08 (s, 3 H, CH_3C).

3-Methyl-3-hydroxymethylquinolizidine Acetates.—A 349-mg sample of the mixture of alcohols was treated with 2 equiv of acetyl chloride and an excess of triethylamine in CH_2Cl_2 overnight at 25°. The mixture was treated with aqueous bicarbonate. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2. The extracts were combined with the original CH_2Cl_2 solution and dried (Na_2SO_4). Evaporation of the solvent gave 422 mg of residue which when passed through neutral alumina (activity I) gave a sample of acetates: ir 1740 cm^{-1}; glc 5 and 5.7 min (0.25-in. 5% Carbowax, 199°, 50% He total flow).

Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.10; H, 10.27; N, 6.02.

Separation of the mixture of acetates by glc gave pure 3(e)-methyl-3(a)-acetoxymethylquinolizidine (3a) [glc 5.0 min (0.25-in. 5% Carbowax, 199°, 50% He total flow; ir 5.75 μ; nmr 4.22 (q, 2 H, J = 9 Hz CH_2OAc), 0.86 (s, 3 H, $CH_3C<$)], and 3(a)-methyl-3(e)-acetoxymethylquinolizidine (3b) [glc 5.7 min; ir 5.75 μ; nmr δ 3.80 (s, 2 H, eq CH_2OAc), 1.10 (s, ax CH_3)].

Treatment of 18 mg of 3(e)-methyl-3(a)-hydroxymethylquinolizidine with acetyl chloride and triethylamine in the manner described above gave 20 mg of pure 3(e)-methyl-3(a)-acetoxymethylquinolizindine (3a): glc 5 min; ir 5.75 μ; nmr δ 4.22 (AB q, J = 9 Hz).

3-Methyl-3-hydroxymethylquinolizidine *p*-Toluenesulfonates.—A 259-mg sample of the alcohol mixture in 2 ml of CH_2Cl_2 was treated with 270 mg of *p*-toluenesulfonyl chloride for 14 hr. The solvent was evaporated and the residue was stored at 0° for 30 hr but no crystalline material formed. Therefore the residue was treated with 10 ml of saturated aqueous bicarbonate and then extracted with CH_2Cl_2 (three 20-ml portions). The combined extracts were dried. Evaporation of the solvent left 384 mg of brown, oily tosylate: nmr δ 7.9 (m, 4 H, SO_2Ar-*o*-H), 7.40 (m, 4 H, SO_2Ar-*m*-H), 4.14 (AB q, J = 8 Hz, 2 H, ax CH_2OTs), 3.68 (s, 2 H, eq CH_2OTs), 2.50, 2.46 (2 s, 6 H, CH_3ArSO_2), 0.84 (s, 3 H, eq $CH_3C<$), and 1.06 (s, 3 H, ax $CH_3C<$).

A 31-mg sample of 3(e)-methyl-3-(a)-hydroxymethylquinolizidine in 0.5 ml of benzene was treated with 33 mg of *p*-toluenesulfonyl chloride at 70–75° for 0.5 hr and at 25° for 14 hr. Removal of solvent by evaporation produced an oil which on cooling gave crystalline 3(e)-methyl-3(a)-hydroxymethylquinolizidine *p*-toluenesulfonate hydrochloride (4a): mp 165–166° (transition point, 126°) (CH_2Cl_2–hexane); nmr δ 4.66, 4.52, 4.38, 4.02 (AB q, 2 H, CH_2OTs), and 0.95 (s, 3 H, ax $CH_3C<$); mass spectrum (unheated, direct inlet) *m/e* (rel intensity) 337 (9), 336 (14), 182 (77), 166 (100); ir OH and Bohlmann bands absent, 4.22, 4.35, 6.24, 6.89, 7.40, 8.40, 8.51, 10.25, 10.48 μ.

Anal. Calcd for $C_{18}H_{28}NSO_3Cl$: C, 57.81; H, 7.55; N, 3.75. Found: C, 57.84; H, 7.31; N, 3.50.

A sample of the hydrochloride was treated with aqueous sodium bicarbonate and shaken with CH_2Cl_2. The extract was dried and the solvent was evaporated to obtain the liquid, free base: nmr δ 4.14 (AB q, J = 8 Hz, 2 H, ax CH_2OTs) and 0.84 (s, 3 H, eq CH_3C); mass spectrum *m/e* (rel intensity) 337 (9), 336 (16), 182 (84), 166 (100); ir OH band absent, 3.40, 3.50, 3.60 (strong, Bohlmann), 6.24, 6.20, 6.89, 6.91, 7.32, 8.40, 8.50, 10.30, 10.50 μ.

3-Methyl-3-methylthiomethylquinolizidine.—A 384-mg sample of 3-methyl-3-hydroxymethylquinolizidine *p*-toluenesulfonate in 2 ml of 2-methoxyethanol was added to a solution of lithium methyl mercaptide prepared by treating 91 mg of lithium hydride with 2 ml of methanethiol and 1 ml of 2-methoxyethanol. The mixture was stored at 50° for 17 hr and at 100° for 2 hr.[14] The reaction mixture was added to 20 ml of benzene and the resulting mixture was passed through 20 g of neutral alumina (activity II). The alumina was washed thoroughly with 150 ml of benzene. Evaporation of the benzene produced 207 mg of oily residue which was chromatographed on a 1-cm-diameter column containing 10 g of neutral alumina (activity II). The chromatography was monitored by glc (0.25-in. 5% Carbowax, 175°, He 75% total flow). Elution with hexane gave a 31-mg fraction and then a 46-mg fraction consisting of two components having glc retention times of 6.65 and 8.95 min. Continued elution with 25% benzene–hexane gave a 77-mg mixture rich in the 6.65-min component. The 46-mg fraction was rechromatographed on 4 g of neutral alumina (activity II) to obtain an analytical sample.

Anal. Calcd for $C_{12}H_{23}NS$: C, 67.55; H, 10.86; N, 6.56; S, 15.03. Found: C, 67.35; H, 11.01; N, 6.50; S, 15.15.

Preparative glc of the 77 mg, 25% benzene–hexane fraction gave 3(e)-methyl-3(a)-methylthiomethylquinolizidine (1a) [glc 6.65 min (0.25-in. 5% Carbowax, 175°, He 75% total flow); uv λ_{max} 220 mμ; mass spectrum *m/e* (rel intensity) 213 (M^+, 59), 198 (100), 167 (51), 166 (100), 152 (28), 150 (20), 138 (38), 136 (22), 110 (20), 98 (100); ir (neat) 3.42, 3.51 (s, CH), 3.59, 3.62 (Bohlmann), 6.95, 7.31, and 8.90 μ; nmr δ 2.80 (s, 2 H, CH_2SCH_3), 2.68 (m, 1 H, eq CHN), 2.49 (m, 1 H, eq CHN), 2.13 (s, 3 H, CH_3S), 1.1–2.0 (m, 13 H), 0.90 (s, 3 H, ax CH_3C)] and 3(a)-methyl-3(e)-methylthiomethylquinolizidine (1b) [glc 8.95 min; mass spectrum *m/e* (rel intensity) 213 (M^+, 42), 198 (66), 167 (43), 166 (100), 152 (22), 150 (18), 138 (32), 136 (18), 110 (17), 98 (100); ir (neat) 3.42, 3.51 (CH), 3.59 3.62 (Bohlmann), 7.0 μ; nmr δ 2.66 (m, 2 H, eq CHN); 2.40 (s, 2 H, eq CH_2S), 2.13 (s, 3 H, CH_3S), 2.0–1.22 (m, 13 H), 1.14 (s, 3 H, ax CH_3)].

3(e)-Methyl-3(a)-methylthiomethylquinolizidine (1a).—A 59-mg sample of the hydrochloride salt of 3(e)-methyl-3(a)-hydroxymethylquinolizidine *p*-toluenesulfonate in a 0.5-ml solution of methyl mercaptan in methylene chloride was heated at 80–90° for 12 hr in a sealed glass tube. The volatiles were removed by evaporation. The nmr of the 57 mg of residue indicated the presence of only starting *p*-toluenesulfonate ester. The residue was treated with 5 ml of saturated, aqueous bicarbonate and then dissolved in CH_2Cl_2 to recover the *p*-toluenesulfonate ester as the free base. The base (42 mg) in CH_2Cl_2 was heated with 1 ml of methanethiol for 16 hr at 80–90° in a sealed glass tube. The volatiles were removed by evaporation. An nmr of the resulting residue (23 mg) showed no starting *p*-toluenesulfonate ester but the presence of the axial CH_2SCH_3 group (δ 2.80). Glc demonstrated the presence of 3(e)-methyl-3(a)-methylthiomethylquinolizidine (6.6 min, 0.25-in. 5% Carbowax, 175°, 75% He total flow). The isomeric sulfide (8.95 min) could not be detected in the product mixture by glc or nmr.

Registry No.—**1a**, 31819-27-9; **1b**, 31819-28-10; **2a**, 31819-29-1; **2b**, 31819-30-4; **3a**, 31883-37-1; **3b**, 31819-31-5; **4a**, 31819-32-6; **4a** HCl, 31819-33-7; **4b**, 31819-34-8.

(14) We thank Professor Richard S. Matthews and Mr. Thomas Neteyer of Syracuse University for disclosing their method of sulfide preparation to us

Gibbane Synthons *via* Hexahydrofluorenones.[1] An Intramolecular Reformatsky Reaction

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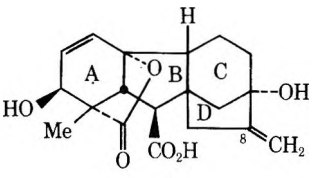
An efficient synthesis of hexahydrofluorene-2,9-dione and 7-methoxyhexahydrofluorene-2,9-dione from the appropriate phenylpyruvic acids is described. Their conversion to α-bromo esters and amides as well as the intramolecular Reformatsky reaction of these substances to provide gibbane synthons is detailed.

Synthetic efforts directed toward the gibberellins [gibberellic acid (**1**)] have led to known gibberellins,[3] degradation products thereof,[4] and gibbane synthons.[5] Our interest in this problem lay in devising an efficient synthetic route to hexahydrofluorenones **7a** and **7b**, which could in turn lead to tetracyclic gibbane synthons.

Although *trans*-2-phenyl-5-oxo-1-cyclohexanecarboxylic acid (**4**) had previously been cyclized to dione **7a**, no yields were specified and, moreover, the acid was obtained as the minor product from the Diels–Alder reaction of 2-ethoxybutadiene and *trans*-cinnamic acid.[6] It seemed reasonable that the corresponding cis acid **5a** would be more amenable to cyclization than its trans counterpart. In addition, the fact that the dissolving metal reduction of 3,4-diphenylcyclohex-2-en-1-one (**3a**) affords *cis*-3,4-diphenylcyclohexanone[7] augured well for a method of preparing the requisite cis acid, since the carboxylate anion of acid **3b** should play a similar role to that of the 3-phenyl substituent in ketone **3a**.

To this end, the condensation between *p*-methoxyphenylpyruvic acid and methyl vinyl ketone was achieved in aqueous methanolic sodium hydroxide, yielding 1-hydroxy-2-(*p*-methoxyphenyl)-5-oxo-1-cyclohexanecarboxylic acid (**2c**) as a single diastereomer in high yield. Several analogous annelations have been reported between phenylpyruvic acid and benzalacetone,[8,9] *p*-methoxybenzylidene acetone,[9] and ethyl styryl ketone.[10] The observation that recrystallization of the acid tended to lower its melting point suggested that thermal dehydration might be occurring. Thus, when the acid **2c** was heated at 180–190°, liquification occurred with concomitant loss of water, providing unsaturated acid **3c** whose nuclear magnetic resonance spectrum exhibited a one-proton doublet at δ 6.84 (J = 1.5 Hz) indicating the presence of a vinyl hydrogen, ruling out the alternative cinnamic acid formulation. Reduction of unsaturated acid **3c** with lithium–ammonia–tetrahydrofuran, as anticipated, gave rise to the cis keto acid **5c** in 54% yield. Alternatively, the use of zinc in refluxing acetic acid produced the desired material in 91% yield.

Catalytic hydrogenation of **3c** over palladized charcoal provided a mixture of the cis keto acid and unsaturated acid **6a**. The stereochemistry of the latter acid was shown to be cis on the basis of the nuclear magnetic resonance spectrum[11] of its methyl ester **6b**. Oxidation of acid **6a** with manganese dioxide[12] in chloroform pro-



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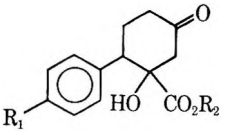
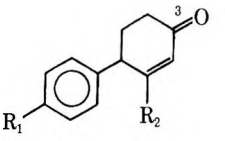
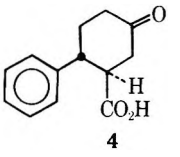


2a, $R_1 = R_2 = H$
b, $R_1 = OMe$; $R_2 = Me$
c, $R_1 = OMe$; $R_2 = H$



3a, $R_1 = H$; $R_2 = Ph$
b, $R_1 = H$; $R_2 = CO_2H$
c, $R_1 = OMe$; $R_2 = CO_2H$



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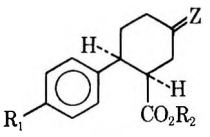
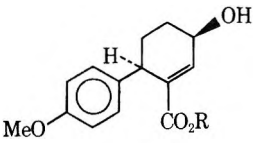


5a, $R_1 = R_2 = H$; $Z = O$
b, $R_1 = H$; $R_2 = Me$; $Z = O$
c, $R_1 = OMe$; $R_2 = H$; $Z = O$
d, $R_1 = OMe$; $R_2 = Me$; $Z = O$
e, $R_1 = R_2 = H$; $Z = (SCH_2)_2$
f, $R_1 = H$; $R_2 = Me$; $Z = (SCH_2)_2$
g, $R_1 = R_2 = H$; $Z = H_2$



6a, R = H
b, R = Me

(1) Taken in part from the Ph.D. thesis of M. E. C., Yale University, 1970; F. E. Ziegler and M. E. Condon, *Tetrahedron Lett.*, 2315 (1969).

(2) National Institutes of Health Postdoctoral Fellow, 1967–1970.

(3) K. Mori, M. Shiozaki, N. Itaya, M. Matsui, and Y. Sumiki, *Tetrahedron*, **25**, 1293 (1969); W. Nagata, T. Wakabayashi, Y. Hayase, M. Narisade, and S. Kamata, *J. Amer. Chem. Soc.*, **92**, 3202 (1970).

(4) Y. Kos and H. J. E. Lowenthal, *J. Chem. Soc.*, 605 (1963); H. J. E. Lowenthal and S. K. Malhotra, *ibid.*, 990 (1965); K. Mori, M. Matsui, and Y. Sumiki, *Agr. Biol. Chem. (Tokyo)*, **25**, 907 (1961); **27**, 527 (1963); **28**, 72 (1964); K. Mori, M. Matsui, and Y. Sumiki, *Tetrahedron Lett.*, 429 (1970).

(5) (a) H. O. House and C. B. Hudson, *J. Org. Chem.*, **35**, 647 (1970), and earlier papers in this series; (b) H. J. E. Lowenthal and H. Rosenthal, *Tetrahedron Lett.*, 3693 (1968); (c) T. Hori and K. Nakanishi, *Chem. Commun.*, 528 (1969); (d) N. N. Gerber, *J. Amer. Chem. Soc.*, **82**, 5216 (1960); (e) V. R. Ghatak, J. Chakravarty, and A. K. Banerjee, *Tetrahedron*, **24**, 1577 (1968); (f) A. Tahara and O. Hoshino, *Tetrahedron Lett.*, 5031 (1966); (g) R. H. B. Galt and J. R. Hanson, *J. Chem. Soc.*, 1565 (1965); (h) K. Shudo, M. Natsume, and T. Okamoto, *Chem. Pharm. Bull.*, **14**, 311 (1966); (i) T. Ogawa, K. Mori, M. Matsui, and Y. Sumiki, *Tetrahedron Lett.*, 2551 (1968); (j) *ibid.*, 4483 (1968); (k) L. J. Dolby and R. J. Mulligan, *J. Amer. Chem. Soc.*, **88**, 4536 (1966); (l) M. D. Bachi, J. W. Epstein, Y. Herzberg-Minzily, and H. J. E. Lowenthal, *J. Org. Chem.*, **34**, 126 (1969); (m) S. K. Dasgupta, R. Dasgupta, S. R. Ghosh, and U. R. Ghatak, *Chem. Commun.*, 1253 (1969); (n) G. Stork, S. Malhotra, H. Thompson, and M. Uchibayashi, *J. Amer. Chem. Soc.*, **87**, 1148 (1965); (o) H. W. Thompson, *J. Org. Chem.*, **32**, 3712 (1967); (p) E. J. Corey, M. Narisada, T. Hiraoka, and R. A. Ellison, *J. Amer. Chem. Soc.*, **92**, 396 (1970); (q) F. E. Ziegler and J. A. Kloek, *Tetrahedron Lett.*, in press.

(6) H. O. House, W. F. Gannon, R. S. Ro, and D. J. Wluka, *J. Amer. Chem. Soc.*, **82**, 1463 (1960).

(7) S. K. Malhotra, D. F. Moakley, and F. Johnson, *Tetrahedron Lett.*, 1089 (1967).

(8) P. Cordier and H. Maximos, *C. R. Acad. Sci.*, **227**, 347 (1948).

(9) M. Kristensen-Reh, *Bull. Soc. Chim. Fr.*, 882 (1956).

(10) M. Kristensen-Reh and P. Cordier, *C. R. Acad. Sci.*, **247**, 2150 (1958).

(11) E. W. Garbisch, Jr., *J. Org. Chem.*, **27**, 4249 (1962).

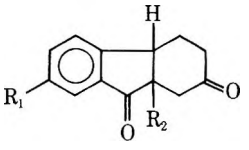
(12) O. Mancera, J. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 2189 (1953).

duced the unsaturated acid **3c**. On the other hand, pure acid **6a** could be obtained by sodium borohydride reduction of the unsaturated acid **3c**.

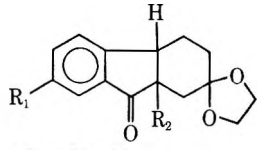
Keto acid **5a** was transformed into its ethylene thioketal **5e**, which, in turn, was converted to its methyl ester **5f** with ethereal diazomethane. Desulfurization with Raney nickel W-2 in refluxing ethanol produced an oil, homogeneous upon thin layer chromatography, whose infrared spectrum exhibited typical ester absorption and whose nuclear magnetic resonance spectrum was devoid of the characteristic thioketal singlet. Saponification of the ester with aqueous methanolic sodium carbonate provided *cis*-2-phenylcyclohexanecarboxylic acid (**5g**), mp 76–77° (lit.[13] mp 77°), thus confirming the stereochemistry of acids **5a** and **5c**.

When the polyphosphoric acid catalyzed cyclization was performed on **5c** at 80–85° at a dilution of 50:1, the yield of ketone **7b** was optimized (55–60%) after 10 min, whereas keto acid **5a** provided diketone **7a** (90%) after 45 min. The lower yield of diketone **7b** compared with **7a** reflects the known difficulties of cyclizing 3-(*p*-methoxyphenyl)propionic acid derivatives.[14]

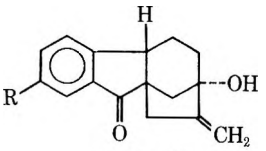
With a viable route for preparing diketones **7a** and **7b**, several investigations were initiated to devise means for constructing ring D. The first approach to the solution of this problem lay in preparing the vinyl bromide **7c**, which, it was anticipated, could undergo reductive cyclization to form tetracyclic **9b**.[15] To this



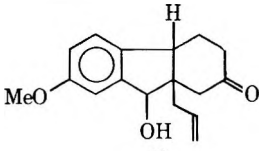
7a, $R_1 = R_2 = H$
b, $R_1 = OMe$; $R_2 = H$
c, $R_1 = OMe$; $R_2 = CH_2CBr{=}CH_2$
d, $R_1 = H$; $R_2 = CH_2CBr{=}CH_2$
e, $R_1 = OMe$; $R_2 = CH_2CH{=}CH_2$



8a, $R_1 = R_2 = H$
b, $R_1 = OMe$; $R_2 = H$
c, $R_1 = OMe$; $R_2 = CH_2CBr{=}CH_2$
d, $R_1 = H$; $R_2 = CH_2CBr{=}CH_2$



9a, R = H
b, R = OMe



10

end, selective ketalization of the more reactive aliphatic carbonyl function in diketone **7b** with ethylene glycol produced the monoketal **8b**. Subsequent alkylation with 2,3-dibromopropene–potassium *tert*-butoxide in 1,2-dimethoxyethane provided the crystalline alkylated ketal **8c**. Removal of the protecting group was achieved under dilute mineral acid conditions to give rise to the desired vinyl bromide **7c**. A similar series of experiments could be executed in the sequence **7a** → **8a** → **8d**[5p] → **7d**.[5p] The cis stereochemical assignment finds ample precedent in other alkylated systems of this type.[16]

In an attempt to effect an intramolecular Grignard addition of the vinyl bromide moiety to the aliphatic ketone in **7c**, the diketone was refluxed in tetrahydrofuran solution for 5 hr in the presence of magnesium affording a mixture of allyl diketone **7e** and the corresponding alcohol **10** in a 4:1 ratio, respectively. Longer reaction times gave more of the latter material at the expense of the former. Oxidation of the alcohol yielded the allyl diketone, which was independently prepared *via* the alkylation sequence from ketal **8b**. The fact that the allyl diketone was isolated indicated that the desired Grignard reagent was being formed, but did not explain its failure to undergo cyclization. The possibility that the Grignard was being protonated upon workup of the reaction mixture was ruled out when it was quenched with deuterium oxide. The nuclear magnetic resonance spectrum of the resultant allyl diketone revealed that the three vinyl hydrogens in the allyl pattern were still intact. Thus, the Grignard was being internally protonated in the reaction medium, presumably by enolization of the aliphatic carbonyl or from degradation of the solvent.

Michael addition of ketal **8b** to methyl α-bromoacrylate in the presence of potassium *tert*-butoxide–*tert*-butyl alcohol–tetrahydrofuran provided bromo ester **11a**, which upon deketalization yielded bromo ester **12a**. The cis bromo ester was obtained as a mixture of diastereomers about the carbon bearing the ester group, as witnessed by the presence of two methyl ester singlets in the nuclear magnetic resonance spectrum. Employing freshly prepared bromo ester **12a**, the Reformatsky reaction[17] was conducted in refluxing benzene in the presence of activated zinc dust followed by quenching of the reaction mixture with acetic anhydride. A mixture of two diastereomeric acetoxy esters, **13a** and **13b**, was formed, with the former predominating over the latter. In a similar fashion, quenching of the reaction mixture with benzoyl chloride provided the corresponding benzoates, **13c** and **13d**. In each case, the major diastereomers (**13a** and **13c**) were reduced with lithium aluminum hydride to a single triol **14a**, while the minor diastereomers provided the triol **14b**.

When the cyclization was conducted in tetrahydrofuran followed by quenching of the reaction mixture with acetic anhydride, the β-hydroxy ester **13e** was isolated with no trace of acetylated products,[18] the stereochemistry of which was determined in the prescribed fashion by conversion to the triol **14a**. No attempt was made to isolate the epimer of the hydroxy ester.

The stereochemistry of the epimeric pairs of diastereomers from the cyclization was determined by an epimeri-

(13) K. Alder, H. Vagt, and W. Vogt, *Justus Liebigs Ann. Chem.*, **565**, 135 (1949).

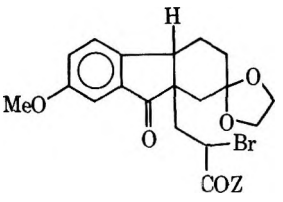
(14) H. O. House and J. K. Larson, *J. Org. Chem.*, **33**, 448 (1968), and references cited therein.

(15) After our investigations on the vinyl bromide **7c** had been completed, the successful cyclization of **7d** to **9a** was accomplished in elegant fashion[5p] by the use of di-*n*-butylcopperlithium.

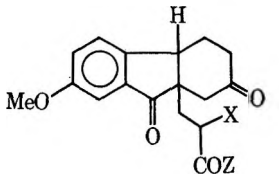
(16) H. O. House and R. G. Carlson, *J. Org. Chem.*, **29**, 74 (1964).

(17) The synthesis of mevalonic acid lactone by an intramolecular Reformatsky reaction has been described: F. H. Hulcher and T. A. Hosick, U. S. Patent 3,119,842 (1964); *Chem. Abstr.*, **60**, 10554*g* (1964).

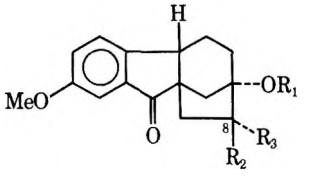
(18) The cleavage of tetrahydrofuran in Reformatsky-like reactions has been reported; *cf.* V. A. Barkhash, G. P. Smirnova, and I. V. Machinskaya, *Zh. Obshch. Khim.*, **33**, 2570 (1963).



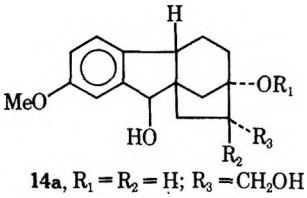
11a, Z = OMe
b, Z = O-*tert*-Bu
c, Z = NMe_2



12a, X = Br; Z = OMe
b, X = Br; Z = O-*tert*-Bu
c, X = Br; Z = NMe_2

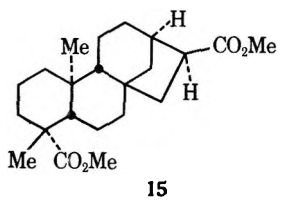


13a, R_1 = Ac; R_2 = H; R_3 = CO_2Me
b, R_1 = Ac; R_2 = CO_2Me; R_3 = H
c, R_1 = Bz; R_2 = H; R_3 = CO_2Me
d, R_1 = Bz; R_2 = CO_2Me; R_3 = H
e, R_1 = R_2 = H; R_3 = CO_2Me
f, R_1 = Ac; R_2 = H; R_3 = CO_2-*tert*-Bu
g, R_1 = Ac; R_2 = CO_2-*tert*-Bu; R_3 = H
h, R_1 = Ac; R_2 = H; R_3 = $CONMe_3$



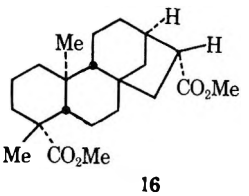
14a, R_1 = R_2 = H; R_3 = CH_2OH
b, R_1 = R_3 = H; R_2 = CH_2OH

zation study conducted on the pair of benzoates, **13c** and **13d**. Treatment of the minor benzoate **13d** with potassium *tert*-butoxide–*tert*-butyl alcohol–tetrahydrofuran effected epimerization to the major benzoate **13c**. Under the same conditions, the major epimer was recovered unchanged. The stereochemical assignment is consonant with the known epimerization, **15** (endo) → **16** (exo).[19]



15

NaOMe–MeOH



16

Two other Reformatsky reactions were investigated, namely those of the α-bromo ester **12b** and α-bromo amide **12c**. Although the mixture of diastereomeric *tert*-butyl esters **13f** and **13g** could be formed in good yield, they were particularly resistant to separation. On the other hand, amide **13h** was obtained with ease, although no attempt was made to seek its epimer.

Clearly, the internal Reformatsky reaction is of particularly synthetic utility, particularly in systems where dehydration to α,β-unsaturated esters can occur.[20]

(19) C. A. Hendricks and P. R. Jefferies, *Aust. J. Chem.*, **17**, 915 (1964).

Experimental Section

General.—Melting points were obtained on a Fisher–Johns apparatus and are corrected.

Microanalyses were performed by Galbraith Laboratories and Bernhardt Microanalytische Laboratorium.

Infrared (ir) spectra were determined on a Perkin-Elmer Model 421 or 237B spectrometer. Nuclear magnetic resonance (nmr) spectra were obtained with Varian Model A-60, A-60A, or HA-100 spectrometers. Chemical shifts are reported in δ units using tetramethylsilane as internal reference. Ultraviolet spectra were taken on a Bausch and Lomb Spectronic 505 recording spectrometer. Absorptions are reported as λ_{max} (ε) in nanometer units. Mass spectra were obtained in part by Professor McMurray of the Yale Medical School using an A.E.I. MS-9 spectrometer and in part on a Hitachi RMU-6 spectrometer. The data are reported as *m/e* (relative intensity).

Except where noted, solvents were reagent grade and were used as received. Thin layer chromatograms (silica gel G) were run using 30% ethyl acetate–benzene as the moving phase unless otherwise noted.

In all work-up procedures the drying process involved swirling over anhydrous magnesium sulfate and filtering prior to evaporation.

2-Methyl-4-(*p*-methoxybenzylidene)oxazol-5-one.—This compound was initially prepared by the method of Niederl and Ziering[21] in 30–35% yield. It was subsequently observed that the use of potassium bicarbonate[22] instead of sodium acetate afforded better yields.

In a 2-l., three-neck flask fitted with a nitrogen inlet, mechanical stirrer, thermometer, and condenser were placed 544 g (4 mol) of *p*-anisaldehyde, 640 ml of acetic anhydride, 200 g (4 mol) of potassium bicarbonate, and 214 g (2 mol) of acetylglycine.[23] On heating the reaction mixture to 70° followed by removal of the external heat, vigorous evolution of carbon dioxide occurred. The reaction temperature then rapidly reached 105° as the reaction mixture became homogeneous. After the evolution of carbon dioxide had subsided, the solution was heated to 135–140° and stirred at this temperature for 1 hr under nitrogen, the temperature being maintained by occasionally applying external heat. After cooling the solution to 80° and pouring it onto 1 kg of crushed ice, 300 ml of methanol was added, and the crude azlactone was filtered and washed with two 200-ml portions of methanol. Upon drying the azlactone to constant weight in a vacuum desiccator, a yield of 300 g (70%, mp 107–111°) was obtained: mp 111–112° (ethyl acetate–hexane) (lit.[21] mp 114°, uncorrected); ir ($CHCl_3$) 1802, 1775, 1662, and 1613 cm^{-1}; nmr ($CDCl_3$) δ 2.35 (3 H, s), 3.84 (3 H, s), 7.05 (1 H, s), and 6.75–8.20 (4 H, m, A_2B_2).

α-Acetamino-*p*-methoxycinnamic Acid.—The "Organic Syntheses"[24] procedure for the preparation of α-acetaminocinnamic acid was adapted, and afforded the acid, mp 227–229° (lit.[21] mp 216°, uncorrected), in 85–90% yield from the above azlactone.

***p*-Methoxyphenylpyruvic Acid.**—The "Organic Syntheses"[25] procedure for the preparation of phenylpyruvic acid was employed, affording the acid, mp 184° dec (depends upon the rate of heating) (lit.[21] mp 184° dec, uncorrected), in 90–95% yield from the above cinnamic acid.

1-Hydroxy-2-(*p*-methoxyphenyl)-5-oxocyclohexanecarboxylic Acid (2c) and Its Methyl Ester 2b.—To a suspension of 132.00 g (0.68 mol) of freshly prepared *p*-methoxyphenylpyruvic acid in 1 l. of methanol maintained under a nitrogen atmosphere was added a solution of 57.12 g (0.82 mol) of methyl vinyl ketone in 100 ml of methanol. The reaction mixture was cooled to 0–5° in an ice bath, and a solution of 32.64 g (0.82 mol) of sodium hydroxide in 300 ml of water (precooled to 5°) was added dropwise at such a rate that the temperature of the reaction mixture was maintained below 15°. The *p*-methoxyphenylpyruvic acid,

(20) K. H. Fung, K. J. Schmalzl, and R. N. Mirrington, *Tetrahedron Lett.*, 5017 (1969).

(21) J. B. Niederl and A. Ziering, *J. Amer. Chem. Soc.*, **64**, 885 (1942).

(22) A. Galat, *ibid.*, **72**, 4436 (1950).

(23) A. H. Blatt, Ed., "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1957 p 11.

(24) Reference 23, p 1.

(25) Reference 23, p 519.

which is relatively insoluble in cold methanol, gradually dissolved on addition of the aqueous base. The reaction vessel was then removed from the ice bath, and the clear solution was stirred at room temperature under nitrogen for 10 hr, during which time the sodium salt of the product partially precipitated from solution.

The reaction mixture was then diluted with 300 ml of water and acidified with concentrated hydrochloric acid, and the resulting clear solution cooled for several hours. The product, which precipitated during this time, was filtered and dried in a vacuum desiccator, affording 153.00 g (86%) of acid: mp 175–177° (ethyl acetate, dehydrates upon melting); ir (KBr) 3500, 3100–2800, 1730, and 1675 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.53; H, 6.35.

Treatment of the above acid with excess ethereal diazomethane afforded the methyl ester **2b** as colorless crystals: mp 122–124° [benzene–petroleum ether (bp 30–60°), dehydrates upon melting]; ir ($CHCl_3$) 3540, 1738, and 1728 cm^{-1} (sh); nmr ($CDCl_3$) δ 1.75–2.65 (4 H, m), 2.88 (1 H, s), 3.10–3.50 (3 H, m), 3.60 (3 H, s), 3.72 (3 H, s), and 6.60–7.25 (4 H, m, A_2B_2).

Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.70; H, 6.70.

1-Hydroxy-2-phenyl-5-oxocyclohexanecarboxylic Acid (2a).—In the manner described (*vide supra*), 72.96 g (0.44 mol) of phenylpyruvic acid[25] in 500 ml of methanol, 27.45 g (0.54 mol) of methyl vinyl ketone in 100 ml of methanol, and 21.40 g (0.54 mol) of sodium hydroxide in 150 ml of water afforded, upon stirring at room temperature under nitrogen for 3 hr, 93.00 g (90%) of acid **2a**: mp 180–182° (ethyl acetate, dehydrates upon melting); ir (KBr) 3455, 3100–2700, 1727, and 1685 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.47; H, 6.18.

3-Oxo-6-(*p*-methoxyphenyl)-1-cyclohexenecarboxylic Acid (3c).—In a flask fitted with a nitrogen inlet was placed 20.00 g (0.076 mol) of hydroxy acid **2c** and the flask was heated at 180–190° in an oil bath until all of the acid had melted (5–10 min). The reaction flask was removed from the oil bath and cooled for several minutes with constant stirring under nitrogen. To the warm yellow, viscous liquid was added 10 ml of benzene and 1 ml of methanol. The product, which crystallized upon cooling to room temperature, was filtered and dried in a vacuum desiccator, yielding 15.88 g of acid: mp 138.5–139.5° (benzene–methanol); ir (KBr) 3200–2800, 1730, 1712, and 1660 cm^{-1}; nmr (CD_3OD) δ 1.84–2.58 (4 H, m), 3.74 (3 H, m), 4.17 (1 H, poorly resolved triplet, $W_{1/2}$ = 5 Hz), 6.84 (1 H, d, J = 1.3 Hz), and 6.70–7.25 (4 H, m, A_2B_2).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.28; H, 5.82.

3-Oxo-6-phenyl-1-cyclohexenecarboxylic Acid (3b).—In the manner described (*vide supra*), dehydration of 13.68 g (0.058 mol) of hydroxy acid **2a** at 190–200° afforded 11.36 g (90%) of acid **3b**: mp 170–171° (benzene–methanol); ir (KBr) 3300–2900, 1730, 1712, and 1650 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.23; H, 5.60.

Catalytic Reduction of 3-Oxo-6-(*p*-methoxyphenyl)-1-cyclohexenecarboxylic Acid (3c). Acids 5c and 6a and Their Respective Methyl Esters, 5d and 6b.—A solution of 5.24 g (0.021 mol) of acid **3c** in 250 ml of absolute ethanol was hydrogenated with 0.250 g of 10% palladized carbon in a Paar shaker. During the hydrogenation, the product partially precipitated from solution, and uptake of hydrogen stopped after consumption of 1 equiv of hydrogen. The reaction mixture was then warmed on a steam bath to effect solution of precipitated materials and filtered through Celite. The ethanol was removed *in vacuo*, and the crystalline mixture of acids was subjected to a series of fractional crystallizations.

Recrystallization from ethanol afforded 2.14 g (40.3%) of relatively pure *cis*-2-(*p*-methoxyphenyl)-5-oxo-1-cyclohexanecarboxylic acid (**5c**), mp 185–189°. An additional fraction (0.225 g) of less pure acid was obtained upon concentrating the mother liquors. Several recrystallizations from ethanol afforded an analytical sample of **5c**: mp 188–190°; ir (KBr) 3200–2800, 1725, and 1695 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 248 (48), 178 (14), 148 (36), 147 (100), 134 (97), 121 (23), and 91 (15).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.82; H, 6.74.

The ethanol was removed from the above mother liquors, and, upon recrystallization from benzene, 1.56 g (29.5%) of *cis*-3-hydroxy-6-(*p*-methoxyphenyl)-1-cyclohexenecarboxylic acid (**6a**) containing a small amount of keto acid **5c** was obtained. Several recrystallizations from benzene afforded an analytical sample of **6a**: mp 195–196.5°; ir (KBr) 3375, 3100–2700, 1695, 1660, and 1605 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 249 (16), 248 (99), 231 (12), 230 (71), 202 (15), 186 (15), 185 (26), 174 (15), 160 (17), 159 (38), 158 (26), 148 (11), 147 (30), 141 (13), 140 (100), 135 (10), 134 (52), 121 (22), 115 (17), 108 (64), 95 (21), and 91 (16).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.95; H, 6.79.

Upon removal of the benzene from the above mother liquors, 1.10 g of a mixture of both acids was obtained.

Treatment of keto acid **5c** with excess ethereal diazomethane afforded keto ester **5d**: mp 100–101° (benzene–petroleum ether); ir ($CHCl_3$) 1725 cm^{-1} (broad); nmr ($CDCl_3$) δ 1.90–2.80 (6 H, m), 3.40 (2 H, m), 3.48 (3 H, s), 3.82 (3 H, s), and 6.80–7.30 (4 H, m, A_2B_2).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.71; H, 6.91.

Treatment of acid **6a** with excess ethereal diazomethane afforded the methyl ester **6b**: mp 84–85° (diisopropyl ether); ir ($CHCl_3$) 3550–3300, 1715, and 1605 cm^{-1}; nmr ($CDCl_3$) δ 1.35–2.13 (4 H, m), 3.43 (1 H, s, concentration dependent), 3.57 (3 H, s), 3.73 (3 H, s), 3.86 (1 H, $W_{1/2}$ = 8 Hz), 4.37 (1 H, $W_{1/2}$ = 16 Hz, poorly resolved triplet), 6.65–7.32 (4 H, m, A_2B_2), and 6.84 (1 H, s).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.68; H, 6.91.

Manganese Dioxide Oxidation of 3-Hydroxy-6-(*p*-methoxyphenyl)-1-cyclohexenecarboxylic Acid (6a).—A solution of 0.496 g (0.002 mol) of acid **6a** in 50 ml of chloroform was refluxed under nitrogen for 3 hr with 2.50 g of manganese dioxide.[12] The manganese dioxide was removed by filtration, boiled with chloroform for 10 min, and refiltered. The combined filtrates were dried and concentrated *in vacuo*. The crude red-brown oil obtained crystallized on trituration with ether to give 0.210 g (35%) of a solid, mp 138–139° (benzene–methanol), which showed no melting point depression upon admixture with an analytical sample of acid **3c**.

Sodium Borohydride Reduction of 3-Oxo-6-(*p*-methoxyphenyl)-cyclohexenecarboxylic Acid (3c).—To a solution of 496 mg (2 mmol) of acid **3c** in 50 ml of 50% aqueous methanol 0–5°, containing a small amount of potassium carbonate, was added 76 mg (2 mmol) of sodium borohydride. After stirring the reaction mixture for 1 hr, the methanol was removed *in vacuo*, and the reaction mixture was diluted with water, acidified with dilute hydrochloric acid, and thoroughly extracted with ethyl acetate. The combined extracts were dried, concentrated *in vacuo*, and triturated with ether giving 441 mg (90%) of acid **6a**, mp 195–196° (benzene), which showed no melting point depression upon admixture with an analytical sample of acid **6a**.

Lithium–Ammonia Reduction of 3-Oxo-6-(*p*-methoxyphenyl)-1-cyclohexenecarboxylic Acid (3c).—To 300 ml of ammonia (from sodium) was slowly added 0.680 g (0.098 g-atom) of lithium, followed by the addition of 4.03 g (0.016 mol) of acid **3c** in 100 ml of dry tetrahydrofuran. After stirring for 2 hr, a few crystals of ferric chloride were added, and the reaction mixture was stirred until discharge of the blue color was complete. After addition of 1 ml of *tert*-butyl alcohol and further stirring for 5 min, solid ammonium chloride was added, and the resulting mixture was left to evaporate overnight.

The residue was taken up in 300 ml of water and acidified with dilute hydrochloric acid, and the solution was saturated with salt and thoroughly extracted with ethyl acetate. The combined extracts were dried and concentrated *in vacuo*. Trituration of the crude residue with ether gave 2.19 g (54%) of acid **5c**, mp 188–189° (ethanol), which showed no melting point depression upon admixture with an analytical sample of acid **5c**. Treatment of a small amount of the acid with excess ethereal diazomethane gave a methyl ester which was homogeneous by analytical thin layer chromatography and identical with an authentic sample of ester **5d**.

Zinc–Aqueous Acetic Acid Reduction of 3-Oxo-6-(*p*-methoxyphenyl)-1-cyclohexenecarboxylic Acid (3c).—A mixture of 37.00 g (0.150 mol) of acid **3c**, 500 ml of glacial acetic acid, 50 ml of water, and 120 g of zinc dust was refluxed under nitrogen for 30 hr. The reaction mixture was cooled to room temperature, the

zinc removed by filtration and washed with glacial acetic acid, and the filtrate evaporated to dryness. The residual solid mixture of product and zinc acetate was partitioned between warm water–ethyl acetate, and the layers were separated. The aqueous layer was cooled to room temperature, salted, and thoroughly extracted with ethyl acetate. The combined extracts, upon drying and concentration, gave 34.00 g (91%) of acid **5c**, mp 188–189° (ethanol), exhibiting no melting point depression upon admixture with an analytical sample of acid **5c**.

***cis*-2-Phenyl-5-oxocyclohexanecarboxylic Acid (5a) and Its Methyl Ester 5b.**—In the manner described (*vide supra*), refluxing a solution of 34.27 g (0.159 mol) of acid **3b** in a mixture of 500 ml of glacial acetic acid, 50 ml of water, and 120 g of zinc dust afforded 32.50 g (94%) of crude acid **5a**: mp 201–202° (ethanol); ir (KBr) 3225 (broad), 1726, and 1695 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.45; H, 6.52.

Treatment of the above acid with excess ethereal diazomethane gave the methyl ester **5b**: mp 114.5–115.5° (methanol); ir ($CHCl_3$) 1725 cm^{-1} (broad); nmr (CDCl) δ 1.85–2.90 (6 H, m), 3.40 (3 H, s), 3.10–3.55 (2 H, m), and 7.00–8.40 (5 H, m).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.29; H, 7.11.

Ethylene Thioketal of *cis*-2-Phenyl-5-oxocyclohexanecarboxylic Acid (5e) and Its Methyl Ester 5f.—To a solution of 6.00 g (0.028 mol) of acid **5a** in 60 ml of hot glacial acetic acid were added 5 ml of boron trifluoride etherate and 5 ml of ethanedithiol.[26] The resulting solution was cooled to room temperature and stored in a refrigerator overnight. The crystalline thioketal was filtered and air-dried: mp 159–160° (ethyl acetate); ir (KBr) 3200–2800 and 1685 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 296 (10), 295 (16), 294 (90), 234 (11), 233 (22), 201 (10), 200 (23), 176 (18), 155 (36), 149 (15), 133 (15), 132 (15), 131 (100), 129 (11), 115 (14), 104 (25), 91 (31), 86 (11), 77 (12), and 61 (17).

Anal. Calcd for $C_{15}H_{18}O_2S_2$: C, 61.21; H, 6.17. Found: C, 61.10; H, 6.11.

Treatment of the above acid with excess ethereal diazomethane gave the methyl ester **5f**: mp 72.5–73.5° (methanol); ir ($CHCl_3$) 1735 cm^{-1}; nmr ($CDCl_3$) δ 1.95–2.32 (4 H, m), 2.42–2.60 (2 H, m), 2.87–3.38 (2 H, m), 3.25 (2 H, m), 3.42 (3 H, s), and 7.00–7.37 (5 H, m).

Anal. Calcd for $C_{16}H_{20}O_2S_2$: C, 62.32; H, 6.54. Found: C, 62.19; H, 6.51.

***cis*-2-Phenylcyclohexanecarboxylic Acid (5g).**—A mixture of 308 mg (1 mmol) of thioketal **5f**, 6.00 g of Raney nickel W-2, and 25 ml of absolute ethanol was refluxed under nitrogen for 17 hr. The reaction mixture was filtered through Celite, and the Raney nickel was washed thoroughly with ethanol. Concentration of the filtrate *in vacuo* yielded 196 mg (90%) of desulfurized product (homogeneous by analytical thin layer chromatography) exhibiting ester absorption at 1725 cm^{-1} in its infrared spectrum, and no thioketal singlet in its nmr spectrum.

The above desulfurized product was hydrolyzed by refluxing it in a mixture of 10 ml of methanol, 10 ml of water, and 212 mg (2 mmol) of sodium carbonate for 18 hr. The solution was cooled to room temperature, saturated with salt, and thoroughly extracted with ether. The combined ether extracts, upon drying and concentration *in vacuo*, yielded 35 mg (17%) of unhydrolyzed ester.

The basic aqueous layer was acidified with dilute hydrochloric acid and thoroughly extracted with ether. Upon drying the combined ether extracts and concentrating *in vacuo*, 105 mg of oil was obtained. The oil completely crystallized on standing to give acid **5g**: mp 76–77° (petroleum ether) (lit.[13] mp 77°); ir (KBr) 3200–2800 and 1700 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 204 (54), 186 (21), 158 (37), 144 (21), 131 (10), 130 (16), 129 (15), 118 (30), 117 (97), 115 (19), 113 (21), 104 (49), 92 (40), 91 (100), 78 (14), and 77 (14).

7-Methoxy-*cis*-1,2,3,4,4a,9a-hexahydrofluorene-2,9-dione (7b).—To 500 g of polyphosphoric acid heated to 80–85° in an oil bath, 10.00 g (0.0404 mol) of finely powdered keto acid **5c** was added in one portion, and the resulting solution was stirred for 10 min. The yellow-brown solution was poured into 1.5 l. of ice-cold water, stirred until decomposition of the polyphosphoric acid was complete, saturated with salt, and extracted with three portions of chloroform (250, 250, and 100 ml). The combined chloroform extracts, after washing with two 100-ml portions of 8% aqueous solium hydroxide, drying, and concentrating *in vacuo*, afforded 7.80 g (84%) of semicrystalline solid. Trituration with ether gave 5.60 g (60%) of crude solid, mp 94–98°, which provided diketone **7b**: mp 103–103.5° (ethanol); ir ($CHCl_3$) 1713 cm^{-1}; uv λ_{max} (EtOH) 322 nm (ϵ 4940) and 251 (11,800); nmr ($CDCl_3$) δ 1.65–2.60 (4 H, m), 2.70 (1 H, m), 2.80 (1 H, s), 3.10 and 3.20 (1 H, m), 3.50–3.80 (1 H, m), 3.85 (3 H, s), and 7.20–7.70 (3 H, m).

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 72.90; H, 6.21.

***cis*-1,2,3,4,4a,9a-Hexahydrofluorene-2,9-dione (7a).**—Following the above procedure, 10.00 g (0.046 mol) of keto acid **5a** (reaction time 45 min) afforded 8.30 g (90%) of neutral oil, which on trituration with ether gave 7.28 g (80%) of **7a**, mp 106–107° (ethyl acetate–hexane) (lit.[6] mp 106–107°).

Monoketal 8b.—A solution of 5.44 g (23.6 mmol) of diketone **7b**, 2.80 g (34.4 mmol) of ethylene glycol, and 0.450 g (2.36 mmol) of *p*-toluenesulfonic acid monohydrate in 50 ml of benzene was refluxed under nitrogen for 3 hr with constant separation of water (Dean–Stark trap). The solution was cooled to room temperature, washed with dilute aqueous sodium hydroxide, and dried. Upon concentration *in vacuo*, 4.51 g (70%) of solid, mp 119–121°, was obtained: mp 122–123° (ethanol); ir ($CHCl_3$) 1706 cm^{-1}; uv λ_{max} (EtOH) 320 (ϵ 4360) and 249 (10,000); nmr ($CDCl_3$) δ 1.30–2.40 (6 H, m), 2.70–3.11 (1 H, m), 3.25–3.60 (1 H, m), 3.80 (3 H, m), 3.86–4.04 (4 H, m), and 7.00–7.45 (3 H, m).

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.93; H, 6.51.

Monoketal 8a.—Reaction of 5.14 g (25.7 mmol) of diketone **7a** with 2.42 g (38.6 mmol) of ethylene glycol and 0.490 g (2.57 mmol) of *p*-toluenesulfonic acid monohydrate in 50 ml of benzene as described above afforded 2.58 g (41%) of crude ketal **8a**, mp 80–81° (diisopropyl ether) (lit.[5p] mp 80–82°). The mother liquors contained ketal **8a** and diketal which could readily be hydrolyzed (*vide infra*) and recycled.

Alkylation of Ketal 8b with 2,3-Dibromopropene.—To a suspension of 2.64 g (22.0 mmol) of freshly prepared dry potassium *tert*-butoxide in 25 ml of dry glyme was added 5.58 g (20.0 mmol) of ketal **8b** in 100 ml of glyme. After stirring the resulting solution at room temperature under nitrogen for 5 min, 4.80 g (24.0 mmol) of freshly distilled 2,3-dibromopropene[27] in 25 ml of glyme was added over a period of 15 min. Stirring under nitrogen was continued for 1 hr, during which time potassium bromide precipitated from solution. The reaction mixture was poured into 200 ml of water, saturated with salt, and extracted with four portions of chloroform (two 100-ml and two 50-ml portions). The combined extracts were dried and concentrated *in vacuo*, affording 6.15 g (77%) of alkylated ketal **8c**: mp 103–104° (ethanol); ir ($CHCl_3$) 1712, 1625, 1110, and 1094 cm^{-1}; nmr ($CDCl_3$) δ 1.15–2.40 (6 H, m), 3.12 (2 H, s), 3.59 (1 H, t, J = 5 Hz), 3.82 (3 H, s), 3.71–4.03 (4 H, m), 5.45 (1 H, d, J = 1.5 Hz), 5.60 (1 H, s, br), and 7.06–7.50 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 394 (<1), 392 (<1), 314 (11), 313 (56), 271 (27), 270 (35), 186 (22), 99 (100), 86 (11), and 54 (13).

Anal. Calcd for $C_{19}H_{21}O_4Br$: C, 58.02; H, 5.38. Found: C, 58.17; H, 5.27.

Diketone 7c from Hydrolysis of Ketal 8c.—A solution of ketal **8c** (4.44 g, 11.3 mmol) was refluxed under nitrogen in 75 ml of methanol containing 25 ml of 5% hydrochloride acid for 1 hr. The solution was poured into 200 ml of water, saturated with salt, and extracted with five portions of chloroform. The solution was dried, concentrated, and triturated with methanol to afford 3.65 g (93%) of diketone **7c**: mp 114–115° (methanol); ir ($CHCl_3$) 1713 and 1623 cm^{-1}; nmr ($CDCl_3$) δ 1.60–2.60 (4 H, m), 2.65 (2 H, s), 2.83 (2 H, s), 3.84 (3 H, s), 3.98 (1 H, m), 5.63 (2 H, m), and 7.10–7.60 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 350 (<1), 348 (<1), 270 (100), 228 (26), 186 (57), and 173 (10).

Anal. Calcd for $C_{17}H_{17}O_3Br$: C, 58.48; H, 4.88. Found: C, 58.50; H, 5.05.

Alkylation of Ketal 8a with 2,3-Dibromopropene.—Following the procedure described (*vide supra*), 6.34 g (26.0 mmol) of ketal **8a** in 50 ml of dry glyme, 3.43 g (28.6 mmol) of freshly prepared dry potassium *tert*-butoxide, and 6.18 g (31.2 mmol) of 2,3-di-

(26) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N. Y., 1967, p 356.

(27) H. Gilman and A. H. Blatt, Ed., "Organic Syntheses," Collect. Vol. I, 2nd ed, Wiley, New York, N. Y., 1958, p 209. The compound was freshly distilled prior to use.

bromopropene in 25 ml of glyme afforded a yellow oil, which on trituration with ether gave 7.16 g (76%) of ketal **8d**, mp 100–102° (ethanol) (lit.[5p] mp 100–102°).

Diketone 7d from Hydrolysis of Ketal 8d.—In the manner described (*vide supra*), 3.00 g (8.29 mmol) of ketal **8d** provided, upon trituration with ether, 2.18 g (83%) of the known[5p] diketone **7d**, mp 74–75°.

Allyl Diketone 7e from Ketal 8b.—To a suspension of 624 mg (5.5 mmol) of freshly prepared dry potassium *tert*-butoxide in 10 ml of dry glyme was added 1.37 g (5 mmol) of ketal **8b** in 30 ml of glyme. After stirring the resulting solution at room temperature under nitrogen for 5 min, 726 mg (6.0 mmol) of allyl bromide in 10 ml of glyme was added over a period of 15 min. Stirring under nitrogen was continued for 1 hr, during which time potassium bromide precipitated from solution. The reaction mixture was then poured into 100 ml of water, saturated with salt, and extracted with four portions of chloroform. The combined extracts were dried and concentrated *in vacuo*, yielding 1.60 g (100%) of alkylated ketal as a yellow oil: ir ($CHCl_3$) 1711, 1642, 1115, 1095, 992, and 905 cm^{-1}; nmr ($CDCl_3$) δ 1.36–2.24 (6 H, m), 2.30 (1 H, d, J_{AB} = 15 Hz), 2.55 (1 H, d, J_{AB} = 15 Hz), 3.22 (1 H, t, J = 6 Hz), 3.82 (3 H, s), 3.70–3.98 (4 H, m), and 4.83–6.00 (3 H, m).

The above ketal (1.60 g, 5 mmol) was refluxed under nitrogen with 25 ml of methanol and 10 ml of 5% hydrochloric acid for 1 hr. The solution was poured into 100 ml of water, saturated with salt, and extracted with four portions of chloroform. After washing the chloroform extracts with water and drying, the solvent was removed *in vacuo* to give 1.24 g (90%) of allyl diketone **7e** as a yellow oil: ir ($CHCl_3$) 1713, 1642, 992, and 905 cm^{-1}; nmr ($CDCl_3$) δ 1.66–2.50 (6 H, m), 3.49 (1 H, t, J = 6 Hz), 3.82 (3 H, s), 4.89–6.06 (3 H, m), and 7.10–7.56 (3 H, m).

Grignard Reaction of Diketone 7c.—To a mixture of 915 mg (37.6 mg-atoms) of 70–80 mesh magnesium, 5 ml of dry tetrahydrofuran, and a crystal of iodine was added two drops of ethylene dibromide, and the mixture was warmed briefly until the color of the iodine had disappeared. The mixture was brought to reflux as 1.13 g (3.76 mmol) of diketone **7c** in 20 ml of tetrahydrofuran was added over a period of 15 min, after which the resulting mixture was refluxed for 5 hr under nitrogen.

The reaction mixture was then cooled to room temperature, filtered through glass wool into 100 ml of saturated aqueous ammonium chloride solution, and thoroughly extracted with chloroform. Upon drying of the extracts and concentration *in vacuo*, 1.3 g of yellow oil was obtained. An analytical thin layer chromatogram indicated that the oil consisted of allyl diketone **7e** and a slower moving component, subsequently shown to be alcohol **10**, and polar material at the origin. The polar material was removed by chromatography of the oil (1.31 g) on Florisil (39 g). Elution with 2–10% ether–benzene afforded 330 mg of a mixture of **7e** and **10**. The nmr spectrum of this oil exhibited methoxyl singlets at δ 3.82 (**7e**) and 3.74 (**10**) in a ratio of 4:1. Separation of the major component was effected by preparative thin layer chromatography (employing 30% ethyl acetate–benzene as the mobile phase), 130 mg of the mixture affording 60 mg of allyl diketone **7e**. The ir and nmr spectra of this material were identical with those of an authentic allyl diketone **7e** (*vide supra*).

In another experiment, the reaction was carried out exactly as described above, except that the reaction mixture was allowed to reflux for a total of 48 hr. Work-up as described above afforded 1.08 g of oil, which, after washing through a column of Florisil (10 g) in benzene, yielded 626 mg of oil. The nmr spectrum of the oil exhibited methoxyl singlets at δ 3.82 and 3.74 in a ratio of 1:5. Separation of the major component was effected by preparative thin layer chromatography employing 30% ethyl acetate–benzene as the mobile phase and afforded 233 mg of alcohol **10** contaminated with a trace of allyl diketone **7e** (analytical thin layer chromatography). The ir spectrum of this oil exhibited broad hydroxyl absorption at 3600–3300 cm^{-1} and carbonyl absorption at 1722 cm^{-1} (alkyl ketone) and displayed a typical allyl multiplet at δ 4.70–6.00 in its nmr spectrum.

Oxidation of 80 mg of the above alcohol **10** with Sarett's reagent afforded 55 mg of oil, having an nmr spectrum identical with that of allyl diketone **7e**.

Addition of Ketal 8b to Methyl α-Bromoacrylate.—To a solution of potassium *tert*-butoxide in *tert*-butyl alcohol (23 mg, 0.60 mmol) was added 548 mg (2.00 mmol) of ketal **8b** in 5 ml of dry tetrahydrofuran followed immediately by a solution of 363 mg (2.20 mmol) of methyl α-bromoacrylate in 5 ml of dry tetrahydrofuran. The resulting solution was diluted with water, saturated with salt, and thoroughly extracted with ether. The extracts were dried and concentrated *in vacuo*. The residue was dissolved in a mixture of 10 ml of tetrahydrofuran and 5 ml of 10% hydrochloric acid and allowed to stand at room temperature for 2 hr. The solution was poured into water, saturated with salt, and thoroughly extracted with ether. After drying and concentrating *in vacuo*, the crude product was washed through a short column of Florisil with benzene, and afforded 523 mg (67% overall) of bromo ester **12a**: ir ($CHCl_3$) 1720 cm^{-1}; nmr ($CDCl_3$) δ 1.60–2.80 (8 H, m), 3.40–3.65 (1 H, m), 3.69 and 3.74 (3 H, s, 3:5 ratio, respectively), 3.85 (3 H, s), 4.20–4.58 (1 H, m) and 7.05–7.60 (3 H, m).

***N,N*-Dimethyl-α-bromoacrylamide.**[28]—The procedure of Drake,[29] *et al.*, for the preparation of α-halo amides was adapted. To a solution of 39.27 g (0.157 mol) of α,β-dibromopropionyl chloride[30] in 100 ml of ether cooled to 0° in an ice bath was added 21 ml (0.314 mol) of dimethylamine in 200 ml of ether (precooled to 0°) with constant stirring under nitrogen. The dimethylamine solution was added at such a rate that the temperature of the reaction mixture was maintained at 0–5°. Enough water to dissolve the precipitated dimethylamine hydrobromide was added, the layers were separated, and the aqueous layer was thoroughly extracted with ether. The combined ether extracts were dried and concentrated *in vacuo*, and the residue was stirred with 100 ml of tetrahydrofuran and 100 ml of 5% aqueous sodium hydroxide for 30 min under nitrogen. The solution was diluted with water, saturated with salt, and extracted with ether, providing 20.20 g (73% overall) of α-bromo-*N,N*-dimethylacrylamide: bp 70° (0.5 mm); nmr ($CDCl_3$) δ 3.05 (6 H, s, br), 5.87 (1 H, d, J = 3 Hz), and 6.21 (1 H, d, J = 3 Hz).

Addition of Ketal 8b to *N,N*-Dimethyl-α-bromoacrylamide.—To a solution of potassium *tert*-butoxide in *tert*-butyl alcohol (398 mg, 10.2 mmol of potassium dissolved in 50 ml of dry *tert*-butyl alcohol) was added 9.29 g (33.9 mmol) of ketal **8b** in 80 ml of dry tetrahydrofuran, followed immediately by a solution of 6.64 g (37.3 mmol) of *N,N*-dimethyl-α-bromoacrylamide in 50 ml of tetrahydrofuran. The resulting solution was stirred at room temperature under nitrogen for 18 hr. The reaction mixture was worked up, hydrolyzed, and passed through a short column of Florisil with benzene as described for bromo ester **12a**, affording 9.19 g (67%) of bromoamide **12c** as a 1:2 mixture of diastereomers: nmr ($CDCl_3$) δ 2.80 (3 H, s), 2.84 (3 H, s), 3.85 (3 H, s), and 4.54 (1 H, dd, J_{AX} = 4, J_{BX} = 10 Hz) for the minor diastereomer and 3.02 (3 H, s), 3.85 (3 H, s), and 4.96 (1 H, dd, J_{AX} = 4, J_{BX} = 10 Hz) for the major diastereomer.

Addition of Ketal 8b to *tert*-Butyl α-Bromoacrylate.—To a solution of potassium *tert*-butoxide in *tert*-butyl alcohol (235 mg, 6 mmol of potassium dissolved in 5 ml of dry *tert*-butyl alcohol) was added 5.48 g (20.0 mmol) of ketal **8b** in 60 ml of dry tetrahydrofuran followed immediately by a solution of 4.55 g (22.0 mmol) of *tert*-butyl α-bromoacrylate in 20 ml of tetrahydrofuran. The resulting solution was stirred at room temperature under nitrogen for 3 hr. Work-up, hydrolysis, and passage of the crude product through a short column of Florisil with benzene as described for bromo ester **12a** afforded 6.19 (71%) of bromo ester **12b** as a mixture of diastereomers: ir ($CHCl_3$) 1720 cm^{-1}; nmr ($CDCl_3$ δ 1.60–2.98 (8 H, m), 1.40 and 1.46 (9 H, 2s, ratio 2:3), 3.40–3.70 (1 H, m), 3.84 (3 H, s), 4.10–4.46 (1 H, m), and 7.20–7.55 (3 H, m).

Reformatsky Reaction of Bromo Ester 12a. Benzoates 13c and 13d.—To a suspension of 19.00 g (0.29 g-atom) of activated zinc dust[31] in 50 ml of dry benzene was added a crystal of iodine. After warming the reaction flask briefly until the color of the iodine had disappeared, a solution of 4.58 g (11.6 mmol) of freshly prepared bromo ester **12a** in 50 ml of dry benzene was added, and the resulting solution was refluxed under nitrogen for 24 hr. The reaction mixture was cooled to room temperature, 10 ml of benzoyl chloride was added, and the mixture was stirred overnight under nitrogen. The excess zinc was removed by filtration and washed with benzene, and excess benzoyl chloride

(28) This compound has been reported in the literature, although no details or data were given: I. R. Knunpants, E. E. Rytslin, and N. P. Gambaryan, *J. Gen. Chem. USSR*, **32**, 1235 (1962).

(29) N. L. Drake, C. E. Baker, and W. Shenk, *J. Amer. Chem. Soc.*, **70**, 677 (1948).

(30) C. S. Marvel, J. Dec, H. G. Cooke, and J. C. Cowan, *ibid.*, **62**, 3495 (1940).

(31) The zinc was activated by washing successively with dilute hydrochloric acid, absolute ethanol, acetone, and ether, and drying *in vacuo*.

was decomposed by stirring the benzene filtrate with aqueous sodium bicarbonate at room temperature. The layers were separated and the aqueous bicarbonate solution was thoroughly extracted with benzene. Upon drying the combined benzene extracts and concentrating *in vacuo*, 3.55 g (69%) of semicrystalline solid was obtained. The thin layer chromatogram of this material indicated two components of almost identical R_f values contaminated with a small amount of polar material. Upon trituration of the residue with ether, 1.09 g (22%) of impure benzoate **13c**, mp 141–146°, was obtained, Recrystallization from methanol afforded pure benzoate **13c**, obtained at different times in two crystalline modifications: needles, mp 153–154°, and rhombs, mp 166–167°. That these two samples were the same material was indicated by their identical infrared, nmr, and mass spectra, as well as a mixture melting point, 166–167°: ir ($CHCl_3$) 1736 and 1700 cm^{-1}; uv λ_{max} (EtOH) 323 nm (ϵ 3750) and 250 (11,000); nmr ($CDCl_3$) δ 1.60–2.55 (8 H, m), 2.60–3.00 (1 H, m), 3.25–3.55 (1 H, m), 3.68 (3 H, s), 3.86 (3 H, s), and 7.15–8.10 (8 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 420 (10), 298 (11), 266 (13), and 105 (100).

Anal. Calcd for $C_{25}H_{24}O_6$: C, 71.41; H, 5.75. Found: C, 71.42; H, 5.84.

Chromatography of the above mother liquor (2.35 g) on Florisil (70 g) afforded 250 mg (5%) of benzoate **13d**, mp 159–160° (methanol), on elution with 1–5% ether–benzene: ir ($CHCl_3$) 1730 and 1710 cm^{-1}; uv λ_{max} (EtOH) 323 nm (ϵ 3330) and 250 (11,500); nmr ($CDCl_3$) δ 1.60–2.70 (8 H, m), 2.83–3.25 (1 H, m), 3.35–3.70 (1 H, m), 3.77 (3 H, s), 3.81 (3 H, s), and 7.15–8.15 (8 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 420 (4), 299 (20), 298 (100), 266 (22), 239 (49), 238 (46), 225 (12), 185 (22), 105 (64), 83 (12), 71 (19), 70 (13), 69 (17), 57 (32), 43 (19), and 41 (22).

Anal. Calcd for $C_{25}H_{24}O_6$: C, 71.41; H, 5.75. Found: C, 71.34; H, 5.94.

Elution with 10% ether–benzene ether gave 600 mg of benzoate **13c**, mp 166–167°, obtained by trituration with ether (total yield of benzoate **13c**, 1.69 g, 35%).

Lithium Aluminum Hydride Reduction of Benzoate 13c.—A mixture of 210 mg (0.5 mmol) of benzoate **13c** and 150 (4 mmol) of lithium aluminum hydride in 15 ml of dry tetrahydrofuran was refluxed under nitrogen for 1 hr. The reaction mixture was cooled for an ice bath, the excess aluminum hydride was decomposed with saturated aqueous sodium sulfate solution, and the resulting mixture was thoroughly extracted with ether, dried, and concentrated, giving 145 mg (100%) of triol **14a**: mp 178–180° (ethyl acetate); ir (KBr) 3400–3200 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 290 (35), 272 (20), 233 (15), 232 (100), 231 (19), 230 (100), 229 (17), 223 (10), 215 (12), 213 (12) 211 (11), 202 (15), 199 (18), 188 (10), 186 (38), 185 (33), 180 (10), 178 (15), 175 (12), 174 (25), 173 (40), 172 (65), 171 (30), 169 (10), 160 (12), 159 (38), 152 (10), 129 (18), 121 (18), 115 (12), 102 (60), 95 (10), 93 (18), 87 (49), 83 (98), 73 (15), 60 (65), 59 (30), and 57 (38).

Lithium Aluminum Hydride Reduction of Benzoate 13d.—A mixture of 30 mg (0.71 mmol) of benzoate **13d** and 10 mg (0.263 mmol) of lithium aluminum hydride in 5 ml of dry tetrahydrofuran was refluxed under nitrogen for 1 hr. Work-up as described (*vide supra*) afforded 18 mg (88%) of triol **14b**: mp 209–210° (acetone); ir (KBr) 3450–3200 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 290 (33), 233 (16), 232 (100), 231 (10), 230 (49), 215 (11), 214 (45), 199 (14), 187 (16), 186 (30), 185 (16), 178 (19), 175 (10), 174 (18), 173 (36), 172 (59), 171 (21), 160 (11), 159 (38), 158 (15), 115 (14), 91 (10), 57 (11), and 41 (18).

Epimerization of Benzoate 13d.—To a solution of 20 mg (0.476 mmol) of benzoate **13d** in 3 ml of dry tetrahydrofuran was added 1.5 ml of 0.046 *M* potassium *tert*-butoxide–*tert*-butyl alcohol solution, and the resulting solution was left at room temperature for 18 hr. The solution was then acidified with 0.1 *N* hydrochloric acid and evaporated to dryness *in vacuo*. The residue was taken up in water and thoroughly extracted with ether. Upon drying and concentrating 18 mg of an oil was obtained. The thin layer chromatogram of this oil indicated that the product was identical with benzoate **13c** contaminated with a small amount of polar material. No trace of starting benzoate **13d** was found.

Treatment of 15 mg (0.36 mmol) of benzoate **13d** as above gave 14 mg of recovered benzoate.

Reformatsky Reaction of Bromo Ester 12a. Acetates 13a and 13b.—In the manner described for the preparation of benzoates **13c** and **13d**, a mixture of 3.55 g (8.45 mmol) of freshly prepared bromo ester **12a** and 13.9 g (0.214 g-atom) of activated zinc dust in 100 ml of dry benzene was refluxed under nitrogen for 24 hr. The reaction mixture was cooled to room temperature, 10 ml of acetic anhydride was added, and the mixture was stirred overnight at room temperature under nitrogen. Work-up (*vide supra*) afforded 2.65 g (88%) of semicrystalline solid, the thin layer chromatogram of which indicated a mixture of two components of almost identical R_f values contaminated with a small amount of polar material. Trituration of the residue gave 1.21 g (40%) of acetate **13a**: mp 181–192° (methanol); ir ($CHCl_3$) 1745, 1738 (sh), and 1712 cm^{-1}; nmr ($CDCl_3$) δ 1.50–2.66 (8 H, m), 1.99 (3 H, s), 2.71–3.00 (1 H, m), 3.10–3.45 (1 H, m), 3.75 (3 H, s), 3.86 (3 H, s), and 7.20–7.50 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 358 (24), 298 (16), 272 (13), 266 (10), 239 (10), 238 (13), 231 (14), 230 (100), 174 (18), and 173 (13).

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 67.26; H, 6.27.

The mother liquors (1.44 g) upon Florisil chromatography afforded 93 mg (3%) of acetate **13b**: mp 129–131° (2–5% ether–benzene eluents); ir ($CHCl_3$) 1738 (sh), 1730, and 1708 cm^{-1}; nmr ($CDCl_3$) 1.60–2.88 (8 H, m), 2.04 (3 H, s), 2.98–3.60 (2 H, m), 3.76 (3 H, s), 3.85 (3 H, s), and 7.10–7.50 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 358 (2), 299 (21), 298 (100), 267 (15), 266 (33), 240 (15), 239 (81), 238 (62), 225 (17), 224 (19), 223 (11), 173 (8), and 43 (13).

The remainder of the material in the mother liquors was eluted in the 10% ether–benzene → ether fractions, and afforded a broad melting (110–170°) mixture of the two diastereomers.

Lithium Aluminum Hydride Reduction of Acetate 13a.—A mixture of 358 mg (1 mmol) of acetate **13a** and 100 mg (2.63 mmol) of lithium aluminum hydride in 20 ml of dry tetrahydrofuran under nitrogen for 1 hr afforded, upon work-up, 248 mg (86%) of triol **14a**, mp 178–180° (ethyl acetate), which exhibited no melting point depression on admixture with a sample of triol **14a** prepared by reduction of benzoate **13c**.

Lithium Aluminum Hydride Reduction of Acetate 13b.—Refluxing a mixture of 50 mg (0.140 mmol) of acetate **13b** and 50 mg (1.3 mmol) of lithium aluminum hydride in 5 ml of dry tetrahydrofuran under nitrogen for 1 hr afforded, upon work-up, 34 mg (84%) of triol **14b**, mp 207–209°. Recrystallization from acetone afforded crystals, mp 209–210°, which gave no melting point depression on admixture with a sample of triol **14b** prepared by reduction of benzoate **13d**.

Reformatsky Reaction of Bromo Ester 12a. Alcohol 13e.—A mixture of 984 mg (2.84 mmol) of freshly prepared bromo ester **12a** and 3.26 g (0.05 g-atom) of activated zinc dust in 20 ml of dry tetrahydrofuran was refluxed under nitrogen for 24 hr. The reaction mixture was cooled to room temperature, 2 ml of acetic anhydride was added, and the reaction mixture was stirred overnight at room temperature under nitrogen. Work-up as described (*vide supra*) afforded 647 mg (82.5%) of a semicrystalline solid, the thin layer chromatogram of which indicated a mixture of two components contaminated with a small amount of polar material. Trituration of the residue afforded 347 mg (44%) of alcohol **13e**: mp 198.5–200° (ethyl acetate); ir (KBr) 3500 and 1710 cm^{-1}; nmr ($CDCl_3$) δ 1.50–3.30 (10 H, m), 3.50–3.70 (1 H, s, br), 3.76 (3 H, s), 3.86 (3 H, s), and 7.10–7.45 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 316 (31), 231 (16), 230 (100), 229 (11), 202 (15), and 175 (11).

Anal. Calcd for $C_{18}H_{20}O_6$: C, 68.34; H, 6.37. Found: C, 68.09; H, 6.25.

Lithium Aluminum Hydride Reduction of 13e.—A mixture of 50 mg (0.16 mmol) of alcohol **13e** and 50 mg (1.3 mmol) of lithium aluminum hydride in 5 ml of dry tetrahydrofuran was refluxed under nitrogen for 1 hr, affording 40 mg (99%) of triol **14a**, mp 178–180° (ethyl acetate), which exhibited no melting point depression on admixture with a sample of triol **14a** prepared by reduction of benzoate **13c**.

Reformatsky Reaction of Bromo Amide 12c. Amide 13h.—A mixture of 2.63 g (6.42 mmol) of freshly prepared bromo amide **12e** and 10.5 g (0.16 g-atom) of activated zinc in 100 ml of dry benzene was refluxed under nitrogen for 24 hr. The reaction mixture was cooled to room temperature, 5 ml of acetic anhydride was added, and the mixture was stirred overnight under nitrogen. Work-up as described for benzoates **13c** and **13d** afforded 1.96 g (82%) of a semicrystalline solid, the thin layer chromatogram (25% methanol–benzene) of which indicated two components of almost identical R_f values contaminated with a small amount of polar material. Trituration of the residue with acetone gave 1.23 g (51%) of amide **13h**: mp 194–196° (methanol); ir ($CHCl_3$) 1727, 1710, and 1644 cm^{-1}; nmr ($CDCl_3$) δ 1.97 (3 H, s), 1.60–

2.95 (8 H, m), 3.00 (3 H, s), 3.13 (3 H, s), 2.95–3.30 (1 H, m), 3.40–3.70 (1 H, m), 3.84 (3 H, s), and 7.10–7.50 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 371 (4), 273 (11), 231 (15), 230 (100), 100 (25), 55 (20), 46 (11), and 43 (18).

No attempt was made to isolate the minor diastereomer from the mother liquors.

Reformatsky Reaction of Bromo Ester 12b. Esters 13f and 13g.—A mixture of 6.19 g (14.2 mmol) of freshly prepared bromo ester **12b** and 23.2 g (0.35 g-atom) of activated zinc dust in 150 ml of dry benzene[32] was refluxed under nitrogen for 4 hr. The reaction mixture was cooled to room temperature, 10 ml of acetic anhydride was added, and the mixture was stirred for 1 hr under nitrogen. Work-up (*vide supra*) afforded 5.14 g (90%) of a semicrystalline solid, the thin layer chromatogram of which indicated a mixture of two components of almost identical R_f contaminated with a small amount of polar material. Trituration of the residue with ether afforded 980 mg (19%) of ester **13f**: mp 153–154° (ethanol); ir ($CHCl_3$) 1732 and 1709 cm^{-1}; nmr ($CDCl_3$) δ 1.50 (9 H, s), 2.00 (3 H, s), 1.30–2.60 (8 H, m), 2.65–3.30 (2 H, m), 3.82 (3 H, s), and 7.10–7.60 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 400 (17), 343 (17), 327 (12), 285 (17), 284 (46), 272 (27), 267 (14), 266 (10), 256 (11), 242 (13), 240 (37), 239 (12), 230 (63), 229 (23), 211 (12), 187 (12), 174 (16), 173 (11), 57 (100), 55 (21), 43 (38), and 41 (25). Chromatography of the mother liquors on Florisil afforded 170 mg (3%) of pure ester **13g**, mp 98–99° (methanol), upon elution with 1–2% ether–benzene: ir ($CHCl_3$) 1710 cm^{-1}; nmr ($CDCl_3$) δ 0.52 (9 H, s), 2.03 (3 H, s), 1.50–2.65 (8 H, m), 2.70–3.70 (2 H, m), 3.82 (3 H, s), and 7.10–7.60 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 400 (1), 343 (10), 285 (24), 284 (100), 267 (14), 266 (15), 265 (10), 240 (14), 239 (46), 238 (41), 237 (26), 211 (17), 57 (32), 55 (18), 43 (36), and 41 (19).

Lithium Aluminum Hydride Reduction of Ester 13f.—A mixture of 50 mg (0.125 mmol) of ester **13f** and 20 mg (0.53 mmol) of lithium aluminum hydride in 5 ml of tetrahydrofuran was refluxed under nitrogen for 1 hr. Work-up (*vide supra*) yielded 34 mg (94%) of triol **14a**, mp 178–180° (ethyl acetate), exhibiting no melting point depression on admixture with a sample of triol **14a** prepared by reduction of benzoate **13c**.

Lithium Aluminum Hydride Reduction of Ester 13g.—A mixture of 30 mg (0.075 mmol) of ester **13g** and 15 mg (0.39 mmol) of lithium aluminum hydride in 3 ml of tetrahydrofuran was refluxed under nitrogen for 1 hr. Work-up (*vide supra*) yielded 24 mg (92%) of triol **14b**, mp 209–210° (ethyl acetate), exhibiting no melting point depression on admixture with a sample of triol **14b** prepared by reduction of benzoate **13d**.

Registry No.—**2a**, 23673-44-1; **2b**, 31729-94-9; **2c**, 23673-45-2; **3a**, 23673-46-3; **3c**, 23673-47-4; **5a**, 23668-27-1; **5b**, 31729-99-4; **5c**, 23668-28-2; **5d**, 31730-01-5; **5e**, 31730-02-6; **5f**, 31730-03-7; **5g**, 24905-74-6; **6a**, 31730-05-9; **6b**, 31730-06-0; **7b**, 23755-91-1; **7c**, 31730-08-2; **7e**, 31730-09-3; **8b**, 31730-10-6; **8c**, 31730-11-7; **12a**, 31730-12-8; **12b**, 31790-82-6; **12c**, 31790-83-7; **12d**, 31730-13-9; **13a**, 31730-14-0; **13b**, 31730-15-1; **13c**, 31730-16-2; **13d**, 31730-17-3; **13e**, 31730-18-4; **13f**, 31730-19-5; **13g**, 31730-20-8; **13h**, 31730-21-9; **14a**, 31730-22-0; **14b**, 31730-23-1; 2-methyl-4-(*p*-methoxybenzylidene)oxazol-5-one, 31730-24-2; α-bromo-*N*,*N*-dimethylacrylamide, 31730-25-3.

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(32) *Cf.* A. E. Opara and G. Read, *Chem. Commun.*, 679 (1969).

The Influence of Reaction Conditions and Stereochemistry on Some Thioacetate Displacements with Carbohydrate Sulfonates[1]

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The reaction of 1,2-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-α-D-apio-L-furanose (**1**) with potassium thioacetate in boiling ethanol gave bis(5-deoxy-1,2-*O*-isopropylidene-α-D-apio-L-furanose-5-yl) disulfide (**2**) in high yield. Deacetylation of the intermediate thiolacetate **6** and subsequent oxidation of the thiol to **2** evidently occurred under these conditions. In aprotic solvents (DMF or acetone), both intramolecular S → O acetyl migration and S acetylation were observed in the reaction of **1** with potassium thioacetate, and a complex mixture of products was obtained. Acid-catalyzed methanolysis of the thiol obtained by reduction of **2** led to migration of the isopropylidene group and the formation of methyl 2,3-*O*-isopropylidene-4-thio-β-D-apio-D-furanoside (**8**). The reaction of methyl 2,3-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-β-D-apio-D-furanoside (**9**) with potassium thioacetate in boiling ethanol gave a mixture of disulfide **12** and monosulfide **13**. In this case, the intermediate thiol is a sufficiently powerful nucleophile to complete with thioacetate ion for **9** and, when thes ame reaction was carried out with 1,2-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-α-D-xylofuranose (**14**), the monosulfide **15** was obtained in 85% yield. Displacement of the sulfonyloxy group of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-allofuranose was readily effected with potassium thioacetate in DMF to give, in high yield, 3-*S*-acetyl-1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-glucofuranose. Oxidative deacetylation of this compound gave the corresponding gluco disulfide and similar treatment of 3-*S*-acetyl-1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-allofuranose gave the isomeric allo disulfide.

The use of potassium thioacetate in nucleophilic displacements of sulfonyloxy groups was reported first by Owen and coworkers in 1950.[3,4] They found that primary sulfonates reacted readily on heating with 2 equiv of potassium thioacetate in acetone or ethanol to give fairly good yields of thiolacetates. An advantage to the use of ethanol is that potassium thioacetate is very much more soluble in this solvent than it is in acetone; and the secondary mesyloxy groups of 1,4:3,6-dianhydro-2,5-di-*O*-methylsulfonyl-D-mannitol can be displaced by potassium thioacetate in ethanol at 110°[4] to give an L-iditol derivative.[5] Deacetylation was observed in this reaction and the reaction mixture was reacetylated prior to isolation of the product. In view of our results (see below), it is probable that transfer of the acetyl group from initially formed thiolacetate to solvent is a rapid reaction in boiling ethanol, catalyzed by the alkalinity of the medium.

(1) Part VI in a series of publications from this laboratory concerning the chemistry of apiose.

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(3) J. H. Chapman and L. N. Owen, *J. Chem. Soc.*, 579 (1950).

(4) P. Bladon and L. N. Owen, *ibid.*, 585 (1950).

(5) A. C. Cope and T. Y. Shen, *J. Amer. Chem. Soc.*, **78**, 3177 (1956).

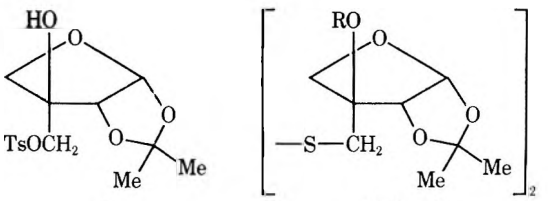
Thioacetate displacements with carbohydrates were reviewed in 1963[6] and, in the past decade, dipolar aprotic solvents, especially *N*,*N*-dimethylformamide (DMF), have been used with notable success in thioacetate displacements of primary[7-9] and secondary[10,11] sulfonyloxy groups. A most convincing demonstration of the nucleophilicity of the thioacetate ion in DMF was the high yield of D-*allo*-thiolacetate obtained with these reagents and 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-glucofuranose,[12] the classic example of a "hindered" sulfonate.

The thiobenzoate ion in DMF has also been used to displace sulfonyloxy groups in carbohydrates[13-16] and the rates of reaction of some 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-hexofuranoses with potassium thiobenzoate in DMF have been measured.[17] Although it appears that the thiobenzoate ion is a stronger nucleophile than thioacetate, the isolated yields obtained from the above displacements of the D-*gluco*- and D-*allo*-thiolbenzoates were both less than 7%,[17] whereas the corresponding thiolacetates were isolated in yields of almost 70% (ref 12 and see below). It therefore seems doubtful that there are any practical advantages to the use of potassium thiobenzoate. Competing thionoacylate formation must be considered as unlikely to occur in detectable amounts in view of the observation that alkylation of potassium thiobenzoate with methyl iodide in acetone gives less than 1% oxygen alkylation.[18]

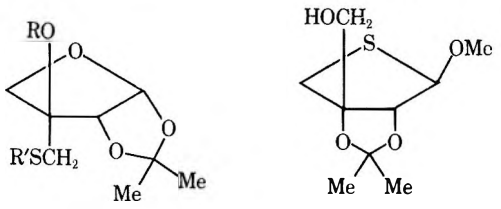
Our interest in thioacetate displacements began with syntheses of analogs of apiose in which the ring oxygen atom is replaced by sulfur, and a preliminary communication of a part of this work has appeared previously.[19] In view of extensive monosulfide formation during a thioacetate displacement with an apiose sulfonate, we have also examined a similar reaction with 1,2-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-α-D-xylofuranose. Displacement of the secondary sulfonyloxy group from 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-allofuranose by thioacetate ion in DMF is also described.

Results

The reaction of 1,2-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-α-D-apio-L-furanose[20,21] [1,2-*O*-isopropylidene-3-*C*-(*p*-tolysulfonyloxymethyl)-β-L-threofuranose] (**1**) with 2 equiv of potassium thioacetate in boiling ethanol was monitored by thin layer chromatography (tlc). After 2 hr, **1** was absent and the major product (shown later to be the thiol **7**) was slowly converted at 0° to a slower moving, uv-absorbing compound. The thiolacetate **6**, presumed to be formed initially, was not observed. After 2 days, bis(5-deoxy-1,2-*O*-isopropylidene-α-D-apio-L-furanose-5-yl) disulfide (**2**) was obtained crystalline in high yield. It appears that the reaction mixture is sufficiently basic to effect rapid transfer of the *S*-acetyl group of **6** to solvent and to promote oxidation of **7** to **2**.



1 **2**, R = H; **3**, R = Ac



4, R = R′ = Ac
5, R = Ac; R′ = H
6, R = H; R′ = Ac
7, R = R′ = H

8

When a similar reaction was carried out in DMF at 100°, **1** was again shown by tlc to be absent after 2 hr and three products were detected and were separated by silica gel chromatography. Initial fractions yielded 3-*O*-acetyl-5-*S*-acetyl-1,2-*O*-isopropylidene-5-thio-α-D-apio-L-furanose (**4**) (an oil) in 25% yield. The second component was obtained crystalline and was shown to be bis(3-*O*-acetyl-5-deoxy-1,2-*O*-isopropylidene-α-D-apio-L-furanose-5-yl) disulfide (**3**) (56% yield). A third fraction, which was mainly one compound, gave a positive thiol test. Treatment of an aliquot with iodine gave the disulfide **3** and S-acetylation with potassium thioacetate in DMF gave the *O*,*S*-diacetate **4**. The major component of this fraction was therefore identified as the thiol **5** and the isolated yield was 9%.

A similar reaction with acetone replacing DMF was complete in 3 days at room temperature and the same products were formed in approximately the same proportions. In an attempt to isolate and fully characterize the thiol **5**, the reaction was modified by using 1 equiv of potassium thioacetate and by rigorous exclusion of oxygen. Disulfide **3** was not detected; the major product after silica gel chromatography was the *O*,*S*-diacetate **4**. The *O*-acetate **5** and the *S*-acetate **6** were isolated as a mixture (21% yield) in an approximate ratio of 3:2, as indicated by nmr spectroscopy. Acetylation of the mixture gave a single compound identical with **4**. A minor constituent of the reaction mixture (*ca.* 10%) was identified as an unsymmetrical disulfide (**2**, with one of the tertiary hydroxyl goups acetylated).

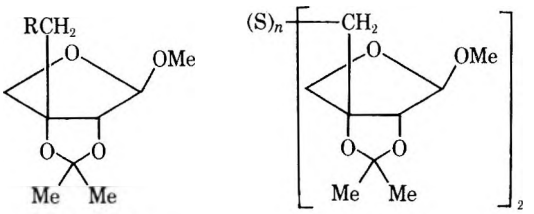
(6) D. Horton and D. H. Hutson, *Advan. Carbohyd. Chem.*, **18**, 123 (1963).
(7) T. J. Adley and L. N. Owen, *Proc. Chem. Soc.*, 418 (1961); *J. Chem. Soc. C*, 1287 (1966).
(8) C. J. Clayton and N. A. Hughes, *Chem. Ind. (London)*, 1795 (1962); *Carbohyd. Res.*, **4**, 32 (1967).
(9) J. M. Cox and L. N. Owen, *J. Chem. Soc. C*, 1121 (1967).
(10) R. L. Whistler, W. E. Dick, T. R. Ingle, R. M. Rowell, and B. Urbas, *J. Org. Chem.*, **29**, 3723 (1964).
(11) L. N. Owen and P. L. Ragg, *J. Chem. Soc. C*, 1291 (1966); L. N. Owen, *Chem. Commun.*, 526 (1967).
(12) U. G. Nayak and R. L. Whistler, *J. Org. Chem.*, **34**, 3819 (1969).
(13) M. A. Bukhari, A. B. Foster, J. Lehman, J. M. Webber, and J. H. Westwood, *J. Chem. Soc.*, 2291 (1963).
(14) E. J. Reist, D. E. Gueffroy, and L. Goodman, *J. Amer. Chem. Soc.*, **85**, 3715 (1963); *ibid.*, **86**, 5658 (1964).
(15) E. J. Reist, L. V. Fisher, D. E. Gueffroy, and L. Goodman, *J. Org. Chem.*, **31**, 1506 (1966).
(16) E. J. Reist, L. V. Fisher, and L. Goodman, *ibid.*, **33**, 189 (1968).
(17) J. M. Heap and L. N. Owen, *J. Chem. Soc. C*, 712 (1970).
(18) S. G. Smith, *Tetrahedron Lett.*, No. 21, 979 (1962).
(19) M. H. Halford, D. H. Ball, and L. Long, Jr., *Carbohyd. Res.*, **8**, 363 (1968).
(20) D. H. Ball, F. A. Carey, I. L. Klundt, and L. Long, Jr., *ibid.*, **10**, 121 (1969).
(21) To preserve the relationship with apiose of the compounds described, the nomenclature used is that suggested by Cahn; see D. J. Bell, F. A. Isherwood, N. R. Hardwick, and R. S. Cahn, *J. Chem. Soc.*, 3702 (1954).

Intramolecular acetyl migration from sulfur to oxygen has been found to occur when the intermediate is a five- or a six-membered ring[22] and is about 30 times faster in the former case.[23] The use of aprotic solvents in the above displacements therefore favors the intramolecular S → O acetyl migration (*via* a five-membered cyclic orthoacetate) to give the thiol **5** from initially formed **6**. The thiol can then be either acetylated to give **4** or oxidized to **3**. It therefore appears that, where such an intramolecular acyl migration is sterically favored, the use of aprotic solvents is likely to give complex mixtures, and the use of protic solvents may be preferable if the disulfide is a useful product. An alternative would be to block the hydroxyl group by, for example, acetylation.

Reduction of **2** with lithium aluminum hydride in ether gave a syrupy thiol which was treated with a 2% solution of hydrogen chloride in methanol. The major product was obtained crystalline after silica gel chromatography and shown to be methyl 2,3-*O*-isopropylidene-4-thio-β-D-apio-D-furanoside (**8**) as anticipated in view of the results obtained with the oxygen analog.[24,25]

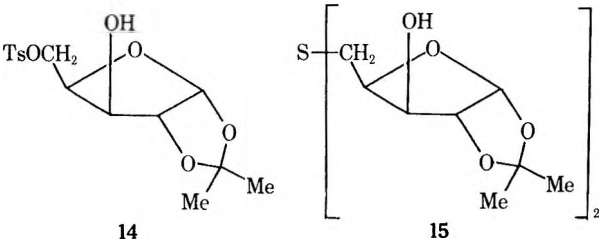
The reaction of methyl 2,3-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-β-D-apio-D-furanoside (**9**)[25] with 2 equiv of potassium thioacetate in boiling ethanol was also examined in the expectation that a disulfide would be the major product. After 2 hr, tlc indicated **9** and a faster moving product (later shown to be the thiol **10**), and these compounds slowly disappeared and were replaced by two slower moving products, one of which was uv absorbing. There was no further change after 24 hr and the mixture was fractionated by chromatography on silica gel. Each of the compounds was obtained as a chromatographically and spectroscopically (nmr) homogeneous syrup. The faster moving, uv-absorbing compound was identified by analytical and spectroscopic data as bis(methyl 5-deoxy-2,3-*O*-isopropylidene-β-D-apio-D-furanoside-5-yl) disulfide (**12**). The slower moving product was similarly characterized as the corresponding monosulfide **13** and the molar ratio of **12**:**13** was determined to be 1:1.3. In this case, it appears that the thiol **10** (formed by rapid deacetylation of the initially formed thiolacetate **11**) is a sufficiently powerful nucleophile to compete with an excess of thioacetate ion for the sulfonate **9**. The remote possibility that the monosulfide **13** could have been formed from the disulfide **12**, a reaction which takes place if the sulfur atom is attached to an active methylene group,[26] was eliminated since no trace of **13** could be detected when a solution of **12** in ethanol was boiled with potassium thioacetate.

When the reaction was repeated with only 1 equiv of potassium thioacetate, **9** and the thiol **10** were still present (together with **12** and **13**) after 48 hr. Fractionation by silica gel chromatography afforded the thiol **10** (15%), starting material (**9**) (5%), and a mixture of **12** and **13** (*ca.* 73%). Integration of the nmr spectrum of the mixture gave the ratio of **12**:**13** as 1:5; *i.e.*, a greater preponderance of monosulfide had been achieved by lowering the concentration of thioacetate ion. Thus, in thioacetate displacements carried out in protic solvents, monosulfide formation is a potential complicating factor. This could also occur in aprotic solvents if intramolecular acetyl migration is possible although the nucleophilicity of the thioacetate ion relative to that of larger thiolate ions may be much greater in these solvents.



9, R = OTs
10, R = SH
11, R = SAc

12, $n = 2$
13, $n = 1$



14 **15**

Adley and Owen[7] found that treatment of 1,2-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-α-D-xylofuranose (**14**) with potassium thioacetate in boiling DMF gave a mixture of 5-*S*-acetyl-1,2-*O*-isopropylidene-5-thio-α-D-xylofuranose and 3-*O*-acetyl-1,2-*O*-isopropylidene-5-thio-α-D-xylofuranose, the product of intramolecular acetyl migration. They also found a small amount of bis(3-*O*-acetyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose-5-yl) disulfide. Neither the *O*,*S*-diacetate nor a monosulfide was found.

When **14** was boiled with 2 equiv of potassium thioacetate in ethanol for 24 hr, tlc indicated the formation of one major product. After silica gel chromatography, the monosulfide **15** was obtained crystalline in 85% yield. There was evidence for the presence of a small amount of the corresponding disulfide but in this case the thiolate ion produced is apparently a more powerful nucleophile and competes very effectively with thioacetate ion for **14**.

The structure of the compound formed by thermal rearrangement of 1,2:5,6-di-*O*-isopropylidene-3-*O*-[(methylthio)thiocarbonyl]-α-D-glucofuranose[27] was shown by nmr spectroscopy to have the D-gluco configuration[28] and is 1,2:5,6-di-*O*-isopropylidene-3-*S*-[(methylthio)carbonyl]-3-thio-α-D-glucofuranose. While the present work was in progress, the spectroscopic evidence was confirmed chemically.[29] An alternative route to 3-thioglucose derivatives is by the reaction of sulfur nucleophiles on the readily available 1,2:5,6-di-*O*-ispropylidene-3-*O*-*p*-tolylsulfonyl-α-D-allofuranose.[30] Treatment of this sulfonate with 3 equiv of potassium thioacetate in DMF at 100° for 2 days gave

(22) J. S. Harding and L. N. Owen, *J. Chem. Soc.*, 1528, 1536 (1954).
(23) R. B. Martin and R. I. Hedrick, *J. Amer. Chem. Soc.*, **84**, 106 (1962).
(24) The product from acid-catalyzed methanolysis of 1,2-*O*-isopropylidene-α-D-apio-L-furanose was incorrectly designated as an α-glycoside in ref 19.
(25) D. H. Ball, F. H. Bissett, I. L. Klundt, and L. Long, Jr., *Carbohyd. Res.*, **17**, 165 (1971).
(26) R. G. Hiskey and A. J. Dennis, *J. Org. Chem.*, **33**, 563 (1968).
(27) K. Freudenberg and A. Wolf, *Ber.*, **60**, 232 (1927).
(28) D. Horton and H. S. Prihar, *Carbohyd. Res.*, **4**, 115 (1967).
(29) J. M. Heap and L. N. Owen, *J. Chem. Soc. C*, 707 (1970).
(30) K. W. Buck, A. B. Foster, R. Hems, and J. M. Webber, *Carbohyd. Res.*, **3**, 137 (1966).

a 70% yield (81% based on unrecovered sulfonate) of 3-*S*-acetyl-1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-glucofuranose, a syrup previously prepared by acetylation of 1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-glucofuranose.[29] The formation of a small amount (<3%) of 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose was attributed to the presence of approximately 10% acetate ion in the potassium thioacetate used (determined by integration of the nmr spectrum). Oxidative deacetylation of the thiolacetate gave bis(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose-3-yl) disulfide in good yield. Deacetylation–oxidation of the isomeric 3-*S*-acetyl-1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-alpofuranose[12] gave crystalline bis(3-deoxy-1,2:5,6-di-*O*-isoprolylidene-α-D-allofuranose-3-yl) disulfide with physical constants very different from those of the gluco isomer.

Experimental Section

Solutions were concentrated under diminished pressure. Melting points were determined in glass capillaries with a Thomas-Hoover apparatus. Thin layer chromatography (tlc) was performed on silica gel GF and developed plates were examined under ultraviolet light and then sprayed with α-naphthol solution and sulfuric acid and heated. Column chromatography was performed on 70–325 mesh ASTM silica gel (E. Merck AG, Darmstadt, Germany; distributed by Brinkmann Instruments, Inc.). Infrared spectra were recorded with a Perkin-Elmer Model 137 spectrophotometer and optical rotations were measured with a Bendix-Ericcson ETL-NPL automatic polarimeter. Ultraviolet spectra were obtained using a Cary Model 14 spectrophotometer. Pmr spectra were recorded at 100 MHz with a Varian Associates HA-100 spectrometer, operating in the "frequency-sweep" mode, and data are for solutions in chloroform-*d* containing tetramethylsilane (τ = 10.00) as internal reference. Microanalyses were by Midwest Microlabs, Inc., Indianapolis, Ind.

Commercial potassium thioacetate (Eastman Organic Chemicals), a dark brown powder, was purified as follows. A suspension of the crude material (25 g) in water (200 ml) was filtered and the resultant orange-red solution was concentrated (bath temperature *ca.* 60°) until crystals began to form. The mixture was cooled at 0° for 30 min and the crystalline product was collected by filtration, washed with tetrahydrofuran until white, and dried *in vacuo* over P_2O_5, yield *ca.* 7 g.

Bis(5-deoxy-1,2-*O*-isopropylidene-α-D-apio-L-furanose-5-yl) Disulfide (2).—To a solution of 1,2-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-α-D-apio-L-furanose (1)[20] (2.0 g, 5.8 mmol) in ethanol (40 ml) was added potassium thioacetate (1.32 g, 11.6 mmol). The solution was boiled under reflux and the reaction was monitored by tlc (chloroform–ethyl acetate, 9:1). After 2 hr, 1 (R_f 0.2) was absent and the major product (R_f 0.3) was weakly uv absorbing; a second, minor product (R_f 0.1) was strongly uv absorbing. After 5 hr, the component with R_f 0.3 was still preponderant; the reaction flask was then stoppered and kept at 0° for 2 days, after which time the component with R_f 0.1 appeared to be the major product. Potassium *p*-toluenesulfonate was removed by filtration and washed with ethanol, and the combined filtrate and washings were concentrated to a pale yellow syrup. At this stage, only a trace of the component with R_f 0.3 could be detected and the mixture was fractionated by chromatography on silica gel (70 g) with ethyl acetate as eluent. The major product (R_f 0.1) was obtained as a syrup (1.15 g, 96%) which crystallized on standing and was shown to be the disulfide 2. Recrystallization from ether afforded pure material with mp 128–129°: $[\alpha]^{26}D$ +182° (*c* 0.77, EtOH); uv max (EtOH) 251 mμ (ε 440); nmr ($CDCl_3$) τ 4.03 (d, 1, $J_{1,2}$ = 3.5 Hz, H_1), 5.65 (d, 1, H_2), 6.12 (s, 2, $H_{4A,4B}$), 6.52, 7.05 (AB quartet, J_{AB} = 14.5 Hz, $H_{5,5'}$), 6.63 (broad s, 1, OH), 8.47, 8.65 (3 H singlets, CMe_2).

Anal. Calcd for $C_{16}H_{26}O_8S_2$: C, 46.81; H, 6.38; S, 15.62. Found: C, 46.82; H, 6.38; S, 15.44.

To a solution of 2 in water (*ca.* 0.01%) was added an equal volume of aqueous potassium cyanide (5%). After 2 min, addition of sodium nitroprusside solution resulted in an immediate, intense purple color. No reaction occurred without pretreatment with potassium cyanide.

Reaction of 1 with Potassium Thioacetate in Aprotic Solvents. A. DMF.—A solution of 1 (0.75 g, 2.2 mmol) and potassium thioacetate (0.50 g, 4.4 mmol) in DMF (15 ml) was heated at 100° in a stoppered flask. After 2 hr, tlc (chloroform–ethyl acetate, 9:1) indicated the absence of 1 and the formation of three products with R_f 0.6 (uv absorbing), 0.4 (uv absorbing), and 0.2. The solution was concentrated to dryness (nitrogen bleed, bath temperature *ca.* 35°) and the residue was extracted with hot chloroform (three 10-ml portions). Concentration of the extracts afforded a syrup which was fractionated by chromatography on silica gel (150 g) with chloroform as eluent. Fractions were concentrated under nitrogen.

Fraction 1 (163 mg), the product with R_f 0.6, was an oil with $[\alpha]^{25}D$ +97° (*c* 0.76, $CHCl_3$): ir ($CHCl_3$) 1735 (OAc) and 1680 cm^{-1} (SAc) consistent with the structure 3-*O*-acetyl-5-*S*-acetyl-1,2-*O*-isopropylidene-5-thio-α-D-apio-L-furanose (4); nmr ($CDCl_3$) τ 4.11 (d, 1, $J_{1,2}$ = 4 Hz, H_1), 5.35 (broad d, 1, $J_{2,4A}$ = 1 Hz, H_2), 5.64, 6.10 (AB quartet, J_{AB} = 10.5 Hz, $H_{4A,4B}$), 6.14, 6.42 (AB quartet, J_{AB} = 15 Hz, $H_{5,5'}$), 7.64 (s, 3, SAc), 7.95 (s, 3, OAc), 8.44, 8.64 (3 H singlets, CMe_2).

Anal. Calcd for $C_{12}H_{18}O_6S$: C, 49.64; H, 6.25; S, 11.04. Found: C, 49.98; H, 6.32; S, 10.77.

Fraction 2 (306 mg), R_f 0.4, crystallized and recrystallization from ether gave the disulfide 3 as white needles: mp 151–152°; $[\alpha]^{25}D$ +170° (*c* 0.78, $CHCl_3$); ir (KBr) 1735 cm^{-1} (ester C=O); nmr ($CDCl_3$) τ 4.11 (d, 1, $J_{1,2}$ = 3.5 Hz, H_1), 5.29 (d, 1, H_2), 5.59, 6.17 (AB quartet, $J_{A,B}$ = 10.5 Hz, $H_{4A,4B}$), 6.49 (s, 2, $H_{5,5'}$), 7.93 (s, 3, OAc), 8.49, 8.66 (3 H singlets, CMe_2).

Anal. Calcd for $C_{20}H_{30}O_{10}S_2$: C, 48.57; H, 6.11; S, 12.97. Found: C, 48.57; H, 6.09; S, 12.94.

Fraction 3 (49 mg), R_f 0.2 gave a purple color with 1% sodium nitroprusside solution and treatment of an aliquot with excess potassium thioacetate in hot DMF resulted in S-acetylation and the formation of 4. Treatment of an aliquot with iodine in aqueous acetone gave crystalline 3 and the major constituent of the fraction was therefore the thiol 5.

B. Acetone.—Substitution of anhydrous acetone for the DMF used above led to a similar series of reactions (complete in 3 days at room temperature), giving the same products in similar proportions. In an attempt to isolate and fully characterize 5, the conditions were modified by the use of less potassium thioacetate and by rigorous exclusion of oxygen.

A solution of 1 (1.72 g, 5.0 mmol) in anhydrous acetone (30 ml) was deoxygenated with a stream of prepurified nitrogen. Potassium thioacetate (0.68 g, 5.5 mmol) was added and the suspension was stirred at 50° under reflux in a stream of nitrogen and with exclusion of water. After 1 hr, tlc (chloroform–ethyl acetate, 9:1) indicated 1 (R_f 0.1) and two products with R_f 0.6 and 0.2; disulfide 3 was absent. After 9 hr, 1 had reacted completely to give the above two major products and small amounts of other compounds. Potassium *p*-toluenesulfonate was removed by filtration under nitrogen and washed with acetone. The combined filtrate and washings were concentrated (nitrogen bleed) to a syrup which was fractionated by chromatography on silica gel (150 g) with dichloromethane as eluent.

Fraction 1 (410 mg) was a syrup identical (ir, nmr) with 4.

Fraction 2 (260 mg) was a syrup: ir (neat) 3450 (OH), 2570 (SH), 1730 (*O*-acetyl C=O), and 1680 cm^{-1} (*S*-acetyl C=O). These data indicate a mixture of compounds 5 and 6 and this was supported by the nmr ($CDCl_3$) which also indicated a ratio of OAc (τ 7.89):SAc (τ 7.60) (and therefore of 5:6) of 3:2. A portion (150 mg) of the syrup was heated at 70° with acetic anhydride and pyridine (1:20, 4 ml). Tlc (chloroform–ethyl acetate, 9:1) indicated complete conversion to a single product after 24 hr. Concentration afforded a yellow residue which was purified by chromatography on silica gel (1.5 g) with chloroform as eluent. The product was identical (tlc, ir, nmr) with 4.

Fraction 3 (120 mg) was a syrup: ir (neat) 3400 (OH), 1730 cm^{-1} (*O*-acetyl C=O). The nmr spectrum was consistent with an equimolar mixture of two compounds or with an unsymmetrical di- (or mono-) sulfide. A portion (45 mg) of the syrup was heated at 70° with acetic anhydride and pyridine (1:20, 0.5 ml). Tlc (dichloromethane–ethyl acetate, 9:1) indicated a slow conversion to a faster moving compound (R_f 0.4), and after 48 hr concentration afforded a syrup which was purified by chromatography on silica gel (1 g) with dichloromethane–ethyl acetate (9:1) as eluent. The crystalline product (35 mg) was identical

with **3** and the original compound was therefore an unsymmetrical disulfide (**2**, with one of the tertiary hydroxyl groups acetylated).

Methyl 2,3-*O*-Isopropylidene-4-thio-β-D-apio-D-furanoside (8).—To a solution of **2** (0.65 g) in anhydrous ether (30 ml) was added lithium aluminum hydride (*ca.* 0.15 g) and the suspension was stirred at room temperature for 3 hr. Water (30 ml) was then added cautiously, followed by acetic acid (5 ml). The solution was extracted with ether (three 50-ml portions) as rapidly as possible and the extracts were concentrated (nitrogen bleed) to a syrup. Tlc (chloroform–ethyl acetate, 1:1) showed a preponderant product (R_f 0.6, chromatographically indistinguishable from the compound initially formed in the preparation of **2**, and presumably the thiol **7**) together with a lesser amount of **2**. The syrup was dried *in vacuo* over P_2O_5 and then taken up in 2% methanolic HCl. A test for thiol (addition to an aliquot of an equal volume of 5% potassium carbonate solution followed by 1% potassium nitroferricyanide), which initially gave an intense violet color, was negative after 24 hr. Tlc (chloroform–ethyl acetate, 1:1) showed, in addition to components with R_f 0.2, a product with the same mobility as the thiol **7**. The solution was neutralized by passage down a column of Dowex 1 (OH^-) analytical grade ion-exchange resin, previously washed with methanol. Concentration of the effluent gave a syrup which was fractionated by chromatography on silica gel (100 g) with chloroform as eluent. Fractions containing the fast-moving component were combined and concentrated to a syrup (0.21 g, 31%) which crystallized on standing. Recrystallization from *n*-heptane afforded analytically pure methyl 2,3-*O*-isopropylidene-4-thio-β-D-apio-D-furanoside (**8**): mp 52.5–53°; $[\alpha]^{28}D$ −264° (*c* 0.8, EtOH); nmr ($CDCl_3$) τ 5.10 (s, 1, H_1), 5.48 (s, 1, H_2), 6.28 (s, 2, $H_{5,5'}$), 6.66 (s, 3, OMe), 6.94, 7.20 (AB quartet, J_{AB} = 12.5 Hz, $H_{4A,4B}$), 7.82 (broad s, 1, OH), 8.44, 8.59 (3 H singlets, CMe_2). Double irradiation experiments indicated small couplings between H_1 and H_2 = 0.7 Hz and H_1 and H_{4A} < 0.5 Hz.[31]

Anal. Calcd for $C_9H_{16}O_4S$: C, 49.07; H, 7.32; S, 14.56. Found: C, 49.14; H, 7.30; S, 14.30.

Reaction of Methyl 2,3-*O*-Isopropylidene-5-*O*-*p*-tolylsulfonyl-β-D-apio-D-furanoside (9) with Potassium Thioacetate in Ethanol. A. With 2 Equiv of Potassium Thioacetate.—To a solution of **9** (1.0 g, 2.8 mmol) in ethanol (20 ml) was added potassium thioacetate (0.64 g, 5.6 mmol) and the mixture was stirred and boiled under reflux with exclusion of moisture. After 2 hr, tlc (benzene–ether, 9:1) showed **9** (R_f 0.4) and a component with R_f 0.5 (not uv absorbing). After 6 hr very little **9** remained but, in addition to the spot at R_f 0.5, two more components, R_f 0.30 (strongly uv absorbing) and R_f 0.25 (not uv absorbing), were observed, and, after 24 hr, only the last two components were present. Potassium *p*-toluenesulfonate was removed by filtration and washed with ethanol, the filtrate was concentrated, and the residue was fractionated by chromatography on silica gel (50 g) with benzene–ether (9:1) as eluent.

Fraction 1 (196 mg) was a syrup, homogeneous by tlc and nmr: $[\alpha]^{25}D$ −230° (c 0.30, $CHCl_3$); uv max (EtOH) 251 mμ (ε 310). The nmr spectrum and analytical data indicated this compound to be the disulfide **12**: nmr ($CDCl_3$) τ 5.09 (s, 1, H_1), 5.70 (s, 1, H_2), 5.99, 6.13 (AB quartet, J_{AB} = 10 Hz, $H_{4A,4B}$), 6.67 (s, 3, OMe), 6.71 (s, 2, $H_{5,5'}$), 8.52, 8.56 (3 H singlets, CMe_2).

Anal. Calcd for $C_{18}H_{30}O_8S_2$: C, 49.29; H, 6.90; S, 14.62. Found: C, 49.01; H, 6.71; S, 14.31.

Fraction 2 (127 mg) was a mixture of the two components.

Fraction 3 (251 mg) was a syrup, homogeneous by tlc and nmr, $[\alpha]^{25}D$ −128° (c 1.0, $CHCl_3$). The nmr spectrum and analytical data indicated this compound to be the sulfide **13**: nmr ($CDCl_3$) τ 5.09 (s, 1, H_1), 5.75 (s, 1, H_2), 5.98, 6.14 (AB quartet, J_{AB} = 10 Hz, $H_{4A,4B}$), 6.68 (s, 3, OMe), 6.92 (s, 2, $H_{5,5'}$), 8.51, 8.55 (3 H singlets, CMe_2).

Anal. Calcd for $C_{18}H_{30}O_8S$: C, 53.18; H, 7.44; S, 7.89. Found: C, 52.96; H, 7.42; S, 7.91.

The ratio **12**:**13** in fraction 2 was determined by integration of the nmr absorptions attributable to the exocyclic methylene groups and the molar ratio of **12**:**13** in the reaction product was 1:1.3.

B. With 1 Equiv of Potassium Thioacetate.—A solution of **9** (0.75 g, 2.1 mmol) and potassium thioacetate (0.24 g, 2.1 mmol) in ethanol (15 ml) was boiled under reflux with exclusion of moisture. Tlc (benzene–ether, 9:1) indicated a reaction similar to that in A except that no change was observed after 48 hr when **9** and the component with R_f 0.5 were still present in small amounts.[32] The reaction mixture was concentrated and the residue was extracted with dry acetone. Residual, insoluble potassium *p*-toluene-sulfonate was washed well with acetone and the combined extracts were concentrated to a syrup which was fractionated by chromatography on silica gel (50 g) with benzene–ether (20:1) as eluent.

Fraction 1 (68 mg) was a syrup, homogeneous by tlc and nmr: $[\alpha]^{25}D$ −121° (*c* 1.4, $CHCl_3$); ir (neat) 2550 cm^{-1} (SH). The nmr and ir spectra and elemental analysis indicated this compound to be the thiol **10**: nmr ($CDCl_3$) τ 5.07 (s, 1, H_1), 5.75 (s, 1, H_2), 5.97, 6.14 (AB quartet, J_{AB} = 10 Hz, $H_{4A,4B}$), 6.68 (s, 3, OMe), 7.06, 7.17 (AB part of an ABX pattern, J_{AB} = 13.5, J_{AX} = 8.7, J_{BX} = 7.3 Hz, $H_{5A,5B}$), 8.28 (X part of ABX pattern, SH), 8.50, 8.56 (3 H singlets, CMe_2).

Anal. Calcd for $C_9H_{16}O_4S$: C, 49.07; H, 7.32; S, 14.56. Found: C, 49.90; H, 7.37; S, 13.75.

Fraction 2 (40 mg) was crystallized and was identical (nmr) with **9**.

Fraction 3 (315 mg) was a syrupy mixture of **12** and **13**. Integration of the nmr spectrum gave the ratio **12**:**13** = 1:5.

Bis(5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose-5-yl) Sulfide (15).—To a solution of 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose (**14**)[33] (1.5 g, 4.35 mmol) in ethanol (15 ml) was added potassium thioacetate (1.0 g, 8.7 mmol) and the solution was boiled under reflux. After 24 hr, tlc (chloroform–ethyl acetate, 1:1) indicated a major product at R_f 0.25 (weakly uv absorbing). The cooled mixture was filtered to remove potassium *p*-toluenesulfonate which was washed with ethanol, and the combined filtrates were concentrated to a syrup. After chromatography on silica gel (200 g) with chloroform–ethyl acetate (3:1) as eluent, the product was obtained as an oil (0.75 g) which crystallized on standing.[34] Recrystallization from dichloromethane gave 0.69 g (85%) of analytically pure monosulfide **15**: mp 161–162°; $[\alpha]^{24}D$ −83° (*c* 1.0, EtOH); nmr ($CDCl_3$) τ 4.09 (d, 1, $J_{1,2}$ = 3.5 Hz, H_1), 5.48 (d, 1, H_2), 5.60–5.88 (m, 2, H_3 and H_4), 6.98–7.20 (m, 2, $H_{5,5'}$), 7.25 (broad d, 1, OH), 8.48, 8.67 (3 H singlets, CMe_2).

Anal. Calcd for $C_{16}H_{26}O_8S$: C, 50.78; H, 6.93; S, 8.47. Found: C, 50.77; H, 6.92; S, 8.46.

3-*S*-Acetyl-1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-glucofuranose.—A solution of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-tolysulfonyl)-α-D-allofuranose[30] (2.07 g, 5 mmol) and potassium thioacetate (1.71 g, 15 mmol) in DMF (25 ml) was heated at 100° in a stream of nitrogen. The reaction was monitored by tlc (ether–hexane, 1:1) and after 48 hr the solution was concentrated, the dark residue was extracted with ether, and the extract was concentrated to an oil which was fractionated on silica gel (225 g) with ether–hexane (1:1) as eluent.

Fraction 1 (1.08 g) was a chromatographically homogeneous syrup with $[\alpha]^{25}D$ −46° (*c* 1.2, $CHCl_3$); ir (CCl_4) 1700 cm^{-1} (*S*-acetyl C=O); nmr ($CDCl_3$) τ 4.21 (d, 1, $J_{1,2}$ = 3.5 Hz, H_1), 5.46 (d, 1, H_2), 5.60–6.10 (m, 5), 7.62 (s, 3, SAc), 8.47, 8.59, 8.67, 8.70 (3 H singlets, $2CMe_2$).

Anal. Calcd for $C_{14}H_{22}O_6S$: C, 52.81; H, 6.96; S, 10.07. Found: C, 52.86; H, 7.20; S, 10.35.

Fraction 2 (0.03 g) was not fully characterized but the nmr spectrum was identical with that of 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose.

Fraction 3 (0.33 g) was unreacted starting material.

Bis(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose-3-yl) Disulfide.—Air was drawn through a solution of 3-*S*-acetyl-1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-glucofuranose (1.0 g) in methanol (25 ml) containing 0.2% w/v sodium methoxide. Tlc (ether–hexane, 1:1) indicated rapid deacetylation followed by slow oxidation to the disulfide which began to precipitate after 1 day. After 1 week, crystalline disulfide (0.59 g) was collected by filtration, and fractionation of the mother liquors on silica gel afforded an additional 50 mg: total yield 0.64 g (74%); mp 163.5–164.5°; $[\alpha]^{25}D$ −285° (*c* 0.95, $CHCl_3$) [lit.[29] mp 165°; $[\alpha]^{21}D$ −281° (*c* 0.5, $CHCl_3$)].

(31) H_{4A} and H_{4B} designate respectively the protons "above" and "below" the plane of the furanose ring.

(32) After treatment of an aliquot of this solution with an equal volume of 5% sodium ethoxide in ethanol at the boiling point for 1 hr, tlc indicated the major product to be the sulfide **13**.

(33) P. A. Levene and A. L. Raymond, *J. Biol. Chem.*, **102**, 317 (1933).

(34) The oil gave a positive test for disulfide (purple color with 1% sodium nitroprusside solution after treatment of an aliquot with 5% potassium cyanide solution for 30 min at room temperature). This, and the weak uv absorption after tlc, indicates probable contamination of **15** with the corresponding disulfide.

Bis(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose-3-yl) Disulfide.—3-*S*-Acetyl-1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-allofuranose[12] (0.25 g) was deacetylated and oxidized as above to give crystalline bis(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose-3-yl) disulfide (0.13 g, 60%). Two recrystallizations from hexane gave pure material with mp 108–109°; $[\alpha]^{25}D$ +64° (c 0.9, $CHCl_3$); uv max 249 mμ (ε 280); nmr ($CDCl_3$) τ 4.20 (d, 1, $J_{1,2}$ = 3.5 Hz, H_1), 5.20 (t, 1, $J_{2,3}$ = 4.5 Hz, H_2), 5.57–6.10 (m, 4, H_4, H_5, $H_{6,6'}$), 6.65 (doublet of doublets, 1, $J_{3,4}$ = 10 Hz, H_3), 8.45, 8.52, 8.62, 8.64 (3 H singlets, $2CMe_2$).

Anal. Calcd for $C_{24}H_{38}O_{10}S_2$: C, 52.35; H, 6.96; S, 11.64. Found: C, 52.48; H, 7.21; S, 11.47.

Registry No.—**2**, 24679-85-4; **3**, 24679-84-3; **4**, 24679-86-5; **5**, 24679-87-6; **6**, 31735-45-2; **8**, 25050-39-9; **10**, 31735-46-3; **12**, 31729-55-2; **13**, 31729-56-3; **15**, 31729-57-4; 3-*S*-acetyl-1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-glucofuranose, 28251-80-1; bis(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose-3-yl) disulfide, 31790-92-8.

Acknowledgment.—The authors wish to thank Mr. F. H. Bissett and Dr. R. C. Chalk for the determination of nmr spectra.

Structure of Anhydro Butenandt Acid

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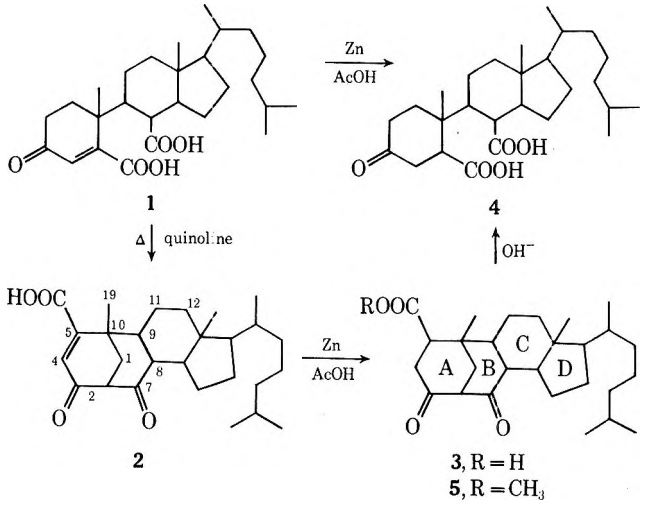
Chemical and spectroscopic evidence has confirmed the structure of anhydro Butenandt acid (**2**), for which an improved preparation is described. The saturated nonenolizable β-diketone **3** obtained from **2** had relatively high intensity ultraviolet absorption indicating the presence of a homoconjugated system. CD measurements on **3** and its methyl ester suggest that it exists as an equilibrium mixture of the boat–chair and twin-chair conformers at room temperature.

In 1953, Fieser,[3] in studies of the oxidation products of cholesterol, reported the preparation of a novel conversion product of Butenandt acid (**1**) for which structure **2** was suggested.



Anhydro Butenandt acid (**2**) was obtained by heating **1** with quinoline or with acetic anhydride and boron trifluoride etherate. The original evidence for structure **2** consisted of (a) the similarity of the ultraviolet spectrum to that of other enedione systems,[3,4] (b) the infrared spectrum, which showed bands assigned to an acid and six-ring ketone, an α,β-unsaturated ketone, and a double bond, and (c) mild base hydrolysis, which gave back **1**, suggesting a β-diketone system.

The nmr spectrum of the anhydro acid **2** supports the suggested structure in complete detail. The nmr spectrum had an ill-resolved triplet centered at δ 3.56 (J = 2 Hz), which was assigned to the bridgehead proton between the two carbonyl groups.[5] The low value of the coupling constant is due to the fixed orientation of the bridgehead proton with respect to the neighboring methylene bridge with an angle such that the coupling constant is near a minimum.[6] The vinyl proton gave rise to a doublet at δ 7.05 (J = 1 Hz). The splitting of this band appears due to long-range coupling with the bridgehead proton.[7] Such coupling across four single bonds appears to be at a maximum when the interacting protons are confined to a planar zigzag configuration. The C-19 methyl resonance occurred at δ 1.57.

Preparation of compound **2** could be improved by exhaustive oxidation of cholesterol,[3,8] isolation of the total acid fraction, and heating this with quinoline without purification. The yield of **2** from cholesterol was thus about 15% in a much shorter working time. Repeated attempts to prepare a 2,4-dinitrophenylhydrazone or semicarbazone of **2** were unsuccessful. However, a high-melting bisoxime could be formed.

Attempted addition of bromine to **2** in glacial acetic acid or chloroform resulted in recovery of starting material. The anhydro acid **2** rapidly took up 1 mol of hydrogen over Pd/C to give **3**. The anhydro acid **2** could also be reduced to **3** by refluxing with excess zinc dust in glacial acetic acid. This latter reaction provides chemical evidence for the presence of an enedione system in **2**. Attempted reduction of the enedione system

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(3) L. F. Fieser, *J. Amer. Chem. Soc.*, **75**, 4386 (1953).

(4) P. Yates and G. F. Fields, *ibid.*, **82**, 5764 (1960).

(5) Similar values can be found for a bridgehead proton between two carbonyl groups in "citrylidenemalonic acid:" C. E. Berkoff and L. Crombie, *J. Chem. Soc.*, 3734 (1960); see also W. Herz and G. Caple, *J. Amer. Chem. Soc.*, **84**, 3517 (1962).

(6) *Cf.* L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 280.

(7) Reference 6, p 334. For similar cases of long-range coupling, see C. Lehmann, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **45**, 1031 (1962); N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 121; N. S. Bhacca, J. E. Gurst, and D. H. Williams, *J. Amer. Chem. Soc.*, **87**, 302 (1965).

(8) L. F. Fieser, W. Huang, and T. Goto, *ibid.*, **82**, 1688 (1960).

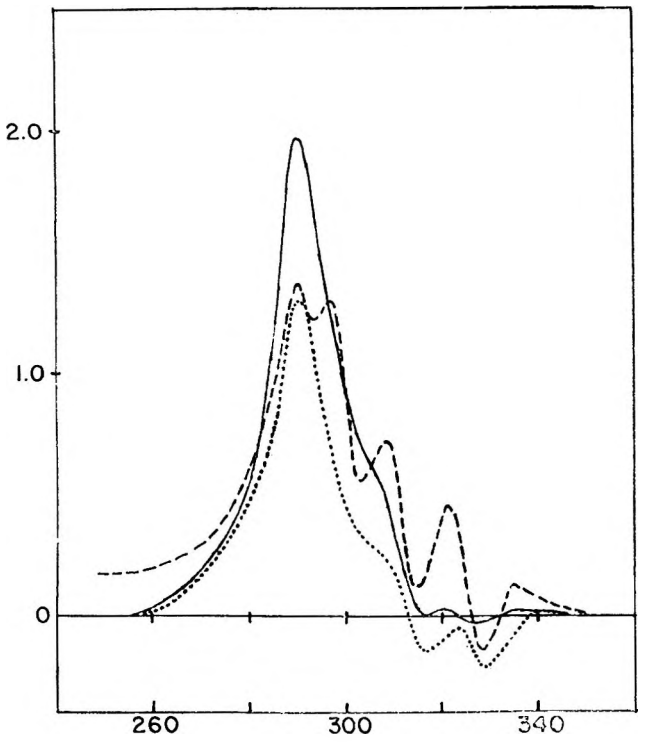


Figure 1.—CD spectrum of **3** at 25°, ····; CD spectrum of **3** at −67°, ----; CD spectrum of **5** at 25°, ——.

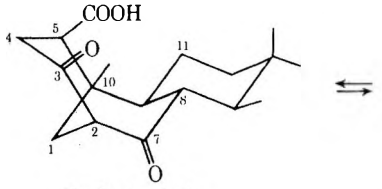
with tin and hydrochloric acid[9] was unsatisfactory possibly because of concurrent hydrolysis of the β-diketone system to dihydro Butenandt acid.

Since the catalytic addition of hydrogen to the double bond of **2** must occur on the least hindered face, the acid group in **3** must be in the β position.

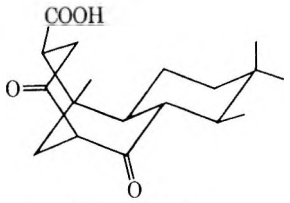
The nmr spectrum of **3** showed the same triplet due to the bridgehead proton at δ 3.60 (J = 3.3 Hz) and a band at δ 1.54 due to the C-19 methyl group.[10] Saponification of **3** with 5% aqueous sodium hydroxide gave dihydro Butenandt acid (**4**). This reaction provides additional chemical evidence for the presence of a β-diketone system in **2** and **3**. The formation of **2** from **1** can be regarded as a further example of an intramolecular Claisen acylation, a reaction which appears to be of some generality for the formation of bridged systems.[11]

The conformation of the A ring in the β-diketone **3** remains to be considered. The dihydro derivative **3** can exist in two possible forms in which the A ring can assume either a boat or a chair conformation.[12] Models indicate that the boat–chair conformation **3a** suffers from 1,4-flagpole interactions as well as badly forcing the carboxyl group into both H-8 and the 11β-hydrogen. In the twin-chair conformation **3b**, the 4β hydrogen is closer to H-8 than in normal boat flagpole interactions, but the carboxyl group is considerably less crowded and is close only to the 1β hydrogen.

The CD curve of the dihydro derivative **3** was temperature dependent, indicating that it was a mixture of the two possible conformers at room temperature. The CD curve showed both positive and negative components and resembled that of other conformationally mobile, temperature-dependent systems.[13]



3a, boat-chair



3b, twin-chair

The CD curves of the dihydro compound **3** measured at 25 and −67° are displayed in Figure 1. These curves may be interpreted as a relatively unstructured broad positive band centered at 300–305 mμ, partly superimposed on a weak negative Cotton effect curve at slightly longer wavelengths which possesses extensive fine structure. Since the extrema of both components of the curve lie well above the 280–285-mμ region associated with the n → π* transition of an isolated carbonyl group, the β-dicarbonyl system as a whole is acting as a single chromophore. The relatively high intensity and position at longer wavelengths of the uv maxima of **3** compared to saturated ketones supports the homoconjugated nature of the chromophore (Table I). Since the positive CD curve is enhanced at the expense of the negative curve with decreasing temperature, one may reasonably postulate an equilibrium between the two conformations (**3a** and **3b**) of the bicyclononadione system. It remains to predict that the sign of the Cotton effect in one of these two conformations and to show that the temperature effect is not due to solvation.

TABLE I

ULTRAVIOLET MAXIMA OF **3** IN DIFFERENT SOLVENTS

Solvent	λ_{max} (ε), mμ				
Methanol	~284		309 (180)		
Acetonitrile	~284	~298	~310	316 (180)	
Methylene chloride	~284	~300	~310	316 (165)	
Dioxane	~284	~302	~311	318 (170)	
Benzene		~300	~312	319 (185)	~328
Cyclohexane[a]	~286	~302	312	321	~330

[a] The low solubility of **3** in cyclohexane makes accurate measurements of the intensities uncertain.

Models indicate that the acid group in the twin-chair conformation **3b** is severely crowded by the axial protons at C-8 and C-11. If this were so, then increasing

(9) J. P. Schaefer, *J. Org. Chem.*, **25**, 2027 (1960).

(10) The keto bands in the infrared of both bicyclic derivatives, **2** and **3**, were shifted toward lower energies by about 35 cm^{-1} from the accepted values. W. J. Wechter and G. Slomp, *J. Org. Chem.*, **27**, 2549 (1962), have remarked on the abnormally low carbonyl frequency of some bicyclic ketones. See also W. Thielacker and W. Schmid, *Justus Liebigs Ann. Chem.*, **570**, 15 (1950); W. Thielacker and E. Wegner, *ibid.*, **664**, 125 (1963); D. J. Cram and H. Steinberg, *J. Amer. Chem. Soc.*, **76**, 2753 (1964).

(11) See, for example, G. Komppa and S. Beckmann, *Ber.*, **69**, 2783 (1936); O. Aschan, *Justus Liebigs Ann. Chem.*, **410**, 240 (1915); W. Herz, *J. Amer. Chem. Soc.*, **79**, 5011 (1957); Z. Valenta, A. H. Gray, D. E. Orr, S. Papadopoulos, and C. Podesva, *Tetrahedron*, **18**, 1433 (1962); K. Wiesner, F. Bickelhaupt, D. R. Babin, and M. Goetz, *ibid.*, **9**, 254 (1960); B. E. Hudson, C. R. Hauser, R. F. B. Cox, and S. M. McElvain, *J. Amer. Chem. Soc.*, **56**, 2459 (1934); R, Fusco and F. Tenconi, *Tetrahedron Lett.*, 1313 (1965).

(12) For a summary of current knowledge on the conformation of bicyclo-[3.3.1]nonanes, see M. Fisch, S. Smallcombe, J. C. Germain, M. A. McKervey, and J. E. Anderson, *J. Org. Chem.*, **35**, 1886 (1970), and references cited therein.

(13) See, for example, C. Djerassi, *Proc. Chem. Soc.*, 314 (1964).

the bulk on the acid group should increase the relative amount of the boat–chair form **3a** at the expense of the twin-chair form **3b**. The contribution of the twin-chair form **3b** to the CD curve should decrease while the intensity of those peaks due to the boat–chair form **3a** should increase. A simple derivative of **3** with increasing bulk on the acid group is its methyl ester **5**. The CD curve of the methyl ester **5** (Figure 1) showed much less contribution by the negative components of the curve. Thus, the broad positive CD band is due to the boat–chair form **3a** and a negative band at longer wavelengths showing fine structure is due to the twin-chair conformation **3b**.

The more symmetrical twin-chair conformation **3b** has a better geometry for overlap between the two keto carbonyl groups. Therefore, the Cotton effect in this conformer is at higher wavelength and has more fine structure, a feature generally associated with homoconjugated systems.

Prediction of the sign of the Cotton effect for **3a** and **3b** from octant rules is not straightforward since vicinal effects of diketones cannot always be predicted and their magnitude appears to depend upon distance and relative positions of the two carbonyl groups.[14]

Experimental Section[15]

Anhydro Butenandt Acid. Δ^4-7(6→2)*abeo*-cholestane-3,7-dion-6-oic Acid (2).[2,8]—A solution of 150 g of sodium dichromate in 400 ml of glacial acetic acid at 10° was added to a solution containing 40 g of cholesterol in 400 ml of glacial acetic acid at 20°. The resulting mixture was kept at 15° for 1 hr and then left overnight at room temperature. A large volume of water was then added and the solution extracted with 5% bicarbonate solution. Further work-up of the neutral fraction gave small amounts of Δ^4-cholestene-3,6-dione and cholestane-3,6-dion-5α-ol.[1] The bicarbonate extracts were backwashed with ether and acidified, and the acid fraction was collected by extracting with ether. The ether was removed to give an off-color glass, to which 15 ml of quinoline was added. The mixture was heated at 180° for 20 min and then at 210–220° for 15 min. This reaction mixture was allowed to cool and then taken up in ether. The ether solution was washed with dilute hydrochloric acid and water. The ether phase was extracted with 20-ml portions of 5% sodium bicarbonate. Each portion was acidified separately with hydrochloric acid. The last portion was occasionally somewhat oily and, if so, was best worked up separately. The acid was collected, washed with water, and dried. The product was crystallized from benzene–petroleum ether (bp 30–60°) or dichloroethane–petroleum ether several times for analysis: mp 223.5–226°; λ_{max} (ethanol) 213 (5300), 239 mμ (7000); λ_{max} (cyclohexane) 236, ~300 mμ; ir (Nujol) ν 1728 (acid and six-ring ketone), 1642 (α,β-unsaturated ketone), 1595 cm^{-1} (double bond); yield 6-8 g (the acid took up 1.1 mol of hydrogen over Pd/C in ethanol); ORD in methanol (*c* 0.009, 30°) $[\alpha]_{400}$ −200°, $[\alpha]_{323}$ +5900°, $[\alpha]_{286}$ −9100°, $[\alpha]_{250}$ +3600°, $[\alpha]_{214}$ −13,100°, $[\alpha]_{210}$ −9200° (last reading) (the profiles of the ORD curves in dioxane and cyclohexane were almost identical with those in methanol); CD (*c* 0.0016, dioxane, 30°) 430 (0), 388 infl (−1.38), 320 (−1.88), 305 (+11.1), 269 (−6.75), 262 (−5.87) (last reading).

Anal. Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.6; H, 9.27.

Dihydro Derivative. 7(6→2)*abeo*cholestane-3,7-dion-6-oic Acid (3).—The anhydro Butenandt acid was refluxed with excess zinc dust in glacial acetic acid for 1.5 hr, cooled, and filtered from the excess zinc dust, and water was added to the cloud point. The dihydro acid **3** separated and was recrystallized several times from acetic acid–water for analysis: mp 202–206°; ir (Nujol) ν 1726 (acid), 1675 cm^{-1} (ketone) (when the reaction was run for 12–24 hr, no product could be isolated in a pure condition); ORD in dioxane (*c* 0.001, 30°) $[\alpha]_{360}$ −1800°, $[\alpha]_{323.5}$ −4720°, $[\alpha]_{324}$ −860°, $[\alpha]_{319}$ −1720°, $[\alpha]_{312}$ +2660°, $[\alpha]_{307.5}$ +2000°, $[\alpha]_{302}$ +4200°, $[\alpha]_{280-270}$ −7720° (broad trough), $[\alpha]_{263}$ −7370°, $[\alpha]_{232}$ −15,500°, $[\alpha]_{225}$ −11,800° (last reading); CD (*c* 0.003, ethanol, 25°) 352 (0), 340 (0.06), 329 (−0.21), 323 (−0.06), 317 (−0.13), 307 infl (0.29), 291 (1.27), 256 (0) (last reading); CD (*c* 0.008, ethanol, −67°) 358 (0), 335 (0.14), 328 (−0.14), 321 (0.46), 315 (0.12) 308 (0.71), 303 (0.56), 297 (1.30), 294 (1.21), 290 (1.38), 256 (0.19), 248 (0.19) (last reading); CD (*c* 0.008, dioxane, 30°) 350 (0), 340 (0.05), 328 (−0.58), 321 (−0.29), 315 (−0.58), 307 (−0.07), 304 (−0.10), 294i (0.80), 290 (0.89), 260 (0), 252–264 (−0.07), 248 (−0.32) (last reading).

Anal. Calcd for $C_{27}H_{42}O_4$: C, 75.3; H, 9.83. Found: C, 75.2; H, 9.84.

Saponification of 3.—The dihydro derivative **3** was dissolved in 5% sodium hydroxide and refluxed for 1.5 hr. The solution was allowed to cool whereupon the sodium salt of **4** crystallized in needles. This was collected, dissolved in methanol, and acidified with hydrochloric acid, and the product was collected with ether, washed, and dried. The product crystallized upon concentration of the ether and addition of petroleum ether, mp 208–209.5°. Mixture melting point with a sample of **4**, prepared according to the method of Fieser,[3] showed no depression. The infrared spectra of the two samples were also identical: ir (Nujol) ν 1736 (acid), 1658 cm^{-1} (ketone).

Bisoxime of Anhydro Butenandt Acid.—Equal weights of **2** and hydroxylamine hydrochloride were refluxed in a 1:1 mixture of anhydrous pyridine and absolute ethanol for 4 hr. The solution was concentrated, water was added, and the solution was then extracted with ether. The ether phase was washed and dried and, upon concentration, the product separated, mp 268–269° dec from ethanol–water. The infrared spectrum showed unresolved hydroxy absorption: (Nujol) ν 1693 (acid), 1640, 1615, 1587 cm^{-1} (C=C and C=N); λ_{max} 265 mμ (ethanol–sodium hydroxide). The oxime was very soluble in ethanol and insoluble in acetic acid.

Anal. Calcd for $C_{27}H_{42}O_4N_2$: C, 70.70; H, 9.23. Found: C, 70.3; H, 9.12.

Methyl Ester of 3 (5).—Compound **3** was treated with excess diazomethane. The ether solvent was removed and the residue filtered through a short column of alumina with benzene. Removal of the benzene gave a gum which appeared homogeneous on tlc but could not be induced to crystallize under a variety of conditions: nmr δ 3.75 (methoxy), 3.25 (H-2), 1.30, 0.92, 0.92, 0.83, 0.67 (*C*-methyls); CD (*c* 0.0007, ethanol, 30°) 350 (0), 335 (0.01) 327 (−0.008), 320 (0.01), 317 (0.008), 306 infl (0.62), 290 (1.98), 255 (0.).

Anal. Calcd for $C_{28}H_{44}O_4$: C, 75.66; H, 9.94. Found: C, 75.8; H, 9.93.

Registry No.—**2**, 32174-69-9; **2** bisoxime, 32256-04-5; **3a**, 32174-70-2; **3b**, 32174-71-3; **5**, 32174-72-4.

Acknowledgment.—The author is grateful to Mr. L. M. White for the analytical data, to Mr. J. Stewart for the ORD and CD curves, and to Dr. W. E. Thiessen for helpful discussions.

(14) G. Snatzke and G. Eckhardt, *Tetrahedron*, **24**, 4543 (1968); G. Snatzke and H. W. Fehlhaber, *ibid.*, **20**, 1243 (1964).

(15) For CD notation see, G. Snatzke, *Tetrahedron*, **21**, 421 (1965). Nmr spectra were obtained at 60 MHz in deuteriochloroform and are given in δ relative to internal TMS. The relative areas of the peaks were consistent with the assignments.

Biogenetic-Like Rearrangements of Tetracyclic Diterpenes

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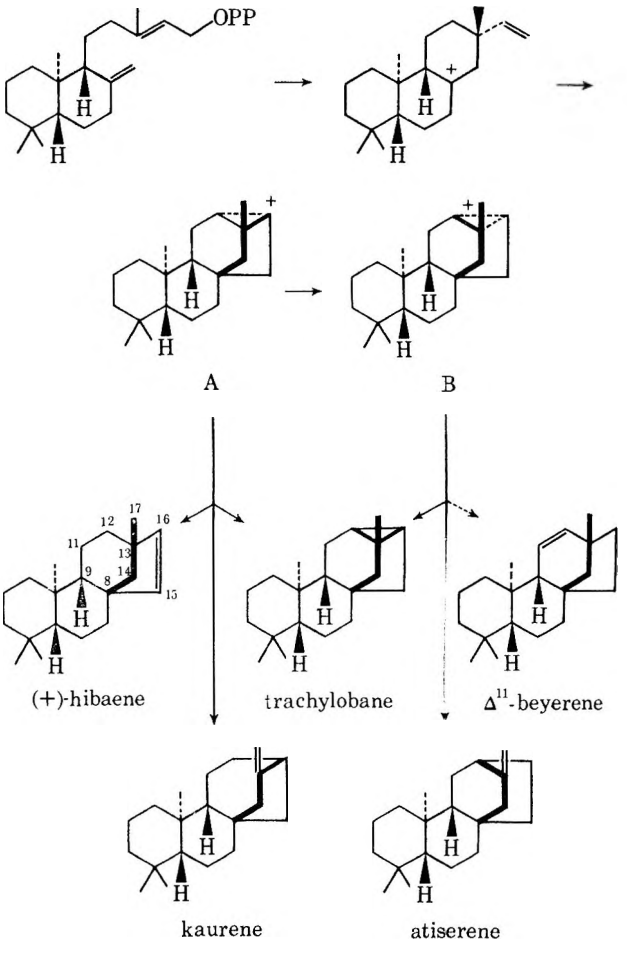
Nitrous acid deamination of methyl *ent*-16-aminobeyeran-19-oate (**1**) in acetic acid gives predominant rearrangement to methyl *ent*-16α-acetoxykauran-19-oate (**2b**) accompanied by small amounts of the isomeric kaurene esters **5** and **6**. Acetolysis of methyl *ent*-16β-tosyloxybeyeran-19-oate (**3c**) and decomposition of the tosylhydrazone **8** of methyl 16-ketobeyeran-19-oate under protic conditions afford the same rearranged, unsaturated esters **5** and **6**; in the latter reaction methyl *ent*-13aα,16-cycloatisan-19-oate (**9**), the C-4 epimer of methyl trachylobanoate, is also produced. Acetolysis of methyl 12β-tosyloxybeyeran-19-oate (**11c**) gives the isoatiserene ester **12** while formolysis of **11c** yields methyl *ent*-16-formyloxyatisan-19-oate (**14d**). Interconversion between these two Wagner–Meerwein rearrangement pairs is achieved through trifluoroacetolysis of **3c** and **11c**. Deuterium incorporation experiments shown that this rearrangement involves an intramolecular 12 ⇄ 16 hydride shift rather than an elimination–addition process by way of **9**. The various rearrangements observed formally correspond to the ring D rearrangements suggested for the biogenesis of these tetracyclic diterpenes.

The great majority of the naturally occurring tetracyclic diterpenes fall into two main classes in which the ethano bridge forming the D ring spans the 8 and either the 12 or 13 positions of the perhydrophenanthrene nucleus.[2,3] In the latter group the two-carbon bridge is found both cis and trans to the proton at C-9 (*e.g.*, kaurene and phyllocladene) and the C-17 carbon may be attached at either positions 13 or 16. Although these rather complex structural variations are inconsistent with the simple isoprene rule, a biogenetic scheme modified to permit skeletal rearrangements suggested by Wenkert[4] provides a concise rationale for the skeletal patterns within this family of natural products. The new diterpenes trachylobane[5a] and atiserene[5b] fit nicely into this biogenetic scheme[6,8-11] (Scheme I).

One particularly attractive feature of this biogenetic scheme is that the interconversions are quite analogous to the carbonium ion rearrangements of bridged bicyclic compounds.[12] It, therefore, seemed of interest to examine the cationic reactions of appropriately substituted tetracyclic diterpenes, to determine the extent to which the chemically induced reactions might follow, or deviate from, the pathways within this biogenetic scheme. In a separate paper we have set forth methods for modifying the available diterpene, isosteviol, with 12 and 16 substituents suitable for generation of carbonium ion intermediates.[13] In the following we describe in detail our investigation of the

SCHEME I



(1) Taken in part from the Ph.D. thesis of E. F. B., University of Illinois, 1970.

(2) (a) J. R. Hanson, "The Tetracyclic Diterpenes," Pergamon Press, London, 1968; (b) R. McCrindle and K. H. Overton, *Advan. Org. Chem.*, **5**, 47 (1965).

(3) The numbering system used throughout this paper conforms to the recommendations ("The Common and Systematic Nomenclature of Cyclic Diterpenes," Third Revision, Oct 1968; Addenda and Corrigenda, Feb 1969) prepared by J. W. Rowe (Forest Products Laboratory, Forest Service, U. S. Department of Agriculture, Madison, Wis. 53705). Both common and systematic names are used in the text as seems appropriate; complete systematic names appear in the Experimental Section. We are grateful to Dr. Rowe for copies of these recommendations.

(4) E. Wenkert, *Chem. Ind. (London)*, 282 (1955).

(5) (a) G. Hugel, L. Lods, J. M. Mellor, D. W. Theobald, and G. Ourisson, *Bull. Soc. Chim. Fr.*, 2882, 2888 (1965); (b) A. H. Kapadi, R. R. Sobti, and S. Dev, *Tetrahedron Lett.*, 2729 (1965).

(6) A face-protonated trachylobane carbonium ion was originally suggested[4] as a possible single precursor to all of the various types of tetracyclic diterpenes. Since the face-protonated structure for the norbornyl cation has now been thoroughly discounted,[7] we prefer to use two separate carbonium ions, A and B. As will be seen, this accords with the chemical behavior.

(7) (a) C. J. Collins and M. H. Lietzke, *J. Amer. Chem. Soc.*, **89**, 6565 (1967); (b) G. A. Olah, A. M. White, J. R. DeMember, A. Commeyras, and C. Y. Lui, *ibid.*, **92**, 4627 (1970); (c) C. J. Collins, *Chem. Rev.*, **69**, 543 (1969).

(8) The reader may choose to consider the bridged representations A and B to correspond to either nonclassical, σ-bridged carbonium ions or transition states between two classical carbonium ions according to his preference. The 2-methylnorbornyl carbonium ion in superacid media is considered to be essentially classical according to spectral data.[7b]

(9) The available biosynthetic evidence is in agreement with these structural relationships; *cf.* J. R. Hanson and B. Achilladelis, *Perfum. Essent. Oil Rec.*, **59**, 802 (1968).

(10) The biosynthesis of some of these diterpenes has been carried out recently with soluble enzyme preparations: D. R. Robinson and C. A. West, *Biochemistry*, **9**, 70, 80 (1970), and references cited therein.

(11) To our knowledge, no naturally occurring Δ^{11}-beyerene derivatives (or their hydrated equivalents) have been isolated, although such compounds might be expected from Scheme I.

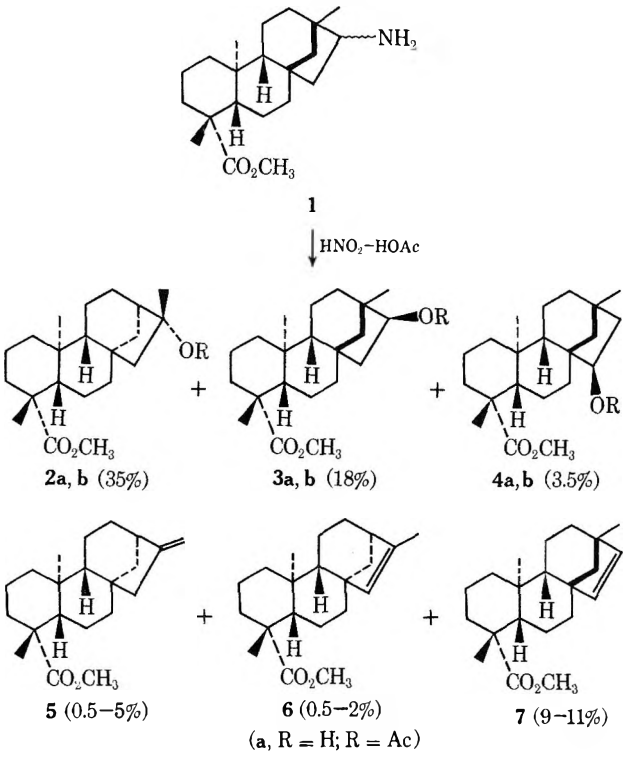
(12) (a) J. A. Berson in "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1963, Part 1, Chapter 3; (b) G. D. Sargent, *Quart. Rev., Chem. Soc.*, **20**, 301 (1966).

(13) R. M. Coates and E. F. Bertram, *J. Org. Chem.*, **36**, 2625 (1971).

biogenetic-like rearrangements of these isosteviol derivatives.[14,15]

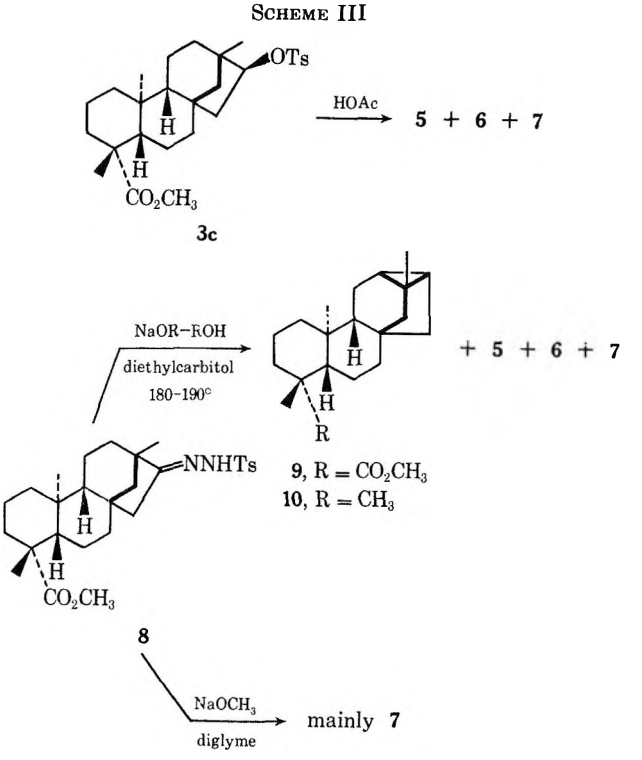
Three different methods for the generation of a cationic intermediate formally equivalent to A were examined: nitrous acid deamination of amine **1**, decomposition of tosylhydrazone **8**, and solvolysis of tosylate **3c**. Treatment of **1**, both as the free amine or in the form of its hydrochloride salt, with nitrous acid in acetic acid afforded a mixture consisting largely of acetates along with lesser amounts of olefinic products (Scheme II). The principal product, tertiary

SCHEME II



acetate **2b**, was identified by hydrolysis to the corresponding hydroxy ester **2a**[20] and dehydration with tosyl chloride in pyridine to a mixture of the exocyclic and endocyclic unsaturated esters **5** and **6**. The structure of the former was established by comparison with an authentic specimen derived from natural kauren-19-oic acid.[21] Iodine-catalyzed equilibration[19] of **5** gave rise to the double bond isomer **6**, and provided independent evidence in support of its constitution. The identity of the secondary acetates **3b** and **4b** was established by comparison with the acetates of the alcohols **3a** and **4a** obtained from hydroboration[13] of the known,[16b] unrearranged olefin **7**. Catalytic hydrogenation of the latter gave rise to methyl *ent*-beyeran-19-oate.[13] Acetolysis of the *exo* tosylate **3c** afforded a mixture of the same three unsaturated esters **5**–**7** in high yield (Scheme III).[22]

SCHEME III



Although none of the trachylobane-type product **9** was detected in the above product mixtures, decomposition of the tosylhydrazone **8** of the methyl ester of isosteviol in a variety of protic media yielded substantial proportions of the pentacyclic ester. With 10% ethylene glycol in diethyl carbitol containing 1.25 equiv of sodium glycolate, conditions which promote bicyclobutane formation from the tosylhydrazone of cyclopropanecarboxaldehyde,[23] **8** produces a mixture of esters in 59% yield. In addition to the same three olefinic esters (**5**–**7**) a fourth ester was obtained in 12% yield (21% of the ester mixture). The absence of both olefinic protons in the nmr spectrum and appreciable end absorption in the ultraviolet spectrum indicated the cyclopropane-containing structure **9**. Transformation

(14) Preliminary reports describing portions of this research are (a) R. M. Coates and E. F. Bertram, *Tetrahedron Lett.*, 5145 (1968); (b) *Chem. Commun.*, 797 (1969); (c) R. M. Coates, "Symposium on the Chemistry of Natural Products and Compounds of Biological Interest," Joint ACS-CIC Meeting, Toronto, Canada, May 1970.

(15) Concurrent, and in part, overlapping studies on the rearrangements of related tetracyclic diterpenes have been published.[16–19]

(16) Epoxide rearrangements: (a) A. H. Kapadi and S. Dev, *Tetrahedron Lett.*, 1255 (1965); (b) J. R. Hanson, *Tetrahedron*, **23**, 793 (1967); (c) A. Yoshikoshi, M. Kitahara, and Y. Kitahara, *ibid.*, **23**, 1175 (1967); (d) J. G. St. C. Buchanan and B. R. Davis, *Chem. Commun.*, 1142 (1967); P. A. Gunn, R. McCrindle, and R. G. Roy, *J. Chem. Soc. C* 1078 (1971); (e) J. R. Hanson, *Tetrahedron*, **26**, 2711 (1970).

(17) Acid-catalyzed rearrangements: (a) G. Hugel, L. Lods, J. M. Mellor, and G. Ourisson, *Bull. Soc. Chim. Fr.*, 2894 (1965); (b) A. J. McAlees, R. McCrindle, and R. D. H. Murray, *Chem. Ind. (London)*, 240 (1966); R. A. Appleton, A. J. McAlees, A, McCormick, R. McCrindle, and R. D. H. Murray, *J. Chem. Soc. C*, 2319 (1966); (c) L. H. Zalkow and A. C. Oehschalager, *J. Org. Chem.*, **32**, 808 (1967).

(18) Solvolytic rearrangements: (a) R. R. Sobti and S. Dev, *Tetrahedron Lett.*, 3939 (1966); (b) E. L. Ghisalberti and P. R. Jefferies, *Aust. J. Chem.*, **19**, 1759 (1966); (c) R. A. Appleton, P. A. Gunn, and R. McCrindle, *Chem. Commun.*, 1131 (1968); *J. Chem. Soc. C*, 1148 (1970).

(19) Iodine-catalyzed rearrangements: (a) K. Mori, M. Matsui, N. Ikekawa, and Y. Sumiki, *Tetrahedron Lett.*, 3395 (1966); K. Mori and M. Matsui, *Tetrahedron*, **24**, 3095 (1968); (b) ref 16c.

(20) The hydroxy acid corresponding to **2b** has recently been isolated: (a) E. P. Serebryakov, A. V. Simolin, V. F. Kucherov, and B. V. Rosynov, *Tetrahedron*, **26**, 5215 (1970); E. P. Serebryakov, N. S. Kobrina, A. V. Simolin, and V. F. Kucherov, *Chem. Ind. (London)*, 1770 (1968); (b) S. C. Pakrashi and E. Ali, *Indian J. Chem.*, **8**, 569 (1970). The properties of **2b** are in good agreement with those reported (see Experimental Section).

(21) C. A. Henrick and P. R. Jefferies, *Aust. J. Chem.*, **17**, 915 (1964). We are very grateful to Professor Jefferies for providing us with a sample of the kaurene ester **5**.

(22) For similar results see ref 18a,b.

(23) (a) J. A. Smith, H. Schechter, J. Bayless, and L. Friedman, *J. Amer. Chem. Soc.*, **87**, 659 (1965); J. Bayless, L. Friedman, J. A. Smith, F. B. Cook, and H. Schechter, *ibid.*, **87**, 661 (1965); see also (b) J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959); (c) P. Clarke, M. C. Whiting, C. Papenmaier, and W. Reusch, *J. Org. Chem.*, **27**, 3356 (1962).

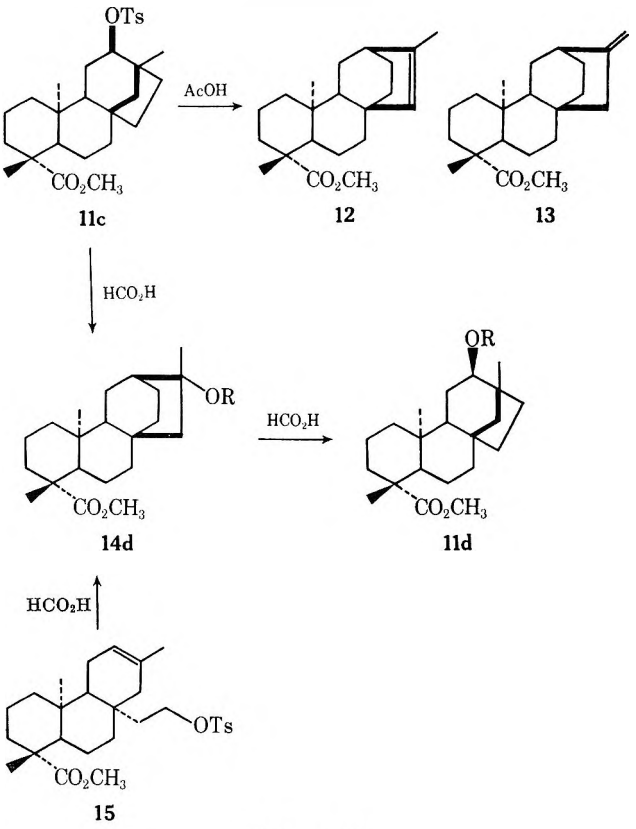
of the carboxyl group to a methyl group furnished the parent hydrocarbon, which proved to be identical with an authentic sample of trachylobane **10**.[5a,24-26]

While all of the protic conditions employed for the tosylhydrazone decomposition afforded **9** in appreciable yields (4–14%, see Experimental Section), a reaction under aprotic conditions (sodium methoxide–diglyme) produced mainly the unrearranged olefinic ester **7**. These results provide an interesting contrast to the corresponding reactions of camphor tosylhydrazone, which give mainly tricyclene (cyclopropane formation) in aprotic media and rearranged olefin (camphene) under protic conditions.[27]

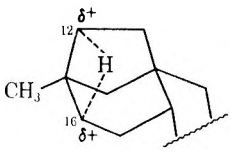
Solvolysis of the 12β tosylate **11c** provided a means for generating a cationic intermediate corresponding to B. In acetic acid, tosylate **11c** underwent Wagner–Meerwein rearrangement and elimination to the isoatiserene ester **12**[13] with little, if any, of the isomeric atiserene ester **13** present. Formolysis, on the other hand, gave rise to the corresponding rearranged substitution product **14d**. The tertiary alcohol (or formate) **14a(d)** upon heating in formic acid reverts to the 12β-beyerane derivative **11d**. The π route originating from tricyclic tosylate **15** also affords the 16-formyloxyatisan-19-oate **14d** upon formolysis,[13] thus implicating a common carbonium ion intermediate (Scheme IV).

The results presented to this point correspond well with the ring D rearrangements in the Wenkert biogenetic scheme (Scheme I). Cation A generated by chemical means does in fact undergo Wagner–Meerwein rearrangement to kaurenes[28a] and under certain conditions transannular proton elimination[28b] to the pentacyclic trachylobane nucleus. Similarly cation B gives the atiserene skeleton under solvolytic conditions. However, the one remaining step in this scheme, the interconversion A $\rightleftarrows$ B by means of a formal 12 $\rightleftarrows$ 16 hydride shift (crossover rearrangement) was not detected in the preceding experiments. This finding stands in contrast to the extremely facile 6 → 2 hydride shifts observed in norbornyl rearrangements.[7b] Furthermore, extensive transannular hydride shifts occur in the solvolysis of 5-*exo*-bicyclo[3.2.1]octyl tosylate[29] and the corresponding norditerpene, *ent*-16β-tosyloxy-17-norbeyerane.[18c] The evident inability of the 16 $\rightleftarrows$ 12 hydride shift to compete with nucleophilic capture and vicinal elimination in the above irreversible solvolysis reactions may be attributed to a combination of two factors. First, in the transition state for the 16 → 12 hydride shift, ring C must adopt a boatlike conformation in order that the 16β proton reach within bonding distance of C-12. This conformational strain must increase the energy of the transition state with respect to the norbornyl system. Second, the presence of the methyl group at C-13 must diminish the effective charge density at the 12 position, thus reducing the probability of hydrogen transfer.[30]

SCHEME IV



(d, R = CHO)



In order to increase the probability of the crossover rearrangement (A → B), we have examined the solvolysis of tosylates **3c** and **11c** in the less nucleophilic media, formic acid and trifluoroacetic acid.[31] A reduction in the rate of nucleophilic capture at the secondary positions (16 and 12) should enhance the relative rate of hydride shift, assuming that the solvent effect upon the latter process is negligible. The results are summarized in Scheme V.[30]

(24) We are grateful to Dr. G. Hugel and G. Ourisson for a sample of trachylobane.[5a]

(25) In view of the recent total synthesis of isosteviol by K. Mori, Y. Nakahara, and M. Matsui [*Tetrahedron Lett.*, 2411 (1970)], the production of **9** and **10** constitute formal total syntheses. Partial syntheses of methyl 13α,16-cycloatisan-19-oate (enantiomer of methyl trachylobanate)[5a] and (+)-**10** (enantiomer of **10**) from levopimaric acid have been reported by W. Herz, R. N. Mirrington, A. Young, and Y. Y. Lin, *J. Org. Chem.*, **33**, 4210 (1968).

(26) The corresponding acid (**9**, R = CO_2H), the C-4 epimer of the previously known trachyloban-18-oic acid,[5a] has recently been isolated from (a) the flowers of *Helianthus annuus* L. by J. St. Pyrek [*Tetrahedron*, **26**, 5029 (1970)] and (b) a *Solidago* species by R. McCrindle (private communication). A direct comparison performed by Professor McCrindle between the methyl ester of the latter and the ester **9** prepared in this work has established the identity of the two compounds.

(27) R. H. Shapiro, J. H. Duncan, and J. C. Clopton, *J. Amer. Chem. Soc.*, **89**, 1442 (1967), and references cited therein.

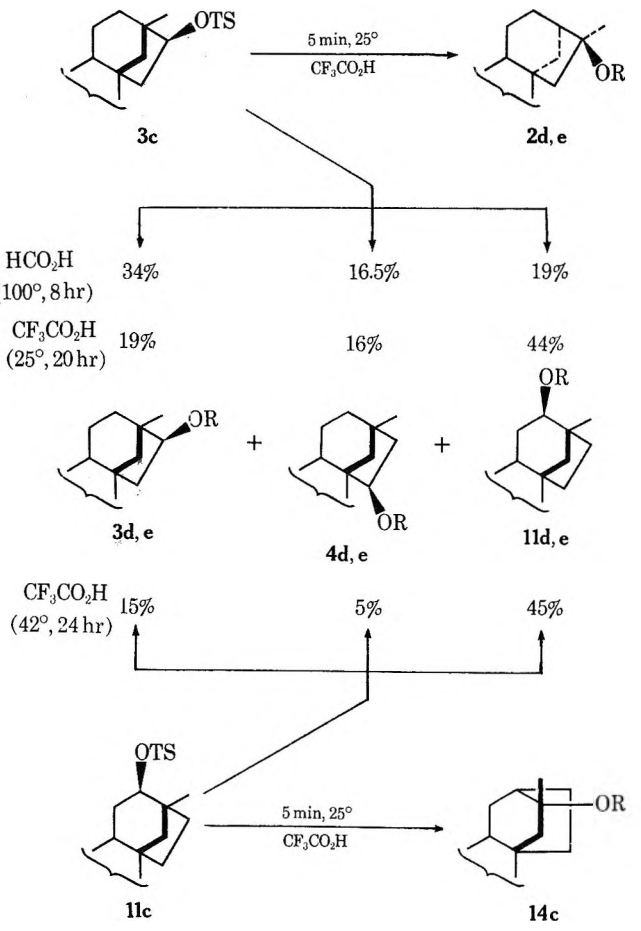
(28) (a) For other examples of this type of C–D rearrangement of beyerane derivatives see ref 16–18 (b). We are assuming that the mechanism of cyclopropane formation in the tosylhydrazone decomposition under protic conditions is cationic (diazonium ion formation with incorporation of a proton from solvent) rather than carbenoid, as has been established for the formation of bicyclobutane from cyclopropyl carboxaldehyde tosylhydrazone: F. Cook, H. Schechter, J. Bayless, L. Friedman, R. L. Foltz, and R. Randall, *J. Amer. Chem. Soc.*, **88**, 3872 (1966); K. B. Wiberg and J. M. Lavanish, *ibid.*, **88**, 5272 (1966).

(29) R. A. Appleton, J. C. Fairlie, R. McCrindle, and W. Parker, *J. Chem. Soc. C*, 1716 (1968).

(30) A small amount (0.5–14%) of crossover rearrangement was detected in the hydrogen chloride catalyzed isomerizations of tetracyclic diterpene hydrocarbons.[17b] A case of apparent crossover rearrangement has also been found in the phyllocladene series.[16d]

(31) P. E. Peterson, R. J. Bopp, D. M. Chevlie, E. L. Curran, D. E. Dillard, and R. J. Kamat, *J. Amer. Chem. Soc.*, **89**, 5902 (1967); J. E. Norlander and W. G. Deadman, *ibid.*, **90**, 1590 (1968); I. L. Reich, A. Diaz, and S. Winstein, *ibid.*, **91**, 5635 (1969).

SCHEME V



c, R = Ts; d, R = CHO; e, R = CF_3CO

Whereas acetolysis of **3c** affords only kaurane-type products (see above), extended formolysis gives 19% of the 12β formate **11d** along with the vicinal rearrangement product **4d**. In the less nucleophilic medium, trifluoroacetic acid, as much as 44% of the 12 substitution product is found. The reverse crossover rearrangement (B → A) is also seen in the trifluoroacetolysis of the 12β tosylate **11c**. In both cases, the initial products are the simple Wagner–Meerwein rearrangement isomers **2e** and **14e**.

The experimental observation of the 12 → 16 hydride shift raises the question of the mechanism of the process. The formation of a trachylobane intermediate, for which precedent now exists, followed by acid-catalyzed ring opening[17a] in the reverse sense would effect overall 12 → 16 hydride transfer. The other possibility is an intramolecular transfer of hydride between positions 12 and 16. These two alternatives were distinguished through solvolysis in deuteriotrifluoroacetic acid; a summary of the data is collected in Table I

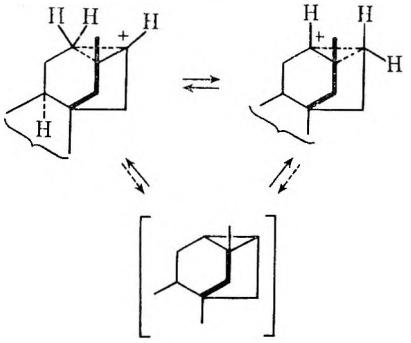


TABLE I

DEUTERIUM INCORPORATION DURING SOLVOLYSIS IN TRIFLUOROACETIC ACID-*O*-*d* WITH VARIOUS DITERPENE SUBSTRATES

	Deuterium incorporation[a]	
Substrate	Into **11b**[b]	Into other products
3c	77% d_5 (4.85)	**3b**,[b] 60% d_4 (3.56)
		4b,[b] 55% d_4 (3.27)
3c		**2a**,[c] 44% d_3 (3.25)
2a	69% d_5 (4.90)	
11a		**14a**,[c] 47% d_5 (4.18)
5	85% d_5 (4.95)	
12	85% d_5 (4.93)	
13	83% d_5 (4.90)	
9	76% d_6 (5.78)	

[a] Percentage of major deuterated species followed by the average deuterium content in parenthesis. Complete deuterium distribution data in Experimental Section. [b] Product isolated as acetate for convenience; deuterium distribution determined on M − 60 fragment. [c] Product isolated as alcohol; deuterium distribution determined on parent peak (M^+).

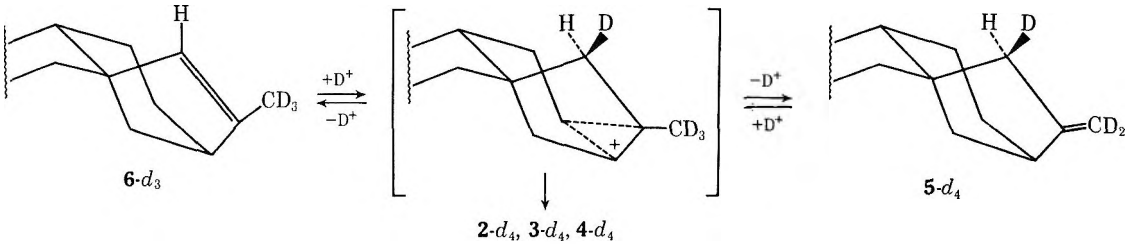
(complete deuterium distributions may be found in the Experimental Section).

From the extensive deuterium incorporation (three to six deuterium atoms), it is clear that extensive elimination–addition occurs in the trifluoroacetic acid medium. This conclusion is confirmed by conversion of the unsaturated esters **5**, **12**, and **13** to **11e** under the standard solvolysis conditions and with the same deuterium incorporation. The disappearance of the C-17 methyl resonance in the nmr spectra of the products locates approximately three of the deuterium atoms. There can be no deuterium at the carbinyl positions (*i.e.*, 12 and 16) of **11b** and **3b**, since the corresponding keto esters (**16** and **17**) had essentially the same deuterium content.

The remainder of the label would be expected to be situated on the carbon adjacent to the methyl group (*i.e.*, position 14 in **3b**, **4b**, and **11b**; position 15 in **2a** and **14a**) in the various products, since the label must be acquired in the deuteron addition to the unsaturated esters **6** and **12**. Some experimental support for this supposition was obtained by dehydration of the labeled **14a** (4.18 *d*, 47.1% d_5) with thionyl chloride in pyridine. The isomeric atiserene-type esters obtained (**12** and **13**) had average deuterium contents of 3.35 *d* and 3.48 *d* with the principal species being d_4 (51.3 and 55.5%) and with essentially no d_5. The nmr spectrum of labelled **13** exhibited a reduced intensity for the allylic methylene group (τ 8.04), and more quantitatively the spectrum of **12** showed only 0.1 proton for the vinyl hydrogen at C-15 (τ 4.42).

Submission of the cyclopropane-containing ester **9** to trifluoroacetic acid-*O*-*d* similarly afforded the 12β-substituted kaurane ester **11**, but now with the clean incorporation of six deuterium atoms. Since **11** was formed in all the other cases with incorporation of five atoms of deuterium (0–6% d_6), the observed crossover rearrangement in trifluoroacetic acid must occur predominantly by way of an intramolecular hydride transfer from C-12 to C-16.

The observation that products **2**–**4** apparently incorporate essentially one less deuterium atom than **11** is attributable to a highly stereoselective elimination–addition sequence with the tertiary kauranol ester **2**. Additions to trigonal carbons on the ethano bridge of kaurenes and beyerenes are well-known to proceed with high exo stereoselectivity.[32] Hence if the deuteron addition to the isokaurene **6** (and its microscopic reverse elimination) proceeds solely from the *exo* (α) side, there will be no opportunity for the endo proton to exchange. On the other hand, additions to atiserenes generally show little selectivity;[32] thus after the crossover rearrangement, nonselective elimination–addition ensues, resulting in the eventual exchange of the one remaining proton.



This investigation and complementary studies in other laboratories[16–19] have established that all of the individual ring D rearrangements in the Wenkert biogenetic scheme (Scheme I) can be mimicked by chemical means.[33] Despite these successes, however, it is clear that the chemical transformations, for the most part, lack the specificity normally found in enzyme-mediated biosynthetic reactions. We find, for example, that elimination under solvolytic conditions gives both kaurene and isokaurene esters, whereas, in the enzymatic biosynthesis of kaurene,[10] only the exocyclic isomer appears to be formed. Although we find that the 12 → 16 hydride shift can be observed in the poorly nucleophilic medium, trifluoroacetic acid, the rearrangement is accompanied by extensive elimination–addition, and under these conditions the product is a 12-substituted beyerane (**11**) rather than an atiserene (**12**). In contrast, the biosynthesis of the carbon nuclei of most terpenes from cyclic precursors appears to proceed in a "nonstop" manner, *i.e.*, without proton elimination *en route*.[36]

It is interesting, albeit highly speculative, to consider in closing the role which an enzyme (or enzymes) might play in the skeletal rearrangements of the actual biosynthetic process. First, the exocyclic specificity in the proton elimination might be effected by the location of a basic center near the C-17 methyl group in the enzyme–substrate complex. The efficiency of the crossover rearrangement could be enhanced through a conformational change imposed upon the diterpene substrate by the shape of the enzyme cavity. If ring C is forced to adopt a boat conformation, the 12 → 16 hydride shift might well occur with facility. Furthermore, it seems likely that a nucleophilic center(s) (and/or counterion) at the active site is closely associated with the various carbonium ions.[37] Reversible nucleophilic capture by this center would help maintain the stereospecificity of the rearrangement, moderate the reactivity of the cationic intermediate(s), and possibly avoid premature elimination.

Experimental Section[38]

Deamination of Methyl *ent*-16-Aminobeyeran-19-oate (1). A. As Hydrochloride.—Sodium nitrite (1.5 g, 21.6 mmol) was added in three equal portions to a solution of the hydrochloride of **1**[13] in acetic acid (25 ml) over a 2-hr period. After 12 hr at room temperature the solvent was evaporated, the residue was dissolved in hexane, and the hexane solution was washed twice with water and then dried (Na_2SO_4) and evaporated. The resulting mixture was separated into eight fractions by column chromatography on silica with chloroform as eluent.

The first fraction (34 mg) contained mainly methyl Δ^{15}-*ent*-beyeren-19-oate (**7**). Glpc analysis indicated the presence of small amounts of the kaurene esters (5:6:7, 5:5:90). The major component was isolated by crystallization from methanol, mp 111–112.5° (lit.[16b] mp 107–109°). The infrared spectrum is identical with a spectrum of **7** obtained from the decomposition of the tosylhydrazone **8**.

The third fraction (86 mg) was crystallized from hexane to give methyl *ent*-16α-acetoxybeyeran-19-oate (**26**): mp 144–148°; nmr τ 9.14, 8.81, 8.38, 8.02, 6.32 (all s, 3 H); ir 1720 cm^{-1}.

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.40; H, 9.65.

The subsequent fractions contained mixtures of three acetates: **2b**, **3b**, and a third acetate. Preparative tlc (silica gel, 1:1 benzene–chloroform as eluent) upon fractions 5 and 6 (69 mg) enabled partial separation of **3b** (25.5 mg) essentially pure by glpc analysis. Several recrystallizations from methanol gave material with mp 91–92° (lit.[13] mp 91–92°). Direct comparison

(32) For specific references see ref 13.

(33) Three of the four preceding cyclization steps in the biogenetic scheme can be effected chemically. Acid-catalyzed cyclizations of acyclic precursors to the proper A–B bicyclic nucleus are well known.[34] In addition, the cationic cyclization of bicyclic diterpenes to the tricyclic stage has also recently been accomplished.[35a,b] Although further cyclization to tetracyclic beyerane derivatives was observed, the pathway is quite different from the biogenetic route in Scheme I.[35c]

(34) A. Eschenmosher, D. Felix, M. Gut, J. Meier, and P. Stadtler in "Biosynthesis of Terpenes and Sterols," Ciba Foundation Lectures, G. E. W. Wolstenholme and M. O'Connor, Ed., J. A. Churchill, London, 1959, p 217; G. Stork and A. W. Burgstahler, *J. Amer. Chem. Soc.*, **77**, 5068 (1955); E. E. van Tamelen, *Accounts Chem. Res.*, **1**, 111 (1968).

(35) (a) O. E. Edwards and R. S. Rosich, *Can. J. Chem.*, **46**, 1113 (1968); E. Wenkert and Z. Kumazawa, *Chem. Commun.*, 140 (1968); (b) T. McCreadie and K. H. Overton, *ibid.*, 288 (1968); *J. Chem. Soc. C*, 312 (1971); (c) O. E. Edwards and B. S. Mootoo, *Can. J. Chem.*, **47**, 1189 (1969); J.-L. Fourrey, J. Polonsky, and E. Wenkert, *Chem. Commun.*, 714 (1969); S. F. Hall and A. C. Oehlschlager, *ibid.*, 1157 (1969).

(36) See, for example, T. T. Tchen and K. Bloch, *J. Amer. Chem. Soc.*, **78**, 1516 (1956); E. Caspi, J. B. Greig, J. M. Zander, and A. Mandelbaum, *Chem. Commun.*, 28 (1969).

(37) The temporary participation of a nucleophilic center in enzyme-catalyzed olefin alkylation reactions has been suggested; *cf.* J. W. Cornforth, *Angew. Chem., Int. Ed. Engl.*, **7**, 903 (1968).

(38) Melting points were taken in open capillary tubes on a Thomas–Hoover melting point apparatus and are uncorrected. Infrared spectra were determined on Perkin-Elmer spectrophotometers, Models 137, 237, or 521. The nmr spectra were obtained in carbon tetrachloride (unless specified otherwise) using tetramethylsilane as internal standard on Varian Associates Models A-60A, A-56-60, or HA-100 spectrophotometers. The mass spectra were determined on an Atlas CH_4 mass spectrometer. Microanalyses were performed by Mr. J. Nemeth and associates at the University of Illinois. The gas chromatograph used was a Hi-Fi Model 600-D (Varian Aerograph) with a 6 ft × 0.125 in. column 5% SE-30 silicone rubber on 60–80 mesh DMCS Chromosorb W (usual temperatures: column 230°, injector 260°). The optical rotations were taken in a Zeiss polarimeter using chloroform as solvent. The ultraviolet spectra were taken on a Cary Model 14 spectrophotometer using ethanol as solvent.

TABLE II
YIELDS AND PRODUCT DISTRIBUTION FROM THE DECOMPOSITION OF TOSYLHYDRAZONE 8

Solvent	Base (equiv)	% yield (less polar fraction)	Relative yields,[e] % 9	5	6	7
DEC[a] + 1.25% H_2O	$NaOCH_3$ (2)	35	30	34	34.5[f]	
DEC + 2% H_2O	NaOH (1.6)	31.3	12.1	17.1	71.5[f]	
DEC + 1.25% H_2O[b]	NaOH (3)	49	24	28.7	6.6	42
DEC + 10% EG[c,d]	$NaOCH_3$ (3)	58	24.2	32.1	43.1[f]	
DEC + 10% EG[c]	$NaOCH_3$ (1)	52	14.8	17	11.2	59
DEC + 10% EG	Na (3)	40	23.6	29.2	6.6	34.8
DEC + 10% EG	Na (1.25)	59	21	35	7	35
Diglyme[c]	$NaOCH_3$ (1)	33		5	5	90

[a] DEC = diethylcarbitol. [b] Additional water added at intervals. [c] Salt formation before the solvent was added. [d] EG = ethylene glycol. [e] By glpc and nmr spectral analysis. [f] Yield of 6 + 7 (inseparable by glpc).

(tlc, glpc, ir, nmr, and mmp 91–93°) established its identity as methyl *ent*-16β-acetoxybeyeran-19-oate (**2b**). The third acetate is tentatively identified as *ent*-16α-acetoxybeyeran-19-oate[13] by glpc comparison.

By means of nmr and glpc analysis upon the mixed fractions, combined with the isolated materials, the following product distribution was calculated: **5** (0.5%), **6** (0.5%), **7** (9%), **2b** (35%), **3b** (15%), and the 16α acetate (<5%).

B. As Amine.—Three portions of sodium nitrite, 3.5 g (50.8 mmol), 2 g (29.0 mmol), and 0.5 g (7.2 mmol), were added to a solution of amine **1**[13] in acetic acid (100 ml) at 0, 0.5, and 15 hr, respectively. After 29 hr at room temperature the product was isolated as described in part A. Direct crystallization from methanol gave **3b** (0.5 g, mp 143–147°).

The mother liquor was evaporated and the residue was chromatographed on silica gel (200 g) using 5% ether in hexane as eluent. The early fractions afforded a mixture of the unsaturated esters (0.414 g) which according to glpc and nmr spectral analysis consisted of **5** (27%), **6** (14%), and **7** (59%). The following fractions gave additional tertiary acetate **3b** after recrystallization (mp 144–148°). The next fractions contained mixtures of **2b**, **3b**, **4b**, and the 16α acetate in varying proportions. From one fraction (502 mg) rich (~90%) in **3b**, crystallization twice from methanol gave pure material, mp 92–93.5°. The material recovered from the mother liquor and the following fraction (enriched in **4b**) were rechromatographed using chloroform as eluent. In this manner relatively pure **4b** was obtained, which after crystallization from methanol gave nmr, ir, glpc, and melting point characteristics identical with those of an authentic specimen.[13]

The final product distribution was estimated to be as follows: **5** (5%), **6** (2%), **7** (10%), **2b** (31%), **3b** (21%), **4b** (3.5%), and 16α acetate (4%).

Methyl *ent*-16α-Hydroxykauran-19-oate (2a).—A solution of **2b** (50 mg, 0.13 mmol) in excess 5% ethanolic sodium hydroxide was heated at reflux temperature for 3 hr. The alcohol was evaporated and the product was isolated by hexane extraction (see above). Recrystallization from hexane afforded the hydroxy ester **2a**: mp 154–155° (lit.[20a] mp 153–156°); nmr τ 9.18, 8.85, 8.70, 6.40 (all s, 3 H) (lit.[20a] τ 9.22, 8.88, 8.69); $[\alpha]^{25}D$ −76° (*c* 33); ir 1720, 3550 cm^{-1}.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.12; H, 10.19.

Methyl Δ[15]-*ent*-Kauren-19-oate (5) and Methyl Δ[16]-*ent*-Kaurene-19-oate (6).—A solution of hydroxy ester **2a** (58.5 mg, 0.17 mmol) and tosyl chloride (300 mg) in 15 ml of pyridine was heated under reflux for 3 hr. The cooled solution was added to dilute hydrochloric acid and the product was extracted from the resulting suspension with three portions of hexane. The combined hexane extracts were washed once with dilute hydrochloric acid and twice with water, dried (Na_2SO_4), and evaporated. The residue was chromatographed on 20% silver nitrate silica gel with ethyl acetate–hexane as eluent. The first two fractions contained **5** (17 mg) and **6** (21 mg), respectively (ir, nmr, tlc, and glpc comparisons). A small amount of unreacted **2a** was found in a later fraction.

Tosylhydrazone 8 of Methyl *ent*-16-Ketobeyeran-19-oate (Isosteviol Methyl Ester).—A solution of isosteviol methyl ester (2.3 g, 6.9 mmol)[13] in 7 ml of glacial acetic acid was heated to reflux temperature. A 3-g (16.3 mmol) portion of *p*-toluenesulfonylhydrazine was slowly added to a second 7-ml portion of glacial acetic acid at reflux temperature. The two hot solutions were then combined and heated at reflux temperature for 1–2 min. After cooling, a fine white crystalline precipitate formed which was filtered and washed first with cold glacial acetic acid and then with 10–20% water in acetic acid. The yield of **8** was 3.36 g (95%): mp 214–215° (from chloroform and hexane); nmr ($CDCl_3$) τ 9.375, 9.00, 8.835, 7.57, and 6.35 (all s, 3 H), 2.70 and 2.17 (A_2B_2, 4 H, J = 8 Hz).

Anal. Calcd for $C_{28}H_{40}N_2O_4S$: C, 67.17; H, 8.05; N, 5.60; S, 6.40. Found: C, 66.91; H, 8.02; N, 5.77.

Decomposition of Tosylhydrazone 8.—Several different conditions were examined (see Table II for summary). A typical procedure is as follows.

The tosylhydrazone **8** (875 mg, 1.7 mmol) was allowed to react with sodium methoxide in methanol (6.0 mmol in 1 ml). The methanol was then removed by gentle heating under a light stream of dry nitrogen. The solvent was added, in this case 10% ethylene glycol in diethylcarbitol, and the solution was quickly brought to reflux temperature (180–190° bath temperature). After 3 hr at reflux temperature, the solution was cooled and the product was isolated by extraction with hexane. The crude product was separated into a less polar fraction (315 mg, 59%) and a more polar fraction by column chromatography on silica gel (chloroform as eluent).

Rechromatography of the less polar fraction on 30 g of 20% silver nitrate–silica gel eluting with 2–10% ethyl acetate–hexane afforded four components. The least polar, pentacyclic ester **9** (methyl *ent*-13α,16-cycloatisan-19-oate)[26] was recrystallized from methanol: mp 101–103° (lit.[26a] mp 98–100°); nmr τ 9.3–9.5 (m), 9.26 (s, 3 H), 8.87 (s, 6 H), 6.38 (s, 3 H) [lit.[26a] τ_{CDCl_3} 9.4 (m), 9.25 (s, 3 H), 8.88 (6 H), 6.40 (s, 3 H)]; $[\alpha]^{25}D$ −67° (*c* 4.5) [lit.[26a] $[\alpha]D$ −70.5° ($CHCl_3$)]; ir 1720 cm^{-1}; uv ϵ_{199} 845; mass spectrum *m/e* 316 (M^+).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.91. Found: C, 79.67; H, 10.11.

The second component was shown to be methyl Δ[16]-kauren-19-oate (**5**) by comparison (ir, mixture melting point, glpc) with an authentic sample:[21] mp 84–85° (lit.[21] mp 88–89°), mmp 83–86.5° (authentic sample, mp 86°); nmr τ 9.18, 8.87, 6.40 (all s, 3 H), 5.27 (m, 2 H); $[\alpha]^{25}D$ −102° (*c* 4.3) (lit.[21] $[\alpha]D$ −107°).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.17. Found: C, 79.57; H, 10.27.

Purification of the third component sometimes required a second column chromatography. An analytical sample was obtained by sublimation and after crystallization from methanol had mp 79–80°; nmr τ 9.165, 18.865, and 6.35 (all s, 3 H), 8.30 (d, 3 H, J = 1.8 Hz), 4.96 (m, 1 H), 4.96 (m, 1 H); $[\alpha]^{25}D$ −54° (*c* 4.1); ir (CCl_4) 1720, 875 cm^{-1}; uv ϵ_{199} 3843.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.92; H, 10.01.

Component four was the unrearranged unsaturated ester **7**: mp 115.1–115.6° (sublimed), 111–112° (recrystallized from methanol) (lit.[16b] mp 107–109°); nmr 9.46, 9.00, and 8.845 (all s, 3 H), 4.3 and 4.60 (AB, d, 2 H, J = 6 Hz); $[\alpha]^{25}D$ +2.48° (*c* 3.6); uv ϵ_{199} 9640.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.56; H, 10.17.

The results with other conditions are summarized in Table II.

Conversion of Methyl Δ[16]-*ent*-Kauren-19-oate (5) into Methyl Δ[15]-*ent*-Kauren-19-oate (6).—A few small crystals of iodine were added to a solution of unsaturated ester **5** (48.5 mg, 1.5 mmol) in xylene (5 ml), and the solution was heated at reflux for 20 min.[19] The reaction mixture was cooled and shaken with mercury (1 g) for several minutes. The precipitate which formed was filtered along with the excess mercury and washed with xylene. Glpc

analysis of the residue obtained after evaporation of the solvent showed three products present in the approximate ratio of 20:80:1 with retention times corresponding to those of 5–7, respectively. Longer reaction times lead to an increase in the third component. Column chromatography on 20% silver nitrate–silica gel separated 25.5 mg of 6 and 11 mg of 5 in order of increasing "polarity." The major component was recrystallized from methanol and was identical (glpc, silver nitrate–silica gel tlc, nmr, and ir comparison) with a sample of 6 isolated from the tosylhydrazone decomposition above.

ent-13α,16-Cycloatisan-19-ol.—A 170-mg (0.43 mmol) sample of 5 was reduced with lithium aluminum hydride (excess) in dry tetrahydrofuran at reflux temperature for 12 hr. The excess lithium aluminum hydride was destroyed with wet tetrahydrofuran. The tetrahydrofuran was evaporated and the residue was dissolved in a hexane and dilute hydrochloric acid mixture. An extractive work-up afforded the pentacyclic alcohol (165 mg, 95%): mp 123–124.4°; nmr ($CDCl_3$) τ 9.23 and 9.39 (both broad m, 1 H), 9.08 (s, 6 H), 8.87 (s, 3 H), 7.76 (d, 1 H, J = 1.2 Hz), 6.52 and 6.36 (AB, d, 2 H, J = 11 Hz); $[\alpha]^{24}D$ −45.4 (c 4.2); ir (KBr) 3380 (OH), 3015 cm^{-1} (Δ H).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.05; H, 11.20.

ent-13α-16-Cycloatisane (Trachylobane, 10).—Oxidation of the pentacyclic alcohol above (60 mg, 0.2 mmol) was carried out with 1 g of the chromium trioxide–dipyridine complex[39] (freshly prepared) in 20 ml of dichloromethane. After 1 min, the mixture was filtered through 20 g of silica gel in a column using 1:4 ether–hexane as eluent. Glpc analysis showed the presence of a new compound with only a trace of starting alcohol; the ir spectrum had bands at 1705 and 2700 cm^{-1} appropriate for the corresponding aldehyde. A 50-mg (0.166 mmol) sample of the aldehyde and 500 mg of 98% hydrazine hydrate were added to a heavy glass tube containing 6 ml of methanol in which 1 g of sodium had been previously dissolved. The tube was sealed and placed in a high-pressure reaction bomb along with 30 ml of methanol. The bomb in turn was sealed and then heated to 210° for 3 hr. After cooling, the product was isolated by hexane extraction. The material obtained (25 mg, 63%) was homogeneous according to glpc analysis and had a retention time corresponding to authentic trachylobane[5a,24] by coinjection. The nmr spectra of the two samples are identical.

A more thorough comparison between hydrocarbon 9 and authentic trachylobane (mp 46–47.5° after recrystallization)[5a,24] was performed with material prepared from another Wolff–Kishner reduction. Repeated crystallization from methanol afforded a sample: mp 44.5–44.6°; mmp 45.5–47°; $[\alpha]^{24}D$ −37° (c 1.2) (lit. $[\alpha]D$ −43°).[5a] The ir and nmr spectra and tlc mobility of the two samples were identical.

Methyl *ent*-16β-Tosyloxybeyeren-19-oate (3c).—A solution of hydroxy ester 3a (360 mg, 1.2 mmol)[13] and tosyl chloride (1.8 g, 10 mmol) in pyridine (25 ml) was allowed to stand for 24 hr at room temperature. After an extractive work-up and crystallization from hexane, tosylate 3c (500 mg, 95%) was obtained: mp 96–97°; nmr ($CDCl_3$) τ 9.26, 9.17, 8.85, 8.57, and 6.39 (all s, 3 H), 5.56 (broad d, 1 H, J = 8 Hz), 2.66 and 2.21 (AB, 2 H each, J = 9 Hz).

Anal. Calcd for $C_{28}H_{40}O_5S$: C, 68.85; H, 8.20. Found: C, 69.33; H, 8.45.

Methyl *ent*-12β-Tosyloxybeyeran-19-oate (11c).—A solution of hydroxy ester 11a (150 mg, 0.46 mmol)[13] and 1 g (5.4 mmol) of tosyl chloride in pyridine (10 ml) was allowed to stand for 15 hr at 10°. An extractive isolation procedure with hexane and recrystallization from hexane gave 200 mg (86%) of 11c: mp 104.5–105.5°; nmr ($CDCl_3$) τ 9.37, 9.13, 8.86, 7.59, and 6.41 (all s, 3 H), 5.60 (s, 1 H, $W_{1/2}$ = 6 Hz), 2.66 and 2.21 (AB, 2 H each, J = 9 Hz); ir (KBr) 1725 cm^{-1}.

Anal. Calcd for $C_{28}H_{40}O_5S_1$: C, 68.85; H, 8.20. Found: C, 68.87; H, 8.22.

Isolation Procedures for Solvolysis Reactions. A.—The solvent (formic acid, acetic acid, or trifluoroacetic acid) was evaporated under reduced pressure with rotary evaporation, and the residue was subjected to hydrolysis with 5% sodium hydroxide in 95% ethanol for 1–2 hr at reflux temperature. The ethanol was removed by rotary evaporation and the product was isolated by extraction with hexane.

B.—After completion of part A, the crude product was heated with 10% acetic anhydride in pyridine for 3 hr at steam bath temperature. The solvents were removed by rotary evaporation and the acetylated product was isolated by hexane extraction.

Solvolysis of Tosylate 3c. A. Acetolysis.—A solution of tosylate 3c (100 mg) in 50 ml of acetic acid (buffered by prior addition of sodium carbonate) was heated at reflux temperature for 15 hr. Glpc and nmr analysis of the product obtained after the isolation procedure A established that the material was a 1:2:1 mixture of the unsaturated esters 5, 6, and 7, respectively.

B. Formolysis at Room Temperature.—A solution of tosylate 3c (210 mg, 0.42 mmol) in 15 ml of formic acid (buffered by prior addition of sodium carbonate) was allowed to stand for 6–7 hr at room temperature. Hydroxy ester 2a (100 mg, 70%), identified by melting point and mixture melting point, crystallized from a hexane solution of the crude product obtained by procedure A. Chromatography of the mother liquor afforded another 20 mg of 2a.

C. Formolysis at Reflux.—A solution of 3c (1.3 g, 2.6 mmol) in 65 ml of formic acid buffered with sodium carbonate (300 mg, 3.0 mmol) was heated at reflux temperature for 8 hr. The product obtained after isolation procedure B was chromatographed on 200 g of silica gel (5% ether–hexane as eluent). The first fraction contained a mixture of unsaturated esters (179 mg, 20%) which was not investigated further. The third fraction (161 mg) afforded methyl *ent*-12β-acetoxybeyeran-19-oate (11b) on crystallization from methanol. The identity of 11b was established by comparison (melting point, glpc, nmr, and ir) with a previously prepared sample.[13] The fifth fraction (228 mg) was a mixture of 3b and 4b (glpc analysis). Crystallization from methanol provided 165 mg of 3b identical (melting point, glpc, nmr, and ir) with a previous sample.[13] By means of rechromatography of the mixed fractions (3b and 4b) on silica gel (chloroform as eluent) 135 mg of 4b could be obtained. Crystallization from methanol afforded pure material identical (melting point, glpc, nmr, and ir) with that previously prepared.[13] The last fraction (79 mg), eluted with ether, proved to be mainly hydroxy ester 2a. A final product distribution could be estimated from the isolated yields and analysis of the mixed fractions by glpc and nmr: 11b (19%), 3b (34%), 4b (16%), and 2a and/or 14a (6%).

D. Trifluoroacetolysis.—A solution of 3c (200 mg, 0.4 mmol) in 25 ml of trifluoroacetic acid buffered with sodium carbonate (200 mg, 1.9 mmol) was allowed to stand at room temperature for 48 hr. After isolation procedure B and purification as described in part C above, there was obtained 11b (44%), 3b (19%), and 4b (19%).

E. Deuteriotrifluoroacetolysis.—The labeled solvent was prepared by adding 4.5 g (0.225 mol, 99.77% pure) of deuterium oxide to 50 g (0.237 mol) of trifluoroacetic anhydride, then buffered with 215 mg (0.002 mol, 0.004 equiv) of sodium carbonate making an 8 × 10^{-2} N solution of sodium trifluoroacetate. A solution of tosylate 3c (900 mg, 1.8 mmol) in buffered deuteriotrifluoroacetic acid (55 ml) was allowed to stand at room temperature for 20 hr; then the product was isolated according to isolation procedure B. Direct crystallization from methanol at this stage gave 250 mg of 11b. Further purification as described in part C afforded 104 mg (15%) of 3b and 60 mg (10%) of 4b as well as additional 11b and mixed fractions.

The nmr spectrum of acetate 11b was identical with that of 11b previously prepared except for the absence of the C-17 methyl signal at τ 9.01. The mass spectrum, after correction for the natural abundance M + 1 and M + 2 peaks in unlabeled 11b, indicated the following deuterium distribution per cent of each deuterated species, followed by the average deuterium content): (M − 60) 2 d_3, 16 d_4, 77 d_5, 5 d_6 (average, 4.85); (M − 75) 7 d_3, 16 d_4, 69 d_5, 5 d_6 (average 4.79).

The nmr spectrum of 3b lacked the signal at τ 9.11. The mass spectrum gave the following deuterium distribution: (M − 60) 4 d_1, 7 d_2, 18 d_3, 60 d_4, 7 d_5 (average 3.56).

The nmr spectrum of 4b had a reduced intensity for the methyl signal at τ 9.03 (s, 1 H). The mass spectrum gave the following deuterium distribution: (M^+) 5 d_0, 15 d_1, 7 d_2, 14 d_3, 48 d_4, 9 d_5 (average 3.23); (M − 60) 4 d_0, 12 d_1, 6 d_2, 14 d_3, 55 d_4, 8 d_5, 1 d_6 (average, 3.27).

Acetates 11b and 3b were hydrolyzed (see isolation procedure A for conditions) to the corresponding hydroxy esters 11a and 3a, then oxidized to the respective keto esters, methyl *ent*-12-ketobeyeran-19-oate (16) and methyl *ent*-16-ketobeyeran-19-oate (isosteviol methyl ester, 17) with excess chromium trioxide dipyridine complex in methylene chloride[39] for 5–10 min at room temperature. After purification by column chromatography and recrystallization, the mass spectra were determined, leading to

(39) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

the following deuterium distribution data: **15** (M^+) 20 d_4, 77 d_5, 0 d_6, 4 d_7 (average, 4.96); **16** (M^+), 2 d_0, 5 d_1, 6 d_2, 18 d_3, 61 d_4, 7 d_5 (average, 3.50).

F. Brief Deuteriotrifluoroacetolysis.—A solution of tosylate **3c** (200 mg, 0.43 mmol) in 25 ml of buffered deuteriotrifluoroacetic acid was allowed to stand at room temperature for 5 min, then quenched quickly with 5% ethanolic potassium hydroxide. The alcohol solution was concentrated, water was added, and the product was isolated by extraction with hexane. Crystallization from hexane afforded 70 mg (52%) of tertiary hydroxy ester **2a**. The nmr spectrum of this material lacked the methyl peak at τ 8.69. Analysis of the mass spectrum gave the following deuterium distribution: (M^+) 3 d_1, 17 d_2, 44 d_3, 38 d_4 (average, 3.25).

Solvolysis of Tosylate 11c. A. Acetolysis.—Tosylate **11c** was subjected to acetolysis as above with **3c** for 25 hr at 85°. Evaporation of the acetic acid and isolation by hexane extraction afforded mainly methyl Δ^{15}-*ent*-atisen-19-oate (**12**) according to nmr analysis on the crude product.

B. Formolysis.—Tosylate **11c** (36 mg) was subjected to formolysis as described above with **3c** for 20 hr at room temperature. The nmr spectrum of the product obtained after isolation procedure A was identical with that of **14a** (methyl *ent*-16-hydroxyatisan-19-oate).[13]

C. Trifluoroacetolysis.—A 900-mg (1.8 mmol) portion of **11c** was added to 40 ml of buffered trifluoroacetic acid. After 5 min at room temperature, a 4-ml aliquot of the solution was removed and subjected to isolation procedure B. On crystallization of the residue from hexane, alcohol **14a** was obtained (by melting point, glpc, analysis, nmr, and ir spectral comparison).[13] After 20 hr at room temperature, a second 4-ml aliquot was removed and treated according to procedure B. Glpc and nmr spectral analyses on the product indicated the presence of **11b** (~80%) along with small amounts of **3b** and **4b**. The reaction was allowed to continue for 96 hr at room temperature and an additional 24 hr at 42°. Isolation according to isolation procedure B and purification by chromatography as described above (part C, formolysis of **3c**) gave **11b** (245 mg, 45%), **3b** (65 mg, 12%), and **4b** (25 mg, 5%). Acetates **11b** and **3b** were identified by melting point glpc and nmr and ir comparisons, acetate **4b** by glpc and nmr comparisons.

Deuteriotrifluoroacetolysis of Hydroxy Ester 11a.—A solution of **11a** in 20 ml of buffered deuteriotrifluoroacetic acid was allowed to stand for 15 min at room temperature. The product was then separated by isolation procedure A. Crystallization of the residue from hexane afforded labeled hydroxy ester **14a** (210 mg, 86%). The nmr spectrum was identical with that of unlabeled **14a**[13] except for the complete absence of the C-17 methyl signal at τ 8.71. Analysis of the mass spectrum gave the following deuterium distribution: (M^+) 1 d_1, 3 d_2, 12 d_3, 33 d_4, 47 d_5, 1 d_6 (average, 4.18); ($M - 18$) 3 d_2, 10 d_3, 34 d_4, 51 d_5 (average, 4.52).

The labeled hydroxy ester **14a** (190 mg, 0.57 mmol) was dehydrated with thionyl chloride (1 ml) in 20 ml of methylene chloride and 8 ml of pyridine and the resulting mixture of atiserene esters **12** and **13** was separated chromatographically on 18% silver nitrate–silica gel as previously described.[13] In the nmr spectrum of the labeled endocyclic isomer **12** (80 mg, 44%, mp 90–91°), the vinyl methyl group (τ 8.28) was reduced to $<1/4$ of the original intensity and the vinyl proton (τ 4.42) to ~0.1 H. Analysis of the mass spectrum gave the following deuterium distribution: (M^+) 5 d_0, 4 d_1, 9 d_2, 28 d_3, 51 d_4 4 d_5 (average 3.35). The nmr spectrum for the exocyclic isomer **13** (40 mg, 21%, mp 125.5–127°) showed a substantially reduced intensity for the vinyl protons (τ 5.3–5.4) and the allylic methylene group (τ 8.04). Analysis of the mass spectrum gave the following deuterium distribution: (M^+) 7 d_0, 3 d_1, 9 d_2, 33 d_3, 55 d_4 (average 3.48).

Deuteriotrifluoroacetolysis of Other Diterpene Substrates.—In each of the following experiments, the substrate was subjected to solvolysis in buffered deuteriotrifluoroacetic acid (10–25 ml) for 20–21 hr at room temperature. After work-up by isolation procedure B, acetate **11b** was isolated by column chromatography and/or crystallization from methanol. The deuterium distribution data were obtained from the mass spectrum of **11b** after correction for ^{13}C natural abundance. The yields were estimated from glpc traces.

A.—Methyl *ent*-16α-hydroxykauran-19-oate (**2a**, 470 mg) in 55 ml of buffered deuteriotrifluoroacetic acid gave, after purification by column chromatography (see part C, formolysis of **3c**), **11b** (46%): ($M - 60$) 4 d_3, 23 d_4, 69 d_5, 5 d_6 (average, 4.78).

B.—Methyl Δ^{16}-*ent*-kauren-19-oate (**5**, 110 mg) in 55 ml of the labeled solvent gave, after purification by column chromatography, **11b** (45%): ($M - 60$), 11 d_4, 85 d_5, 5 d_6 (average, 4.95).

C.—Methyl Δ^{15}-*ent*-atisen-19-oate (**12**, 50 mg)[13] gave **11b** in ~80% yield: ($M - 60$) 11 d_4, 85 d_5, 4 d_6 (average 4.93).

D.—Methyl Δ^{16}-*ent*-atisen-19-oate (**13**, 56 gm)[13] gave **11b** in ~80% yield: ($M - 60$) 1 d_3, 12 d_4, 83 d_5, 4 d_6 (average 4.90).

E.—Methyl *ent*-13α,16-cycloatisan-19-oate (**9**, 24 mg) gave **11b** in ~80% yield: ($M - 60$) 4 d_4, 18 d_5, 76 d_6, 3 d_7 (average, 5.78); ($M - 75$) 20 d_5, 80 d_6, 1 d_7 (average, 5.85).

Registry No.—**1**, 21682-55-3; **2a**, 22376-08-5; **3c**, 31819-20-2; **5**, 5524-25-4; **6**, 18671-79-9; **7**, 14699-35-5; **8**, 21682-50-8; **11c**, 31819-24-6; **26**, 30288-12-1; *ent*-13α,16-cycloatisan-19-ol, 31819-26-8.

Studies on the Syntheses of Heterocyclic Compounds. CDL. Total Synthesis of Androcymbine

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Photolysis of the diazonium salts **4** and **14** of 6,7-dimethoxy- (**3**) and 7-benzyloxy-6-methoxy-1-(2-amino-4-benzyloxy-3,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-2-methylisoquinoline (**13**) gave *O*-benzylandrocymbine (**8**), which was debenzylated to afford (±)-androcymbine (**2**). Also the same reaction of a diazonium salt **19**, however, gave the abnormal product, homoproaporphine (**20**).

Androcymbine (**2**),[1] the principal member of a family of 1-phenethylisoquinoline alkaloids, has been biosynthesized from the diphenolic phenethylisoquinoline (**1**)[2] (Scheme I). Three synthetic methods have been developed for androcymbine-type compounds: the first by phenol oxidation,[3] the second by Pschorr reaction,[4] and the third by photolysis of diazonium salts.[5] Herein we wish to report the total synthesis of androcymbine by the photolysis of the diazonium salts **4** and **14** and the abnormal reaction during the photolysis of the phenolic diazonium salt **19**.

(1) J. Hrbek, Jr., and F. Šantavý, *Collect. Czech. Chem. Commun.*, **27**, 255 (1962); A. R. Battersby, R. B. Herbert, L. Pijewska, and F. Šantavý, *Chem. Commun.*, 228 (1965).

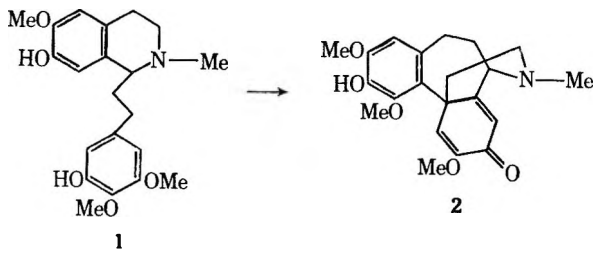
(2) A. C. Baker, A. R. Battersby, E. McDonald, R. Ramage, and J. H. Clements, *ibid.*, 36 (1967), and references cited therein.

(3) T. Kametani, K. Fukumoto, M. Koizumi, and A. Kozuka, *ibid.*, 1605 (1968); *J. Chem. Soc. C*, 1295 (1969).

(4) T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *Chem. Commun.*, 1001 (1968); *J. Chem. Soc. C*, 3084 (1968).

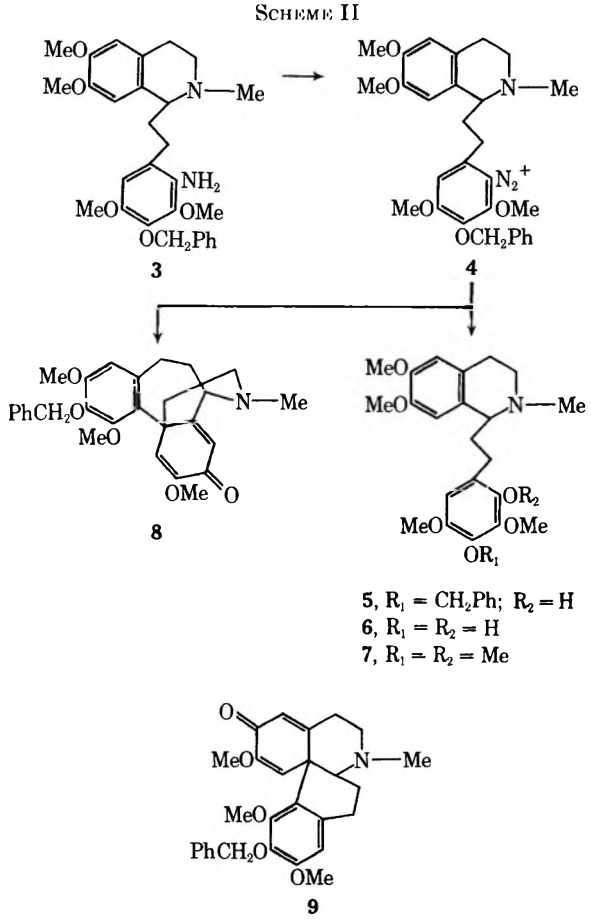
(5) T. Kametani, M. Koizumi, and K. Fukumoto, *Chem. Commun.*, 1157 (1970); *J. Chem. Soc. C*, 1792 (1971).

SCHEME I



Diazotization of the 2′-aminophenethylisoquinoline **3**[6] in the usual way, followed by photolysis with a Hanovia 450-W mercury lamp using a Pyrex filter at 5–10°, gave four compounds after separation by silica gel column chromatography (Scheme II).

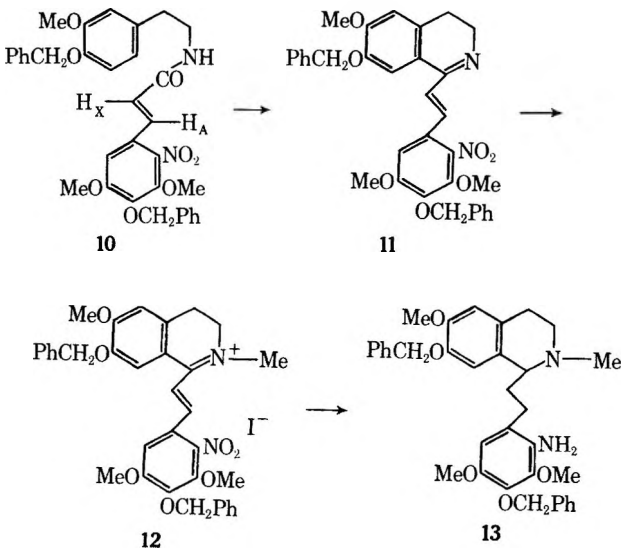
SCHEME II



The first compound in 0.5% yield was assigned as 4-benzyloxy-3,5-dimethoxybenzaldehyde by direct comparison with the authentic sample.[6] The second eluent afforded 3,4-dihydro-6,7-dimethoxy-2-methylisocarbostyril in 1% yield; this was identical in all aspects with the authentic sample.[7] The third compound in 9.2% yield was assigned as 1-(4-benzyloxy-2-hydroxy-3,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (**5**) by the following evidence. The infrared spectrum revealed this compound to be a phenolic isoquinoline and the ultraviolet spectrum showed this compound to be 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline. The nmr spectrum revealed three aromatic protons with one *O*-benzyl, four *O*-methoxy, and one *N*-methyl resonances. Debenzylation of **5**, followed by O-methylation with diazomethane, gave hexamethoxyphenethylisoquinoline (**7**), which was identical with the authentic sample.[5] The fourth compound in 1.4% yield had the molecular formula $C_{28}H_{31}NO_5$ by mass spectrometry, and showed the typical cross-conjugated α-methoxycyclohexadienone system in infrared and ultraviolet spectra.[3-5] The nmr spectrum showed an *N*-methyl (τ 7.63), three *O*-methyls (6.4, 6.23, and 6.02), and the methylene of one benzyloxy group (5.05). Also two olefinic and one aromatic protons at τ 3.76, 3.73, and 3.26 were observed, each as singlets. According to the above data, the possible structure could be either the desired *O*-benzylandrocymbine (**8**) or **9**. However, structure **9** was ruled out by the following evidence.

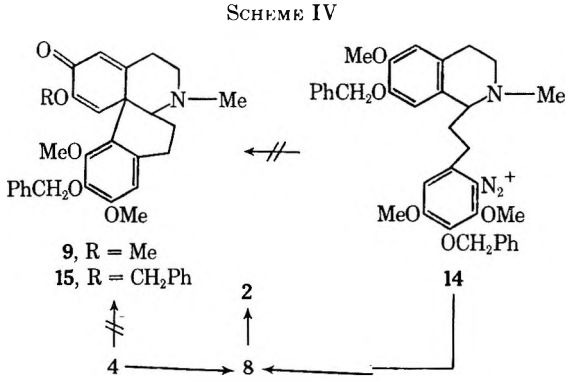
If the structure of the dienone were **9**, the products from the aminoisoquinoline **3** and **13** should be different. On the grounds of this consideration, we examined photolytic decomposition of the diazonium salt **14** derived from aminoisoquinoline **13**, which was synthesized as described in the Experimental Section and Scheme III.

SCHEME III



The diazotization of **13**, followed by photolysis of the diazonium salt **14** in a manner similar to the above, gave the same dienone **8** (Scheme IV).

SCHEME IV



Thus it was apparent that in both cases intramolecular reaction had occurred between the 2′ and 4a posi-

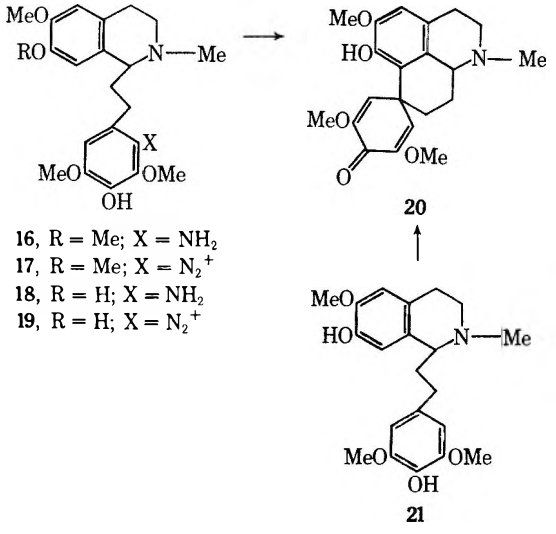
(6) T. Kametani, K. Takahashi, T. Sugahara, M. Koizumi, and K. Fukumoto, *J. Chem. Soc. C.*, 1032 (1971).

(7) T. Kametani, M. Koizumi, and K. Fukumoto, *J. Pharm. Soc. Jap.*, **90**, 1331 (1970).

tions in the isoquinoline skeleton. Debenzylation of **8** gave (±)-androcymbine (**2**), an alkaloid from *Androcymbium melanthioides* var. *stricta*, the spectral data of which were superimposable upon those of natural androcymbine.[1]

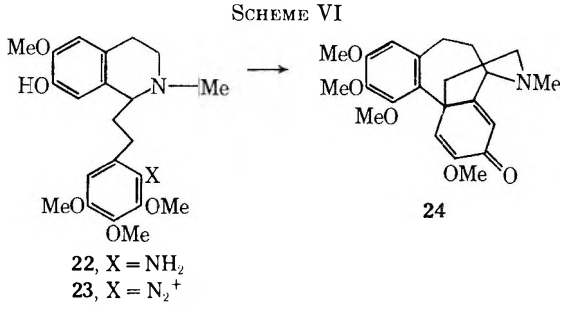
Moreover, in order to obtain androcymbine directly, the photolysis of the diazonium salts **17** and **19** was investigated. The irradiation of a diazonium salt **17**, obtained by the usual method from **16**, which was prepared from the 4′-benzyloxy derivative **3**, under the same conditions as above, gave only isocarbostyril. On the other hand, the diazotization of diphenolic aminoisoquinoline **18**, prepared from **13**, gave the diazonium salt **19**, which was photolyzed with a mercury lamp under the same conditions as above to give an unexpected compound, homoproaporphine **20**, as the main product. The spectra of the compound were superimposable upon those of an authentic sample of **20**,[8] prepared from a diphenolic isoquinoline **21** by phenolic oxidation (Scheme V).

SCHEME V



However, the photolysis of the diazonium salt **23** from a monophenolic aminoisoquinoline **22** afforded a normal product, *O*-methylandrocymbine **24**[9] (Scheme VI).

SCHEME VI



Therefore, we hypothesize that a phenolic hydroxy group on the phenethyl residue played an important role in this abnormal reaction. When the diazonium salt **19** was treated at 5–10° for 4 hr in dilute sulfuric acid without irradiation, no homoproaporphine **20** was obtained. Moreover, the photolysis of a diphenolic isoquinoline **21** and the presence of nitrous acid recovered the starting material **21**. Therefore, the homoproaporphine **20** would have been formed *via* the radical intermediates **25**, **26**, and **27** (Scheme VII).

Thus, we have accomplished the total synthesis of (±)-androcymbine and confirmed that its structure is **2** as suggested by Battersby.[1]

(8) T. Kametani, K. Fukumoto, H. Yagi, and F. Satoh, *Chem. Commun.*, 878 (1967); T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Org. Chem.*, **33**, 690 (1968).

(9) T. Kametani, M. Koizumi, K. Shishido, and K. Fukumoto, *J. Chem. Soc. C*, 1923 (1971).

Experimental Section

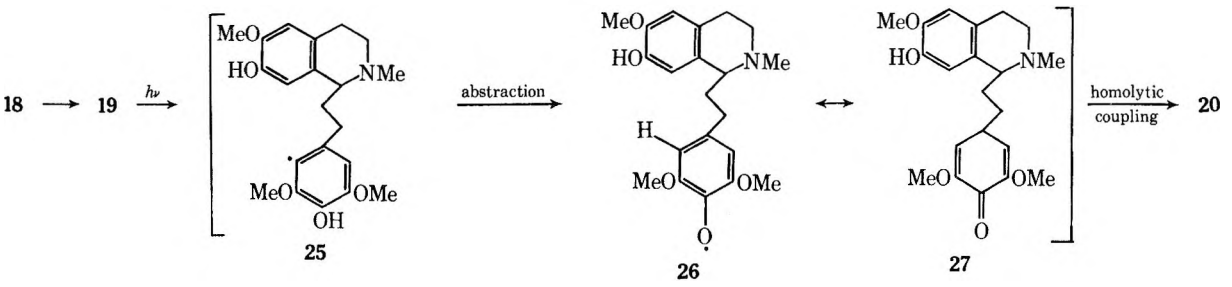
Melting points were determined on a Yanagimoto microapparatus (MP-S2) and are uncorrected. Infrared spectra were obtained on a Hitachi EPI-3 recording spectrophotometer in chloroform solution. Ultraviolet spectra were recorded on a Hitachi recording spectrophotometer (EPS-3) in methanol. Nuclear magnetic resonance spectra of deuteriochloroform solution containing tetramethylsilane ($\delta = 10\ \tau$) as internal standard were taken on a Hitachi R-20 spectrometer. Mass spectra were taken on a Hitachi RMU-7 spectrometer.

Photolysis of Diazonium Salt of 3.—To a stirred solution of 4.0 g (8.2 mmol) of aminoisoquinoline **3**[6] in 200 ml of 1 *N* sulfuric acid and 60 ml of acetic acid was added dropwise a solution of 700 mg (10.3 mmol) of sodium nitrite in 7 ml of water during 30 min at 3° and the stirring was continued for a further 1 hr at the same temperature. After decomposition of the excess of nitrous acid with urea, followed by dilution to a volume of 2 l. with water, the reaction mixture was irradiated with a Hanovia 450-W mercury lamp using a Pyrex filter at 5–10° for 4 hr. The reaction mixture was then made basic with concentrated ammonia and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to afford 3.8 g of a dark brown gum, which was subjected to chromatography on 100 g of silica gel with chloroform (fractions 1–13, each 200 ml) and chloroform–methanol (99:1 v/v; fractions 14–36) as eluents inspecting with thin layer chromatography, infrared, and ultraviolet spectra. Fraction 2 gave 10 mg (0.5%) of 4-benzyloxy-3,5-dimethoxybenzaldehyde as a pale yellow glass. The thin layer chromatography and infrared spectrum of this product were identical with those of an authentic sample.[6] Fraction 7 gave 18 mg (1%) of 3,4-dihydro-6,7-dimethoxy-2-methylisocarbostyril as colorless plates, mp 124–125° (lit.[7] 124–125°) (from ethyl acetate), infrared C=O at 6.1 μ (s), which was identical with the authentic sample.[7] Fractions 16–23 gave 370 mg (9.2%) of 1-(4-benzyloxy-2-hydroxy-3,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (**5**) as a viscous syrup: infrared hydroxy group at 2.86 μ (s); ultraviolet 283 nm; nmr τ 7.62 (3, s, NCH_3), 6.31 (9, s, 3 OCH_3), 6.22 (3, s, OCH_3), 5.11 (2, s, benzyl CH_2), 3.77 (1, s, 6′-HO), 3.65 (2, s, 5 H and 8 H), 3.76 (5, s, benzyl C_6H_5). Fractions 28–34 gave 210 mg of the crude compound **8** which was rechromatographed on 15 g of silica gel using chloroform containing 1% methanol as an eluent to give 105 mg of a pale brown syrup. Further purification was achieved through chromatography on 15 g of alumina using benzene containing 30% chloroform as an eluent. Evaporation of the appropriate fractions gave 50 mg (1.4%) of (±)-*O*-benzylandrocymbine (**8**) as a pale yellow viscous syrup: infrared cyclohexadienone system at 6.02 (s), 6.11 (s), and 6.20 μ (s); ultraviolet 237 and 281 nm (log ϵ 4.31 and 3.70); nmr spectrum τ 7.63 (3, s, NCH_3), 6.4 (3, s, OCH_3), 6.23 (3, s, OCH_3), 6.02 (3, s, OCH_3), 5.05 (2, s, benzyl CH_2), 3.76, 3.73, 3.26 (3, each s, an aromatic and two olefinic protons); mass spectum *m/e* 461 (M^+), 370 ($M^+ - 91$). Recrystallization of the methiodide of **8** from methanol–ether gave colorless needles, mp 251–253°.

Anal. Calcd for $C_{28}H_{31}NO_5 \cdot CH_3I$: C, 57.72; H, 5.68. Found: C, 57.68; H, 5.45.

***N*-(4-Benzyloxy-3-methoxyphenethyl)-4-benzyloxy-3,5-dimethoxy-2-nitrocinnamide (10).**—A solution of 32 g (85 mmol) of 4-benzyloxy-3,5-dimethoxy-2-nitrocinnamoyl chloride [prepared from 31 g (86.5 mmol) of the corresponding carboxylic acid and 25 g of phosphorus pentachloride in 250 ml of chloroform] was added dropwise to a solution of 30 g (115 mmol) of 4-benzyloxy-3-methoxyphenethylamine in 150 ml of 5% sodium hydroxide solution with stirring at 20°. After the stirring had been continued for 3 hr, the organic layer was separated, washed with 10% hydrochloric acid and water, dried over sodium sulfate,

SCHEME VII



and evaporated to give a residue, to which was added 10 ml of methanol. The separated crystals were collected by filtration, and recrystallization from methanol gave 46 g (90%) of the cinnamide **10** as yellow prisms: mp 152–153°; infrared amide NH at 2.94 (m), amide C=O at 6.00 (s), C=C at 6.13 μ (m); nmr spectrum τ 6.16 (6, s, $2OCH_3$), 6.09 (3, s, OCH_3), 4.98 (2, s, benzyl CH_2), 4.92 (2, s, benzyl CH_2), 3.76 (1, d, J = 16 Hz, H_X), 2.64 (1, d, J = 16 Hz, H_A).

Anal. Calcd for $C_{34}H_{34}N_2O_8 \cdot 0.5\ H_2O$: C, 67.21; H, 5.81; N, 4.61. Found: C, 67.50; H, 5.93; N, 4.76.

7-Benzyloxy-1-[(4-benzyloxy-3,5-dimethoxy-2-nitrophenyl)-vinyl]-3,4-dihydro-6-methoxyisoquinoline (11).—A mixture of 15 g (25 mmol) of the amide **10**, 15 ml of phosphoryl chloride, and 150 ml of dry chloroform was heated under reflux for 45 min. An excess of hexane was added to the reaction mixture and the yellow precipitate, which was collected by filtration, was washed with hexane. After it had been dissolved in chloroform, the resultant solution was poured into cooled ammonia with stirring. The solvent layer was separated, washed with water, dried over sodium sulfate, and evaporated to give 10 g (69%) of **11** as a yellow syrup: infrared C=N at 6.12 (m), C=C at 6.17 μ (m); nmr spectrum τ 6.18 (6, s, $2OCH_3$), 6.10 (3 H, s, OCH_3), 4.97 (2, s, benzyl CH_2), 4.98 (2, s, benzyl CH_2). Recrystallization of the hydrochloride from methanol gave pale yellow needles, mp 184–185°.

Anal. Calcd for $C_{34}H_{32}N_2O_7 \cdot HCl$: C, 66.18; H, 5.39; N, 4.54. Found: C, 66.48; H, 5.44; N, 4.41.

7-Benzyloxy-1-[(4-benzyloxy-3,5-dimethoxy-2-nitrophenyl)-vinyl]-3,4-dihydro-6-methoxyisoquinoline Methiodide (12).—A mixture of 10 g (17 mmol) of the 3,4-dihydroisoquinoline **11** and 20 ml (320 mmol) of methyl iodide was allowed to stand at room temperature for 12 hr, and the excess of methyl iodide was distilled off to leave 11 g (87%) of methiodide **12** as yellow crystals, the recrystallization of which from methanol–ether gave yellow needles, mp 110–112°.

Anal. Calcd for $C_{34}H_{32}N_2O_7 \cdot CH_3I$: C, 58.18; H, 4.88; N, 3.88. Found: C, 58.31; H, 4.97; N, 3.68.

1-(2-Amino-4-benzyloxy-3,5-dimethoxyphenethyl)-7-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (13).—Within 1.5 hr at a temperature below 5°, 60 g (917 mg-atoms) of zinc powder was added in small portions to a stirred mixture of 11 g (15 mmol) of the above methiodide (**12**), 250 ml of concentrated hydrochloric acid, and 250 ml of glacial acetic acid. The stirring was continued at the same temperature for 6 hr. After removal of zinc by filtration, the filtrate was made basic with concentrated ammonia and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and distilled to leave 8 g of the aminoisoquinoline, which was hydrogenated with hydrogen on 400 mg of Adams catalyst in 600 ml of methanol to give 7 g (82%) of **13** as a pale brown viscous syrup: nmr spectrum τ 7.59 (3, s, NCH_3), 6.28 (3, s, OCH_3), 6.19 (6 H, s, $2OCH_3$), 5.01 (2, s, benzyl CH_2), 4.95 (2, s, benzyl CH_2), 3.68 (1, s, 6′ H), 3.47 (2, s, 5 H and 8 H), 2.71 (5, s, benzyl C_6H_5), 2.68 (5, s, benzyl C_6H_5). This was used because of difficulty in crystallization.

Photolysis of Diazonium Salt of 13.—To a stirred solution of 2.2 g (3.9 mmol) of aminoisoquinoline **13** in 100 ml of 1 *N* sulfuric acid was added dropwise a solution of 280 mg (4 mmol) of sodium nitrite in 3 ml of water at 3° during 30 min. The stirring was continued at 5° for 1 hr. After decomposition of the excess of nitrous acid with urea, followed by dilution to a volume of 1 l. with water, the reaction mixture was irradiated with a Hanovia 450-W mercury lamp using a Pyrex filter at 5–10° for 4 hr. The reaction mixture was treated in the same manner as in the case of **3**, giving the following substances: 13 mg (1.2%) of 7-benzyloxy-3,4-dihydro-6-methoxy-2-methylisocarbostyril as a pale brownish viscous syrup, infrared C=O at 6.11 μ (s), which was identical with the authentic sample,[5] and 10 mg (0.6%) of *O*-benzylandrocymbine (**8**) as a pale yellow viscous syrup, which was identical with the authentic sample described before.

(±)-Androcymbine (2).—A mixture of 60 mg (0.12 mmol) of *O*-benzylandrocymbine (**8**), 6 ml of 48% hydrobromic acid, and 18 ml of methanol was heated at 55° on a water bath for 45 min. After evaporation of the solvent *in vacuo*, the residue was treated with 10% ammonia and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give 53 mg of a pale brown viscous syrup, which was purified by preparative thick layer chromatography on silica gel in chloroform–methanol (10:1 v/v) to give 3 mg (6.2%) of (±)-androcymbine (**2**) as a pale yellow viscous syrup together with 12 mg of the starting material **8**. Infrared, ultraviolet, and nmr spectra of the former compound (**2**) were identical with those of natural androcymbine: infrared hydroxy group at 2.86 (s), cyclohexadienone system at 6.02 (s), 6.12 (s), and 6.20 μ (s); ultraviolet 240 and 279 nm (log ϵ 4.18 and 3.62); nmr spectrum τ 7.62 (3, s, NCH_3), 6.39 (3, s, OCH_3), 6.19 (3, s, OCH_3), 5.99 (3, s, OCH_3), 3.76 (1, s, aromatic proton), 3.76 and 3.23 (2, each s, olefinic protons); mass (*m/e*) calcd for $C_{21}H_{25}NO_5$, 371.173 (found, 371.171).

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2,3,4,5-tetramethoxyphenethyl)-2-methylisoquinoline (7).—A mixture of 200 mg (0.4 mmol) of **5**, 4 ml of ethanol, and 4 ml of concentrated hydrochloric acid was heated on a water bath for 3 hr. Evaporation of the solvent gave a viscous syrup, the solution of which in water was made basic with 10% ammonia and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give 140 mg (87.5%) of the 1,2,3,4-tetrahydro-1-(2,4-dihydroxy-3,5-dimethoxyphenethyl)-6,7-dimethoxy-2-methylisoquinoline (**6**) as a pale brown viscous syrup: infrared hydroxy group at 2.86 μ (s); nmr spectrum τ 7.57 (3, s, NCH_3), 6.21 (6, s, $2OCH_3$), 6.15 (3 H, s, OCH_3), 6.11 (3 H, s, OCH_3), 3.60 (1, s, 6′ H), 3.43 (1, s, 5 H), 3.40 (1, s, 8 H). To a solution of 140 mg (0.35 mmol) of the above dihydroxyisoquinoline (**6**) in 4 ml of methanol was added an excess of diazomethane [prepared from *p*-toluenesulfonyl-*N*-methyl-*N*-nitrosamide (5 g)] and the mixture was allowed to stand at room temperature for 48 hr. The excess diazomethane and solvents were distilled off and the residue was distilled *in vacuo* to give 70 mg (47%) of **7** as a viscous syrup, bp 250–255° (0.5 mm), which was identical with an authentic sample.[5]

1-(2-Amino-4-hydroxy-3,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (16).—A mixture of 2 g (4.1 mmol) of benzylisoquinoline (**3**), 40 ml of ethanol, and 40 ml of concentrated hydrochloric acid was heated on a water bath for 3 hr. Evaporation of the solvent gave a viscous syrup, the aqueous solution of which was made basic with 10% ammonia and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give 1.2 g (78%) of **16** as a pale brown viscous syrup: infrared hydroxy group at 2.86 μ (s); nmr spectrum τ 7.69 (3, s, NCH_3), 6.23 (6, s, $2OCH_3$), 6.19 (6, s, $2OCH_3$), 3.69 (1, s, 6′ H), 3.52 (2, s, 5 H and 8 H). This was labile in air and therefore used without purification.

Photolysis of the Diazonium Salt of 16.—To a solution of 1.2 g (3 mmol) of phenolic isoquinoline **16** in 70 ml of 1 *N* sulfuric acid and 10 ml of acetic acid was added dropwise a solution of 208 mg (3 mmol) of sodium nitrite in 2 ml of water during 20 min at 3° and the stirring was continued for a further 1 hr at the same temperature. After decomposition of the excess of nitrous acid with urea, followed by dilution to a volume of 1 l. with

water, the reaction mixture was treated in a similar manner to that of the above compound (3) to give 11 mg (1.6%) of 3,4-dihydro-6,7-dimethoxy-2-methylisocarbostyril as colorless plates, which were identical with the authentic sample described before.

1-(2-Amino-4-hydroxy-3,5-dimethoxyphenethyl)-7-hydroxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (18).—A mixture of 7 g (12.3 mmol) of **13**, 140 ml of ethanol, and 140 ml of concentrated hydrochloric acid was refluxed for 3 hr. The reaction mixture was treated in the same manner as in the case of **16** to give 4.2 g of **18** as a brown viscous syrup, which was purified by chromatography on 100 g of silica gel using chloroform containing 1% methanol as an eluent. Evaporation of the appropriate fraction gave 1.2 g (25%) of **18** as a viscous syrup: infrared hydroxy group at 2.86 μ (s); nmr spectrum τ 7.60 (3, s, NCH_3). 6.25 (3, s, OCH_3), 6.19 (6, s, $2OCH_3$), 3.67 (1, s, 6′ H), 3.51 (2, s, 5 H and 8 H). This was labile in air and therefore used immediately.

Photolysis of the Diazonium Salt of 18.—A solution of diazonium salt [prepared from 1.2 g (3.1 mmol) of diphenolic isoquinoline **18**, 70 ml of 1 *N* sulfuric acid, 10 ml of glacial acetic acid, and 214 mg (3.1 mmol) of sodium nitrite] was diluted to a volume of 1 l. which was irradiated with a Hanovia 450-W mercury lamp under the same conditions as in the case of **3**. The crude product (520 mg) was chromatographed on 15 g of silica gel using chloroform containing 1% methanol as an eluent inspecting with thin layer chromatography, infrared and ultraviolet spectra. Evaporation of the appropriate fraction gave 180 mg (15%) of homoproaporphine (**20**): mp 176–178° (lit.[8] mp 176–178°); infrared hydroxy group at 2.86 (s), enone C=C at 6.06 (s) and 6.18 μ (s); ultraviolet 232 and 278 nm (log ϵ 4.04 and 4.03); nmr spectrum τ 7.65 (3, s, NCH_3), 6.44 (3, s, OCH_3), 6.37 (3, s, OCH_3), 6.22 (3, s, OCH_3), 4.14 and 4.0 (2, each d, J = 2.5 Hz, olefinic protons), 3.57 (1, s, aromatic proton). These spectral data were superimposable upon those of an authentic sample (**20**).[8]

Registry No.—**2**, 31730-26-4; **5**, 31836-46-1; **6**, 31730-27-5; **8**, 31735-04-3; **8** methiodide, 31735-03-2; **10**, 31735-05-4; **11** 31735-06-5; **11** HCl, 31735-11-2; **12**, 31735-07-6; **13**, 31735-08-7; **16**, 31735-09-8; **18**, 31735-10-1.

Acknowledgments.—We thank Professor F. Šantavý, The Chemical Institute, Palacky University for a gift of androcymbine. We also thank Miss R. Kato, Miss A. Kawakami, Miss R. Suzuki, Miss U. Tadano, Miss T. Yoshida, Miss C. Yoshida, and Mr. T. Ohuchi for microanalyses and spectral measurements.

Studies on the Syntheses of Heterocyclic Compounds. CDLI. Alternative Photolytic Total Syntheses of *O*-Methylandrocymbine and Kreysigine

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Received May 21, 1971

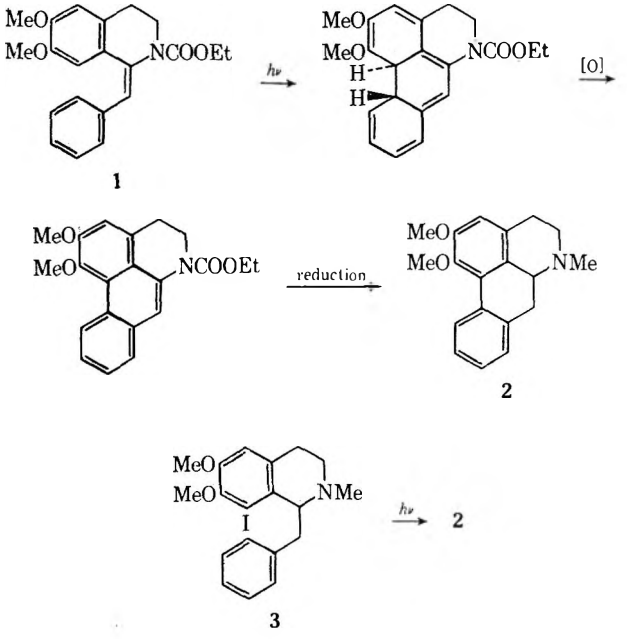
The total syntheses of (±)-*O*-methylandrocymbine (**8**) and (±)-kreysigine (**17**) by photolysis of 1-(2-bromo-3,4,5-trimethoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (**13b**) are reported. The same reaction of the demethoxy analog **13a** to the homomorphinandienone **14** and homoaporphine **15** is also described.

Photolytic electrocyclic reactions[1] have constituted the backbone of the synthesis of the cyclic compounds by carbon–carbon bond formation and are extremely useful in natural product synthesis.[2] These useful reactions involve cyclization of conjugated olefinic systems and have been applied to the photolytic synthesis of aporphine alkaloids,[3] as shown in the total synthesis of (±)-nuciferine (**2**) from the substituted stilbene **1**.[4]

Moreover, Kupchan[5] reported a new application of the photolytic cyclization of iodoaromatic compounds (**3**) in an intramolecular reaction in order to accomplish the synthesis of (±)-nuciferine (**2**) (Scheme I).

We achieved the photolytic conversion of the diazotized isoquinoline **4** to the morphinandienone **5**[6] in addition to the aporphine **7** and applied this reaction to the synthesis of (±)-*O*-methylandrocymbine (**8**).[7] In this reaction, an aromatic radical **5** formed by the decomposition of a diazonium group participates in the coupling reaction of both aromatic rings.[8] Therefore,

SCHEME I

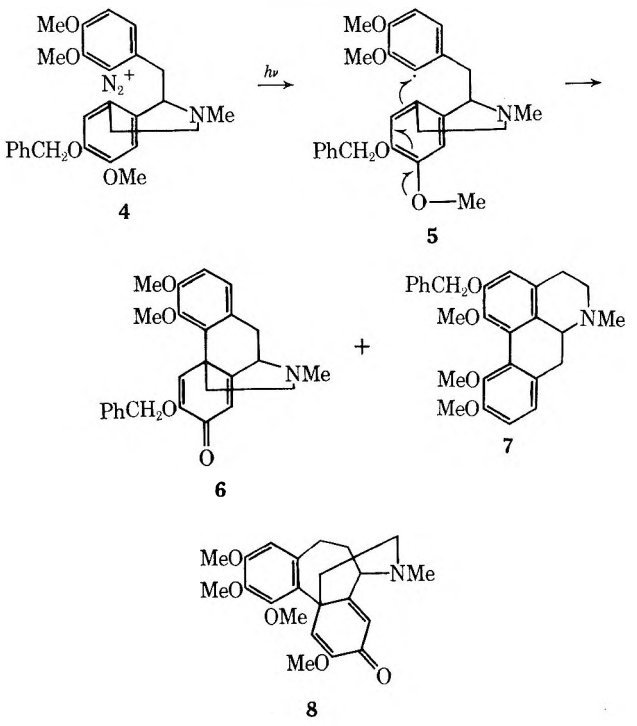


we examined the photolysis of the bromoisoquinoline. Herein we wish to report the syntheses of (±)-*O*-methylandrocymbine (**8**) and (±)-kreysigine (**17**) (Scheme II).

Since the formation of a seven-membered-ring system by a radical coupling reaction is not so easy, the pre-

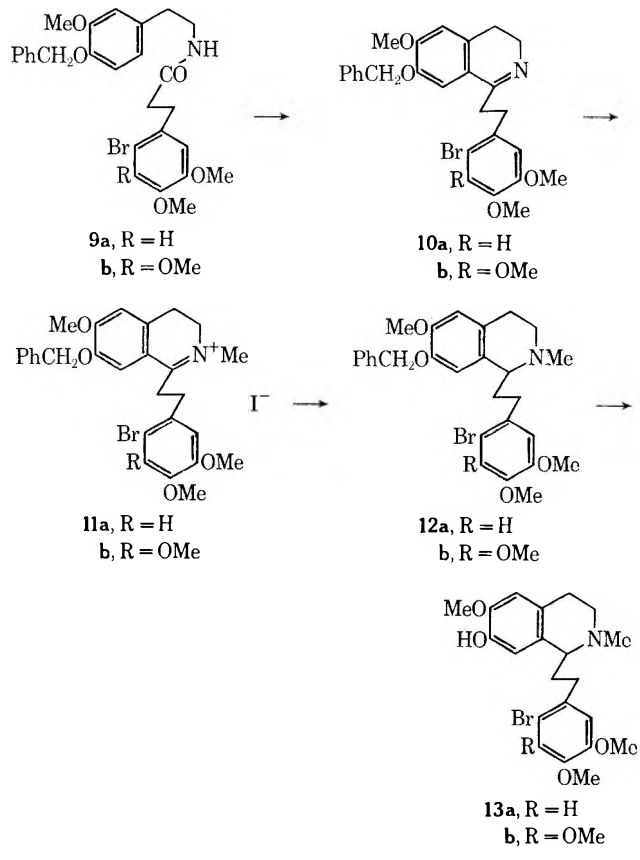
(1) R. B. Woodward and R. Hoffmann, "The Conversion of Orbital Symmetry," Academic Press, New York, N. Y., 1970.
(2) P. G. Sammers, *Quart. Rev. Chem. Soc.*, **24**, 37 (1970).
(3) N. C. Yang, G. R. Lenz, and A. Shani, *Tetrahedron Lett.*, 2941 (1966).
(4) M. P. Cava, S. C. Havlicek, A. Lindert, and R. J. Spangler, *ibid.*, 2937 (1966).
(5) S. M. Kupchan and R. M. Kanojia, *ibid.*, 5353 (1966).
(6) T. Kametani, K. Fukumoto, and K. Shishido, *Chem. Ind. (London)*, 1566 (1970).
(7) T. Kametani, M. Koizumi, and K. Fukumoto, *Chem. Commun.*, 1157 (1970).
(8) A. Schonberg, "Preparative Organic Photochemistry," Springer-Vorlag, New York, N. Y., 1968, p 313, and references cited therein.

SCHEME II



liminary experiment was carried out as follows using material easily available; namely, 2′-bromophenolic isoquinoline (**13a**) was synthesized from 2-bromo-4,5-dimethoxyphenylpropionic acid[9] and 4-benzyloxy-3-methoxyphenethylamine in the usual way (see Scheme III and Experimental Section).

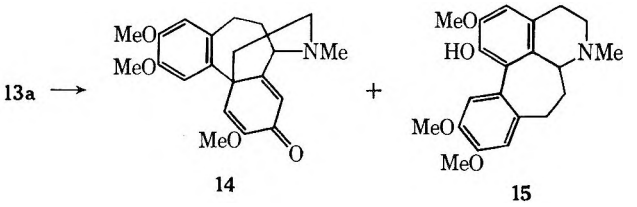
SCHEME III



(9) H. G. Graftree and R. Robinson, *J. Chem. Soc.*, **113**, 871 (1918).

Irradiation of **13a** with a Hanovia 450-W mercury lamp surrounded by a Pyrex filter in ethanolic sodium hydroxide aqueous solution at room temperature for 7 hr gave two compounds. Purification on silica gel column chromatography showed that the first one, characterized as its methiodide, could be assigned to the homomorphinandienone **14** by comparison of spectroscopic data with an authentic sample.[10] The second compound, $C_{21}H_{25}O_4N$, *m/e* 355 (M^+), showed a typical homoaporphine system in its uv spectrum[11,12] (λ_{max} 262.5 and 290 nm). This hypothesis was supported by mass spectrum[12] revealing an ion at *m/e* 388 ($M^+ -$ OH, base peak) and also by nmr spectrum[11] showing three aromatic protons resonanced at τ 3.43, 3.27, and 2.92. Therefore, the second compound was assigned as 1-hydroxy-2,10,11-trimethoxyhomoaporphine (**15**) (Scheme IV).

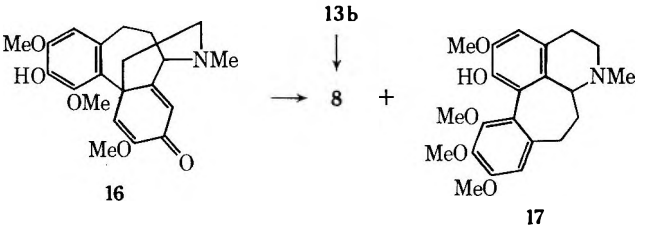
SCHEME IV



Thus, we developed a new synthetic route to the homomorphinandienone and homoaporphine type compounds which have the basic skeleton of the alkaloids found in *Liliaceae* species.[13]

Total Syntheses of (±)-*O*-Methylandrocymbine (8) and (±)-Kreysigine (17).—The above synthesis of the homomorphinandienone **14** and homoaporphine **15** should function, in principle, also with 1-(2-bromo-3,4,5-trimethoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (**13b**), thus leading to the total synthesis of (±)-*O*-methylandrocymbine (**8**) and (±)-kreysigine (**17**) (Scheme V).

SCHEME V



The starting phenolic isoquinoline **13b** was synthesized from 2-bromo-3,4,5-trimethoxyphenylpropionic acid[14] by the usual method. Photolysis of **13b**, under conditions similar to the reaction of **13a**, yielded two components in addition to the starting material. The first one was identical with *O*-methylandrocymbine (**8**)[7] prepared from natural androcymbine (**16**) by spectral

(10) T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *J. Chem. Soc. C*, 3084 (1968).

(11) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *ibid.*, 1003 (1968); 382 (1970).

(12) A. R. Battersby, R. B. Bradbury, R. G. Herbert, M. H. G. Munro, and R. Ramage, *Chem. Commun.*, 450 (1967).

(13) T. Kametani, "The Chemistry of the Isoquinoline Alkaloids," Hirokawa, Tokyo, and Elsevier, Amsterdam, 1968, pp 222 and 258.

(14) H. F. Frank, P. E. Fanta, and D. S. Tarbell, *J. Amer. Chem. Soc.*, **70**, 2314 (1948).

comparisons. The second compound, which showed the same molecular formula, $C_{22}H_{27}O_5N$, as *O*-methylandrocymbine, was assigned (±)-kreysigine (**17**), an alkaloid found in *Kreysigia multiflora*,[12] by comparison of spectroscopic data with those of the authentic sample[15] prepared by a photo-Pschorr reaction.

Thus, we achieved the alternative syntheses of (±)-*O*-methylandrocymbine and (±)-kreysigine in similar yields. The photolysis of the phenolic bromo aromatic compounds would be a useful method for the synthesis of the dienone type compound such as salutaridine.[16]

Experimental Section[17]

N-(**4-Benzyloxy-3-methoxyphenethyl**)-**3**-(**2-bromo-4,5-dimethoxyphenyl**)**propionamide** (**9a**).—A mixture of 8 g of 4-benzyloxy-3-methoxyphenethylamine and 8.7 g of 2-bromo-4,5-dimethoxyphenylpropionic acid was heated at 190° for 1 hr and the mixture was extracted with chloroform. The extract was washed with 10% sodium hydroxide and water and dried over sodium sulfate. Evaporation of the solvent gave 15.5 g of **9a** as colorless needles, mp 150–152° (from methanol), $\nu_{max}^{CHCl_3}$ 3400 (NH) and 1660 cm^{-1} (C=O).

Anal. Calcd for $C_{27}H_{30}BrNO_5$: C, 61.41; H, 5.73; N, 2.65. Found: C, 61.61; H, 5.60; N, 2.84.

7-Benzyloxy-1-(2-bromo-4,5-dimethoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline (**10a**).—A mixture of 11 g of the preceding amide, 7 g of phosphoryl chloride, and 100 ml of dry benzene was refluxed for 1.5 hr. The precipitate was collected and recrystallized from methanol to give 9 g of the isoquinoline **10a** hydrochloride, mp 210–212°, $\nu_{max}^{CHCl_3}$ 1650 (>C=N⁺–) cm^{-1}.

Anal. Calcd for $C_{27}H_{28}BrNO_4 \cdot HCl$: N, 2.52. Found: N, 2.41.

A suspension of 8.5 g of the hydrochloride in 10% ammonia was extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give 7.5 g of the isoquinoline **10a**, mp 115–117° (from methanol), $\nu_{max}^{CHCl_3}$ 1625 cm^{-1} (–C=N).

Anal. Calcd for $C_{27}H_{28}BrNO_4$: C, 63.58; H, 5.53; N, 2.75. Found: C, 63.34; H, 5.45; N, 3.05.

7-Benzyloxy-1-(2-bromo-4,5-dimethoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline Methiodide (**11a**).—A mixture of 7 g of **10a**, 10 ml of methyl iodide, and 50 ml of methanol was allowed to stand at room temperature. The pale yellowish precipitate was collected by filtration and recrystallized from methanol to give 9 g of **11a** as pale yellowish needles, mp 200–202°, $\nu_{max}^{CHCl_3}$ 1625 cm^{-1} (>C=N⁺–).

Anal. Calcd for $C_{28}H_{31}BrINO_4$: C, 51.58; H, 4.79; N, 2.16. Found: C, 51.72; H, 4.55; N, 2.20.

7-Benzyloxy-1-(2-bromo-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (**12a**).—To a stirred solution of 8 g of **11a** in 150 ml of methanol was added in small portions 3 g of sodium borohydride. After the stirring had been continued for 1 hr, the solvent was evaporated. The resulting residue was diluted with water and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give 6 g of **12a** as a pale brownish oil, $\nu_{max}^{CHCl_3}$ 2780 cm^{-1} (NCH_3). The methiodide prepared as usual was recrystallized from methanol to afford colorless needles, mp 165–166°.

Anal. Calcd for $C_{29}H_{35}BrINO_4$: C, 52.04; H, 5.13; N, 2.09. Found: C, 51.90; H, 5.10; N, 2.38.

1-(2-Bromo-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (**13a**).—A mixture of 5 g of the preceding isoquinoline **12a**, 50 ml of concentrated hydrochloric acid, and 50 ml of ethanol was refluxed for 2 hr. After removal of the solvent, the resulting residue was made basic with 28% ammonia and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give 3.8 g of **13a** as a pale brownish oil, $\nu_{max}^{CHCl_3}$ 3490 (OH) and 2730 cm^{-1} (NCH_3). The methiodide prepared as usual gave colorless needles, mp 230–233°.

Anal. Calcd for $C_{22}H_{29}BrINO_4$: C, 45.71; H, 4.88; N, 2.42. Found: C, 45.86; H, 5.15; N, 2.51.

Photolysis of 13a.—A stirred mixture of 2 g of the phenolic isoquinoline **13a**, 1 g of sodium hydroxide, 500 ml of ethanol, and 500 ml of water was irradiated using a 450-W Hanovia mercury lamp with a Pyrex filter under water cooling for 7 hr. The solvent was evaporated and extracted with chloroform after the addition of an excess of crystalline ammonium chloride. The extract was washed with water, dried over sodium sulfate, and evaporated to leave 1.5 g of a brownish oil. This was chromatographed on silica gel (45 g). After the chloroform fractions (fractions 1–9, each fraction 90 ml) had been discarded, the elution with methanol–chloroform (1:99) (fractions 10–16) gave the phenolic isoquinoline **13a**, and the elution with methanol–chloroform (2:98) (fractions 17–19) afforded 105 mg of a mixture of the dienone **14** and homoaporphine **15**. Finally, the elution with the same solvent (fractions 20–27) as above afforded 200 mg of **15** as colorless needles: mp 195–196° (from methanol–ether); nmr ($CDCl_3$) τ 2.92, 3.27, 3.43 (3 H, each singlet, aromatic protons), 6.12 (6 H, singlet, $2OCH_3$), 6.16 (3 H, singlet, OCH_3), 7.63 (3 H, singlet, NCH_3); mass spectrum *m/e* 355 (M^+), 338 ($M^+ - OH$).

Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.75; H, 7.30; N, 3.93.

The former mixture chromatographed on 5 g of neutral alumina using benzene–chloroform (8:2) gave 20 mg of the dienone **14** as a colorless oil, whose spectroscopic data were identical with those of an authentic specimen.[10]

N-(**4-Benzyloxy-3-methoxyphenethyl**)-**3**-(**2-bromo-3,4,5-trimethoxyphenyl**)**propionamide** (**9b**).—A mixture of 10 g of 4-benzyloxy-3-methoxyphenethylamine and 12.4 g of 2-bromo-3,4,5-trimethoxyphenylacetic acid was heated at 140° for 20 min and then at 180° for 1.5 hr. The mixture was extracted with benzene. The extract was washed with water, dried over sodium sulfate, and evaporated. The residual oil was recrystallized from benzene–hexane to give 18 g of **9b** as colorless needles: mp 104.5–106.5°; $\nu_{max}^{CHCl_3}$ 3400 (NH), 1660 cm^{-1} (C=O); nmr ($CDCl_3$) τ 6.20–6.03 (12 H, broad singlet, $4OCH_3$), 4.89 (2 H, singlet, OCH_2Ph), 2.74 (1 H, broad singlet, NHCO), 3.55, 3.12 (4 H, multiplet, aromatic protons), 2.74–2.46 (5 H, broad singlet, aromatic protons).

Anal. Calcd for $C_{28}H_{32}BrNO_6$: C, 60.22; H, 5.78; N, 2.51. Found: C, 60.22; H, 5.60; N, 2.55.

7-Benzyloxy-1-(2-bromo-3,4,5-trimethoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline (**10b**).—A mixture of 12 g of the preceding amide **9b**, 12 ml of phosphoryl chloride, and 100 ml of dry chloroform was refluxed for 2 hr. The solvent was evaporated and the residual oil was washed with hexane. Recrystallization of the crude hydrochloride from methanol–ether afforded 8 g of **10b** as colorless needles, mp 184–185°, $\nu_{max}^{CHCl_3}$ 1650 cm^{-1} (>C=N⁺–).

Anal. Calcd for $C_{28}H_{30}BrNO_5 \cdot HCl$: C, 58.29; H, 5.42; N, 2.43. Found: C, 58.01; H, 5.58; N, 2.61.

A solution of 7 g of the preceding hydrochloride in 50 ml of chloroform was washed with 10% ammonia and water. The solvent was evaporated to give 6 g of the isoquinoline **10b** as a pale brownish oil: $\nu_{max}^{CHCl_3}$ 1625 cm^{-1} (>C=N–); nmr ($CDCl_3$) τ 6.53–6.86 (12 H, $4OCH_3$), 4.89 (2 H, singlet, OCH_2Ph), 3.38 (2 H, singlet, aromatic protons), 2.88–2.42 (6 H, multiplet, aromatic protons).

7-Benzyloxy-1-(2-bromo-3,4,5-trimethoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline Methiodide (**11b**).—A mixture of 6 g of **10b**, 5 ml of methyl iodide, and 50 ml of methanol was left at room temperature. The yellow precipitate was filtered and recrystallized from methanol–ether to give 4 g of **11b** as pale yellowish needles, mp 193–195°, $\nu_{max}^{CHCl_3}$ 1628 cm^{-1} (>C=N⁺–).

Anal. Calcd for $C_{29}H_{33}BrINO_5$: C, 51.05; H, 4.87; N, 2.05. Found: C, 51.19; H, 4.92; N, 2.13.

7-Benzyloxy-1-(2-bromo-3,4,5-trimethoxyphenethyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (**12b**).—To a cooled mixture of 3.5 g of **11b**, 80 ml of methanol, 20 ml of chloroform, and 1 drop of water was added in portions 1.5 g of sodium borohydride under stirring. The mixture was stirred for a further 1 hr and then refluxed for 0.5 hr. The solvent was evaporated, and the remaining residue was diluted with water and extracted with chloroform. The extract was washed with water, dried over

(15) T. Kametani, M. Koizumi, K. Shishido, and K. Fukumoto, *J. Chem. Soc. C*, 1923 (1971).

(16) T. Kametani, M. Ihara, K. Fukumoto, and H. Yagi, *ibid.*, 2030 (1969), and references cited therein.

(17) Melting points are not corrected. Infrared spectra were measured with a type EPI-3 Hitachi recording spectrometer, and nmr spectra were taken with a Hitachi R-20 spectrometer using tetramethylsilane as an internal reference. Mass spectra were taken with a Hitachi RMU-7 spectrometer.

potassium carbonate, and evaporated to give 2.6 g of **12b** as a colorless oil, bp 205–210° (bath temperature) (0.05 mm), after purification by distillation, $\nu_{max}^{CHCl_3}$ 2780 cm^{-1} (NCH_3).

Anal. Calcd for $C_{29}H_{34}BrNO_5$: C, 62.59; H, 6.16; N, 2.52. Found: C, 62.33; H, 6.13; N, 2.40.

1-(2-Bromo-3,4,5-trimethoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (**13b**).—A mixture of 2.6 g of the preceding isoquinoline (**12b**), 30 ml of concentrated hydrochloric acid, and 30 ml of ethanol was refluxed for 4 hr. The solvent was evaporated, and the remaining residue was basified with 10% ammonia and extracted with chloroform. The extract was washed with water and dried over potassium carbonate. Evaporation of the solvent afforded 1.8 g of **13b** as a pale brownish oil, which was difficult to crystallize and therefore used in the following reaction without purification, $\nu_{max}^{CHCl_3}$ 3510 (OH) and 2730 cm^{-1} (NCH_3).

Photolysis of 13b.—A stirred mixture of 1.8 g of the phenolic isoquinoline **13b**, 0.5 g of sodium hydroxide, 250 ml of ethanol, and 750 ml of water was irradiated using a 450-W Hanovia mercury lamp with a Pyrex filter under water cooling for 7 hr. The mixture was extracted with chloroform after the addition of 6 g of ammonium chloride. The extract was washed with water, dried over potassium carbonate, and evaporated to leave 1.6 g of a brownish oil which was chromatographed on silica gel (50 g). Removal of the eluate with 1% methanol–chloroform gave a dienone fraction (440 mg), which was further rechromatographed on silica gel (10 g). Evaporation of the eluate with chloroform–methanol (99:1) afforded 210 mg of the dienone fraction, which was again rechromatographed on 10 g of neutral alumina. The elution with benzene–chloroform (19:1) gave 50.5 mg of *O*-methylandrocymbine (**8**). Recrystallization from ether–hexane afforded colorless prisms, mp 154–156.6°,[18] the spectroscopic data of which were identical with those of an authentic specimen.[7]

Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55, H, 7.06. Found: C, 68.68; H, 7.24.

Removal of the subsequent elution after collection of the dienone fraction afforded 40 mg of kreisigine (**17**): mp 187–188° (from ethanol) (lit.[15] mp 187–188°); $\nu_{max}^{CHCl_3}$ 3500 cm^{-1} (OH); λ_{max}^{MeOH} 258 and 291 nm (log ϵ 4.02 and 3.82); nmr ($CDCl_3$) 7.60 (3 H, singlet, NCH_3), 6.38 (3 H, singlet, OCH_3), 6.12 (9 H, singlet, $3OCH_3$), 3.41 (1 H, singlet, aromatic proton), 3.38 (1 H, singlet, aromatic proton); mass spectrum *m/e* 385 (M^+), 368 ($M^+ - 17$). The spectral data were identical with those of an authentic sample.[15]

Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.68. Found: C, 68.35; H, 7.28; N, 3.62.

Registry No.—**8**, 31735-12-3; **9a**, 31735-13-4; **9b**, 31790-84-8; **10a**, 31735-15-6; **10a** HCl, 31735-14-5; **10b**, 31790-85-9; **10b** HCl, 31735-16-7; **11a**, 31790-87-1; **11b**, 31735-17-8; **12a** methiodide, 31735-18-9; **12b**, 31735-19-0; **13a** methiodide, 31790-86-0; **13b**, 31735-20-3; **15**, 31735-21-4; **17**, 31735-22-5.

Acknowledgments.—We thank Miss Y. Tadano for nmr determination, Miss A. Kawakami and Miss C. Yoshida for microanalysis, and T. Ohuchi for mass spectral measurements.

(18) In a previous paper,[7] we reported *O*-methylandrocymbine to be an oil, but, after being allowed to stand for a long time, it crystallized.

Bufadienolides. 14. Synthesis of Bufotalien, 15α-Hydroxybufalin, and Resibufogenin[1]

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Received April 6, 1971

Conversion of 14-dehydrobufalin (**2a**) to bufotalien (**4a**) was accomplished. Peracid oxidation of 3β-acetoxy-14-dehydrobufalin (**2b**) was employed to obtain 14α,15α-epoxide **5b**. Sulfuric acid catalyzed opening of epoxide **5b** was used to complete a route to 15α-hydroxybufalin (**6b**). Treatment of diol **6b** with methanesulfonyl chloride led to a new synthesis of 3β-acetoxyresibufogenin (**3b**). Conversion of 14-dehydrobufalin to the halohydrins represented by structures **6d–g** followed by treatment with basic alumina or hot pyridine afforded resibufogenin in good yield. The epoxide formation catalyzed by alumina was also shown to yield 14α-artebufogenin (**8b**).

Interest in the chemistry and physiological action of amphibian venom constituents, for example, from the family Bufonidae, continues to increase.[2] We recently summarized a total synthesis of bufalin (**1a**) and resibufogenin (**3a**) employing 14-dehydrobufalin (**2a**) as relay.[3] The study was subsequently expanded to preparation of bufotalien[4] and to establish alternative routes from 14-dehydrobufalin to resibufogenin. A summary of these new conversions now follows.

To verify the structure of bufotalin[4] it became necessary to extend the total synthesis of 14-dehydrobufalin[3,5] to bufotalien (**4a**). An extensive attempt to convert olefin **2b** to diene **4b** by means of sulfur dehydrogenation proved impractical. However, mild treatment of olefin **2b** with *N*-bromosuccinimide followed by pyridine-catalyzed dehydrohalogenation did afford 3β-acetoxybufotalien (**4b**). Selective saponification of acetate **4b** to bufotalien (**4a**) was achieved using alumina. The synthetic diene (**4a**) was identical with a specimen prepared by acid-catalyzed dehydration of bufotalin (**1d**) essentially as previously reported.[6]

As part of the bufotalin investigation we were led to restudy the *m*-chloroperbenzoic acid oxidation of 14-dehydrobufalin.[3] When the oxidation was carried out with more recently purchased samples of *m*-chloroperbenzoic acid, formation of 14α,15α-epoxide **5** was obtained in high yield. The oxidation was repeated several times each with alcohol **2a** and acetate **2b** in chloroform or benzene with the same result (**5**). Unlike the initial study[3] no isolatable amounts of β-epoxide **3** were detected. Thus it became important to more firmly establish tranformation of 14-dehydrobufalin (**2a**) to resibufogenin (**3a**). Toward this

(1) For paper 13 (Steroids and Related Natural Products. 67), refer to G. R. Pettit and J. Dias, *J. Org. Chem.*, **36**, 3207 (1971).

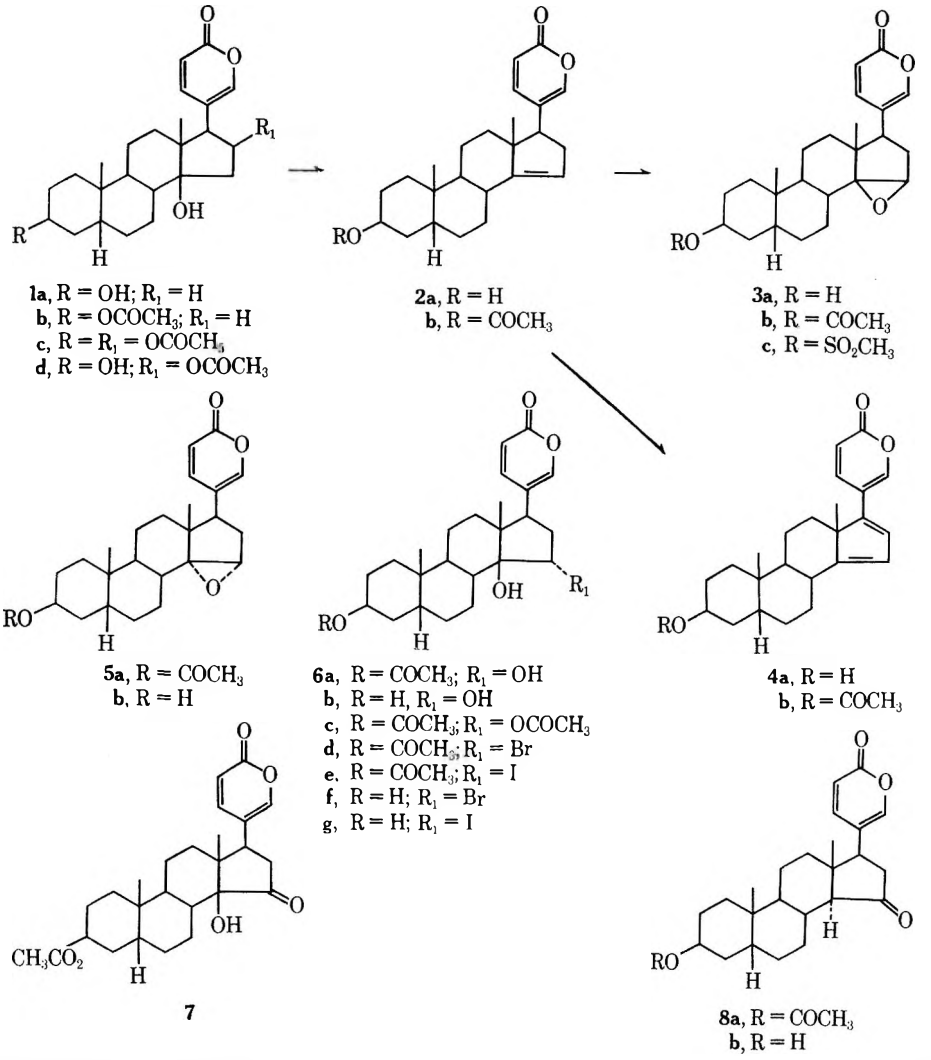
(2) For example, see G. Habermehl, *Naturwissenschaften*, **56**, 615 (1969); Y. Kamano, *Kagaku No Ryoiki*, **24** (4), 57 (1970); Y. Kamano, *ibid.*, **24** (5), 27 (1970); G. R. Pettit, B. Green, and G. L. Dunn, *J. Org. Chem.*, **35**, 1367 (1970); and W. Haede, W. Fritsch, K. Radscheit, U. Stache, and H. Ruschig, *Justus Liebigs Ann. Chem.*, **741**, 92 (1970).

(3) G. R. Pettit, L. E. Houghton, J. C. Knight, and F. Bruschweiler, *J. Org. Chem.*, **35**, 2895 (1970).

(4) The bufotalien synthesis reported herein in detail was summarized in a preliminary communication: G. R. Pettit, P. Brown, F. Bruschweiler, and L. E. Houghton, *Chem. Commun.*, 1566 (1970).

(5) F. Sondheimer, W. McCrae, and W. G. Salmond, *J. Amer. Chem. Soc.*, **91**, 1228 (1969).

(6) K. Meyer, *Helv. Chim. Acta*, **32**, 1993 (1949); H. Wieland, J. Hesse, and R. Huttel, *Justus Liebigs Ann. Chem.*, **524**, 203 (1936); H. Kondo and S. Ikawa, *J. Pharm. Soc. Jap.*, **53**, 23 (1933); *Chem. Abstr.*, **27**, 1887 (1933).



end the mild aqueous sulfuric acid catalyzed opening of epoxide **5** was viewed. Both acetate **5a** and alcohol **5b** led in good conversion to diol **6a** and triol **6b**, respectively. Compelling evidence for the 15α-hydroxybufalin structure (**6a,b**)[7] was obtained from mass spectral[8] proton magnetic resonance and optical rotatory dispersion measurements. Further diol **6a** was easily oxidized by chromium trioxide to ketone **7** and when treated with methanesulfonyl chloride provided a useful route to 3β-acetoxyresibufogenin (**3b**). The same reaction was applied to triol **6b** to provide 3β-methanesulfonyloxyresibufogenin (**3c**) which was also easily prepared by reaction between methanesulfonyl chloride and resibufogenin.

In addition to the synthesis of resibufogenin *via* α-epoxide **5**, a variety of bromohydrin approaches were also evaluated and found to be particularly useful.[5,9] When 3β-acetoxy-14-dehydrobufalin (**2b**) was treated with *N*-bromoacetamide in dioxane–water containing perchloric acid, bromohydrin **6d** was obtained in high yield. When the crude bromohydrin was chromatographed on basic alumina, 3β-acetoxyresibufogenin (**3b**) was obtained in 83% yield. When the bromohydrin was heated in pyridine, the same product (**3b**) was isolated in 75% yield. Comparable results were realized with the same bromohydrin from *N*-bromosuccinimide and from iodohydrin **6e** derived from an *N*-iodosuccinimide sequence. An even more direct synthesis of resibufogenin was achieved by applying the NBA, NBS, and NIS halohydrin pathways to 14-dehydrobufalin (**2a**). Here both the basic alumina- and pyridine-catalyzed elimination reactions led to 56–66% overall yields of resibufogenin. Also noteworthy was the isolation of small amounts of 14α-artebufogenin[10] (**8b**) from the products obtained using basic alumina. Whether the 14α-artebufogenin arose from resibufogenin or a precursor was not determined.

The preceding experiments conclusively demonstrated that the halohydrin approach to resibufogenin from 14-dehydrobufalin is convenient and reliable. The simplicity and dependability of this synthesis of resibufogenin-type β-epoxides should eventually facilitate total syntheses of related bufadienolides such as bufotalinin and marinobufagin.[2]

Experimental Section

All melting points were observed using a micro hot-stage apparatus (Reichert, Austria) and are uncorrected. Proton magnetic resonance (deuteriochloroform solution), ultraviolet

(7) *Cf.* D. Satoh, M. Horie, and J. Morita, *Chem. Pharm. Bull. (Tokyo)*, **14**, 613 (1966).

(8) A detailed mass spectral study of bufadienolides has been prepared by P. Brown, Y. Kamano, and G. R. Pettit, *Org. Mass Spectrum*, in press.

(9) Addition of hydrobromic acid to a 14-olefin system has been employed a number of times in cardenolide chemistry to form a bromohydrin which on reductive dehalogenation provided a practical synthesis of 14β-hydroxycardenolides. See, *e.g.*, P. D. Meister and H. C. Murray, U. S. Patent 2,930,-791 (March 29, 1960); *Chem. Abstr.*, **54**, 17471 (1960); U. Stache, W. Fritsch, W. Haede, K. Radscheit, and K. Fachinger, *Justus Liebigs Ann. Chem.*, **726**, 136 (1969); and F. Becke and J. Gnad, *ibid.*, **726**, 110 (1969).

(10) H. Linde and K. Meyer, *Experientia*, **15**, 238 (1958).

(95% ethyl alcohol), infrared (potassium bromide pellets), and mass spectral data (by Messrs. Richard Scott and Gene Kelley) were recorded as indicated in the experimental introductions to parts 5 and 10 of this series.[11] The *m*-chloroperbenzoic acid was used as purchased from Aztec Chemicals, Elyria, Ohio. The bufalin and resibufogenin were isolated from the Chinese medicinal preparation *Ch'an Su*. General experimental and chromatographic techniques (acetone–chloroform–*n*-hexane, 3:3:4,[12] were used here as tlc solvent systems) as well as commercial materials have been noted in the experimental introduction to part 5.[11]

3β-Hydroxy-14-dehydrobufalin (2b).—A solution of 3β-acetoxybufalin (**1b**, 0.20 g) in methanol (10 ml) containing concentrated hydrochloric acid (0.4 ml) was heated at reflux 2 hr. The mixture was poured into ice–water and the solid was collected and washed with water. Recrystallization of the crude product (0.196 g) from acetone gave 0.16 g of olefin **2b** melting at 191–193°. The product was identical[13] with a specimen obtained by acetylating 14-dehydrobufalin (**2a**).

Bufotalien (4a).—A solution prepared from carbon tetrachloride (40 ml), 3β-acetoxy-14-dehydrobufalin (**2b**, 0.18 g), and *N*-bromosuccinimide (0.10 g) was heated at reflux for 3.5 hr. The solvent was evaporated and the residue treated (3 hr) with pyridine (3 ml)–acetic anhydride (2.4 ml). The mixture was concentrated under reduced pressure, and a solution of the residue in chloroform was washed with 1 *N* hydrochloric acid, 10% aqueous sodium bicarbonate, and water. The solvent was evaporated and the crude product in benzene was chromatographed on a column of silica gel (10 g). Elution with benzene–chloroform (1:1, 5-ml fractions) afforded 0.028 g of 3β-acetoxybufotalien in the seventh and eighth fractions. Crystallization from chloroform and recrystallization from methanol–ether provided yellow crystals melting at 189–191°: mass spectrum M^+ 408 (base peak), 348, 333, 241, 197, and 107; uv $\lambda_{max}^{CH_3OH}$ 300 mμ (log ε 4.20); ir ν_{max} 1750–1730, 1650, 1620, 1560, 1260–1220, 950, 770; pmr δ 1.08 (18-methyl), 1.12 (19-methyl), 2.05 (acetate H), 5.03 (3α proton), 5.94 (t, J = 2 Hz, H-16), 6.34 (q, J = 1.8 and 9 Hz, H-23), 6.52 (d, J = 2 Hz, H-15), 7.50 (d, J = 2 Hz, H-21), 7.60 (q, J = 2 and 9 Hz, H-22). The specimen of bufotalien acetate (**4b**) prepared by this procedure was identical[13] with a sample by heating (3 hr) 3β-acetoxybufotalin (**1c**) in refluxing ethyl alcohol (3 ml) containing 3% concentrated hydrochloric acid followed by reacetylation. Selective saponification of 3β-acetoxybufotalien to bufotalien (**4a**) was achieved using activated alumina as reported previously for the preparation of resibufogenin.[3] The specimens of diene **4a** prepared from 14-dehydrobufalin (**2a**) and bufotalin (**1d**) were found to be identical.[13]

3β-Acetoxy-14α,15α-epoxy-5β-bufa-20,22-dienolide (5b). Method A. From 14-Dehydrobufalin (2a).—To a solution of 14-dehydrobufalin (**2a**, 0.81 g) in chloroform (20 ml) was added *m*-chloroperbenzoic acid (0.46 g). After a 2.5-hr period at room temperature the mixture was diluted with chloroform and washed consecutively with aqueous potassium iodide, sodium thiosulfate, sodium bicarbonate, and water. Solvent was removed under reduced pressure and the crystalline residue (0.82 g) was recrystallized from acetone to afford 0.70 g, melting at 235–237°, of **3β-hydroxy-14α,15α-epoxy-5β-bufa-20,22-dienolide (5b)** identical[14] with a specimen prepared from 14-dehydrobufalin (**2a**) by perbenzoic acid oxidation.[14]

A 0.35-g sample of alcohol **5b** was acetylated and the product purified by column chromatography on silica gel. Elution with ligroin–acetone (9:1 and 6:1) afforded 0.31 g of acetate **5a** as a colorless amorphous solid identical[13] with a sample obtained by the perbenzoic acid oxidation route.

Method B. From 3β-Acetoxy-14-dehydrobufalin (2b).—A 0.10-g amount of 3β-acetoxy-14-dehydrobufalin (**2b**) was oxidized with *m*-chloroperbenzoic acid (0.065 g) as summarized in method A. The crude product (0.098 g) was chromatographed in ligroin–acetone (6:1) on a column of silica gel. Elution with the same solvent gave 0.072 g of acetate **5a** as an amorphous solid. The samples of 14α,15α-epoxide obtained by both methods A and B were identical.

3β-Acetoxy-14β,15α-dihydroxy-5β-bufa-20,22-dienolide (6a, 3β-Acetoxy-15α-hydroxybufalin). Method A. From α-Epoxide 5b.—A solution composed of acetone (20 ml), water (1.5 ml), and 1 *N* sulfuric acid (5.0 ml) was added to a solution of α-epoxide **5b** (0.15 g) in chloroform (10 ml). After 24 hr at room temperature the mixture was diluted with chloroform and poured into water. The chloroform layer was washed consecutively with water, 1% potassium bicarbonate, and water. Solvent was evaporated and the residue (0.15 g) was chromatographed on a column of silica gel. Elution with ligroin–acetone (3:1) and recrystallization of the product from acetone gave 0.12 g (71%) of 3β,14β,15α-trihydroxy-5β-bufa-20,22-dienolide (**6b**, 15α-hydroxybufalin) as colorless needles melting at 272–273°: mass spectrum M^+ 402, 384 ($M^+ - H_2O$), 366 ($M^+ - 2H_2O$); uv λ_{max} 301 mμ (log ε 2.16); ir ν_{max} 3580, 3400, 1760, 1740–1720, 1640, 1550, 955, 903, 755, and 745 cm^{-1}; pmr δ (1:3 deuteriochloroform–pyridine), 0.92 (18-methyl), 0.98 (19-methyl), 6.28 (d, J = 10 Hz, H-23), 7.39 (d, J = 3 Hz, H-21), and 7.94 (q, J = 10 and 3 Hz, H-22).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.44; H, 8.33.

Triol **6b** (40 mg) was acetylated (18 hr at room temperature) and the product was chromatographed on a column of silica gel. Elution with ligroin–acetone (5:1) and recrystallization of the acetate from acetone provided 34 mg (85%) of needles melting at 281–283°. The specimen of acetate **6a** was identical[13] with the product obtained by method B directly below.

Method B. From Acetate 5a.—A 0.10-g amount of acetate **5a** was treated with 1 *N* sulfuric acid (2.5 ml) and the product isolated as described above in method A (*cf.* **6a**). Recrystallization from acetone led to 0.065 g (65%) of needles melting at 280–283°: mass spectrum; M^+ 444, 426 ($M^+ - H_2O$), 408 ($M^+ - 2H_2O$), 384 ($M^+ - CH_3CO_2H$), 366, 351, 348, 232, 217, 123, 109, 95, and 67; uv λ_{max} 301 mμ (log ε 2.56); ir ν_{max} 3350, 1740, 1700, 1630, 1540, 1260, 1230, 955, 900, 755, 743 cm^{-1}; pmr δ 0.69 (18-methyl), 0.91 (19-methyl), 2.03 (3-acetate), 5.09 (3α proton), 6.31 (d, J = 10 Hz, H-23), 7.34 (d, J = 3 Hz, H-21), and 7.73 (q, J = 10 and 3 Hz, H-22).

Anal. Calcd for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 69.70; H, 8.04.

3β,15α-Diacetoxy-14β-hydroxy-5β-bufa-20,22-dienolide (6c, 3β,15α-Diacetoxybufalin).—A 38-mg sample of triol **6b** was acetylated (60 hr at room temperature) and the crude product was chromatographed on a column of silica gel. A pure sample of diacetate **6c** (30 mg, 80% yield) was obtained as a colorless solid by the fraction eluted by ligroin–acetone (6:1) from acetone–*n*-hexane. A later chromatography fraction led to 4 mg of monoacetate **6a**, mp 279–281°. The diacetate exhibited in the mass spectrum M^+ 486, 468 ($M^+ - H_2O$), 426 ($M^+ - CH_3CO_2H$), and 408 ($M^+ - CH_3CO_2H - H_2O$); uv λ_{max} 299 mμ (log ε 2.87); ir ν_{max} 3600, 1760–1720, 1650, 1550, 1270, 1260, 1230, 953, 905, 754–745 cm^{-1}; pmr δ 0.74 (18-methyl), 0.92 (19-methyl), 2.05 (3-acetate), 2.09 (15-acetate), 5.20–5.10 (3α,15β protons), 6.30 (d, J = 10 Hz, H-23), 7.27 (d, J = 3 Hz, H-21), and 7.67 (q, J = 10 and 3 Hz, H-22).

Anal. Calcd for $C_{28}H_{38}O_7$: C, 69.11; H, 7.87. Found: C, 68.80; H, 7.78.

Acetylation (30 hr, room temperature) of monoacetate **6a** and purification of the product as described directly above gave 19 mg (92%) of diacetate **6c**.

3β-Acetoxy-14β-hydroxy-15-oxo-5β-bufa-20,22-dienolide (7, 3β-Acetoxy-15-oxobufalin). Method A. From α-Epoxide 5b.—To a solution of α-epoxide **5a** (0.15 g) in acetic acid (3 ml) was added a solution composed of acetic acid 0.3 ml), water (0.04 ml), and chromium trioxide (0.04 g). The mixture was stirred at room temperature for 1.5 hr. Excess chromium trioxide was reduced by adding methanol. The mixture was diluted with water and extracted with chloroform. The combined extract was washed with aqueous sodium bicarbonate and water. Solvent was removed and the product (0.13 g) was chromatographed on a column of silica gel. Recrystallization of the fraction eluted by ligroin–acetone (6:1) from acetone led to 0.09 g (60%) of ketone **7** melting at 260–261°: mass spectrum M^+ 442, 424 ($M^+ - H_2O$), 414 ($M^+ - CO$), 399, 396, 382 ($M^+ - CH_3CO_2H$), 364, 292, 232, 151, 123, 109, and 95; uv λ_{max} 300 mμ (log ε 2.88); ir ν_{max} 3530, 1740, 1720, 1640, 1540, 1250, 1230, 960, 905, 755, and 765 cm^{-1}; pmr δ 0.86 (18-methyl), 0.94 (19-methyl),

(11) G. R. Pettit, C. L. Herald, and J. P. Yardley, *J. Org. Chem.*, **35**, 1389 (1970); J. C. Knight, G. R. Pettit, and P. Brown, *ibid.*, **35**, 1415 (1970).

(12) K. Manki, Y. Kamano, and M. Suzuki, *Bunseki Kagaku*, **14**, 1049 (1965).

(13) The results of thin layer chromatographic, infrared spectral, and proton magnetic resonance comparisons served to confirm the identical composition of both specimens.

(14) Y. Kamano, *Chem. Pharm. Bull.*, **17**, 1711 (1969).

2.07 (3-acetate), 2.64 (broad singlet, 16-methylene), 5.10 (3α proton), 6.29 (d, J = 10 Hz, H-23), 7.41 (d, J = 2.5 Hz, H-21), and 7.86 (q, J = 10 and 2.5 Hz, H-22).

Anal. Calcd for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.46; H, 7.74.

Method B. From Alcohol 6a.—Oxidation of alcohol **6a** (26 mg) was conducted as summarized in method A with epoxide **5a**. After chromatographic purification and recrystallization from acetone, the ketone (16 mg) was obtained as needles melting at 259–262°. The specimens of ketone **7** prepared by methods A and B were mutually identical.[14]

3β-Acetoxyresibufogenin (3b). Method A. From Diol 6a.—Methanesulfonyl chloride (0.05 ml) was added to a cold (ice bath) solution of diol **6a** (40 mg) in pyridine (0.4 ml). The mixture was maintained at approximately 10° for 24 hr and then poured into ice–water (50 ml). The mixture was extracted with chloroform, and the combined extract was washed with water, dilute hydrochloric acid, and water. Removal of solvent led to 45 mg of residue which was chromatographed on a column of silica gel. The fraction eluted by ligroin–acetone (6:1) was recrystallized from acetone to yield (19 mg, 47%) of 3β-acetoxyresibufogenin as needles melting at 235–239°.

Method B. From Olefin 2b Using N-Bromoacetamide.—In a typical experiment a solution of N-bromoacetamide (0.35 g) in dioxane (3 ml) was added to a mixture prepared from 3β-acetoxy-14-dehydrobufalin (**2b**, 0.36 g) in dioxane (15 ml)–water (2.6 ml)–70% perchloric acid (0.45 ml). Before adding a solution prepared from sodium sulfite (0.35 g) and water (7 ml), the mixture was stirred for 20 min at room temperature. The solution was concentrated under reduced pressure to approximately one-third of the original volume and poured into ice–water with stirring. Solid was collected and washed with water to yield 0.37 g of crude bromohydrin **6d**. The bromohydrin was used without further purification as follows. A solution of bromohydrin **6d** (0.20 g) in benzene was chromatographed on basic alumina. The fraction (0.18 g) eluted by benzene–ethyl acetate (9:1) was crystallized from acetone to afford 0.17 g (83%) of 3β-acetoxyresibufogenin as needles melting at 234–239°.

Alternatively the crude bromohydrin (95 mg) was heated 30 min in refluxing dry pyridine (10 ml). Concentration to dryness *in vacuo* gave 98 mg of a residue which was dissolved in chloroform and washed with dilute hydrochloric acid and water. Recrystallization of the crude product (76 mg) from acetone gave 71 mg (75%) of 3β-acetoxyresibufogenin as needles melting at 228–232°.

Method C. Using N-Bromosuccinimide.—The preceding reaction (method B with NBA) was repeated using 0.20 g of olefin **2b** and 0.20 g of N-bromosuccinimide. In this example the reaction time was 15 min at room temperature and the yield of bromohydrin **6d** was 0.22 g. The basic alumina- (5 g) catalyzed elimination applied to bromohydrin **6d** (0.11 g) provided 0.073 g (66%) of 3β-acetoxyresibufogenin (**3b**), mp 230–235°. Application of the pyridine (5 ml) method to 0.11 g of bromohydrin **6d** led to a 75% yield (81 mg) of product **3b** melting at 229–233°.

Method D. Using N-Iodosuccinimide.—When N-iodosuccinimide (0.16 g) was substituted for NBA as described in method B above, olefin **2b** (0.20 g) led to 0.22 g of crude iodohydrin **6e**. Conversion of the iodohydrin (0.10 g) to 3β-acetoxyresibufogenin by the basic alumina technique resulted in a 68% yield (68 mg) of product, mp 233–236°. The pyridine (5 ml) route with iodohydrin **6e** (98 mg) provided a 73% yield (72 mg) of product (**3b**) melting at 230–235°.

The sample of 3β-acetoxyresibufogenin (**3b**) prepared by methods A–D were found identical[14] with material prepared from natural resibufogenin.

Resibufogenin (3a). Method A. From 14-Dehydrobufalin (2a) Using N-Bromoacetamide.—The procedure summarized from preparation of 3β-acetoxyresibufogenin (**3b** using N-bromoacetamide) was repeated employing 14-dehydrobufalin (**2a**, 0.20 g). The resulting crude bromohydrin (**6f**, 0.23 g) led, by the basic alumina (10 g) route, to 0.13 g (65%) of resibufogenin (**3a**). Recrystallization from acetone–hexane afforded a pure sample melting at 108–120 and 162–166°. Continued elution of the alumina column led to 16 mg of 14α-artebufogenin[14] (**8b**) as prisms, mp 263–265°.

Method B. By N-Bromosuccinimide.—Preparation of bromohydrin **6d** from 14-dehydrobufalin (0.10 g) was repeated using N-bromosuccinimide (0.10 g); after chromatography of the bromohydrin (**6f**) on basic alumina and recrystallization of the product from acetone–hexane, 56 mg (56%) of resibufogenin melting at 115–130 and 164–172° was obtained. In addition 12 mg of 14α-artebufogenin (**8b**), mp 262–264°, was obtained following recrystallization from acetone.

Method C. By N-Iodosuccinimide.—The general procedure (*cf.* **3b**, method D) was applied to 95 mg of 14-dehydrobufalin using 90 mg of N-iodosuccinimide. The crude iodohydrin (**6g**, 99 mg) was heated in refluxing dry pyridine (4 ml) for 40 min. Following column chromatography on silica gel (3.5 g), elution by ligroin–acetone (5:1), and recrystallization from acetone–hexane, pure resibufogenin (66% yield, 63 mg) was obtained with the characteristic double melting point at 117–122 and 157–166°.

Each of the resibufogenin samples obtained by methods A–C were identical[13] with natural resibufogenin, and the specimens of 14α-artebufogenin were identical[13] with material prepared from resibufogenin.[14]

3β-Methanesulfonyloxyresibufogenin (3c). Method A. From Triol 6b.—A solution prepared from pyridine (0.4 ml), triol **6b** (36 mg), and methanesulfonyl chloride (0.05 ml) was allowed to remain at approximately 10° for 20 hr. The mixture was poured into ice–water and extracted with chloroform. The combined extracts were washed with 2% hydrochloric acid and water. Removal of solvent and recrystallization of the residue (31 mg) from methanol provided 26 mg (71%) of mesylate **3c** as prisms melting at 160–162°. The product was identical[13] with the corresponding sample prepared from resibufogenin as described below.

Method B. From Resibufogenin (3a).—Extension of the procedure just described (*cf.* **3c**, method A) to resibufogenin (0.10 g) led to 90 mg (90%) of mesylate **3c** melting at 161–162°: mass spectrum 366 ($M^+ - CH_3OSO_2H$), 348, 333, 312, 294, 216: uv λ_{max} 301 mμ (log ε 3.09); ir ν_{max} 3040, 1760–1720, 1640, 1540, 1320, 1300, 1255, 1180, 1170, 1155, 950, 750, and 745 cm^{-1}; pmr δ 0.80 (18-methyl), 1.03 (19-methyl), 3.05 (3-methanesulfonyl), 3.55 (s, 15α proton), 5.10 (s, 3α proton), 6.27 (d, J = 10 Hz, H-23), 7.29 (d, J = 2.5 Hz, H-21), and 7.91 (q, J = 10 and 2.5 Hz, H-22).

Anal. Calcd for $C_{25}H_{34}O_6S$: C, 64.90; H, 7.40; S, 6.93. Found: C, 64.92; H, 7.27; S, 7.15.

Registry No.—**3a**, 465-39-4; **3b**, 4029-64-5; **3c**, 31444-07-2; **4a**, 474-53-3; **4b**, 31444-09-4; **6a**, 4534-19-4; **6b**, 31444-11-8; **6c**, 31489-85-7; **7**, 31444-12-9; **8b**, 468-86-0.

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Electroreduction of α,β-Unsaturated Esters. I. A Simple Synthesis of *rac*-Deoxypicropodophyllin by Intramolecular Diels–Alder Reaction Plus Trans Addition of Hydrogen[1a,b]

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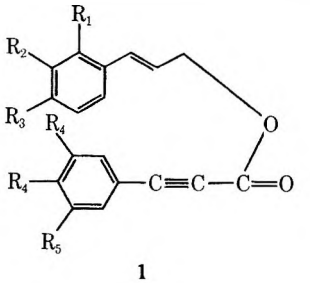
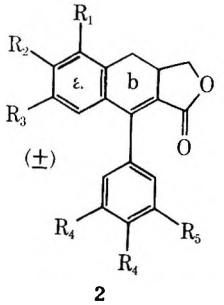
A one-step synthesis of dihydrocyclolignan lactones (including γ-apopicropodophyllin, **2c**) from *trans*-cinnamyl chlorides and sodium phenylpropiolates is described. Studies on polarographic and macroscale electroreductions of model α,β-unsaturated esters in the solvent-electrolyte acetonitrile–tetraethylammonium bromide are presented. In particular, electroreduction of **2c** at controlled cathode potential gives *rac*-deoxypicropodophyllin (**3**) by trans addition of hydrogen to the conjugated carbon–carbon double bond.

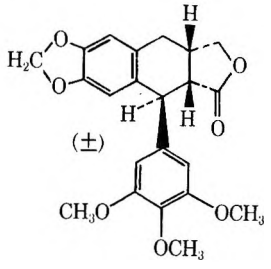
In previous papers[2-4] we reported syntheses of cyclolignan lactones **2** by means of the intramolecular Diels–Alder reaction of *trans*-cinnamyl phenylpropiolates (**1**) in refluxing acetic anhydride. Formation of **1** from the corresponding phenylpropiolyl chloride and *trans*-cinnamyl alcohol, however, proved to be difficult or capricious in many cases.[5] We now report an alternative synthetic procedure for **2** wherein the ester **1** is formed (from the corresponding *trans*-cinnamyl chloride and sodium phenylpropiolate) in refluxing anhydrous dimethylformamide (DMF) and is cyclized *in situ*.[6] Thus, cyclolignans **2a–c** were obtained by this method in yields of 18–51% from the corresponding phenylpropiolic acids. At least in these three cases, the DMF method offers a more convenient, reliable route to **2**, as well as an overall yield of magnitude comparable to that found with use of acetic anhydride.



1



2



3

a, $R_1 = R_2 = R_3 = R_4 = R_5 = H$
b, $R_1 = R_5 = H$; $R_2 = R_3 = R_4 = OCH_3$
c, $R_1 = H$; $R_2R_3 = OCH_2O$; $R_4 = R_5 = OCH_3$
d, $R_1 = R_4 = R_5 = OCH_3$; $R_2R_3 = OCH_2O$

Reduction of the carbon–carbon double bond of **2** should lead to cyclolignans of the 1-phenyl-3-hydroxymethyl-1,2,3,4-tetrahydro-2-naphthoic acid lactone type. Catalytic hydrogenation of γ-apopicropodophyllin (**2c**) to the *cis,cis*-tetrahydrolactone, *rac*-isodeoxypicropodophyllin (**4**), in 19–37% yield has been described previously.[7] Particularly, when platinum oxide (in acetic acid) was used as a catalyst, the major product isolated (30% yield)[7] resulted from hydrogenation of ring a plus dehydrogenation of ring b. It seemed likely that electrochemical reduction of compounds of structure **2** at constant cathode potential should allow saturation of the lactone α,β-carbon–carbon double bond without attendant reaction elsewhere in the molecule. This has been accomplished on a synthetic scale by use of a mercury cathode and **2c** in an anhydrous mixture of acetonitrile (solvent), hydrogen bromide (proton source), and tetraethylammonium bromide (supporting electrolyte) to give crystalline *trans-cis*-tetrahydrolactone (**3**), *rac*-deoxypicropodophyllin. Assignment of stereochemistry to **3** is based on (a) the presence of a cis lactone band[7] at 1765 cm^{-1}; (b) identity of its infrared spectrum with that reported[7] for (+)-deoxypicropodophyllin; and (c) nonidentity of **3** and **4**.

Only limited information on the stereochemistry of electroreduction of α,β-unsaturated esters is available. Elving, *et al.*,[8] obtained diethyl fumarate from trans reduction of diethyl acetylenedicarboxylate at a mercury cathode in aqueous HCl–KCl containing some ethanol. Ono[9] obtained ethyl cinnamate (presumably trans) from reduction of ethyl phenylpropiolate at controlled cathode potential in aqueous acidic ethanol. The conversion of **2c** into **3** appears to be the first pertinent example of trans electroreduction of a carbon–carbon double bond which is conjugated with an ester function.

In order to facilitate the selection of experimental conditions of cathode potential and proton availability for use in syntheses, preliminary polarographic studies

(1) (a) This investigation was supported by Research Grant No. GM 12730 from the National Institute of General Medical Sciences, U. S. Public Health Service. Paper VII in the series on Intramolecular Diels–Alder Reactions. (b) For paper VI, see L. H. Klemm, R. A. Klemm, P. S. Santhanam, and D. V. White, *J. Org. Chem.*, **36**, 2169 (1971). (c) Research Assistant, 1968–present. (d) Research Associate, 1969–1970.

(2) L. H. Klemm, K. W. Gopinath, D. H. Lee, F. W. Kelly, E. Trod, and T. M. McGuire, *Tetrahedron*, **22**, 1797 (1966).

(3) L. H. Klemm, D. H. Lee, K. W. Gopinath, and C. E. Klopfenstein, *J. Org. Chem.*, **31**, 2376 (1966).

(4) L. H. Klemm and P. S. Santhanam, *ibid.*, **33**, 1268 (1968).

(5) L. H. Klemm, K. W. Gopinath, G. C. Karaboyas, G. L. Capp, and D. H. Lee, *Tetrahedron*, **20**, 871 (1964).

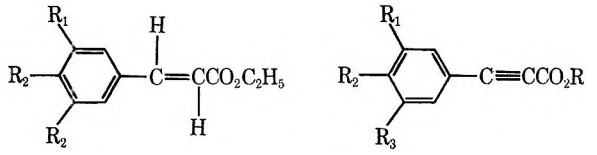
(6) The syntheses of phenylpropargyl and *trans*-cinnamyl propiolates in DMF have been described previously.[1b] These propiolates underwent intramolecular Diels–Alder reaction in acetic anhydride, but they gave unidentified reaction(s) in DMF.

(7) A. W. Schrecker and J. L. Hartwell, *J. Amer. Chem. Soc.*, **75**, 5916 (1953).

(8) I. Rosenthal, J. R. Hayes, A. J. Martin, and P. J. Elving, *ibid.*, **80**, 3050 (1958).

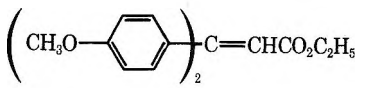
(9) S. Ono, *Nippon Kagaku Zasshi*, **77**, 665 (1956); *Chem. Abstr.*, **52**, 9020 (1958).

were made on a series of seven β-aryl α,β-unsaturated esters (**2d**, **5**–**7**) which were available in our laboratory (Table I).



5a, $R_1 = H$; $R_2 = OCH_3$
b, $R_1 = R_2 = OCH_3$

7a, R = Et; $R_1 = R_2 = R_3 = H$
b, R = Et; $R_1 = R_3 = OCH_3$; $R_2 = H$
c, R = Me; $R_1 = H$; $R_2R_3 = OCH_2O$



6

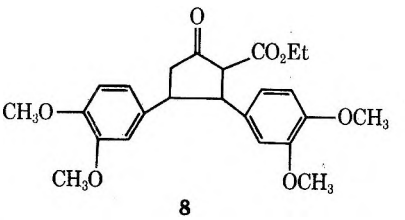
TABLE I
POLAROGRAPHIC HALF-WAVE REDUCTION POTENTIALS[a] FOR SOME β-ARYL α,β-UNSATURATED ESTERS

Substrate no.	Solvent–electrolyte[b]	First wave $-E_{1/2}$	Second wave $-E_{1/2}'$	Third wave $-E_{1/2}''$
2d	A	1.78[c]	2.00	
	B	1.69[d]		
5a	A	1.94[c]	2.26	
	B	1.83[e]	1.99	
	C	1.79[e]	1.93	
5b	A	1.87[c]	2.23	
	B	1.78[e]	1.93	
6	A	1.91[e]	2.06	
7a	A	1.94[f]	2.21	2.55
	B	~1.81[g]		
7b	A	1.91[f]	2.15	2.52
	B	~1.78[g]		
7c	A	1.97[f]	2.23	2.62
	B	1.82		
	D	1.74		

[a] In volts *vs.* the saturated aqueous calomel electrode. [b] A, 0.05 *M* Et_4NBr in anhydrous MeCN; B, solvent A diluted with 3.85 vol. % water; C, solvent A diluted with 7.7 vol. % water; D, 0.4 mg of phenol per ml of solvent B. [c] The first and second waves have approximately equal heights. [d] Wave height is twice that of the first wave in solvent A. [e] The first and second waves overlap but have nearly equal heights. [f] The three waves have unequal heights. [g] Irregular wave.

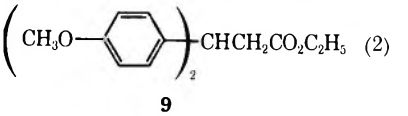
From the table one notes that the trans cinnamates **5**, as well as the β-arylcinnamates **2d** and **6**, show two reduction waves of approximately equal heights under conditions of low proton availability (anhydrous acetonitrile solvent). When water (a better proton source) is added to the solvent both waves are shifted to less negative potentials, though the second wave is moved further than the first one. That each of the two waves corresponds to the uptake of one electron is apparent from products obtained on macroscale syntheses. Thus, controlled reduction of **5a** under anhydrous conditions at a cathode potential of *ca.* −2.12 V (on the plateau of the first reduction wave) gave dimerization–cyclization to **8**, as per eq 1.[10] On the other hand, reduction of **6** at *ca.* −2.17 V (on the plateau of the second wave) gave simple hydrogenation of the conjugated carbon–carbon double bond, as per eq 2. Petrovich, *et al.*,[11] also found two well-separated reduction waves of equal heights on polarography of ethyl cinnamate in anhydrous DMF which contained tetraethylammonium perchlorate. Addition of water (1 *M*) shifted both waves to less negative potentials in the same manner as in MeCN. In neutral or acidic aqueous solution (containing as much as 50% ethanol or dioxane) methyl, ethyl, and benzyl cinnamates gave only one two-electron wave.[12,13] It was proposed[13] that in the pH range of 6–8 the protonated ester is the reducible species.

25a + $2e^-$ + H^+ →



+ EtO^- (1)

8

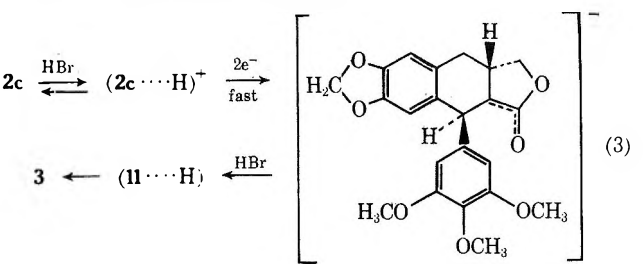


(2)

9

The phenylpropiolates **7** showed three waves of unequal heights on polarography under anhydrous conditions. When water or aqueous phenol (solvent–electrolyte D) was added to the acetonitrile in order to increase proton availability the three waves coalesced into a single (or nearly single) wave at a less negative $E_{1/2}$ value than for the first wave. When ethyl phenylpropiolate (**7a**) was electroreduced at *ca.* −2.06 *V* (plateau of the first wave) under anhydrous, low protic conditions only a small amount of the saturated compound ethyl β-phenylpropionate (**10**) was isolated. No ethyl cinnamate was found. This is not surprising in view of the fact that $E_{1/2}$ for ethyl cinnamate should be slightly less negative (perhaps at −1.91 V) than that for **5a** under these conditions. Macroscale reduction of **7a** at −2.06 V under anhydrous, high protic conditions (obtained by addition of a four molar quantity of anhydrous hydrogen bromide per mole of substrate) raised the yield of **10** to 55%. Compound **10** was also obtained by Ono[9] from electroreduction of **7a** in aqueous acidic ethanol at a cathode potential sufficiently negative as to lie on the plateau of the second wave (no third wave observed) present under his reaction conditions.

Equation 3 shows a plausible mechanism for the con-



(3)

11

(10) To be described in paper II in this series; *cf.* J. P. Petrovich, M. M. Baizer, and M. R. Ort, *J. Electrochem. Soc.*, **116**, 749 (1969).

(11) J. P. Petrovich, M. M. Baizer, and M. R. Ort, *ibid.*, **116**, 743 (1969).

(12) S. Ono, *Nippon Kagaku Zasshi*, **76**, 631 (1955); *Chem. Abstr.*, **61**, 17525 (1957); S. Ono and M. Uehara, *Nippon Kagaku Zasshi*, **78**, 929 (1957); *Chem. Abstr.*, **54**, 4485 (1960); S. Ono and T. Hayashi, *Bull. Chem. Soc. Jap.*, **26**, 268 (1953).

(13) M. J. D. Brand and B. Fleet, *J. Electroanal. Chem.*, **16**, 341 (1968).

version of **2c** into **3** in electrosynthesis. Protonation of **2c** is presumed to occur in the substrate solution and thereby to produce a single reduction wave (*cf.* **2d**, Table I). On contact with the cathode this protonated species takes up two electrons rapidly to give the intermediate anion **11**. In **11** the added proton is placed on C-1, since this allows the remaining negative charge to reside partially on the carbonyl oxygen atom. The preferred transition state for the protonation at C-1 should have the aryl group trans (rather than cis) to the methylene group at C-3. Sites of protonation in $(\mathbf{2c}\cdots H)^+$ and $(\mathbf{11}\cdots H)$ are uncertain, but it is possible that the latter complex is the enol form of **3** which tautomerizes to give the thermodynamically preferred cis lactone and trans-1,2 configurations of **3**.

The difference in net electronic effect of a meta (electron withdrawing, as compared to hydrogen) and a para alkoxy substituent (electron donating) in the benzene ring is noted when one compares half-wave reduction potentials for the α,β-unsaturated ester systems in **5** and **7**. Thus, **7b** (two meta MeO groups) reduces more readily than the unsubstituted compound **7a**, while **7c** (OCH_2O group attached both meta and para) reduces less readily than **7a**. Likewise **5b** reduces more readily than **5a**. This effect is also observed in polarographic reduction of 3- and 4-substituted benzaldehydes[14] and in chemical and catalytic reductions of β,β-diarylitaconic acids.[15]

Experimental Section[16]

1-Phenyl-3-hydroxymethyl-3,4-dihydro-2-naphthoic Acid Lactone (2a).—A mixture of 5 g of phenylpropiolic acid (Aldrich), 2.88 g (equimolar amount) of anhydrous $NaHCO_3$, and 10 ml of MeOH was warmed until gas evolution (CO_2) ceased. Solvent was removed *in vacuo*. A mixture of the residual sodium phenylpropiolate, 5.2 g (equimolar amount) of *trans*-cinnamyl chloride, and 40 ml of anhydrous dimethylformamide was refluxed (nitrogen atmosphere) for 5 hr. The white precipitate (NaCl) which formed in the cooled mixture was removed by filtration. Cooling the filtrate to −20° gave 3.1 g (mp 190–191.5°) of **2a**, identified by direct comparison with an authentic sample.[3] Additional **2a** was obtained by evaporation of the mother liquor and addition of benzene–petroleum ether (bp 30–60°), total yield 4.6 g (51%), mp 185–191.5°.

1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-3-hydroxymethyl-3,4-dihydro-2-naphthoic Acid Lactone (2b).—Sodium 3,4-dimethoxyphenylpropiolate was prepared in the preceding manner. *trans*-3,4-Dimethoxycinnamyl chloride was obtained by slow addition at 0° of a mixture of 1.2 ml (0.015 mol) of pyridine, 0.94 ml (0.013 mol) of thionyl chloride, and 20 ml of $CHCl_3$ to a solution of 2.1 g (0.011 mol) of *trans*-3,4-dimethoxycinnamyl alcohol[5] in 50 ml of $CHCl_3$. The mixture was refluxed for 1 hr, washed with water, dried (Na_2SO_4), and evaporated to yield the crude organic chloride. As for **2a**, these components were refluxed in DMF to form **2b**, isolated on addition of MeOH to the evaporated solution, yield 18%, mp 220.5–222° (lit.[2] 221–222°).

***rac*-γ-Apopicropodophyllin (2c).**—This was prepared in the foregoing manner from *trans*-3,4-methylenedioxycinnamyl alcohol[5] and 3,4,5-trimethoxyphenylpropiolic acid.[5] The residue from evaporation of the DMF solution was diluted with water and extracted with $CHCl_3$ (dried). Evaporation of the organic extract and addition of ether to the residue gave **2c** (29%), mp 243–246° (lit.[2] 252–253°).

Chemicals for Electroreductions.—In both polarography and electrosynthesis the solvent was anhydrous, spectral grade acetonitrile (used without further purification). The supporting electrolyte was tetraethylammonium bromide (originally 99% pure, recrystallized repeatedly from reagent grade 1-butanol, and stored in the dark *in vacuo* and in the presence of anhydrous $CaSO_4$). In polarography the concentration of Et_4NBr was 0.05 *M*; in synthesis it was 0.1 *M*. In some polarographic studies, water or aqueous phenol was added to the solvent to serve as a proton source (see Table I). In electrosynthesis anhydrous HBr was oftentimes used for this purpose. Without added H_2O or HBr, the MeCN itself is presumed to be the main proton source. Substrate molecules were available either commercially or from studies in our own laboratory.[1b,5,6,17]

Polarography.—The apparatus and the general procedure (but not the solvent–electrolyte) were the same as described previously.[18] Concentrations of each substrate were varied over the range of $2.2\text{–}5.8 \times 10^{-4}$ *M*. Correction for *iR* drop was negligibly small. Reproducibility in $E_{1/2}$ values was ±0.01 V.

Electrosynthesis.—Macroscale electroreductions were conducted in a cell made from a 250-ml beaker which contained a mercury pool cathode and a horizontal silver disk anode (2.6 cm radius), separated from one another by means of a sintered-glass partition of medium porosity. The cathode potential was maintained constant by means of an American Instrument Co. Redox-O-Trol. The solvent–electrolyte (50 ml) was preelectrolyzed until the current fell to a small value (3–4 mA). During preelectrolysis and electrosynthesis purified nitrogen (>99.99%) was bubbled through the catholyte (stirred magnetically). For **6**, the neat substrate (a liquid) was added to the catholyte in one portion. For **2c**, a solution of the substrate, plus slightly more than a 2-*M* quantity of anhydrous HBr in MeCN was added to the catholyte during the course of the electroreduction. Addition of **7a**, with or without HBr, was portionwise. Electroreduction was continued until the current again became small. Combined solutions from anode and cathode compartments were evaporated to dryness and the residue was extracted with $CHCl_3$ (plus water). Evaporation of the dried (Na_2SO_4) organic layer gave the crude product.

***rac*-Deoxypicropodophyllin (3).**—A mixture of 178 mg (0.45 mmol) of **2c**, mp 245–246.5°, 1.1 mmol of anhydrous HBr, and 8 ml of MeCN was added to the catholyte (cathode potential −2.10 V) over a period of 10 min and electroreduction was continued for 5 min longer. Crude product was crystallized from 2-propanol, yield 121 mg (68%), mp 196–201°. Recrystallizations from 2-propanol and methanol gave needles: mp 210–211°, depressed to 186–196° on admixture with *rac*-isodeoxypicropodophyllin (**4**),[2] mp 203–204.5°; ir ($CHCl_3$) identical with that reported[7] for (+)-deoxypicropodophyllin but different from that of **4** in the range of 1000–1020 cm^{-1}; pmr ($CDCl_3$) δ 2.6–3.4 (m, 4, H-2, H-3, H-4), 3.80 (s, 3, CH_3O at C-4′) and 3.85 (s, 6, 2 CH_3O at C-3′ and C-5′) which overlap 3.7–4.2 (m, 10 total, including H-1), 4.2–4.6 (broad s, 2, $CH_2OC{=}O$), 5.96 (broadened s, 2, OCH_2O), 6.3–6.9 (m, 4, aromatic protons); mass spectrum *m/e* 398 (100, M^+).

Anal. Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.46; H, 5.52.

Ethyl β,β-Bis(4-methoxyphenyl)propionate (9).—Electroreduction of 778 mg of **6** [obtained by dehydration of ethyl β-hydroxy-β,β-bis(4-methoxyphenyl)propionate][17] over a period of 18 min and chromatography of the crude product by means of silica gel (4 g) and CH_2Cl_2 (to remove tar) gave 300 mg (39%) of crude **9**: ir 1720 cm^{-1}, identified by direct spectral comparison with an authentic sample of **9** [pmr (CCl_4) δ 1.01 (t, 3, J_{Et} = 7 Hz, CH_3), 2.89 (d, 2, $J_{\alpha\beta}$ = 8 Hz, $CHCH_2C{=}O$), 3.57 (s, 6, 2 MeO), 3.93 (q, 2, CH_2CH_3), 4.43 (t, 1, $CHCH_2$), 6.91 (d of d, 8, J_{ortho} = 8.5 Hz, Δδ = 20.8 Hz, aromatic protons)][19] from catalytic hydrogenation of **6**[17] and by hydrolysis to β,β-bis(4-methoxyphenyl)propionic acid, mp 137–138° (from benzene–hexane), undepressed on admixture with an authentic sample.[17]

Electroreduction of Ethyl Phenylpropiolate (7a).—A solution

(14) P. Zuman, "Substituent Effects in Organic Polarography," Plenum Press, New York, N. Y., 1967, p 76.

(15) L. H. Klemm and C. D. Lind, *J. Org. Chem.*, **21**, 258 (1956), and references cited therein.

(16) Microanalyses were performed by M-H-W Laboratories, Garden City, Mich. Infrared spectra were determined on $CHCl_3$ solutions by means of Beckman IR-5A and Perkin-Elmer Model 700 spectrometers; mass spectra, by means of a CEC Model 21-110 instrument at 70 eV; pmr spectra, by means of a Varian A-60 spectrometer, with tetramethylsilane used as internal standard.

(17) L. H. Klemm and G. M. Bower, *J. Org. Chem.*, **23**, 344 (1958).

(18) L. H. Klemm, W. C. Solomon, and A. J. Kohlik, *ibid.*, **27**, 2777 (1962).

(19) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, pp. 89–90.

of 1.12 g of **7a** in 25 ml of MeCN was added to the cell over a period of 60 min and reduction was continued for 100 min longer. Vpc (10% silicone rubber on Chromosorb W, 200°) of the $CHCl_3$-soluble product indicated the formation of ethyl β-phenylpropionate (**10**) (11%), identified by comparison with an authentic sample. Acidification of the aqueous layer to pH 1 and extraction with $CHCl_3$ gave 400 mg (43%) of phenylpropiolic acid.

Repetition of the procedure but with 2 equiv of anhydrous HBr added to the substrate solution raised the yield of **10** to 26%. With 4 equiv of HBr the yield of **10** was 55%.

Registry No.—**2a**, 31892-93-0; **2c**, 6258-32-8; **2d**, 31892-95-2; **3**, 31892-96-3; **5a**, 24393-65-5; **5b**, 31892-98-5; **6**, 31892-99-6; **7a**, 2216-94-6; **7b**, 29577-38-6; **7c**, 31893-02-4.

Nucleosides. XIV. Synthesis of 3′-Deoxyadenosine and 9-(3-Deoxy-α-L-*threo*-pentofuranosyl)adenine

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Treatment of methyl 9-(2,3-*O*-isopropylideneribofuranosyluronate)adenine (**3**) with sodium isopropoxide at room temperature leads to isopropyl 3′-deoxy-3′-adenosinene 5′-carboxylate (**4**) in 70% yield. The latter on catalytic (Pd/C) hydrogenation affords a mixture of two (C-4′) epimeric esters **5** and **6**, one of which (**5**) on reduction with sodium bis(2-methoxyethoxy)aluminum hydride furnished 3′-deoxyadenosine (**7**, cordycepin). The other ester (**6**), subjected to the same conditions of reduction, gave 9-(3-deoxy-α-L-*threo*-pentofuranosyl)-adenine (**8**). Compounds **7** and **8** could also be obtained in a more efficacious manner by column chromatography (Dowex 1) of the mixture derived by performing the reductions consecutively without separation of the isomeric intermediates **5** and **6**.

Recent reports from this laboratory[2a-c] described the introduction of 3′,4′ unsaturation into both pyrimidine and purine 2′-deoxynucleosides *via* corresponding 2′-deoxy-β-D-*erythro*-pentofuranosyluronic acid derivatives. Concurrently, Jones and Moffatt[2d,e] and Howgate,[3] *et al.*, reported the facile conversion of 2′,3′-*O*-alkylidene ribonucleoside 5′-carboxaldehydes (**1**) into 3′,4′-unsaturated nucleosides (**2**) and derivatives thereof under relatively mild basic conditions. The present communication describes the application of the latter approach to methyl 9-(2,3-*O*-isopropylideneribofuranosyluronate)adenine (**3**) which led to a practical synthesis of the antibiotic 3′-deoxyadenosine (**7**, cordycepin) and its C-4′ epimer, 9-(3-deoxy-α-L-*threo*-pentofuranosyl)-adenine[4] (**8**). The fact that **7** is a strong inhibitor of RNA synthesis, which generally accounts for its cytostatic activity,[5] stimulated our interest in **8** (Scheme I).

The conversion of **1** to **2** has been effected with a relatively wide spectrum of bases[2d,e] ranging from sodium bicarbonate or sodium carbonate in DMF to alkali metal alkoxides in both protic and dipolar aprotic media. By contrast, **3** was recovered unchanged after prolonged treatment with sodium carbonate in DMF. Moreover, triethylamine in DMF, the system of choice for the conversion of ethyl 3′-*O*-methylsulfonylthymidine 5′-carboxylate[2b] into ethyl 3′-deoxy-3′-thymidinene 5′-carboxylate,[6] proved equally ineffective after 13 hr at 80°. The desired elimination was effected, along with transesterification, by the action of sodium isopropoxide[7] in 2-propanol to give isopropyl 3′-deoxy-3′-adenosinene 5′-carboxylate[6] (**4**) in 70% yield after 0.5 hr at ambient temperature. The structure of the olefinic ester **4** was readily deduced from its nmr spectrum which showed, *inter alia*, a doublet at τ 6.53 ppm characteristic of the C-3′ vinyl proton in the sugar moiety.[2b]

Jones and Moffatt[2d,e] reported the occurrence of epimerization at C-4′, along with elimination when nucleoside 5′-carboxaldehydes (**1**) were brought into contact with adsorbents such as silica gel. There was no evidence of epimerization in our experiments. However, a small amount of the corresponding 3′,4′-unsaturated acid was occasionally isolated along with the ester (**4**) which is apparently generated from **4** during the work-up of the reaction mixture.

It would appear that, with the exception of a need for a stronger base to effect the process of elimination in the case of **3** relative to the nucleoside 5′-carboxaldehyde, the two elimination reactions probably proceed *via* similar paths. However, the scope of the present study precludes any firm conclusion in regard to the exact mechanism(s).

Catalytic hydrogenation (Pd/C) of **4** yielded two saturated esters **5** and **6** in the ratio of 1.5:1 which were separated on preparative tlc. The faster moving component **5**, on reduction with sodium bis(2-methoxyethoxy)aluminum hydride in tetrahydrofuran, yielded 3′-deoxyadenosine (**7**) in 50% yield. The slower moving ester **6**, subjected to the same conditions of reduction, afforded the epimeric structure, 9-(3-deoxy-α-L-*threo*-pentofuranosyl)adenine (**8**), in virtually the same yield.

(1) To whom correspondence should be addressed: Detroit Institute of Cancer Research.

(2) (a) J. Zemlicka, R. Gasser, and J. P. Horwitz, Abstracts, 160th National Meeting of the American Chemical Society, Chicago, Ill., 1970, Abstract No. CARB 3; (b) *J. Amer. Chem. Soc.*, **92**, 4744 (1970); (c) Abstracts, Joint Conference Chemical Institute of Canada and American Chemical Society, Toronto, Canada, 1970, Abstract No. CARB 5; (d) G. H. Jones and J. G. Moffatt, Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., 1969, Abstract No. CARB 15; (e) U. S. Patent 3,457,255 (1969); *Chem. Abstr.*, **72**, 3727 (1970).

(3) P. Howgate, A. S. Jones, and J. P. Tittensor, *Carbohyd. Res.*, **12**, 403 (1970).

(4) This compound has been described (*cf.* ref 2e), but corresponding physical constants have not been disclosed.

(5) For pertinent references, see R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley, New York, N. Y., 1970, p 50.

(6) See J. P. Horwitz, J. Chua, M. A. Da Rooge, M. Noel, and J. T. Donatti, *J. Org. Chem.*, **31**, 205 (1966), for the basis of this nomenclature.

(7) This base system was chosen because the ester **3** was relatively insoluble in both methanol and ethanol.

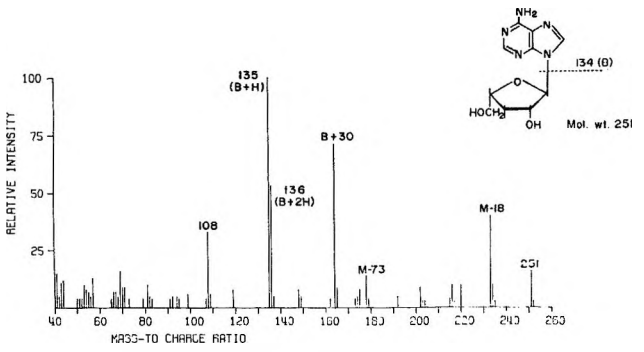
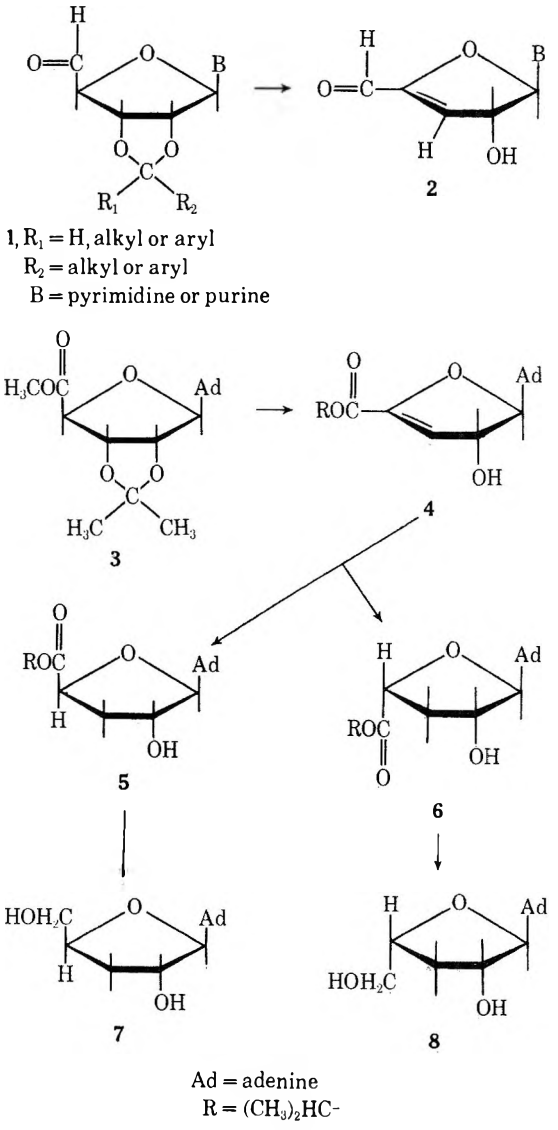


Figure 1.—Mass spectrum of 9-(3-deoxy-α-L-*threo*-pentofuranosyl)adenine.

SCHEME I



A more convenient route to **7** and **8** consisted of performing consecutively the catalytic and chemical reductions of **4** and then resolving the mixture of β-D and α-L isomers on column chromatography (Dowex-1).[8] The ratio of yields of products **7** and **8** obtained in the two procedures is essentially the same.

The formation of two products (**5** and **6**) from the hydrogenation of **4** differs from the course of reduction of ethyl 3′-deoxy-3′-thymidinene 5′-carboxylate which gave ethyl 3′deoxythymidine 5′-carboxylate as the sole product.[9] This difference probably can be ascribed in part to the presence of the 2′-OH in **4** coupled with the relative influence of the purine moiety vis-à-vis a thymine residue.

The nmr spectrum of **7** has been reported by two groups of workers.[10,11] As the compounds **7** and **8** differ in their configuration at C-4′, an attempt was made to assign the signal of this proton in the nmr spectra of the two isomers. Unfortunately, this signal is obliterated in both compounds by strong HDO absorption at τ 5.30 ppm. Moreover, efforts to resolve the C-4′ proton in solvents such as methyl sulfoxide and pyridine were equally unsuccessful. The spectra of **7** and **8** were generally similar and the anomeric proton in both structures shows essentially identical chemical shifts. However, the coupling constant of the anomeric proton of **8** (J = 3.5 Hz) is significantly larger than that of **7** (J = 2.0 Hz). A comparable difference prevailed as well in the precursory esters (**5** and **6**).

The absorption due to 3′-CH_2 in the L-threo compound **8** appears as a series of ten lines centered at 2.67 ppm and spread from 2.10 to 3.25 ppm. The corresponding multiplet for the isomer **7** consists of four lines that are poorly resolved and spread over a narrower range (2.52–2.69 ppm).[10,11]

Mass spectrometric evidence in support of the structure of cordycepin was provided by Hanessian, *et al.*[12] Interpretation of the mass spectrum of **8** lends additional support to the assigned structure. Thus the molecular ion m/e 251, which corresponds to a deoxyriboside of adenine, is common (Figure 1) to both spectra. Moreover, the structural identities of the most significant peaks in **8**, namely m/e 135, 136 (B + H and 2 H, respectively, where B = adenine residue) and 164 (B + 30) follow the previous interpretation of **7**. Thus the ion at 164 (B + 30) agrees with the presence of 2′-OH group and the one at 178 as in **7** indicates the absence of this group at C-3′.

Unlike **7**, its C-4′ epimer, **8** shows a prominent peak at m/e 233 (M − 18) due to the loss of water, but there is an absence of the peak at 221 (M − 30) characteristic of the loss of the elements of formaldehyde from the 5′-hydroxy group. The appearance of the peak (M − 30) requires that the labile hydrogen of the 5′-hydroxyl function be in relatively close proximity to the aglycon.[13] Since the 5′-OH in **8** is oriented trans to the base across the furanose ring, the labile hydrogen in this group becomes sterically inaccessible to the base which would explain the absence of a peak at m/e 221. A similar situation exists in 9-α-xylofuranosyladenine and 2′-deoxy-9-α-adenosine[13] which have the same geometrical relationship between the 5′-OH and the base as exists in **8**. The former does not exhibit the loss of the elements of formaldehyde, whereas the peak in the latter due to this loss (M − 30) is of low abundance as compared to its β isomer, 2′-deoxyadenosine. Biological

(8) C. A. Dekker, *J. Amer. Chem. Soc.*, **87**, 4027 (1965).

(9) J. Zemlicka and J. P. Horwitz, unpublished results.

(10) W. W. Lee, A. Benitez, C. D. Anderson, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **83**, 1906 (1961).

(11) E. A. Kaczka, E. L. Dulaney, C. O. Gitterman, H. B. Woodruff, and K. Folkers, *Biochem. Biophys. Res. Commun.*, **14**, 452 (1964).

(12) S. Hanessian, D. C. DeJongh, and J. A. McCloskey, *Biochim. Biophys. Acta*, **117**, 480 (1966).

(13) S. J. Shaw, D. M. Desiderio, K. Tsuboyama, and J. A. McCloskey, *J. Amer. Chem. Soc.*, **92**, 2510 (1970).

and biochemical studies with **8** are currently in progress and the results will be reported elsewhere.

Experimental Section

General Procedures.—Evaporations were carried out *in vacuo* at a bath temperature below 45°. Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Thin layer chromatography (tlc) was performed on silica gel GF (Merck); preparative tlc was carried out on 20 × 20 cm glass plates coated with 1-mm layers of the same absorbent. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter. The ir spectra were measured in a Perkin-Elmer Model 21 spectrophotometer. Nuclear magnetic resonance spectra were obtained using a Varian A-60A spectrometer and mass spectra using an AEI MS-902 instrument with a direct inlet system and an ionizing voltage of 70 eV. Ultraviolet spectra were obtained by using a Cary recording spectrometer.

Isopropyl 3′-Deoxy-3′-adenosinene 5′-Carboxylate (4).—To a solution of 0.335 g (1 mmol) of methyl 9-(2,3-*O*-isopropylideneribofuranosyluronate)adenine (**3**),[14] dissolved by heating in 150 ml of dry 2-propanol, was added at room temperature 20 ml of 2-propanol containing 0.04 g of sodium (1.73 g-atoms) and the clear solution, protected from moisture, was stirred magnetically for 0.5 hr. The pH of the reaction mixture was adjusted to *ca.* 7 by dropwise addition of glacial acetic acid and the solution was evaporated to dryness. The residue was triturated with water and collected. The air-dried product crystallized from aqueous methanol as colorless needles: wt 0.215 g (70% yield); mp *ca.* 200° with prior softening *ca.* 115°; ir (KBr) 1733 cm^{-1} (ester C=O); uv max (95% EtOH) 256 nm (ε 15,800); nmr (acetone-d_6) δ 8.19 (s, 1, H-8) 8.10 (s, 1, H-2), 6.82 (s, 2, exchanges with D_2O, NH_2) 6.25 (d, 1, $J_{1',2'}$ = 2.5 Hz, H-1′), 6.53 (d, 1, $J_{2',3'}$ = 3.3 Hz, H-3′), 5.71 (t, 1, H-2′), 5.07 (m, 1, isopropyl hydrogen), 1.18 and 1.28 (s, isopropyl methyls); $[\alpha]^{24}D$ −145°; $[\alpha]^{24}_{578}$ −151° (*c* 0.5, methanol).

Anal. Calcd for $C_{13}H_{15}N_5O_4$: C, 51.14; H, 4.91; N, 22.95. Found: C, 50.97; H, 5.00; N, 23.01.

Isopropyl 9-(3-Deoxy-β-D-ribofuranosyluronate)adenine (5) and Isopropyl 9-(3-Deoxy-α-L-*threo*-ribofuranosyluronate)adenine (6).—A solution of 4 (0.305 g, 1 mmol) in 95% alcohol (40 ml) containing 0.3 g of 10% palladium/charcoal catalyst was shaken for 2 hr under 1 atm of hydrogen at 25°. The catalyst was filtered through Celite and the Celite was washed with alcohol. The combined filtrate and washings were evaporated to dryness and the residue (0.261 g), dissolved in methanol, was applied to five silica gel (20 × 20) plates ($CHCl_3$:CH_3OH, 4:1). Elution of the faster moving component with 95% ethanol gave **5** (148 mg, 49% yield), whereas the slower moving band furnished **6** (96 mg, 31% yield). Compound **5** was recrystallized from a mixture of ethanol and water: mp *ca.* 210° with a prior softening at *ca.* 105°; ir (KBr) 1753 cm^{-1} (ester C=O); uv max (95% EtOH) 260 nm (ε 16,300); nmr (acetone-d_6, TMS internal standard) δ 8.38 (s, 1, H-8), 8.18 (s, 1, H-2), 6.64 (s, 2, exchanges with D_2O, NH_2), 6.10 (d, 1, $J_{1',2'}$ = 1.5 Hz, H-1′), 2.40 (m, 2, 3′-CH_2), 1.15 and 1.25 (isopropyl methyls); $[\alpha]^{23}D$ −11.6°; $[\alpha]^{23}_{578}$ −13° (*c* 0.5, methanol).

Anal. Calcd for $C_{13}H_{17}N_5O_4 \cdot 0.5H_2O$: C, 49.36; H, 5.68; N, 22.19. Found: C, 49.03; H, 5.28; N, 21.89.

Compound **6** was recrystallized from isopropyl alcohol: mp *ca.* 235° with prior softening *ca.* 180°; ir (KBr) 1750 cm^{-1} (ester C=O); uv max (95% EtOH) 259 nm (ε 16,100); nmr (acetone-d_6, TMS internal standard) δ 8.19 (s, 1, H-8), 8.08 (s, 1, H-2), 6.57 (s, 2, exchanges with D_2O, NH_2), 6.15 (d, 1, $J_{1',2'}$ = 3.0 Hz, H-1′), 2.83 (m, 2, 3′-CH_2), 1.18 and 1.28 (s, isopropyl methyls); $[\alpha]^{24}D$ −17.5°; $[\alpha]^{24}_{578}$ −18.8° (*c* 0.5, methanol).

Anal. Calcd for $C_{13}H_{17}N_5O_4$: C, 50.81; H, 5.53; N, 22.80. Found: C, 50.60; H, 5.57; N, 22.96.

9-(3-Deoxy-α-L-*threo*-pentofuranosyl)adenine (8).—To a solution of **6** (0.1 g, 0.32 mmol) in dry THF (5 ml), cooled externally by an ice bath, was added 0.64 ml (0.128 g, 2 equiv) of a 21% benzene–THF solution of sodium bis(methoxyethoxy)aluminum hydride. The turbid mixture was stirred at room temperature for 1.25 hr after which additional (2 equiv) reducing agent was introduced and the stirring was continued for 3 hr. The reaction mixture was cooled by an ice bath and treated with 15 ml of ethanol and excess Dowex-50 (NH_4^+). The mixture was stirred at room temperature for 1.5 hr and the resin was removed by filtration. The filtrate and combined alcohol washings were evaporated to dryness. The residue, dissolved in methanol, was applied to a nonadhering (loose layer) silica gel (70–235 mesh) glass plate (20 × 20 cm) and the preparative tlc was developed in $CHCl_3$–CH_3OH, 4:1 (v/v). The principal and slower moving band was eluted with ethanol and the filtered solution, on evaporation, left a residue which crystallized from water: wt 0.039 g (48% yield); $[\alpha]^{25}D$ − 52°; $[\alpha]^{25}_{578}$ −54° (*c* 0.5, H_2O); uv max (95% EtOH) 260 nm (ε 13,100); nmr (D_2O, external standard TMS) δ 8.58 (s, 1, H-8), 8.53 (s, 1, H-2), 6.43 (d, 1, $J_{1',2'}$ = 3.5 Hz, H-1′), 4.18 (m, 2, 5′-CH_2), 2.67 (m, 2, 3′-CH_2).

Anal. Calcd for $C_{10}H_{13}N_5O_3 \cdot 0.75H_2O$: C, 45.36; H, 5.48; N, 26.46. Found: 45.25; H, 5.37; N, 26.65.

3-Deoxyadenosine (7).—The reduction of **5** (0.1 g, 0.32 mmol) with sodium bis(methoxyethoxy)aluminum hydride (0.64 ml diluted to 10 ml in THF) was effected in exactly the same manner described above for the corresponding reductions of **5**. Preparative tlc afforded 0.042 g of a solid (52% yield), after crystallization from water: mp 222–224°; $[\alpha]^{25}D$ −44°; $[\alpha]^{25}_{578}$ −46° (*c* 0.5, H_2O);[15] uv max (95% EtOH) 260 nm (ε 13,500); nmr[10,11] (D_2O, external standard TMS) δ 8.63 (s, 1, H-8), 8.51 (s, 1, H-2), 6.40 (d, 1, $J_{1',2'}$ = 2.0 Hz, H-1′), 4.25 (m, 2, 5′-CH_2), 2.66 (m, 2, 3′-CH_2).

An Alternate Route to 7 and 8.—A mixture of **5** and **6** (307 mg, 1 mmol) as obtained from the (Pd/C) hydrogenation of **4** was reduced with 4 equiv of sodium bis(2-methoxyethoxy)aluminum hydride in THF, as described above, to give 148 mg of a mixture of **7** and **8**. A sample (0.1 g) of the mixture, dissolved in 30% methanol (20 ml), was put on a column (2.5 × 38 cm) of Dowex-1 (OH-, 200–400 mesh), and the column was eluted with 1.6 l. of 30% methanol. Removal of the solvent from the faster moving product contained in fractions 48–65 (each fraction was of 15 ml) furnished **7** (53 mg), and the slower moving component (fractions 85–100) yielded **8** (34 mg). Both **7** and **8** were recrystallized from water and were found to be identical with the compounds obtained according to the method described above.

Registry No.—**4**, 31735-23-6; **5**, 31735-24-7; **6**, 31735-25-8; **7**, 73-03-0; **8**, 26302-05-6.

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(14) P. J. Harper and A. Hampton, *J. Org. Chem.*, **35**, 1988 (1970).

(15) The following physical constants have been recorded (see ref 5, 10, and 11) for this compound: mp 230–231°; $[\alpha]^{26}D$ −35° (*c* 9.452, H_2O); uv max (pH 4) 259 nm (ε 13,100).

Oligomerization during the Acylation of *O*-(Benzyloxycarbonylsarcosyl-L-*N*-methylvalyl)-L-threonyl-D-valyl-L-proline with 2-Nitro-3-benzyloxy-4-methylbenzoic Acid[1,2]

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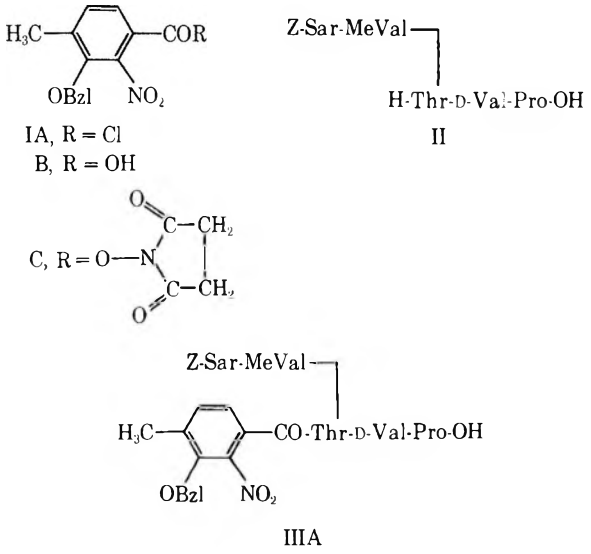
Reaction of the β-pentadepsipeptide *O*-(benzyloxycarbonylsarcosyl-L-*N*-methylvalyl)-L-threonyl-D-valyl-L-proline, with 2-nitro-3-benzyloxy-4-methylbenzoyl chloride resulted in considerable oligomerization. Oligomers up to the pentamer were isolated by means of LH-20 chromatography and characterized. Other methods of activation of the benzoyl moiety were investigated including mixed carbonic carboxylic anhydride, *N*,*N*′-carbonyldiimidazole, *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, *N*-hydroxysuccinimide ester, symmetrical anhydride, and azide. The best yields of the desired monomer were obtained from the symmetrical anhydride generated by the reaction of dicyclohexylcarbodiimide with 2-nitro-3-benzyloxy-4-methylbenzoic acid, although dimer and trace amounts of trimer were also formed. Monomer only was obtained from (a) the acid chloride by controlling the addition of base and (b) the azide, but the total yields were low in these procedures.

The reaction of 2-nitro-3-benzyloxy-4-methylbenzoyl chloride (IA)[4] with *O*-(benzyloxycarbonylsarcosyl-L-*N*-methylvalyl)-L-threonyl-D-valyl-L-proline (II) was described in an earlier communication on the synthesis of actinomycin D.[5] Purification of the crude product by column chromatography on Sephadex LH-20 in methanol or ethanol gave five discrete peaks of peptide derivatives (Figure 1).[6]

The desired intermediate for the synthesis of actinomycin D, *O*-(benzyloxycarbonylsarcosyl-L-*N*-methylvalyl)-*N*-(2-nitro-3-benzyloxy-4-methylbenzoyl)-L-threonyl-D-valyl-L-proline (IIIA) was contained in the largest and slowest moving peak, A. Isolation and examination of the four faster moving peaks by carboxyl group titration revealed that they were due to dimer IIIB, trimer IIIC, tetramer IIID, and pentamer IIIE (Figure 2). Authentic dimer was subsequently synthesized from *O*-(benzyloxycarbonylsarcosyl-L-*N*-methylvalyl)-*N*-(2-nitro-3-benzyloxy-4-methylbenzoyl)-L-threonyl-D-valyl-L-proline (IIIA) and *O*-(benzyloxycarbonylsarcosyl-L-*N*-methylvalyl)-L-threonyl-D-valyl-L-proline (II), and its physical characteristics agreed with the dimer IIIB obtained from chromatographic fractionation of the crude reaction mixture.



The occurrence of oligomerization can be explained by intermediate mixed anhydride formation due to nucleophilic attack by the carboxylate of the C-terminal proline residue on 2-nitro-3-benzyloxy-4-methylbenzoyl chloride (IA). Kopple, *et al.*, previously observed and discussed the rationale of oligomer formation during reactions of benzyl chloroformate with tripeptides.[7] Indeed, the first recorded peptide synthesis occurred during benzoylation of silver glycinate.[8]

To obtain optimal yields of monomer required for the synthesis of actinomycin D and analogs, several other methods of activation of 2-nitro-3-benzyloxy-4-methylbenzoic acid were investigated. In these experiments the overall yield of monomer in relation to the degree of oligomer formation was an important factor in choosing a suitable method of activation. The results are summarized in Table I.

The mixed carbonic carboxylic anhydride method utilizing isobutyl chloroformate[9] gave a low yield of the monomer IIIA and substantially more oligomerization than the acid chloride reaction. Likewise, the *N*,*N*′-carbonyldiimidazole[10] and the *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ)[11] methods gave similar results.

The *N*-hydroxysuccinimide[12] ester (IC) of 2-nitro-3-benzyloxy-4-methylbenzoic acid gave only monomer

(1) Contribution VII in the series, Syntheses of Actinomycin and Analogs. Part VI: J. Meienhofer, R. Cotton, and E. Atherton, *Peptides, Proc. Eur. Symp., 11th*, in press.

(2) This work was supported in part by Public Health Service Research Grants C-6516 from the National Cancer Institute and FR-05526 from the Division of Research Facilities and Resources, National Institutes of Health. Abbreviations follow the rules of the IUPAC-IUB Commission on Biochemical Nomenclature in *Biochemistry*, **5**, 1445, 2485 (1966); **6**, 362 (1967); *J. Biol. Chem.*, **241**, 2491 (1966).

(3) To whom correspondence should be addressed.

(4) H. Brockmann and H. Muxfeldt, *Chem. Ber.*, **91**, 1242 (1958); S.-W. Chow, Y. S. Kao, C.-H. Chou, and B. Hou, *Sci. Sinica (Peking)*, **12**, 49 (1963).

(5) J. Meienhofer, *J. Amer. Chem. Soc.*, **92**, 3771 (1970).

(6) Additional peaks of by-products and side products of lower molecular weight were observed eluting after the peptide monomer. One of these peaks was identified as 2-nitro-3-benzyloxy-4-methylbenzoic acid.

(7) K. D. Kopple, T. Saito, and M. Ohnishi, *J. Org. Chem.*, **34**, 1631 (1969).

(8) T. Curtius, *J. Prakt. Chem.*, **26**, 175 (1882).

(9) T. Wieland and H. Bernhard, *Justus Liebigs Ann. Chem.*, **572**, 190 (1951); R. A. Boissonnas, *Helv. Chim Acta*, **34**, 874 (1951); J. R. Vaughan, Jr., *J. Amer. Chem. Soc.*, **73**, 3547 (1951).

(10) G. W. Anderson and R. Paul, *ibid.*, **80**, 4423 (1958); **82**, 4596 (1960).

(11) D. Belleau and G. Malek, *ibid.*, **90**, 1651 (1968).

(12) G. W. Anderson, J. E. Zimmerman, and F. Callahan, *ibid.*, **85**, 3039 (1963).

TABLE I

PROPERTIES OF THE OLIGOMERS AND YIELDS FOR VARIOUS METHODS OF ACTIVATION

	Mp, °C	$[\alpha]^{26}D$, deg	Formula, (mol wt)	Calcd (found) C, %	H, %	N, %	Mol wt[a] by titration	% yields Acid chloride	Mixed anhydride	N,N'-Carbonyldiimidazole	EEDQ	N-Hydroxysuccinimide ester	Symmetrical anhydride	Acid chloride base control	Azide
Monomer IIIA	115–120	−2.3 (*c* 1, MeOH)	$C_{46}H_{58}N_6O_{13}$ (903.0)	61.19 (61.18)	6.47 (6.84)	9.31 (9.02)	985	55.0	7.7	15.0	10.0	48.2	80.0	33.0	28.0
Dimer IIIB	116–120	−19.9 (*c* 1, MeOH)	$C_{77}H_{103}N_{11}O_{21}$ (1518.73)	60.90 (60.82)	6.84 (7.05)	10.15 (9.98)	1532	21.0	11.0	20.0	19.3	Trace	5.5	0	0
Trimer IIIC	119–124	−25.6 (*c* 1, MeOH)	$C_{108}H_{149}N_{16}O_{29}$ (2134.45)	60.77 (60.94)	6.99 (7.38)	10.50 (10.06)	2000	1.5	24.5	5.0	11.0	0	Trace	0	0
Tetramer IIID	123–126	−54.5 (*c* 0.29, MeOH)	$C_{139}H_{193}N_{21}O_{37}$ (2750.18)	60.69 (60.26)	7.08 (7.19)	10.69 (10.58)	2682	Trace	Trace	0	4.7	0	0	0	0
Pentamer IIIE	127–131	−41.0 (*c* 0.29, MeOH)	$C_{170}H_{238}N_{26}O_{45}$ (3365.91)	60.65 (60.48)	7.14 (7.12)	10.82 (10.71)		Trace	Trace	0	1.5	0	0	0	0

[a] Molecular weights were determined by titration of an aqueous ethanolic solution of each oligomer with a standardized solution of sodium hydroxide.

Figure 1.—Uvicord recording of a chromatographic fractionation of the product obtained from a reaction of 2-nitro-3-benzyloxy-4-methylbenzoyl chloride with *O*-(benzyloxycarbonylsarcosyl-L-*N*-methylvalyl)-L-threonyl-D-valyl-L-proline, Sephadex LH-20 column (190 × 5 cm) using ethanol at 5° as eluent and collecting 15-ml fractions.

IIIA and trace amounts of dimer IIIB. Formation of the dimer in this instance could occur through ester interchange involving transfer of the *N*-hydroxysuccinimide ester from the 2-nitro-3-benzyloxy-4-methylbenzoyl moiety to the peptide moiety[13] or through a mixed anhydride intermediate.[14] The low overall yield of monomer, however, rendered this method unsuitable.

Reaction of the symmetrical anhydride,[15,16] generated *in situ* by the action of dicyclohexylcarbodiimide on 2-nitro-3-benzyloxy-4-methylbenzoic acid, with the pentadepsipeptide II produced a high yield of monomer IIIA. A small amount of dimer was observed and trace amounts of trimer. In this reaction 1 equiv of base was initially used to neutralize the pentadepsipeptide hydrochloride and another 1.2 equiv was added over a period of 2 hr, thus optimizing conditions for obtaining the monomer and minimizing the chance of oligomer formation.

This method of controlled addition of base, utilized in the symmetrical anhydride reaction, was tried in a reexaminition of the acid chloride method. The experiment resulted in monomer formation only; however, the yield was quite low. Similarly, the azide[17] method of activation gave monomer only but in low yield.

In these series of experiments conditions were found under which oligomerization was suppressed, chiefly through controlled addition of base. Furthermore, weak activation minimized oligomer formation. However, under such conditions of comparatively slow reaction, the desired monomer was obtained in low yields, probably due to degradation of the pentadepsipeptide. It was concluded that the best method of activation of 2-nitro-3-benzyloxy-4-methyl benzoic acid, in the reaction under investigation, was the generating of its symmetrical anhydride. Although some dimer and trace amounts of trimer were formed, the best overall yields of monomer IIIA (70–80%) were obtained.

Experimental Section

Details on materials and methods have been described before.[5] *O*-(**Benzyloxycarbonylsarcosyl-L-*N*-methylvalyl)-L-threonyl-D-**

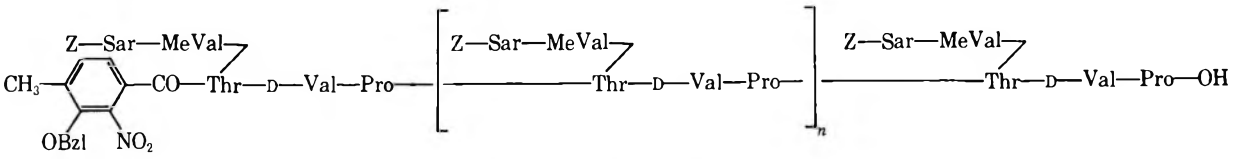
(13) Similar observations were made by C. N. C. Drey and J. Lowbridge in the synthesis of β-alanine peptides using the trichlorophenyl activated ester: communication of the Chemical Society, Protein Group, Liverpool, 1969.

(14) M. Bodanszky, *Peptides, Proc. Eur. Symp., 9th*, 150 (1968).

(15) I. Muramatsu and A. Hagitani, *J. Chem. Soc. Jap.*, **80**, 1497 (1959).

(16) F. Weygand, P. Huber, and K. Weiss, *Z. Naturforsch., B*, **22**, 1084 (1967).

(17) T. Curtius, *Ber.*, **35**, 3226 (1902).



IIIB, $n = 0$; IIIC, $n = 1$; IIID, $n = 2$; IIIE, $n = 3$

Figure 2.—The structure of oligomers formed during N-acylation of *O*-(benzyloxycarbonylsarcosyl-L-*N*-methylvalyl)-L-threonyl-D-valyl-L-proline.

valyl-L-proline II. **A. Trifluoroborate.**—This was prepared in a similar manner to that described previously.[5]

B. Hydrochloride.[18]—The trifluoroborate salt of II was dissolved in dioxane and treated with a slight excess of 2.5 *N* HCl in ether. An oil was formed which on trituration with anhydrous ether solidified to a fine white solid (80–90% yields), mp 158–163°, $[\alpha]^{20}D$ −43° (*c* 1, methanol).

Acylation of *O*-(Benzyloxycarbonylsarcosyl-L-*N*-methylvalyl)-L-threonyl-D-valyl-L-proline with 2-Nitro-3-benzyloxy-4-methylbenzoic Acid.—All procedures described were carried out in reduced light. The general work-up procedure was the same in every reaction. After completion, the reaction mixture was poured into water and the oily suspension which formed was extracted into ethyl acetate. The ethyl acetate solution was washed with dilute acid two times, followed by saturated NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The oil obtained was dissolved in 95% ethanol and chromatographed at 5° on a 190 × 5 cm column of Sephadex LH-20 using ethanol as the eluent. Fractions obtained were concentrated under reduced pressure and precipitated from ethyl acetate by the addition of hexane. The results are summarized in Table I.

Methods of Activation. A. Acid Chloride.[5]—The trifluoroborate salt of II (6.00 g, 9.45 mmol) was dissolved in 25 ml of dioxane and cooled to 0°. *N*-Methylmorpholine (3.16 ml, 28.26 mmol) was added, followed by Ia[4] (2.88 g, 9.42 mmol). The reaction mixture was allowed to warm to room temperature and after stirring for 1 hr was worked up as described above.

B. Mixed Carbonic Carboxylic Anhydride.—To a stirred solution of IB (102.1 mg, 0.36 mmol) in dioxane (2 ml) at room temperature was added *N*-methylmorpholine (0.04 ml, 0.36 mmol) and isobutyl chloroformate (0.047 ml, 0.36 mmol). After 1 min a solution of the trifluoroborate salt of II (250 mg, 0.36 mmol) and *N*-methylmorpholine (0.12 ml, 1.07 mmol) in dioxane (2 ml) was added. After stirring for 1 hr, the reaction mixture was worked up as described.

C. *N,N'*-Carbonyldiimidazole.—IB (86 mg, 0.30 mmol) was dissolved in dioxane (5 ml). *N,N'*-Carbonyldiimidazole (47 mg, 0.30 mmol) was added and the mixture was stirred for 10 min at room temperature. The hydrochloride of II (200 mg, 0.30 mmol) was dissolved in 5 ml of dioxane and *N*-methylmorpholine (0.1 ml, 0.90 mmol) was added. The two solutions were mixed and stirred at room temperature for 16 hr and then worked up as described.

D. *N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline.—The hydrochloride of II (1 g, 1.49 mmol) was dissolved in dimethylformamide (5 ml) cooled to 0° and *N*-methylmorpholine (0.33 ml, 2.98 mmol) was added. IB (0.43 g, 1.49 mmol) and *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline were dissolved in dimethylformamide at 0° and stirred for approximately 30 sec before the addition of the peptide solution. The mixture was stirred for 19 hr at room temperature and worked up as described after the addition of two drops of concentrated HCl.

E. *N*-Hydroxysuccinimide Ester.—IC[19] (157 mg, 0.41 mmol) was added to a dimethylformamide (5 ml) solution of the hydrochloride of II (0.25 g, 0.37 mmol) preneutralized with triethylamine (0.064 ml, 0.45 mmol). The mixture was stirred for 24 hr and worked up as previously described. Unreacted IC was filtered off before column chromatography.

F. Symmetrical Anhydride.—IB (0.944 g, 3.27 mmol) was dissolved in ethyl acetate (15 ml) and dicyclohexylcarbodiimide (0.323 g, 1.56 mmol) in ethyl acetate (7 ml) was added. The mixture was warmed slightly and allowed to stir at room temperature for approximately 5 min, before the addition of the hydrochloride of II (1 g, 1.49 mmol) dissolved in dimethylformamide (5 ml), and neutralized with *N*-methylmorpholine (0.166 ml, 1.49 mmol). After intervals of 1 and 2 hr, 0.083 ml and 0.12 ml of *N*-methylmorpholine were added respectively. After 3.5 hr, *N,N'*-dicyclohexylurea was filtered off and the mixture was worked up as described.

G. Acid Chloride with Controlled Addition of Base.—The hydrochloride of II (1 g, 1.49 mmol) was dissolved in dimethylformamide (10 ml) and *N*-methylmorpholine (0.167 ml, 1.49 mmol) was added, followed by IA (0.455 g, 1.49 mmol). Over the next 30 min at intervals of 5, 10, 20, and 30 min, *N*-methylmorpholine (0.04 ml each) was added. After 3 hr of stirring at room temperature, the mixture was worked up as described previously.

H. Azide. 2-Nitro-3-benzyloxy-4-methylbenzoylhydrazide.—IC (1.36 g, 3.5 mmol) was dissolved in dimethylformamide (5 ml) and hydrazine hydrate (3.5 ml, 70 mmol) was added. A dark yellow solution resulted which after standing 18 hr at room temperature turned to a solid green mass. The mixture was diluted with water (50 ml) and filtered, and the filtrate was washed with water and then dried to give 0.9 g of hydrazide. Crystallization from ethyl acetate–hexane gave colorless crystals, mp 162–163°.

Anal. Calcd for $C_{15}H_{15}N_3O_4$ (301.31): C, 59.80; H, 5.02; N, 13.95. Found: C, 60.27; H, 5.03; N, 13.92.

2-Nitro-3-benzyloxy-4-methylbenzoyl Azide.—The hydrazide (0.5 g, 1.66 mmol) was dissolved in acetic acid (1 ml) and water (4 ml), cooled to 0°, and sodium nitrite (0.114 g) dissolved in water (2 ml) was added. The mixture was stirred for 20 min at 0° and allowed to warm to room temperature. The solid formed was extracted into ethyl acetate and washed with 1 *M* $NaHCO_3$ and water and dried ($MgSO_4$). Evaporation under reduced pressure gave an oil. Unchanged hydrazide (90 mg) was removed by filtration after treatment with ethyl acetate–hexane. On evaporation of the mother liquor pure solid azide was obtained: 200 mg (38.5%); mp 72–73°; ir (KCl) 2075 cm^{-1} (strong singlet).

Anal. Calcd for $C_{15}H_{12}N_4O_4$ (312.28): C, 57.68; H, 3.87; N, 17.94. Found: C, 57.52; H, 3.98; N, 17.03.

Coupling Reaction.—2-Nitro-3-benzyloxy-4-methylbenzoyl azide (124 mg, 0.39 mmol) was dissolved in dimethylformamide and cooled to 0°. The hydrochloride of II (250 mg, 0.37 mmol) was dissolved in dimethylformamide, cooled to 0°, and *N*-methylmorpholine (0.041 ml, 0.37 mmol) was added. After 30 sec the two solutions were mixed and stirred for 24 hr at room temperature and worked up as described.

Synthesis of Authentic Dimer IIIB.—To a stirred solution of monomer IIIA (200 mg, 0.22 mmol) in tetrahydrofuran at −10° was added *N*-methylmorpholine (0.025 ml, 0.22 mmol) followed by isobutyl chloroformate (0.029 ml, 0.22 mmol). After 2 min a solution of the trifluoroborate salt of II (156 mg) and *N*-methylmorpholine (0.075 ml, 0.66 mmol) in dioxane (2 ml) was added and the mixture was stirred for 30 min at −10° and 17 hr at room temperature. It was worked up as described above to yield dimer 65%, trimer 12%, and trace amounts of tetramer and pentamer.

Registry No.—IB, 6623-31-0; II, 31729-72-3; II HCl, 21148-62-9; IIIA, 21148-63-0; IIIB, 31729-75-6; IIIC, 31729-76-7; IIID, 31729-77-8; IIIE, 31729-78-9; 2-nitro-3-benzyloxy-4-methylbenzoylhydrazide, 31729-79-0; 2-nitro-3-benzyloxy-4-methylbenzoyl azide, 31729-80-3.

Acknowledgments.—We wish to thank Dr. S. Sengupta for a generous supply of 2-nitro-3-benzyloxy-4-methylbenzoic acid and Mrs. E. Judkins for technical assistance.

(18) J. Meienhofer, *Experientia*, **24**, 776 (1968).

(19) J. Meienhofer, *J. Org. Chem.*, **32**, 1143 (1967).

The Effect of Triethylamine on the Deoxydative Substitution of Pyridine *N*-Oxides by Mercaptans[1]

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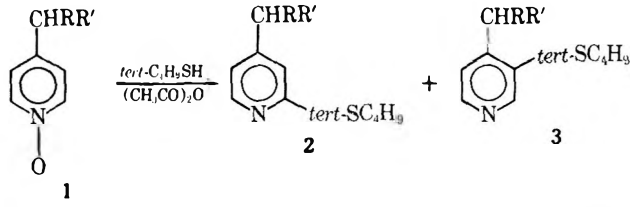
The reaction of a number of pyridine 1-oxides with mercaptans in acid anhydrides was studied in the presence of 2 equiv of triethylamine. 2- and 3-pyridyl sulfides were isolated, with a notable increase of the 2 isomer from those cognate reactions in which triethylamine had been omitted. The reaction of 4-picoline and 4-ethyl-, 4-*n*-propyl-, and 4-isopropylpyridine 1-oxides with *tert*-butyl mercaptan in acetic anhydride containing triethylamine furnished a new series of 1-acetyl-2-acetoxy-3-*tert*-butylthio-4-alkylidene-1,2,3,4-tetrahydropyridines. When triethylamine was absent, similar reactions of 4-*n*- and 4-isopropylpyridine 1-oxides produced the expected 1-acetyl-2-acetoxy-3,6-di(*tert*-butylthio)-4-alkyl-1,2,3,6-tetrahydropyridines. Pyridine and 3-picoline 1-oxide reacted with *tert*- and *n*-butyl mercaptan in acetic anhydride and triethylamine to give rise to another series of 1-acetyl-2-alkylthio-3,4-diacetoxy-1,2,3,4-tetrahydropyridines. The structure of the piperideines was established by spectral analysis.

It was discovered that triethylamine influenced the reaction of pyridine *N*-oxides with mercaptans in acetic anhydride. Basically, two distinct changes were observed when the reaction was conducted in the presence of 2 equiv of triethylamine. The percentage of α over β substitution rose sharply compared to that observed when triethylamine was omitted,[4] and a number of new tetrahydropyridines were isolated which were not encountered previously.[5,6]

The reaction of a number of 4-substituted pyridine 1-oxides **1** with *tert*-butyl mercaptan in acetic anhydride produced the expected sulfides **2** and **3** whose yields and isomer distributions are listed in Table I.



The change in the ratio of **2** and **3** due to the inclusion of triethylamine is interpreted in terms of the mechanisms proposed for α and β substitution.[5] Triethylamine can facilitate removal of the α proton from the intermediate 1-acetoxy-2-*tert*-butylthio-1,2-dihydropyridine[4] and thus expedite the process which would lead to an increased proportion of **2**.

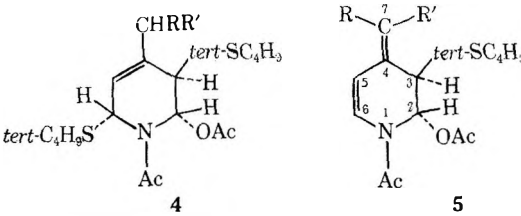
The reaction of a number of pyridine 1-oxides with *tert*-butyl mercaptan in acetic anhydride had yielded previously a series of 1-acetyl-2-acetoxy-3,6-di(*tert*-butylthio)-1,2,3,6-tetrahydropyridines **4** (Ac = CH_3CO).[5,6] In this reported work, the reactions of 4-picoline and 4-ethyl-, 4-*n*-propyl-, and 4-isopropylpyridine 1-oxides with *tert*-butyl mercaptan in acetic anhydride containing triethylamine produced a series of 1-acetyl-2-acetoxy-3-*tert*-butylthio-4-alkylidene-1,2,3,4-tetrahydropyridines **5**. Spectral data established for the previous piperideines **4**[5,6] were utilized in the determination of the structure of type **5**.

TABLE I

SUBSTITUTION PATTERN OF SULFIDES OBTAINED FROM THE REACTION OF PYRIDINE 1-OXIDES WITH *tert*-BUTYL MERCAPTAN IN ACETIC ANHYDRIDE, WITH AND WITHOUT TRIETHYLAMINE

Substituent on *N*-oxide	Method[a]	Yield, %	Isomer distribution—2-Substitution	Isomer distribution—3-Substitution
	A	62[b]	70	30
	B	41	90	10
3-CH_3	A	66[b]	64[c]	36[c]
	B	20	95[d]	5[e]
4-CH_3	A	41[b]	71	29
	B	33	82	18
4-C_2H_5	A	49	67	33
	B	32	87	13
4-*n*-C_3H_7	A	54	63	37
	B	45	70	30
4-*i*-C_3H_7	A	61	62	38
	B	39	80	20
4-*tert*-C_4H_9	A	48[b]	83	17
	B	48	96	4

[a] Experiments designated by method A are those performed without triethylamine and those by method B contained 2 equiv of triethylamine. [b] Reported initially in ref 4. [c] Distributed over positions 2 and 6 in the ratio of 45:19 (ref 4). [d] Ratio of 2 and 6 substitution was determined to be 61:34 (gc). [e] Represents 5-*tert*-butylthio-3-picoline.



a, R = R′ = H; **b**, R = R′ = CH_3; **c**, R = CH_3, R′ = H; **c′**, R = H, R′ = CH_3; **d**, R = CH_3, R′ = D; **d′**, R = D, R′ = CH_3; **e**, R = C_2H_5, R′ = H; **e′**, R = H, R′ = C_2H_5

Corresponding members of the series **4** and **5** differed by $C_4H_{10}S$, which is equivalent to *tert*-butyl mercaptan. Unlike the pmr spectra of **4**[6] which were complicated due to restricted rotation about the N–Ac bond at 35°, those of **5** were more readily analyzed (see Experimental

(1) Part X. The Chemistry of Pyridine. Presented in part at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969 and at the Third Great Lakes Regional Meeting, Northern Illinois University, DeKalb, Ill., June 1969.

(2) Taken in part from the Ph.D. dissertation of B. A. M., University of Illinois (Medical Center), June 1971.

(3) National Science Foundation Trainee.

(4) F. M. Hershenson and L. Bauer, *J. Org. Chem.*, **34**, 655 (1969).

(5) F. M. Hershenson and L. Bauer, *ibid.*, **34**, 660 (1969).

(6) R. S. Egan, F. M. Hershenson, and L. Bauer, *ibid.*, **34**, 665 (1969).

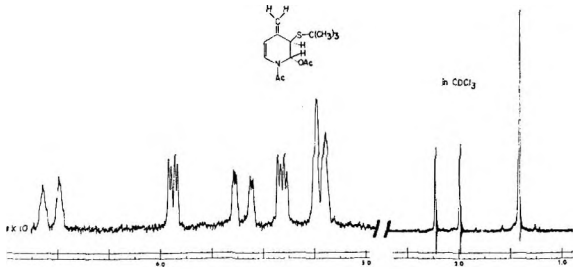


Figure 1.—100-MHz spectrum of **5a** in $CDCl_3$.

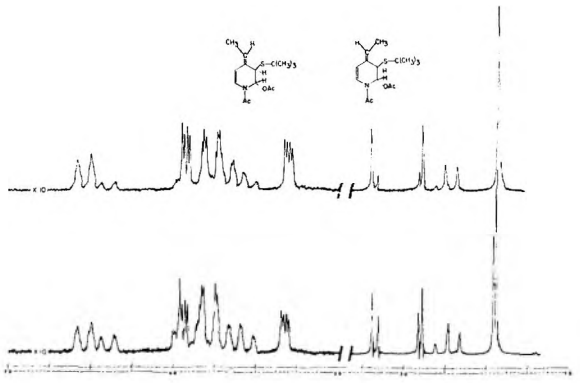


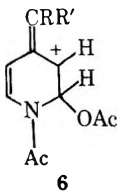
Figure 2.—100-MHz spectrum of **5c**, **5c′** in C_5D_5N; the top spectrum is enriched in **5c**.

Section). Singlets expected from $NCOCH_3$, $OCOCH_3$, and *tert*-SC_4H_9 protons were found in the upfield region. Characteristic signals due to the 4-alkyl groups were absent, but appropriate resonances downfield suggested the presence of additional alkene protons in **5**. These facts are accommodated by the presence of an 4-alkylidene group which locks the double bond of the piperideines **5**, into the α,β position. In accordance with this partial picture, the α-enamido proton (H-6) comes into resonance furthest downfield and its large coupling constant ($J_{5,6}$ = 8 Hz) clearly demonstrated that C-5 was unsubstituted. The absence of characteristic CH_2 resonances dictated that C-2 and C-3 bore one substituent each.

Pyrolysis of each member in the series **5** furnished the corresponding 3-*tert*-butylthio-4-alkylpyridine. This proved that the sulfide is attached to C-3 and the formula of **5** is completed by attaching the acetoxy group to C-2.

An analysis of the 100-MHz spectra of **5** provided the coupling constant, $J_{2,3}$ (3.0 ± 0.1 Hz). The magnitude of this coupling constant is remarkably close to that reported previously for members of series **4** ($J_{2,3}$ = 2.0–2.4 Hz) and this would place the H-2 and H-3 trans diequatorial and the sulfide and ester in both **4** and **5** are then trans diaxial.

Additional structure proof was provided by the mass spectra of **5**. The molecular ion was visible in each spectrum and the ensuing major fragmentation was common to each member of **5**. This pattern involved the loss of *tert*-$C_4H_9S\cdot$ to produce an (M − 89) ion **6**



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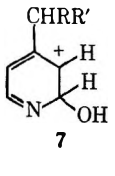

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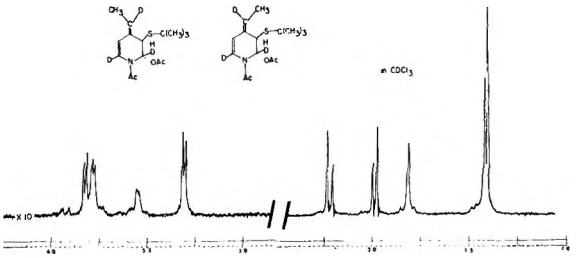


Figure 3.—100-MHz spectrum of **5d**, **5d′** in $CDCl_3$.

which eliminated ketene, twice, to produce **7** (shown as the 2,3-dihydropyridine tautomer) which represents a logical precursor for the molecular ion of the corresponding 4-alkylpyridine after the loss of HO·.

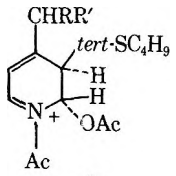
Although the spectra of **5a** and **5b** represented single compounds (Figure 1), the product from 4-ethylpyridine 1-oxide was clearly a mixture (Figure 2) which was obtained in varying composition from chromatography and crystallization. The results are readily explained in terms of the geometric isomers **5c**, **5c′**. Pmr parameters for the major and minor isomers were identified in the 100-MHz spectrum of the 2,6,7-d_3 analogs **5d**, **5d′** (Figure 3) which were synthesized from 4-ethylpyridine-2,6,7,7-d_4 1-oxide. By using nuclear Overhauser effects[7] (NOE; see Experimental Section), it was found that the major isomer was **5d**, subsequently related to the proton analog **5c**, and it is the one in which the methyl is trans to the bulky *tert*-butylthio group. This assignment gave rise to another interesting observation. In this fixed 4-alkylidene-Δ^2-piperideine system, compared to H-7, the CH_3 group at C-7 deshielded the ring protons closest to it, *viz.*, H-3 and H-5. Thus, in **5c** and **5d**, H-5 is 0.24-ppm downfield when contrasted to the chemical shifts of H-5 in **5c′** and **5d′**; similarly, H-3 is 0.52-ppm downfield in **5c′** and **5d′** compared to **5c** and **5d**. These findings corroborate the report by Cárdenas that in a fixed system, alkyl groups exert considerable magnetic anisotropic effects on nearby hydrogen atoms.[8]

A similar stereochemical problem was anticipated from the products of the cognate reaction of 4-*n*-propylpyridine 1-oxide. However, the crystalline solid which was isolated appeared to be uniform and was assigned structure **5e**, from a close comparison of the chemical shift data of **5c** and **5d** in identical solvents. This conclusion was based primarily on the excellent correspondence of the chemical shifts of H-3 and H-5 in **5e** with those in **5c** and **5d**, in $CDCl_3$ and C_5D_5N. These structure assignments of **5c**, **5d**, and **5e** logically follow the expectation that, in the thermodynamically more stable isomer, the alkyl group on C-7 is situated on the side opposite to the bulky *tert*-butyl sulfide group on C-3.

The mechanism for the formation of **5** is in line with that advanced for the previously reported products.[5] The change in forming **5** rather than **4** is attributed to triethylamine in solution. It is proposed that **1** is converted to **8**, *via* an episulfonium intermediate,[5] in which the acidic H-7 is neutralized by triethylamine to form **9**, which is the dipolar form of **5**. In the absence of triethylamine, *tert*-butyl mercaptan attacks C-6 of **8** to afford **4**. As a matter of fact, reaction of 4-*n*-propyl-

(7) For a summary of NOE, see P. D. Kennewell, *J. Chem. Educ.*, **47**, 278 (1970).

(8) C. G. Cárdenas, *Tetrahedron Lett.*, 4013 (1969); *J. Org. Chem.*, **36**, 1631 (1971).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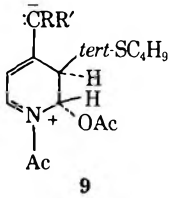
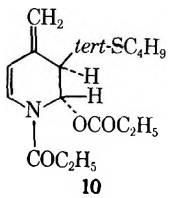

9

and 4-isopropylpyridine 1-oxides with *tert*-butyl mercaptan in acetic anhydride, without triethylamine, yielded the sulfides (Table I) and the tetrahydropyridines **4e** and **4b**, respectively. Their structures were established in the manner reported previously.[4-6] The reaction of 4-picoline 1-oxide with *tert*-butyl mercaptan in propionic anhydride and triethylamine produced both types of tetrahydropyridines **10** and **11** which were identified by means of their spectra.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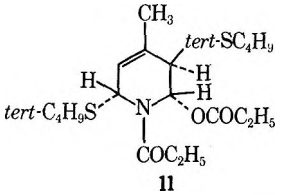
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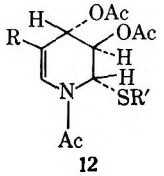
The presence of triethylamine during the reaction of pyridine 1-oxide with *tert*-butyl mercaptan in acetic anhydride produced yet another series of tetrahydropyridines, represented by the general structure **12**.


12

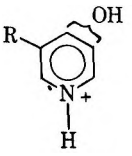
a, R = H, R′ = *tert*-C_4H_9; **b**, R = H, R′ = *n*-C_4H_9; **c**, R = CH_3, R′ = *tert*-C_4H_9; **d**, R = CH_3, R′ = *n*-C_4H_9

Although triethylamine was essential to produce **12a** from pyridine 1-oxide, the homolog **12c** was isolated from 3-picoline 1-oxide, with or without added base. The reaction was extended to *n*-butyl mercaptan with pyridine and 3-picoline 1-oxides to give (in the presence of triethylamine) **12b** and **12d**, respectively. Structure elucidation was aided by the availability of the 2,6-d_2 analogs of **12a** and **12c**.

The molecular ions for **12** and their ir and pmr spectra confirmed that each of these piperideines possessed two acetoxy groups and one acetamido and one butyl sulfide group. Their uv maxima narrowed the number of isomers to the 1,2,3,4-tetrahydropyridine system (*i.e.*, the double bond $\alpha\beta$ to the ring nitrogen) and the characteristic α-enamido proton resonance downfield (H-6) reinforced this assumption. Furthermore, the large coupling constant, $J_{5,6}$ for **12a**, **12b**, confined substitution to C-2, C-3, and C-4. At first impulse, and without decisive pmr data for this series and with analogy to structure **4**, one might place the sulfide group at C-3. Subsequent experiments proved that the sulfide group is attached to C-2 in this series.

Pyrolysis of **12a** at 200° for 0.5–1 hr produced 2- and 3-*tert*-butylthiopyridines (83:17), acetic anhydride, and acetic acid, identified by gc. Similarly, **12c** was decomposed thermally to a mixture of 2- and 3-*tert*-butylthio-5-picoline (3:1). Since all criteria pointed to the homogeneity of **12**, the sulfide group is attached at C-2 and it is assumed that in this system some of the sulfide migrated to C-3 under the condition of the pyrolysis. This behavior of **12** differs from **4** and **5**, which pyrolyzed to give the 3-sulfide only. The mass spectral fragmentation of **12** also departed from the pattern consistently shown by **4**.[5]

From the molecular ion of **4**, characteristic losses followed this order: a butylthio radical from C-6, followed by acetic acid, and then ketene and isobutylene. At 70 eV, the major fragmentation of **12** consisted of consecutive losses of an alkylthio radical, acetic acid, and then ketene, twice, leading to the aromatic ion **13**. However, at 10 eV, this path competed with one in which the first loss is acetic acid, followed by acetoxy radical leading to the 1-acetyl-2-alkylthiopyridinium cation **14**. When the 2,6-d_2 analogs of **12a** and **12c** were prepared from the corresponding 2,6-d_2 1-oxides, their fragmentation at 70 eV to **13** retained two deuterium atoms, while the alternate path at 10 eV involved the loss of CH_3CO_2D leading to **14**, which contained one deuterium atom (on C-6). The fragmentations upon electron impact of the *n*-butyl analogs **12b** and **12d** were quite analogous.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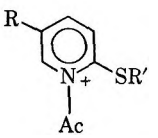

14

The 100-MHz spectra of **12** revealed $J_{2,3}$ to be around 3.0 Hz which agrees with the trans-diequatorial arrangement of H-2,H-3 and the sulfide and acetoxy groups at C-2 and C-3 would again be trans-diaxial. The small coupling constant $J_{3,4}$ in the order of 1.5 Hz indicated a trans-diequatorial arrangement of H-3,H-4 and the stereochemistry of the esters at C-3 and C-4 is trans diaxial. The molecules of type **12** appeared to be conformationally stable at 35° since the pmr spectra indicated no other species in solution.

The mechanism advanced for the formation of **4** and **5** can explain that of **12** also. Attack of acetate ion at C-3 can occur either by direct neutralization of the positive charge as the acetate departs from nitrogen of the 1-acetoxy-2-alkylthio-1,2-dihydropyridine intermediate[4,5] to yield the 2-alkylthio-3-acetoxy-2,3-dihydropyridine, *or*, by ring opening of the episulfonium ion.[5] The role of triethylamine so vital in forming **12a** is not clearly understood since **12c** is produced in its absence. Quaternization of this 2,3-dihydropyridine as suggested for the formation of **4** and **5** would produce 1-acetyl-2-alkylthio-3-acetoxy-2,3-dihydropyridinium acetate which, in the particular milieu, could be attacked preferentially at the electrophilic C-4 site by acetate, instead of mercaptan, to produce **12**.

Experimental Section[9]

Starting Materials.—We gratefully acknowledge generous gifts of *n*- and *tert*-butyl mercaptans (from Penn-Salt Chemical

(9) Boiling and melting points (Thomas-Hoover apparatus) are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill., and those for nitrogen, in this Department, using a Coleman, Model D29 analyzer. Uv spectra were recorded on a Beckman DK-1, ir spectra on a Perkin-Elmer 337 spectrophotometer. Pmr spectra were obtained on either a Varian A-60 or a HA-100 spectrometer. Mass spectra were obtained by Mr. Richard Dvorak using a Hitachi Perkin-Elmer RMU-6D mass spectrometer.

Co. and Phillips Petroleum Co.) and 4-ethylpyridine, 4-*n*- and 4-isopropylpyridine, pyridine, and 4-picoline 1-oxides (from Reilly Tar and Chemical Co.). *N*-Oxides were synthesized by literature methods.[4] 4-Ethylpyridine 1-oxide: bp 160–163° (0.02 mm); mp 108–109° [lit.[10] bp 201–203° (2 mm), mp 108–110°]; pmr ($CDCl_3$) δ 8.18 (H-2, H-6), 7.18 (H-3, H-5), 2.69 (CH_2), 1.22 (CH_3). 4-*n*-Propylpyridine 1-oxide: mp 53–55° [lit.[11] bp 124–125° (1 mm)]; pmr ($CDCl_3$) δ 8.28 (H-2, H-6), 7.27 (H-3, H-5), 2.62 ($CH_2C_2H_5$), 1.63 ($CH_2CH_2CH_3$), 0.90 (CH_3). 4-Isopropylpyridine 1-oxide: mp 77–79° (lit.[12] mp 78–79°); pmr ($CDCl_3$) δ 8.12 (H-2, H-6) 7.12 (H-3, H-5), 2.85 (CH), 1.15 (CH_3).

3-Picoline-2,6-d_2 1-oxide was prepared by heating the *N*-oxide (15 g) with D_2O (25 ml) at 160° for 30 hr in a Monel bomb. Solvents were removed and the residue was reheated with D_2O (30 ml) under similar conditions. This procedure could not be applied to synthesize 4-ethylpyridine-2,6,7,7-d_4 1-oxide. Extensive charring occurred. The exchange was conducted according to an adaptation of the published procedure.[13] The *N*-oxide (15 g) was boiled with 1% NaOD (50 ml) and the exchange followed by pmr. After 3 hr, one-half of the solvent was removed and fresh D_2O was added and boiling continued for 1 hr longer. The solution was neutralized by 38% DCl to pH 6, solvents were removed *in vacuo*, and the residue was distilled [bp 130–133° (0.01 mm)].

General Considerations for the Reactions of Mercaptans with *N*-Oxides.—The reactions were carried out along the lines described previously.[4,5] One example is described in detail and only pertinent details are reported on the others.

Extreme care was exercised in handling *tert*-butyl mercaptan.[4] Exits from reaction flasks and distillations were connected to a long tower filled with 1/8-in. pellets of Purafil Odoroxidant (Marbon Chemical Co., Division of Borg-Warner Corp.).

Reactions of *N*-Oxides with *tert*-Butyl Mercaptan in Acetic Anhydride, with Triethylamine. A. 4-Ethylpyridine 1-Oxide.—4-Ethylpyridine 1-oxide (12.3 g, 0.1 mol) was dissolved with stirring in acetic anhydride (100 ml) containing *tert*-butyl mercaptan (32 ml, 0.3 mol) at ambient temperature. Triethylamine (28 ml, 0.2 mol) was slowly added (5 min) and the resultant solution heated at 95° (steam bath) for 2 hr. The solution was cooled somewhat and a low-boiling fraction distilled at 20 mm from a steam bath. This distillate consisted of aliphatic materials (pmr) and was not examined further. Further fractionation yielded a yellow liquid, 44.2 g, bp 42–94° (0.02 mm). The bath temperature during this distillation should be kept at a minimum and not to exceed 150°. No attempt was made to separate triethylamine and acetic acid by distillation at this stage since these did not interfere in the subsequent isolation of the products.[5] The following compounds were collected by means of gc (injection temperature 100°).[14]

4-(1-Acetoxyethyl)pyridine (5.6%, rt 38.4 min): pmr ($CDCl_3$) δ 8.45 (H-2, H-6), 7.10 (H-3, H-5), 5.87 (CHOAc), 2.10 ($OCOCH_3$), 1.51 ($CHCH_3$). *Anal.* Calcd for $C_9H_{11}NO_2$: N, 8.48. Found: N, 7.95.

3-Acetoxy-4-ethylpyridine (3.1%, rt 40.7 min): pmr ($CDCl_3$) δ 8.42 (H-6), 8.33 (H-2), 7.24 (H-5), 2.58 (CH_2CH_3), 2.32 ($OCOCH_3$), 1.20 (CH_2CH_3). *Anal.* Calcd for $C_9H_{11}NO_2$: N, 8.48. Found: N, 8.78.

2-*tert*-Butylthio-4-ethylpyridine (31.6%, rt 56.4 min): pmr ($CDCl_3$) δ 8.42 (H-6), 7.19 (H-3), 6.90 (H-5), 2.57 (CH_2CH_3), 1.50 (*tert*-C_4H_9), 1.20 (CH_2CH_3). *Anal.* Calcd for $C_{11}H_{17}NS$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.38; H, 8.73; N, 7.14.

3-*tert*-Butylthio-4-ethylpyridine (4.7% rt 58.0 min): pmr ($CDCl_3$) δ 8.70 (H-2), 8.50 (H-6), 8.08 (H-5), 2.98 (CH_2CH_3), 1.30 (*tert*-C_4H_9), 1.21 (CH_2CH_3). *Anal.* Calcd for $C_{11}H_{17}NS$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.41; H, 8.58; N, 6.92.

Based on the starting *N*-oxide, the yield of the sulfides was 31.6%, and the yield of the acetates was 8.4%.

The dark brown residue (8.0 g) which remained after high-vacuum distillation was chromotagraphed on alumina (Alcoa, Grade F-20, 180 g). Elution with benzene (500 ml) afforded, after removal of the solvent, a yellow oil. Addition of 15 ml of petroleum ether (bp 30–60°) precipitated a colorless solid which was recrystallized from petroleum ether (bp 30–60°) to give **1-acetyl-2-acetoxy-3-*tert*-butylthio-4-ethylidene-1,2,3,4-tetrahydropyridine** (5c and 5c′) (0.9 g, 3.0%, mp 94–95°): ir 1750 (ester C=O), 1690 cm^{-1} (amide C=O); pmr for major isomer 5c ($CDCl_3$) δ 6.54 (H-6), 5.93 (H-2), 5.77 (H-5), 5.67 (H-7), 5.30 (H-3), 2.24 ($NCOCH_3$), 1.98 ($OCOCH_3$), 1.82 (7-CH_3), 1.41 (*tert*-C_4H_9) ($J_{2,3}$ = 3.0, $J_{2,6}$ = 1.2, $J_{3,5}$ = 1.5, $J_{3,7}$ = 0.5, $J_{5,6}$ = 8.2, $J_{7,6}$ = 1.2, J_{7,CH_3} = 7.2, J_{3,CH_3} = J_{5,CH_3} ~ O, J_{6,CH_3} ~ 0.5 Hz).

The pmr parameter for the minor isomer 5c′ in $CDCl_3$ could not be ascertained. In C_5D_5N, some of these data could be extracted from the spectrum in that solvent (Figure 2). The chemical shifts for H-6 in 5c and 5c′ are most discernible around δ 6.75 in Figure 2; the bottom spectrum was typical of the mixture of 5c, 5c′ usually isolated by the procedure outlined above. In an attempt to obtain additional quantities of 5c, 5c′, the filtrates from the solid were concentrated and the oily residue was subjected to molecular distillation. The solid which crystallized subsequently proved to be a mixture rich in 5c, as shown in the top half of Figure 2; the mass spectra (70 eV) of all mixtures were similar, *m/e* (rel intensity) 297 (6), 238 (3), 209 (6), 208 (47), 196 (4), 167 (11), 166 (100), 149 (10), 139 (25), 138 (20), 125 (6), 124 (64), 123 (5), 122 (5), 108 (3), 107 (29), 106 (42), 105 (4), 104 (4), 96 (4), 94 (6), 80 (4), 79 (8), 78 (4), 77 (5), 57 (17), 45 (4), 43 (37), 42 (3), 41 (14), 39 (6), 29 (7), 28 (10); at 8.5 eV, ion *m/e* 208 was the base peak and *m/e* 297, 237, 149, and 107 were most prominent. *Anal.* Calcd for $C_{15}H_{23}NO_3S$: C, 60.59; H, 7.80; N, 4.71. Found: C, 61.28; H, 7.82; N, 4.82.

Pyrolysis of 5c, 5c′ (0.5 g) at 200 ± 10° for 0.25 hr yielded, after distillation *in vacuo*, 3-*tert*-butylthio-4-ethylpyridine (75 mg), identified by its pmr spectrum.

B. 4-Ethylpyridine-2,6,7,7-d_4 1-Oxide.—From a reaction analogous to A, there was isolated 5d, 5d′ (0.4 g, 1.1%), mp 92–94°, in the ratio of 64:36 (Figure 3), and the following pmr parameters were established in $CDCl_3$: for 5d, δ 5.30 (H-3), 5.78 (H-5), 2.24 ($NCOCH_3$), 1.98 ($OCOCH_3$), 1.81 (7-CH_3), 1.40 (*tert*-C_4H_9); for 5d′, δ 5.82 (H-3), 5.54 (H-5), 2.20 ($NCOCH_3$), 2.00 ($OCOCH_3$), 1.81 (7-CH_3), 1.42 (*tert*-C_4H_9) $J_{3,5}$ = 1.5 Hz). The following NOE effects were observed. Irradiation of the CH_3 groups at C-7 (with identical chemical shifts) caused the integrated intensity of H-5 in 5d to be increased by 32.4%, that of H-3 in 5d′ by 20.0%, while that of H-5 in 5d′, H-3 in 5d remained unchanged. Irradiation of the *tert*-SC_4H_9 protons of 5d caused an increase in the integrated intensity of H-3 in 5d by 22.6% and in 5d′ by 11.3%, while H-5's were unaffected. Irradiation of the close-by *tert*-SC_4H_9 protons in 5d′ increased the integration of H-3 in 5d by 13.6%, H-3 in 5d′ by 14.8%, and again caused no effect on either H-5's. The mass spectrum (70 eV) of the mixture was *m/e* (rel intensity) 301 (2), 300 (5), 299 (2), 241 (4), 240 (3), 212 (14), 211 (44), 210 (16), 199 (6), 198 (3), 171 (4), 170 (25), 169 (100), 168 (34), 167 (5), 157 (4), 156 (13), 155 (7), 143 (5), 142 (18), 141 (22), 140 (10), 139 (3), 128 (16), 127 (71), 126 (30), 125 (10), 124 (4), 113 (5), 112 (3), 111 (13), 110 (56), 109 (75), 108 (33), 107 (10), 106 (5), 105 (4), 57 (34), 43 (98), 41 (49).

C. 4-Picoline 1-Oxide.—The reaction was performed as delineated under A. The volatile fraction contained 3-acetoxypyridine (14.7%), 4-picolyl acetate (19.6%), 2-*tert*-butylthiopyridine (52.6%), 3-*tert*-butylthiopyridine (11.3%), and 4-picolyl *tert*-butyl sulfide (1.6%) which were identified as described previously.[4] Chromatography of the nonvolatile fraction afforded, on elution with benzene, **1-acetyl-2-acetoxy-3-*tert*-butylthio-4-methylene-1,2,3,4-tetrahydropyridine** (5a) (3.1 g, 10.6%): mp 85–87°; uv max (95% ethanol) 275 mμ (log ϵ 4.29); ir 1751 (ester C=O), 1690 cm^{-1} (amide C=O); pmr at 100 MHz (C_5D_5N) δ 6.78 (H-6), 6.28 (H-2), 5.69 (H-5), 5.60 (H-3), 5.25 (H-7, H-7′), 2.19 ($NCOCH_3$), 1.90 ($OCOCH_3$) 1.41 (*tert*-

(10) M. Shimizu, T. Naito, G. Ohta, T. Yoshikawa, and R. Dohmori, *J. Pharm. Soc. Jap.*, **72**, 1474 (1952) [*Chem. Abstr.*, **47**, 8077 (1953)]; P. F. Holt and H. Lindsay, *J. Chem. Soc., B*, 54 (1969).

(11) S. Ghersetti, G. Maccagnani, A. Mangini, and F. Montanari, *J. Heterocycl. Chem.*, **6**, 859 (1969).

(12) W. M. Schubert, J. Robins, and J. M. Craven, *J. Org. Chem.*, **24**, 943 (1959).

(13) Y. Kawazoe, M. Ohnishi, and Y. Yoshioka, *Chem. Pharm. Bull.*, **15**, 1225 (1967).

(14) Preparative gas chromatography utilized the Varian Aerograph Autoprep, Model 700. All separations (0.005–0.2 ml) were carried out on a 3/8 in. × 20 ft coiled aluminum column containing 20% silicone gum rubber (SE-30) on Chromosorb W (40–60 mesh), unless stated otherwise. By selecting a power setting of "50" during these separations, the column was heated using a nonlinear temperature program. The samples were collected at room temperature. Retention times (rt) are quoted for a particular run and the composition of the mixture is expressed in mole per cent. The yield of sulfides in Table I are based on the starting *N*-oxide.

C_4H_9S); pmr ($CDCl_3$) δ 6.53 (H-6), 5.94 (H-2), 5.59 (H-5), 5.40 (H-3) ($J_{2,3}$ = 2.9, $J_{2,6}$ = 1.2, $J_{3,5}$ = 1.5, $J_{5,6}$ = 8.0, $J_{5,7}$ = $J_{5,7'}$, ~ 1.0, $J_{6,7'}$ ~ 1.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 283 (5), 195 (6), 194 (40), 182 (3), 153 (8), 152 (88), 142 (3), 135 (4), 126 (3), 125 (12), 124 (4), 111 (7), 110 (100), 109 (5), 93 (19), 92 (9), 80 (8), 65 (4), 57 (12), 43 (35), 41 (10), 39 (5); the primary fragmentation at 8.5 eV was *m/e* 283, 194 (base peak) 181, 135; at 10 eV, in addition to these ions, *m/e* 224, 152, 125, an 93 became prominent; the metastable ion at *m/e* 133.0 also appeared as a broad peak for the transition *m/e* 283 → 194 (m* 133.0). *Anal.* Calcd for $C_{14}H_{21}NO_3S$: C, 59.35; H, 7.47; N, 4.94; S, 11.29. Found: C, 59.22; H, 7.48; N, 4.88; S, 11.26.

D. 4-*n*-Propylpyridine 1-Oxide.—Reaction of the *N*-oxide on three times the (molar) scale as A yielded a fraction (37.3 g), bp 90–98° (0.01 mm), which was separated by gc[14] but this time using 5% DEGS on Chromosorb (injection temperature 80°).

3-Acetoxy-4-*n*-propylpyridine (3.1%, rt 43.3 min): pmr ($CDCl_3$) δ 8.35 (H-6), 8.28 (H-2), 7.18 (H-5), 2.50 ($CH_2CH_2CH_3$), 2.28 ($CCOCH_3$), 1.52 ($CH_2CH_2CH_3$), 0.93 ($CH_2CH_2CH_3$). *Anal.* Calcd for $C_{10}H_{13}NO_2$: N, 7.82. Found: N, 8.04.

4-(1-Acetoxypropyl)pyridine (3.0%, rt 45.6 min): pmr ($CDCl_3$) δ 8.60 (H-2, H-6), 7.26 (H-3, H-5), 5.67 ($CHOCOCH_3$), 2.10 ($OCOCH_3$), 1.81 (CH_2CH_3), 0.89 (CH_2CH_3). *Anal.* Calcd for $C_{10}H_{13}NO_2$: N, 7.82; Found: N, 8.04.

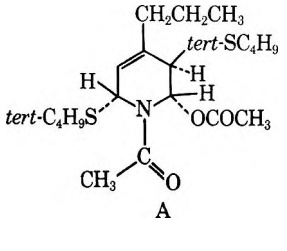
2-*tert*-Butylthio-4-*n*-propylpyridine (43.0%, rt 35.8 min): pmr ($CDCl_3$) δ 8.43 (H-6), 7.17 (H-3), 6.88 (H-5), 2.50 ($CH_2CH_2CH_3$), 1.60 ($CH_2CH_2CH_3$), 1.51 (*tert*-C_4H_9), 0.93 ($CH_2CH_2CH_3$). *Anal.* Calcd for $C_{12}H_{19}NS$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.64; H, 9.13; N, 6.64.

3-*tert*-Butylthio-4-*n*-propylpyridine (6.2%, rt 37.5 min): pmr ($CDCl_3$) δ 8.72 (H-2), 8.47 (H-6), 7.20 (H-5), 2.92 ($CH_2CH_2CH_3$), 1.62 ($CH_2CH_2CH_3$), 1.28 (*tert*-C_4H_9), 0.97 ($CH_2CH_2CH_3$). *Anal.* Calcd for $C_{12}H_{19}NS$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.96; H, 9.29; N, 6.77.

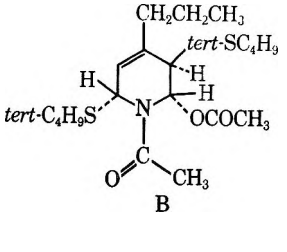
4-(1-*tert*-Butylthiopropyl)pyridine (1.2%, rt 40.8 min): pmr ($CDCl_3$) δ 8.55 (H-2, H-6), 7.32 (H-3, H-5), 3.68 (CHS), 1.84 (CH_3CH_2), 1.20 (*tert*-C_4H_9), 0.90 (CH_3). *Anal.* Calcd for $C_{12}H_{19}NS$: N, 6.69. Found: N, 6.82.

Chromatography of the nonvolatile fraction and elution with benzene afforded initially some 2-*tert*-butylthio-4-*n*-propylpyridine and their fractions enriched in **5e**. The pure solid was obtained by removing benzene and crystallizing the residue from petroleum ether (bp 30–60°) at −60°: mp 67–69° (2.2 g, 2.4%); pmr ($CDCl_3$) δ 6.53 (H-6), 5.96 (H-2), 5.79 (H-5), 5.34 (H-3), 5.64 (H-7), 2.24 ($NCOCH_3$), 2.00 ($OCOCH_3$), 1.42 (*tert*-C_4H_9), 2.24 (CH_2CH_3), 1.06 (CH_2CH_3); pmr (C_5D_5N) δ 6.84 (H-6), 6.41 (H-2), 5.92 (H-5), 5.63 (H-3), 5.71 (H-7), 2.23 ($NCOCH_3$), 1.92 ($OCOCH_3$), 1.47 (*tert*-C_4H_9), 2.10–2.25 (CH_2CH_3), 0.94 (CH_2CH_3) ($J_{2,3}$ = 3.0, $J_{2,6}$ = 1.2, $J_{3,5}$ = 1.6, $J_{5,6}$ = 8.0, $J_{5,7}$ = 1.1, $J_{6,7}$ = 1.2, J_{7,CH_2} = 7.4, J_{CH_2,CH_3} = 7.4 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 311 (2), 252 (2), 223 (6), 222 (4), 210 (3), 181 (11), 180 (100), 164 (2), 163 (12), 162 (6), 154 (3), 153 (9), 152 (8), 139 (7), 138 (68), 137 (3), 136 (6), 125 (9), 124 (2), 123 (5), 121 (22), 120 (25), 119 (5), 118 (7), 117 (2), 110 (6), 109 (2), 108 (4), 107 (4), 106 (55), 93 (8), 92 (10), 57 (19), 43 (62). *Anal.* Calcd for $C_{16}H_{25}NO_3S$: C, 61.72; H, 8.09; N, 4.50. Found: C, 61.94; H, 8.16; N, 4.38.

The mother liquor contained some **4e** but this compound was obtained more readily in a cognate reaction (0.1 mol of *N*-oxide) in which triethylamine was omitted. The nonvolatile material was chromatographed as above and elution with benzene yielded a fraction which, when crystallized from petroleum ether at −60° produced 1-acetyl-2-acetoxy-3,6-di(*tert*-butylthio)-4-*n*-propyl-1,2,3,6-tetrahydropyridine (**4e**) (0.3 g, 0.75%), mp 96–97°. The structure of **4e** was established in a fashion quite analogous to that described for the lower homologs.[5,6] Its pmr spectrum (30°) showed the two rotamers, A and B, in the ratio of 55:45:



A



B

for A, (C_5D_5N) δ 6.64 (H-2), 5.48 (H-3), 5.98 (H-5), 5.68 (H-6), 2.44 ($NCOCH_3$), 2.02 ($OCOCH_3$), 1.46, 1.42 (*tert*-C_4H_9), 0.88 ($CH_2CH_2CH_3$); for B, (C_5D_5N) δ 5.54 (H-2), 5.44 (H-3), 5.98 (H-5), 6.35 (H-6), 2.25 ($NCOCH_3$), 2.06 ($OCOCH_3$), 1.48, 1.42 (*tert*-C_4H_9), 0.88 ($CH_2CH_2CH_3$) ($J_{2,3}$ = 2.2, $J_{5,6}$ = 3.7, J_{6,CH_2} = 1.7, J_{5,CH_2} = 1.2, J_{CH_2,CH_3} = 7.2 Hz) (at 115–120°, signals due to H-2 and H-6 broadened into the base line); mass spectrum (70 eV) *m/e* (rel intensity) 401 (0.1), 312 (15), 252 (12), 223 (2), 222 (15), 212 (2), 211 (4), 210 (22), 209 (13), 196 (3), 181 (5), 180 (38), 163 (7), 155 (7), 154 (28), 153 (57), 152 (11), 139 (4), 138 (38), 132 (7), 126 (3), 125 (36), 124 (7), 57 (100), 56 (11), 41 (52); at 12.5 eV, ion *m/e* 312 (base peak), 252 (40), 222 (85), 209 (54), and 153 (70) are most prominent. *Anal.* Calcd for $C_{20}H_{35}NO_3S_2$: C, 59.83; H, 8.73; N, 3.49. Found: C, 59.94; H, 8.82; N, 3.35.

E. 4-Isopropylpyridine 1-Oxide.—The reaction using 0.3 mol of the *N*-oxide produced 38.6 g [bp 90–110° (0.01 mm)] which was separated on a 5% DEGS column.[14]

2-*tert*-Butylthio-4-isopropylpyridine (44.5%, rt 38.8 min): pmr ($CDCl_3$) δ 8.42 (H-6), 7.20 (H-3), 6.94 (H-5), 2.83 [$CH(CH_3)_2$], 1.50 (*tert*-C_4H_9), 1.22 ($CH(CH_3)_2$]. *Anal.* Calcd for $C_{12}H_{19}NS$: N, 6.69. Found: N, 6.45.

3-*tert*-Butylthio-4-isopropylpyridine (4.3%, rt 41.7 min): pmr ($CDCl_3$) δ 8.70 (H-2), 8.51 (H-6), 7.27 (H-5), 3.86 [$CH(CH_3)_2$], 1.28 (*tert*-C_4H_9), 1.21 [$CH(CH_3)_2$). *Anal.* Calcd for $C_{12}H_{19}NS$: N, 6.69. Found: N, 6.72.

Benzene eluted **5b** from alumina (0.95 g, 1%). It was recrystallized from petroleum ether (bp 30–60°) at −60°: mp 107–108.5°; pmr (C_5D_5N) δ 6.71 (H-6), 6.43 (H-2), 5.96 (H-5), 6.19 (H-3), 1.86, 1.78 (C-7 CH_3's), 2.20 ($NCOCH_3$), 1.96 ($OCOCH_3$), 1.50 (*tert*-C_4H_9) ($J_{2,3}$ = 3.1, $J_{2,6}$ = 1.4, $J_{3,5}$ = 1.6, $J_{5,6}$ = 8.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 311 (6), 252 (2), 223 (7), 222 (51), 181 (11), 180 (100), 164 (4), 163 (30), 162 (11), 153 (8), 152 (12), 138 (24), 137 (3), 136 (5), 125 (6), 124 (3), 122 (7), 121 (57), 120 (75), 119 (6), 118 (7), 110 (11), 108 (7), 107 (5) 106 (37), 92 (10), 79 (10), 32 (99), 41 (69). *Anal.* Calcd for $C_{16}H_{25}NO_3S$: C, 61.72; H, 8.09; N, 4.50. Found: C, 61.97; H, 8.05; N, 4.41.

There were indications that the mother liquor contained some **4b**, but a purer product (**4b**) was obtained when the above reaction was carried out omitting triethylamine. Using 0.1 mol of *N*-oxide and an identical work-up, the solid (0.5 g, 1.2%) from the column, crystallized from petroleum ether (bp 30–60°) at −60°, mp 89–90°. The pmr data in C_5D_5N at 30° is given for rotamers A and B (85:15), analogous to those described in section D: for A, δ 6.53 (H-2), 5.49 (H-3), 5.93 (H-5), 5.66 (H-6), 2.20 ($NCOCH_3$), 1.98 ($OCOCH_3$), 1.21 (*tert*-C_4H_9), 1.00, 1.03 [$(CH_3)_2CH$]; for B, δ 5.43 (H-2), 5.43 (H-3), 5.93 (H-5), 6.29 (H-6), 2.10 ($NCOCH_3$), 2.01 ($OCOCH_3$), 1.21, 1.23 (*tert*-C_4H_9), 1.00, 1.03 [$(CH_3)_2CH$] ($J_{2,3}$ = 2.4, $J_{5,6}$ = 3.7, $J_{6,CH}$ = 1.0, J_{CH,CH_3} = 7.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 401 (1), 342 (1), 314 (5), 313 (12), 312 (64), 254 (2), 253 (5), 252 (33), 223 (5), 222 (33), 212 (2), 211 (6), 210 (41), 209 (13), 196 (11), 181 (10), 180 (79), 164 (9), 163 (35), 156 (3), 155 (11), 154 (49), 153 (46), 152 (11), 139 (5), 138 (35), 137 (4), 136 (5), 132 (10), 125 (25), 123 (5), 122 (42), 121 (27), 120 (24), 112 (5), 107 (12), 106 (15), 99 (7), 90 (12), 57 (100), 56 (11), 55 (8), 45 (10), 43 (49), 42 (5), 41 (55), 39 (14), 32 (9), 29 (25), 28 (27); at 13 eV, ion *m/e* 312 (base peak), 252 (34), 222 (29), 209 (15), and 153 (26) are most prominent. *Anal.* Calcd for $C_{20}H_{35}NO_3S_2$: C. 59.83; H, 8.79; N, 3.49. Found: C, 60.14; H, 8.98; N, 3.52.

F. 4-Picoline 1-Oxide and Propionic Anhydride.—The reaction (0.3 mol, *N*-oxide) yielded 2- and 3-*tert*-butylthio-4-picoline (30%, ratio 91:9). Chromatography of the nonvolatile fraction produced a mixture of tetrahydropyridines which were separated as follows. Crystallization of the residues from the benzene eluates, from petroleum ether (bp 30–60°) afforded 1-propionyl-2-propionoxy-3,6-di-(*tert*-butylthio)-4-methyl-1,2,3,6-tetrahydropyridine (**11**) (1.8 g, mp 111–113°) shown to exist as two rotamers, A and B, *analogous* to those in section D: for A, (C_5D_5N) δ 6.65 (H-2), 5.43 (H-3), 5.97 (H-5), 5.66 (H-6), 2.74 ($NCOCH_2CH_3$), 1.23 ($NCOCH_2CH_3$), 2.32 ($OCOCH_2CH_3$), 1.08 ($OCOCH_2CH_3$), 1.45 (*tert*-C_4H_9S), 1.79 (4-CH_3); for B, δ 5.62 (H-2), 5.37 (H-3), 5.97 (H-5), 6.31 (H-6), 2.81 ($NCOCH_2CH_3$), 1.25 ($NCOCH_2CH_3$), 2.37 ($OCOCH_2CH_3$), 1.10 ($OCOCH_2CH_3$), 1.45 (*tert*-C_4H_9S), 1.81 (4-CH_3) ($J_{2,3}$ = 2.2, $J_{5,6}$ = 3.7, J_{6,CH_3} = 2.0, J_{6,CH_3} = 1.8, $J_{CH_2,CH_3(OCO)}$ = 7.6, $J_{CH_3,CH_2(NCO)}$ = 7.1 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 401 (1), 327 (1), 313 (2), 312 (7), 311 (33), 256 (4),

240 (1), 239 (4), 238 (24), 222 (8), 214 (1), 200 (2), 184 (5), 183 (13), 182 (100), 181 (3), 167 (4), 166 (41), 150 (6) 145 (4), 141 (4), 128 (3), 127 (9), 126 (72), 125 (25), 124 (3), 111 (4), 110 (56), 95 (6), 94 (78), 93 (20), 92 (9), 90 (5), 57 (90), 41 (52), 39 (2), 32 (12), 29 (75), 29 (4), 27 (21). *Anal.* Calcd for $C_{20}H_{35}NO_3S_2$: C, 59.83; H, 8.79; N, 3.49. Found: C, 59.95; H, 8.87; N, 3.29.

Distillation of the mother liquors of **11** yielded a viscous oil, bp 140–160° (0.01 mm), which crystallized on being triturated with petroleum ether (bp 30–60°) to produce 1-propionyl-2-propionoxy-3-*tert*-butylthio-4-methylene-1,2,3,4-tetrahydropyridine (**10**) (0.5 g): mp 64–65°; pmr ($CDCl_3$) δ 6.58 (H-6), 5.99 (H-2), 5.44 (H-3), 5.63 (H-5), 5.27, 5.22 (H-7,7′), 2.50 ($NCOCH_2CH_3$), 1.21 ($NCOCH_2CH_3$), 2.26 ($OCOCH_2CH_3$), 1.11 ($OCOCH_2CH_3$), 1.45 (*tert*-C_4H_9S); mass spectrum (70 EV) *m/e* (rel intensity) 311 (3), 238 (1), 223 (3), 222 (27), 208 (1), 198 (5), 167 (10), 166 (94), 149 (3), 142 (4), 126 (3), 125 (10), 124 (5), 111 (7), 110 (100), 109 (4), 97 (4), 94 (3), 93 (35), 92 (8), 80 (8), 57 (45), 41 (15), 39 (6), 29 (47), 28 (15), 27 (9). *Anal.* Calcd for $C_{16}H_{25}NO_3S$: C, 61.72; H, 8.09; N, 4.50. Found: C, 61.82; H, 8.15; N, 4.56.

G. Pyridine 1-Oxide.—From the reaction (0.1 mol, *N*-oxide) as described in section A, there were isolated, in the benzene eluate, 1-acetyl-2-*tert*-butylthio-3,4-diacetoxy-1,2,3,4-tetrahydropyridine (**12a**) (2.5 g): mp 91–93°; uv max (hexane) 237 mμ (log ε 4.23), 199 (4.02); ir (CCl_4) 1752 (ester C=O), 1700 (amide C=O), 1655 cm^{-1} (C=C); pmr (C_5D_5N) δ 1.38 (*tert*-C_4H_9), 1.88, 2.02 ($OCOCH_3$), 2.18 ($NCOCH_3$), 6.13 (H-2), 5.49 (H-3), 5.11 (H-4), 5.24 (H-5), 6.95 (H-6), ($J_{2,3}$ = 3.0, $J_{3,4}$ = 1.4, $J_{4,5}$ = 4.4, $J_{5,6}$ = 8.2, $J_{2,4}$ = 1.2, $J_{2,6}$ = 1.2, $J_{3,5}$ = 1.8, $J_{4,6}$ = 1.2, $J_{3,6}$ = 0.4 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 329 (8), 240 (5), 210 (5), 198 (12), 181 (5), 180 (40), 170 (4), 168 (4), 139 (9), 138 (100), 128 (12), 114 (4), 113 (4), 112 (12), 111 (7), 97 (6), 96 (87), 80 (17), 79 (5), 68 (5), 57 (20), 43 (65), 41 (14), 39 (4), 29 (7); mass spectrum (10 eV) *m/e* (rel intensity) 331 (11), 330 (21), 329 (100), 269 (5), 241 (16), 240 (63), 239 (11), 210 (32), 181 (16), 180 (95) 167 (11), 91 (5). *Anal.* Calcd for $C_{15}H_{23}NO_5S$: C, 54.71; H, 6.99; N, 4.25; S, 9.72. Found: C, 54.87; H, 7.00; N, 4.22; S, 9.78.

Pyrolysis of **12a** at 200° for 50 min yielded a dark liquid on distillation at 0.2 mm; gc separation[14] proved to contain (enrichment method) 2-*tert*-butylthiopyridine (66%), acetic anhydride (16%), 3-*tert*-butylthiopyridine (13%), and acetic acid (6%). The ratio of 2- to 3-sulfide is 85:15.

Pyridine-2,6-d_2 1-oxide[6] yielded the 2,6-d_2 analog of **12a**: pmr (C_5D_5N) δ within 0.05 ppm of **12a** listed above; mass spectrum (10 eV) *m/e* (rel intensity) 332 (9), 331 (33), 270 (2), 243 (7), 242 (35), 241 (7.3) 212 (9), 211 (7), 183 (15), 182 (100), 191 (9), 109 (11). In this fragmentation, *m/e* 331 → 270 loses CH_3CO_2D while at 10 eV **12a**, *m/e* 329 → 269, involves the loss of CH_3CO_2H.

H. 3-Picoline 1-Oxide.—The solid, on elution from alumina, proved to be **12c**: mp 123–124° (1% yield, based on *N*-oxide); uv max (hexane) 239 mμ (log ε 4.25), 200 (3.96); ir (CCl_4) 1760 (ester C=O), 1702 (amide C=O), 1680 cm^{-1} (C=C); pmr (C_5D_5N) δ 1.40 (*tert*-C_4H_9), 1.88, 2.08 ($OCOCH_3$) 2.20 ($NCOCH_3$), 1.78 (CH_3), 6.40 (H-2), 5.57 (H-3), 5.27 (H-4), 6.85 (H-6) ($J_{2,3}$ = 2.7, $J_{2,4}$ = 1.2, $J_{2,6}$ = 1.2, $J_{3,4}$ = 1.3, $J_{4,6}$ = 1.2 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 344 (3), 343 (11), 284 (3), 254 (12), 224 (7), 212 (8), 195 (6), 194 (43), 182 (8), 153 (9), 152 (97), 142 (11), 126 (20), 125 (8), 111 (8), 110 (100), 100 (12), 94 (28), 93 (8), 92 (6), 82 (8), 81 (6), 57 (37), 55 (8), 43 (93), 41 (28), 39 (9), 32 (16), 29 (19). The mass spectrum of the 2,6-d_2 analog at 10 eV gave ions *m/e* (rel intensity) 345 (100), 286 (2), 256 (25), 228 (10), and 196 (95) indicating that the two deuterium atoms are retained. *Anal.* Calcd for $C_{16}H_{25}NO_5S$: C, 55.97; H, 7.29; N, 4.08; S, 9.32. Found: C, 56.02; H, 7.36; N, 4.04; S, 9.43.

When **12c** (290 mg) was pyrolyzed at 200 ± 5° for 0.5 hr, a dark liquid was distilled (0.2 mm) which was revealed to be (by pmr) 2-*tert*-butylthio-5-picoline (75%) and 3-*tert*-butylthio-5-picoline (25%) as well as acetic anhydride and acetic acid.

Omission of triethylamine from this reaction changed the sulfide ratio (Table I) but actually improved the yield of **12c** slightly.

I. Pyridine 1-Oxide and *n*-Butyl Mercaptan.—Using method A, and neglecting an analysis of the sulfide fraction, the nonvolatile residue was chromatographed. Elution of **12b** was accomplished by benzene–dichloromethane (1:1) and dichloromethane. The solid crystallized from petroleum ether (bp 30–60°) at −60°, mp 58–59° (0.8% yield based on the *N*-oxide). Its pmr spectrum was compatible with the proposed structure, the most significant feature being the downfield doublet ($CDCl_3$) at δ 6.87 (H-6, $J_{5,6}$ = 8.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 329 (4), 270 (1), 269 (1), 240 (9), 211 (2), 210 (16), 199 (1), 198 (13), 181 (4), 180 (37), 169 (3), 168 (17), 167 (3), 139 (9), 138 (100), 112 (6), 96 (94), 80 (20), 79 (13), 43 (87). *Anal.* Calcd for $C_{15}H_{23}NO_5S$: C, 54.70; H, 7.04; N, 4.25. Found: C, 54.76; H, 6.91; N, 4.42.

J. 3-Picoline 1-Oxide and *n*-Butyl Mercaptan.—Using the procedure outlined in A and I, a solid, mp 117.5–118.5°, was isolated which proved to be **12d**: mass spectrum (70 eV) *m/e* (rel intensity) 343 (0.8), 284 (0.8), 283 (0.8), 255 (2), 254 (11), 224 (6), 213 (4), 212 (31), 195 (2), 194 (16), 182 (11), 153 (3), 152 (30), 111 (8), 110 (100), 109 (4), 94 (17), 93 (11), 92 (7), 84 (3), 82 (9), 65 (4), 57 (7), 56 (5), 55 (5), 45 (5), 43 (54), 41 (9), 39 (5), 32 (11), 29 (6). *Anal.* Calcd for $C_{16}H_{25}NO_5S$: C, 54.35; H, 7.37; H, 4.88. Found: C, 54.38; H, 7.44; N, 4.97.

Registry No.—**4b**, 31579-80-3; **4e**, 31579-81-4; **5a**, 31579-82-5; **5b**, 31579-83-6; **5c**, 31579-84-7; **5c′**, 31579-85-8; **5d**, 31579-86-9; **5d′**, 31579-87-0; **5e**, 31579-88-1; **10**, 31579-89-2; **11**, 31579-90-5; **12a**, 31579-91-6; **12** 2,6-d_2 analog, 31571-03-6; **12b**, 31571-04-7; **12c**, 31571-05-8; **12d**, 31571-06-9; triethylamine, 121-44-8; 4-ethylpyridine 1-oxide, 14906-55-9; 4-*n*-propylpyridine 1-oxide, 25813-87-0; 4-isopropylpyridine 1-oxide, 22581-87-9; 4-(1-acetoxyethyl)pyridine, 2555-02-4; 3-acetoxy-4-ethylpyridine, 31571-11-6; 2-*tert*-butylthio-4-ethylpyridine, 31579-73-4; 3-*tert*-butylthio-4-ethylpyridine, 31579-74-5; 3-acetoxy-4-*n*-propylpyridine, 31579-75-6; 2-*tert*-butylthio-4-*n*-propylpyridine, 31579-76-7; 3-*tert*-butylthio-4-*n*-propylpyridine, 31615-27-7; 4-(1-*tert*-butylthiopropyl)pyridine, 31579-77-8; 2-*tert*-butylthio-4-isopropylpyridine, 31579-78-9; 3-*tert*-butylthio-4-isopropylpyridine, 31579-79-0.

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Photochemistry of Benzo[b]thiophenes Addition of Acetylenes

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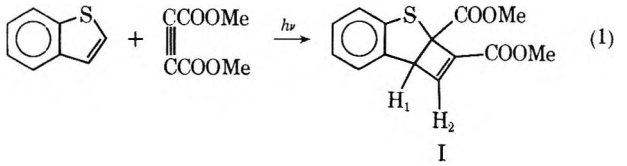
The photochemical addition of dimethyl acetylenedicarboxylate, methyl propiolate, and methyl phenylpropiolate to benzo[b]thiophene leads to cyclobutene derivatives of unexpected structure. Methyl propiolate adds in a direction opposite to the direction of methyl phenylpropiolate suggesting that the excited state of benzo[b]thiophene is highly polarized. The cyclobutenes formed are thermally unstable and rearrange, with loss of sulfur, to naphthalenes.

Photochemical addition reactions of acetylenes to aromatic compounds have been studied as possible routes to cyclobutadienes.[2-12] Addition reactions involving heteroaromatic compounds and acetylenes, though reported less frequently, are similarly attractive as routes to substituted cyclobutadienes. We have studied the addition of acetylene derivatives to the naphthalene-like heterocycle benzo[b]thiophene[13] and report the addition of several acetylenes to this heterocycle and some of its alkylated derivatives.

Results

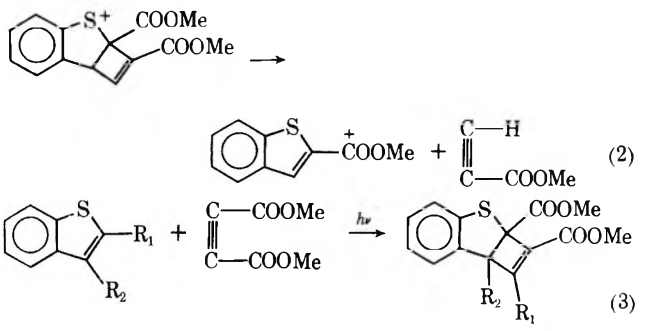
Direct and photosensitized addition of dimethyl acetylenedicarboxylate to benzo[b]thiophene leads to the formation of a cyclobutene derivative in 51% yield (eq 1). The nmr spectrum of the adduct (Table I) confirms that the structure of the product is I,



(1)

I

in that protons 1 and 2 are weakly coupled doublets ($J_{1,2} < 1$ Hz), an observation characteristic of vinyl and allylic protons in cyclobutenes.[14,15] The mass spectra of similar compounds allow us to predict retrocleavage in a direction such that the benzo[b]-thiophene nucleus would remain as a major peak (Table II).[16] Thus, the peak height of fragment II (*m/e* 192) represents 90% of the parent peak (eq 2). Similar additions (eq 3) are observed with 2-methylbenzo[b]-thiophene, 2,3-dimethylbenzo[b]thiophene, and 3-methylbenzo[b]thiophene. The nmr spectra of these

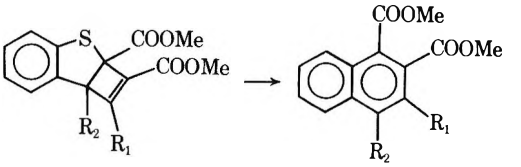


(2) (3)

III, R_1 = Me; R_2 = H
IV, R_1 = H; R_2 = Me
V, R_1 = Me; R_2 = Me

adducts (Table I) and mass spectra (Table II) are consistent with the assigned structures.

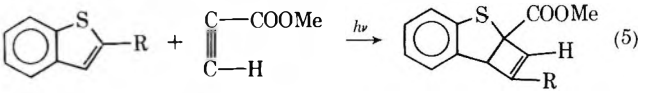
Cyclobutene adducts prepared from dimethyl acetylenedicarboxylate and alkyl benzo[b]thiophenes are thermally unstable. These adducts rearrange to naphthalene derivatives (eq 4) *via* a sulfur extrusion process.[17]



(4)

XX, $R_1 = R_2$ = H
XXI, R_1 = H; R_2 = Me
XXII, R_1 = Me; R_2 = Me

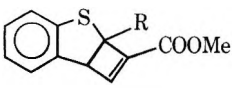
Sensitized addition of methyl propiolate (eq 5) to benzo[b]thiophene derivatives proceeds similarly.



(5)

VI, R = H
VII, R = Me

Yields are as high as 33% when benzo[b]thiophene is used. In all cases additions of methyl propiolate appeared slower than similar additions of dimethyl acetylenedicarboxylate. The addition of methyl propiolate is highly selective and the vapor phase chromatogram of the crude reaction mixture shows only a few per cent of stereoisomers of VI and VII which are VIII



VIII, R = H
IX, R = Me

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(2) D. Bryce-Smith, A. Gilbert, and J. Grzonka, *Chem. Commun.*, 498 (1970).

(3) D. Bryce-Smith, A. Gilbert, and B. H. Orger, *ibid.*, 512 (1966).

(4) D. Bryce-Smith and J. E. Lodge, *Proc. Chem. Soc.*, 333 (1961).

(5) D. Bryce-Smith and J. E. Lodge, *J. Chem. Soc.*, 695 (1963).

(6) J. C. Atkinson, D. E. Ayer, G. Büchi, and E. W. Robb, *J. Amer. Chem. Soc.*, **85**, 2257 (1963).

(7) W. H. F. Sasse, P. J. Collin, and G. Sugowdz, *Tetrahedron. Lett.*, 3373 (1965).

(8) P. J. Collin and W. H. F. Sasse, *ibid.*, 1689 (1968).

(9) W. H. Sasse, *Aust. J. Chem.*, **6**, 1257 (1969).

(10) R. J. McDonald and B. K. Selinger, *Tetrahedron Lett.*, 4791 (1968).

(11) E. H. White and R. L. Stern, *ibid.*, 193 (1964).

(12) R. M. Bowman and J. J. McCullough, *Can. J. Chem.*, **47**, 4503 (1969).

(13) D. C. Neckers, J. H. Dopper, and H. Wynberg, *Tetrahedron Lett.*, 2913 (1969).

(14) E. A. Hill and J. D. Roberts, *J. Amer. Chem. Soc.*, **89**, 2047 (1967).

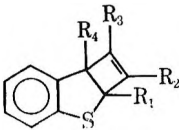
(15) L. Paquette, and W. C. Farley, *J. Org. Chem.*, **32**, 2725 (1967).

(16) D. C. Neckers, J. H. Dopper, and H. Wynberg, *ibid.*, **35**, 1582 (1970).

(17) H. Hofmann, H. Westernacher, and H. J. Haberstroh, *Chem. Ber.*, **102**, 2592 (1969).

TABLE I

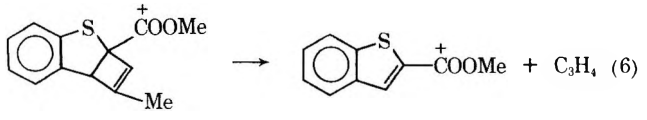
NMR SPECTRA OF SUBSTITUTED CYCLOBUTENE SYSTEMS[a]



Compd	H_5–H_8	R_1	R_2	R_3	R_4
I		COOMe	COOMe	H	H
	7.05 s	3.72 s	3.76 s	6.78 d	4.69 d
	4 H	3 H	3 H	1 H	1 H
				$J_{3,4}$ <1.0 Hz	
IV		COOMe	COOMe	H	CH_3
	7.11 s	3.76 s	3.80 s	6.76 s	1.58 s
	4 H	3 H	3 H	1 H	3 H
III		COOMe	COOMe	CH_3	H
	7.06 s	3.76 s	3.80 s	1.95 s	4.68 s
	4 H	3 H	3 H	3 H	1 H
V		COOMe	COOMe	CH_3	CH_3
	7.12 s	3.76 s	3.80 s	1.95 s	1.58 s
		3 H	3 H	3 H	3 H
VI		COOMe	H	H	H
	7.09 s	3.76 s	6.24 d	6.19 d	4.87 s
			$H_{2,3}$ AB system	$J_{2,3}$ = 1.8 Hz	
	4 H	3 H	1 H	1 H	1 H
VII		COOMe	H	CH_3	H
	7.14 s	3.76 s	5.92 q	1.75 d	4.74 br s
			$J_{2,3}$ <1 Hz		
	4 H	3 H	1 H	3 H	1 H
XI		Phenyl	COOMe	CH_3	H
	7.0–7.1	7.0–7.6 m	3.78 s	2.07 d	4.19 q
					$J_{3,4}$ = 1.4 Hz
	(9 H)		3 H	3 H	1 H
XIII		COOMe	Phenyl	CH_3	H
	7.0–7.1	3.76 s	7.0–7.6 m	1.87 d	4.52 q
					$J_{3,4}$ <1 Hz
	4 H	3 H	5 H	3 H	1 H
X		Phenyl	COOMe	H	H
	7.07 s	7.1–7.6 m	3.69 s	6.66 d	4.28 d
					$J_{3,4}$ = 1 Hz
	(9 H)		3 H	1 H	1 H
XV		H	H	Cl	H
	7.04 s	4.81 d	6.00 s		4.59 d
		H_1 and H_4	AB doublet		$J_{1,4}$ = 4 Hz
	4 H	1 H	1 H		1 H
XVI		CH_3	H	Cl	H
	7.07 s	1.78 s	5.89 s		4.09 s
	4 H	3 H	1 H		1 H
XVII		CH_3	Cl	H	H
	7.06 s	1.78 s		6.01 d	4.22 d
					$J_{3,4}$ = 1.5 Hz
	4 H	3 H		1 H	1 H
XVIII		H	H	Cl	CH_3
	7.03 s	4.36 s	6.00 s		1.68 s
	4 H	1 H	1 H		3 H

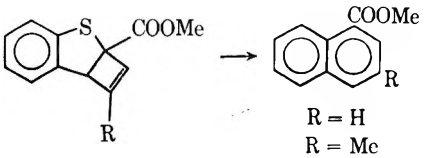
[a] All data in ppm, δ scale, s = singlet, d = doublet, m = multiplet, q = quartet, br = broad.

and IX. The nmr spectrum of VI (Table I) shows an AB quartet between the vinyl protons and a very weak coupling between vinyl and allylic protons. The predominant mass spectral fragment, *m/e* 192, is proof of the derived structure (eq 6).



(6)

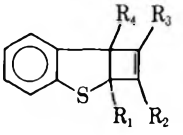
Chemical proof for the structure of the products VI and VII again derives from the thermal rearrangement of the products. Thus, at 240° (2 min), rearrangement takes place (eq 7) to the corresponding naphthalene



(7)

ester. The derived product from VI has an identical infrared spectrum with that of α-naphthoic acid methyl ester.

TABLE II
MASS SPECTRAL DATA



I, $R_1 = R_2 = CO_2CH_3$; $R_3 = R_4 = H$

$M^+ = 276$		90%
M − 31 = 245	$-OCH_3$	65%
M − 32 = 244	−S	100%
M − 59 = 217	$-CO_2CH_3$	40%
M − 84 = 192	$-HC{\equiv}CCO_2Me$	90%
M − 142 = 134	$-H_3CO_2C{\equiv}CCO_2CH_3$	25%

IV, $R_1 = R_2 = CO_2CH_3$; $R_3 = H$; $R_4 = CH_3$

$M^+ = 290$		95%
M − 31 = 259	$-OCH_3$	30%
M − 32 = 258	−S	100%
M − 59 = 231	$-CO_2CH_3$	25%
M − 84 = 206	$-HC{\equiv}CCO_2Me$	85%
M − 142 = 148	$-CH_3O_2CC{\equiv}CCO_2CH_3$	14%

V, $R_1 = R_2 = CO_2Me$; $R_3 = R_4 = CH_3$

$M^+ = 304$		100%
M − 31 = 273	$-OCH_3$	50%
M − 32 = 272	−S	60%
M − 59 = 245	$-CO_2CH_3$	85%
M − 98 = 206	$-CH_3C{\equiv}CCO_2Me$	65%
M − 142 = 162	$-CH_3O_2CC{\equiv}CCO_2Me$	50%

VII, $R_1 = COOMe$; $R_3 = CH_3$; $R_2 = R_4 = H$

$M^+ = 232$		100%
M − 31 = 201	$-OCH_3$	40%
M − 32 = 200	−S	60%
M − 40 = 192	$-C_3H_4$	50%
M − 59 = 173	$-CO_2CH_3$	45%
M − 71 = 161	$-C_2H_4$-OCH_3	50%
M − 84 = 148	$-HC{\equiv}CCO_2CH_3$	15%

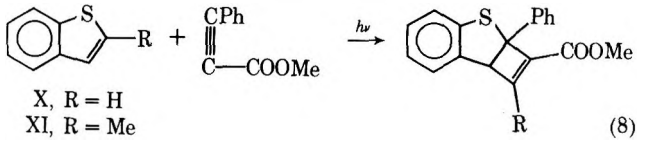
XI, R_1 = Ph; $R_2 = CO_2Me$; $R_3 = CH_3$; $R_4 = H$

$M^+ = 308$		45%
M − 31 = 277	$-OCH_3$	13%
M − 32 = 278	−S	16%
M − 59 = 249	$-CO_2CH_3$	21%
M − 63 = 245		8%
M − 74 = 234		20%
M − 98 = 210		25%
M − 116 = 192		60%

XIV, $R_1 = R_4 = H$; $R_2 = R_3$ = Ph

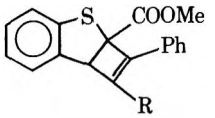
$M^+ = 312$		45%
M − 32 = 280	−S	60%
M − 102 = 210	$-HC{\equiv}CPh$	10%
M − 134 = 178		100%
M − 178 = 134	$-PhC{\equiv}CPh$	50%

Additions of methyl phenylpropiolate to benzo[b]-thiophene (eq 8) give a 52% yield of an adduct to which



X, R = H
XI, R = Me (8)

we assign the structure shown. The reaction is directionally selective and only a few per cent of the other possible isomers, XII and XIII, can be detected. The

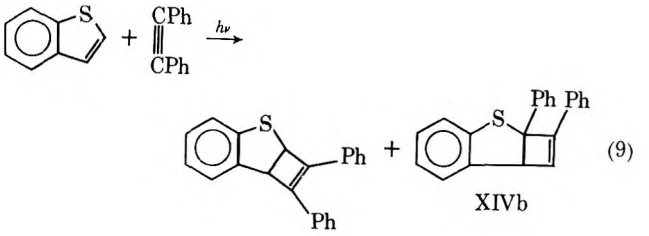


XII, R = H
XIII, R = Me

selectivity is greater in additions to benzo[b]thiophene than it is to 2-methylbenzo[b]thiophene. As before, all adducts rearrange to the corresponding naphthalenes.

Addition of diphenylacetylene to benzo[b]thiophene is a very slow reaction unless special precautions are taken to remove last traces of oxygen. Dimers of diphenylacetylene are detected among the products of the addition reaction (eq 9).

Removal of last traces of oxygen affords ~30% yield of the rearranged adduct XIVb as reported by Sasse.[18] The efficiency of the photochemical addition of benzo[b]thiophene to diphenylacetylene is dependent on the concentration ratio of benzo[b]thiophene to diphenylacetylene as well. In order to obtain maximum yield of 1:1 adducts, several molar excesses of benzo[b]-thiophene must be used.



XIVa (9)

XIVb

Although it appeared initially that the ring-opening reaction of fused benzo[b]thiophene cyclobutenes might provide facile entry into the relatively inaccessible benzo[b]thiepin system,[13] we have not succeeded in trapping thiepins in thermal rearrangements of our products. Either the temperature required for ring opening is too high for the thiepin to survive, or the mechanism for the ring opening is nonconcentrated and the thiepins have no existence in our system.

Nevertheless the thermal rearrangement provides a very easy way to prepare highly substituted naphthalenes, some of which are not easily obtained by conventional procedures. The reaction is general, as our earlier work with halocyclobutenes fused to benzo-[b]thiophenes has shown.[16] Overall yields of these reactions approach 75% (see Table III).

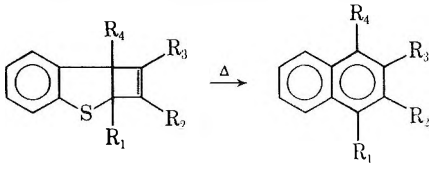
Discussion

The scope of addition reactions to benzo[b]thiophenes is shown by the data in Table IV. This data assumes

(18) W. H. F. Sasse, P. J. Collin, and D. B. Roberts, *Tetrahedron Lett.*, 4791 (1969).

TABLE III

REARRANGEMENT TO NAPHTHALENES



R_1	R_2	R_3	R_4	
CO_2Me	COOMe	H	H	I → XX
COOMe	COOMe	H	CH_3	IV → XXI
COOMe	COOMe	CH_3	CH_3	V → XXII
COOMe	H	H	H	VI → XXIII
COOMe	H	CH_3	H	VII → XXIV
Ph	COOMe	CH_3	H	XI → XXV
Ph	COOMe	H	H	X → XXVI
H	H	Cl	H	XV → XXVII
CH_3	H	Cl	H	XVI → XXVIII

TABLE IV

RATES OF ADDITIONS OF ACETYLENES TO BENZO[b]THIOPHENES

Acetylene AC≡CB	Ease of adduct formation
A = B = COOMe	++++
A = H; B = COOMe	+++
A = Ph; B = COOMe	++++
A = Ph; B = acetyl	+
A = B = Ph	+[a]
A = Ph; B = Me	±
A = B = CH_2Cl	−
A = B = CH_2OMe	−

[a] The addition of diphenylacetylene to benzo[b]thiophene is concentration and oxygen dependent.

that the energy is eventually accepted by the benzo[b]-thiophene so that it is the heteroaromatic compound that is absorbing the light, either directly or by energy transfer.

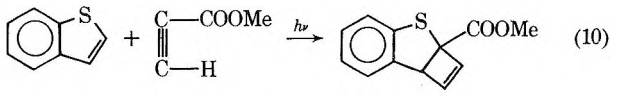
In order for acetylene additions to benzo[b]thiophenes to be efficient, the acetylene must be substituted with strong electron-attracting groups. Further, sensitizers with triplet energies higher than 68.5 kcal/mol increase the efficiency of the additions though sensitizers have no effect on the products.

The ultraviolet spectra of several fused heterocyclic compounds, including benzo[b]thiophene and its 2-methyl derivative, show sharp absorption maxima at wavelengths in the 287–300-nm region. In the case of benzo[b]thiophene the maximum absorption is at 296.5 nm (hexane) (ϵ 4600) while for the 2-methyl derivative the maximum in hexane is at 297.0 nm (ϵ 5400). These maxima shift very slightly to the blue in methanol and have been attributed to n–π^* excitations requiring the nonbonded electrons of the sulfur atom, a result corroborated by the disappearance of these bands in the corresponding benzo[b]thiophene 1,1-dioxide, though there is certainly no consensus that these long wavelength bands derive from n–π^* absorptions.[19]

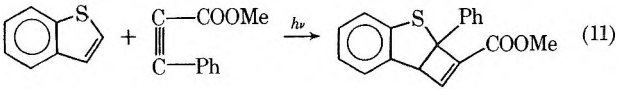
Absorption maxima of dimethyl acetylenedicarboxylate, methyl propiolate, and methyl phenylpropiolate lie below the position of the absorption maxima of the benzo[b]thiophenes and are weaker. In the direct radiation reaction involving these acetylenes most of the light must initially be absorbed by the benzo[b]-thiophene or alkyl derivative. In the sensitized reaction employing benzophenone or acetophenone as the sensitizer, most of the reaction derives from energy transfer from the carbonyl compound to the heteroaromatic compound. Triplet energy levels of the acetylene esters are too high to be competitive in the transfer process, since the triplet-state energy of benzo[b]thiophene is 68.9 kcal/mol.[20] Though benzo[b]thiophene fluoresces efficiently, this fluorescence is only weakly quenched by additives which react with the heterocyclic compound.[21]

Charge distribution in the excited benzo[b]thiophene triplet derives from the direction of addition of unsymmetrical acetylenes, methyl propiolate, and methyl phenylpropiolate to benzo[b]thiophene and its 2-methyl derivative.

Sensitized addition of methyl propiolate to benzo[b]-thiophene produces exclusively the adduct with the carboxymethyl group attached to the 2 position of the benzo[b]thiophene nucleus (eq 10). Addition of methyl phenylpropiolate places the phenyl group at the 2 position of the benzo[b]thiophene and the COOMe group ends up on the cyclobutene ring (eq 11).



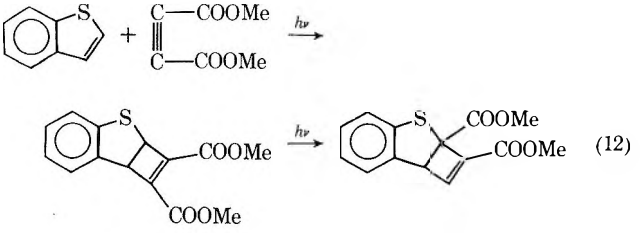
(10)



(11)

From the studies of Huisgen and coworkers[22] it is known that methyl propiolate and methyl phenylpropiolate add dipolar species in opposite directions. A charged excited state of the benzo[b]thiophene might select the carbon of the carbomethoxy group in methyl propiolate while selecting the carbon of the phenyl group in methyl phenylpropiolate, thereby accounting for the observed directional difference in methyl propiolate and methyl phenylpropiolate.

In our first publication describing studies of photochemical addition by dimethyl acetylenedicarboxylate to benzo[b]thiophenes, we suggested that the rearranged product we observed might derive from a 2-quantum process. The initial addition of 1 mol of the acetylene to the benzo[b]thiophene would thereby have to produce a photolabile cyclobutene (eq 12).



(12)

XXIX

There are at least two other mechanisms that could just as well account for the observed rearrangement. Both of these mechanisms involve additions to the sulfur

(19) H. H. Jaffé, and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962, p 240.

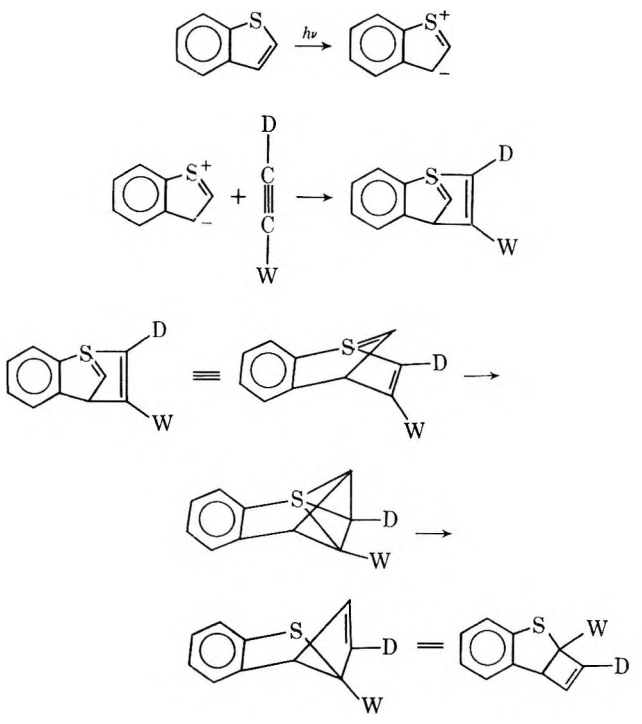
(20) R. C. Heckman, *J. Mol. Spectrosc.*, **2**, 27 (1958).

(21) The peak in the fluorescence spectrum of benzo[b]thiophene at 285 nm appears to be selectively quenched at higher concentrations of benzo[b]-thiophene.

(22) R. Huisgen, H. Golhard, and R. Grashey, *Chem. Ber.*, **101**, 536 (1968).

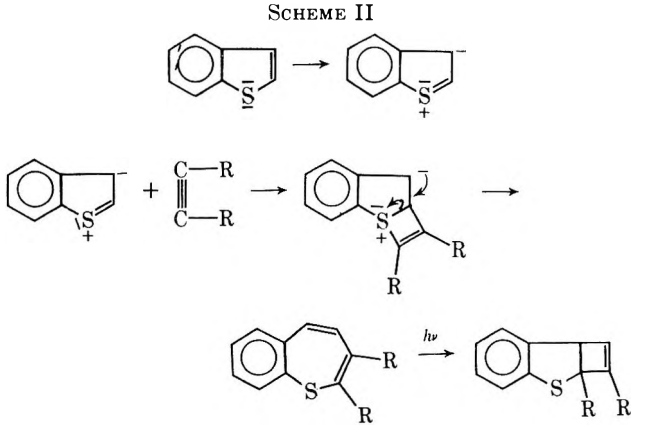
atom. In one mechanism, a 1,3 addition to the sulfur atom and the 3 carbon of the benzo[b]thiophene is the first step followed by bond rearrangement. This mechanism is shown in Scheme I.

SCHEME I



The second possible mechanism involving the sulfur atom requires a 1,2 addition to the sulfur and the 2 carbon of the benzo[b]thiophene. This 1,2-addition mechanism is shown in Scheme II.

SCHEME II



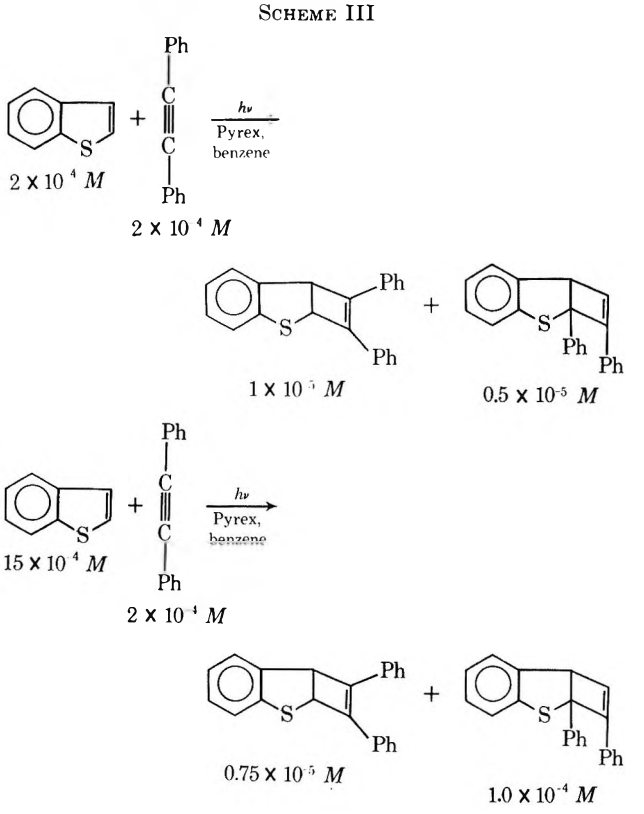
XXX

There are several pieces of information which bear on the question of mechanism, none of which seems all-conclusive, but all of which we list below.

First, in both the 2,3-addition mechanism (eq 12) and the 1,2-addition mechanism (Scheme II), isolable intermediates should be obtained. In the 2,3-addition mechanism, the intermediate should have the structure XXIX (eq 12); *i.e.*, the first formed product should be a cyclobutene with both substituent groups attached to the double bond of the cyclobutene. In the 1,2-cycloaddition process, the product should be a benzo[b]-thiepin, XXX (Scheme II). In no case have we observed either said intermediate even when the additions are carried out to low conversion in a nmr tube, when acetylenes with carbomethoxy groups, –COOMe, are attached. Only in the addition of diphenylacetylene to benzo[b]thiophene[18] have unrearranged adducts been observed.

To our knowledge, diphenylacetylene is the only alkyne from which an unrearranged 1:1 adduct to benzo[b]thiophene can be isolated, (Scheme III). Even

SCHEME III



this adduct accounts, however, for only $^1/_{30}$th of the total adduct yield under the most favorable conditions. Even though this unrearranged adduct can be shown to rearrange to the major isolated adduct, there is compelling evidence which suggests that diphenylacetylene is a special case. This evidence is twofold. First, diphenylacetylene absorbs light in the same region of the spectrum as benzo[b]thiophene and some ten times more strongly.[19] Thus, unless benzo[b]thiophene is in substantial excess, most of the light is absorbed by diphenylacetylene. Second, there is a substantial concentration dependence on the yield of adducts. When solutions which are 1 *M* in benzo[b]-thiophene and 1 *M* in diphenylacetylene are irradiated, both adducts form very slowly and the unrearranged adduct predominates, albeit in very low total yield. As the molar ratio of benzo[b]thiophene is increased, the yield of rearranged adduct grows while the yield of unrearranged adduct decreases slightly for a comparable irradiation time.

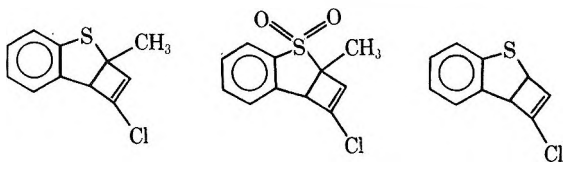
The concentration dependence of benzo[b]thiophene additions to diphenylacetylene suggests that competitive photochemical processes are occurring in this case. One photochemical process, the process producing the unrearranged adduct, involves light absorption and excited-state formation from diphenylacetylene. The other photochemical process, the pro-

cess producing the rearranged adduct, derives from an excited state of the benzo[*b*]thiophene and must be regarded as the normal *modus operandi* in benzo[*b*]-thiophene–alkyne systems.

Second, in both the 2,3-addition mechanism (eq 12) and the 1,2-addition mechanism (Scheme II), a secondary photochemical rearrangement reaction is required to obtain the observed products. We have isolated several related cyclobutenes (Chart I), and,

CHART I

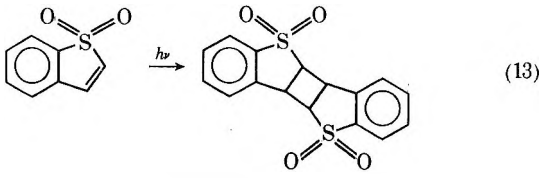
STABLE ADDUCTS OF BENZO[*b*]THIOPHENE



though the models have some significant drawbacks, these compounds are not observed to rearrange under the conditions of our experiments.

The rearrangement of benzo[*b*]thiepins like that proposed in Scheme II has not been observed. Benzo[*b*]-thiepins are rather elusive compounds,[23] and we have not succeeded in isolating them as yet. Nevertheless, their photochemical rearrangement is predicted and has been observed in the corresponding oxepins.[24]

Third, both the 1,3-addition mechanism (Scheme I) and the 1,2-addition mechanism (Scheme II) require the sulfur atom of the benzo[*b*]thiophene to have available unshared electrons. The 2,3-addition mechanism does not. Therefore, it is significant that benzo-[*b*]thiophene 1,1-dioxide fails to add either acetylenes or related derivatives. Instead, benzo[*b*]thiophene 1,1-dioxide undergoes a cinnamic acid type dimerization (eq 13). Other heterocyclic compounds which contain

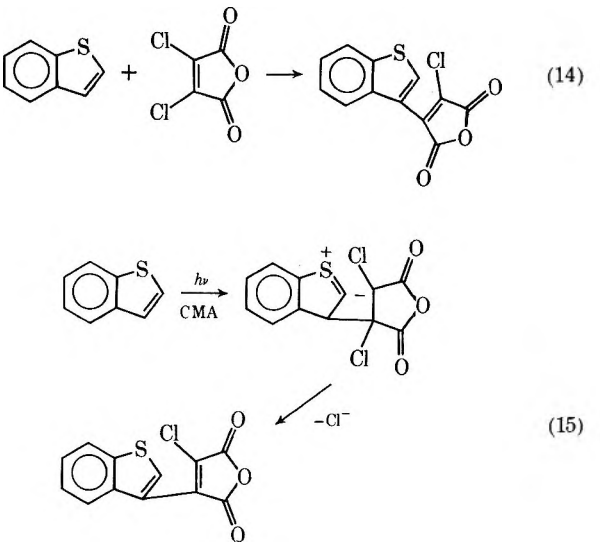


(13)

atoms with a lesser ability to accommodate more than eight electrons than sulfur also undergo just dimerization and do not add acetylenes.[25]

Finally, thermal additions of many acetylene derivatives to a variety of heteroaromatic compounds involve dipolar additions. Thus, dimethyl acetylenedicarboxylate adds to thiazole and benzothiazole *via* a dipolar intermediate.[26]

At this point, we feel that either of the mechanisms involving the sulfur atom, Scheme I or II, probably accounts for the experimental facts better than does the secondary rearrangement mechanism (eq 12). This statement is reinforced by the observation that some reactions of benzo[*b*]thiophene, *e.g.*, the photochemical addition of dichloromaleic anhydride, occur with substitution rather than addition (eq 14). A dipolar mechanism, like that shown (eq 15), accounts for this



(14)

(15)

observation. Experiments are continuing in an effort to isolate the intermediates suggested by the 1,2-dipolar addition mechanism and the 2,3-addition process above.

Examination of the mass spectra of the fused cyclobutene adducts point to the observation that one might at least predict the facile loss of sulfur by the adducts, particularly since the parent peak minus sulfur is significant in all the mass spectra. The cyclobutanes show no tendency to lose sulfur in the same sort of process. Thus, as others as well as ourselves have pointed out before, there is a distinct parallel between thermal, photochemical, and mass spectral fragmentation reactions.[27]

Experimental Section

All melting points are uncorrected. Infrared spectra were taken either in carbon tetrachloride solution or in pure form using a Perkin-Elmer 621. Nmr spectra were taken (10% in CCl_4 or $CDCl_3$) using a Varian A-60 spectrometer. Reference is to tetramethylsilane. Mass spectra were recorded on an A.E.I. MS9 equipped with an A-700 F & M vpc with thermalconductivity detectors. Uv spectra were taken on a Cary 14. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Starting Materials.—Benzo[*b*]thiophene, dimethyl acetylenedicarboxylate, methyl propiolate, diphenylacetylene, phenylacetylene, 1,4-dichlorobutyne-2, dichloromaleic anhydride, hexafluorobutyne-2, benzophenone, and acetophenone were commercial materials purified when necessary by conventional methods. 2-Methylbenzo[*b*]thiophene, 3-methylbenzo[*b*]thiophene, and 2,3-dimethylbenzo[*b*]thiophene were prepared as previously described.[16] 1,4-Dimethoxybutyne-2 was prepared from 1,4-dihydroxybutyne-2.[28] Phenylmethylacetylene was prepared from phenylacetone.[29] 2-Phenyl-1-acetoacetylene was prepared from phenylacetylene.[30] Phenyl methylpropiolate was prepared from phenylpropiolic acid (Aldrich) (nmr phenyl δ 7.18–7.68 (m, OCH_3) and 3.77, ir $\nu_{C\equiv C}$ 2220 (s), $\nu_{C=O}$ 1720 cm^{-1}). Benzo[*b*]thiophene 1,1-dioxide was prepared by oxidation of benzo[*b*]thiophene, with *m*-chloroperbenzoic acid in chloroform,[16] mp 140–141° (lit.[31] mp 142°).

General Irradiation Procedures.—Irradiations were carried out using a Hanau S81 or a Hanovia 450-W medium pressure mercury

(23) H. Hofmann and H. Westernacher, *Chem. Ber.*, **102**, 205 (1969).

(24) See, *e.g.*, L. A. Paquette, "Modern Heterocyclic Chemistry," W. A. Benjamin, New York, N. Y., 1968.

(25) T. H. Barton and coworkers, private communication.

(26) See, *e.g.*, O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **498**, 16 (1932); E. Winterfeldt, *Chem. Ber.*, **98**, 3537 (1965); D. H. Reid, F. S. Skelton, and W. Bonthrone, *Tetrahedron. Lett.*, 1797 (1964).

(27) N. J. Turro, D. C. Neckers, *et al.*, *J. Amer. Chem. Soc.*, **87**, 4097 (1965).

(28) G. F. Hennion and F. P. Kuiecki, *J. Org. Chem.*, **18**, 1601 (1953).

(29) C. D. Hurd and A. Tochman, *ibid.*, **23**, 1087 (1958).

(30) J. W. Kroeger and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **58**, 1961 (1936).

(31) E. N. Karaalova, O. Sh. Meilanova, and G. D. Ga'pern, *Dokl. Akad. Nauk SSSR*, **123**, 99 (1958).

arc lamp. All irradiations were carried out using Pyrex filters. The temperature was held at 25°.

Addition of Dimethyl Acetylenedicarboxylate to Benzo[b]thiophene.—Benzo[b]thiophene (3.0 g, 0.22 mol), dimethyl acetylenedicarboxylate (3.5 g, 0.024 mol), and benzophenone (0.5 g, 0.0027 mol) were dissolved in 400 ml of pure benzene and the solution was irradiated for 7 days. The benzene was removed *in vacuo* on a rotating evaporator and vpc analysis (column SE-30, oven temperature 250°) of the crude mixture showed formation of one product in 51% yield. The dimethyl acetylenedicarboxylate and part of the benzo[b]thiophene was distilled *in vacuo*. The orange-colored residue was chromatographed over a silica gel column using CCl_4 as elution agent. With CCl_4, unreacted benzo[b]thiophene eluted. Changing solvents carefully from CCl_4 to $CHCl_3$ separated benzophenone and a little dimethyl acetylenedicarboxylate. Changing from $CHCl_3$ as elution agent to $CHCl_3$–CH_2Cl_2 (1:1) and finally to pure CH_2Cl_2 delivered 2.7 g (45%) of pure product (I) as a bright yellow oil; nmr is in Table I, mass spectrum in Table II. For purposes in which very pure material is required, the adduct can be purified further using preparative thin layer chromatography techniques. On a 20 × 100 cm glass plate a 2-mm layer of silica gel (Merck PF-254) was prepared and activated at 110° for 1 hr. One gram of material was dissolved in 25 ml of CH_2Cl_2 and added carefully to the plate with a 50-ml syringe. The elution was carried out using CH_2Cl_2. The products were removed from the silica gel by extracting for 12 hr with methanol. After removing the MeOH *in vacuo*, the dissolved silica gel was separated from the product by stirring the mixture for 2 hr with $CHCl_3$. After filtration, the solution was dried over sodium sulfate and after filtering, the $CHCl_3$ was removed. After 6 months, the adduct crystallized to a white solid, which could be further purified by washing with pentane. The adduct, mp 79–81°, had λ_{max} at 305 nm (ϵ 1350), 293 (1700), 281 (1750), and 235 (16,700); calcd mol wt[32] for $C_{14}H_{12}O_4S$, 276.0456 (found, 276.0458).

Similar methods were used for the addition of 3-methylbenzo[b]thiophene to dimethyl acetylenedicarboxylate (yield ~40%), [calcd mol wt for $C_{15}H_{14}O_4S$, 290.06128 (found, 290.0613)] and for the other alkylbenzo[b]thiophenes. For example, for the adduct of 2,3-dimethylbenzo[b]thiophene and dimethyl acetylenedicarboxylate, the following data were obtained: mp 89–92°; λ_{max} 308 nm (ϵ 1900) and 229 (23,800). *Anal.* Calcd for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.30; S, 10.54; mol wt, 304.07693. Found: C, 62.80; H, 5.19; S, 10.65; mol wt, 304.0766.

Addition of Methyl Propiolate to Benzo[b]thiophene.—Benzo[b]thiophene (3.5 g, 0.026 mol), methyl propiolate (3 g, 0.035 mol), and acetophenone (0.5 g, 0.0025 mol) were dissolved in 400 ml of benzene and irradiated for 7 days. The benzene and methyl propiolate were removed *in vacuo* on a rotating evaporator and vpc analysis (5-ft Carbowax 20-m, 10%, oven temperature 220°) of the crude mixture showed formation of one product in 33% yield. The acetophenone and part of the benzo[b]thiophene was distilled off *in vacuo*. (Note: One should not use a higher pot temperature than 100°, because rearrangements to the corresponding naphthalene of the cyclobutene derivatives will become a serious side reaction). The dark-colored residue was chromatographed over a silica gel column using CCl_4 as the elution agent. With CCl_4 unreacted benzo[b]thiophene could be separated first. After that the product VI and a little acetophenone were separated. The total weight of the almost pure fractions was 1.30 g (23%). In order to purify this mixture further the 1.30 g was chromatographed again over silica gel using cyclohexane as an elution agent. Acetophenone separated first and after that 1.18 g of pure product could be obtained as a light yellow oil: calcd mol wt for $C_{12}H_{10}O_2S$, 218.04015 (found mol wt, 218.0403).

Addition of Methyl Propiolate to 2-Methylbenzo[b]thiophene.—Additions were carried out in exactly the same way as described for benzo[b]thiophene. Yields of VI were as high as 35%: calcd mol wt for $C_{13}H_{12}O_2S$, 232.0559 (found, 232.0560).

Addition of Phenylpropiolic Acid Methyl Ester to Benzo[b]thiophene.—Benzo[b]thiophene (3 g, 0.22 mol), methyl phenylpropiolate (3.5 g, 0.022 mol), and acetophenone (0.5 g, 0.0038 mol) were dissolved in 400 ml of benzene and the solution was irradiated for 7 days. The benzene was removed *in vacuo* on a rotating evaporator and vpc analysis (column SE-30, oven temperature 250°) of the crude mixture showed formation of one product (52%). The acetophenone and part of the other starting material were distilled *in vacuo*. The dark-colored residue was chromatographed over a Florisil column (Fisher F-100) with cyclohexane as the eluting agent. With cyclohexane, benzo[b]thiophene and methyl phenylpropiolate eluted. Changing solvents from cyclohexane to $CHCl_3$ separated (45%) 2.9 g of X.

Addition of Methyl Phenylpropiolate to 2-Methylbenzo[b]thiophene.—Additions were carried out in exactly the same way as described for benzo[b]thiophene. The total (XI + XIII) was 50%.

Preparative Addition of Diphenylacetylene to Benzo[b]thiophene.—Benzo[b]thiophene (2 g, 0.015 mol) and diphenylacetylene (2.8 g, 0.016 mol) were dissolved in 400 ml of benzene and irradiated for 10 days. The benzene was removed *in vacuo* on a rotating evaporator and vpc analysis of the crude mixture (column SE-30, oven temperature 285°) showed formation of two products. The yields were very low and certainly not more than 1% where the solutions were not degassed. Taking mass spectra of the two major products from a vpc column GE-SE-30 showed the product with the lowest retention time to be a 1:1 adduct, mass 312. On the basis of the cracking pattern (Table II) the structure XIV was assigned. The product with the highest retention time on the vpc showed a mass of 356 and is probably derived from a dimer or tetramer of diphenylacetylene.

Nmr Studies of Diphenylacetylene and Benzo[b]thiophene Photoadditions.—Five samples of diphenylacetylenes (35.6 mg, 2×10^{-4} mol) were added to five separate clear Pyrex nmr tubes and 1 ml of benzene was added to each tube. A constant quantity of *tert*-butylbenzene was added to each tube as an nmr integration standard. To each successive tube sufficient benzo[b]thiophene was added so that the molar ratio of benzo[b]thiophene to diphenylacetylene in tube 1 was 1:1, in tube 2, 2.5:1, in tube 3, 5.0:1, in tube 4, 7.5:1, and in tube 5, 10.0:1. Each tube was outgassed three times and sealed, after which the tubes were strapped around a Hanovia lamp and irradiated. The molar concentration of product was calculated from integration of the *tert*-butylbenzene singlet at 1.20 ppm and the two vinyl region protons of the adducts at 5.00 and 6.45 ppm. Spectra were taken at various time intervals and the buildup in product was recorded as a function of time.

Additions of Other Acetylenes to Benzo[b]thiophenes.—A solution of 1 g (0.008 mol) of benzo[b]thiophene, 1.3 g (0.011 mol) of 1,4-dimethoxybutyne-2, and 0.2 g (0.001 mol) of benzophenone in 100 ml of benzene irradiated for 7 days showed, after removal of the benzene, by vpc analysis (GE-SE-30 column, oven temperature 230°) no products. Even after prolonged radiation no products could be detected. 1,4-Dichlorobutyne-2 behaved similarly. When the same experiments were carried out using phenylacetylene and methylphenylacetylene, vpc analysis showed the formation of two products, but the yield was too small to identify these products even after prolonged radiation.

Addition of 2-Phenylacetylacetylene to Benzo[b]thiophene.—Benzo[b]thiophene (2 g, 0.015 mol), 2-phenyl-1-acetylacetylene (2.5 g, 0.017 mol), and acetophenone (0.5 g, 0.03 mol) were dissolved in 400 ml of benzene and irradiated for 20 hr. The benzene was removed on a rotating evaporator and vpc analysis (5-ft Carbowax, 10%, oven temperature 210°) showed the formation of two products in 4% yield.

Addition of Dichloromaleic Anhydride to Benzo[b]thiophene.—Benzo[b]thiophene (3 g, 0.022 mol), dichloromaleic anhydride (3 g, 0.017 mol), and benzophenone (0.25 g, 0.001 mol) were dissolved in 400 ml of benzene and irradiated for 16 hr. The benzene was removed on a rotating evaporator and vpc analysis (column GE-SE-30, oven temperature 240°) of the crude residue showed the formation of two products in 4 and 2% yield. The acetophenone and part of the benzo[b]thiophene were distilled *in vacuo*, and the dark residue was separated by preparative vpc (column GE-SE-30, oven temperature 225°). Isolated was 60 mg of XXIX which had the lowest retention time as very fine yellow needles: mp 149–150°; nmr δ 6.82 (s, 1 H) and 6.9–7.75 (phenyl H); ir 1245 (CO), 1622 (C=C), and 1784 and 1838 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity, fragment) 266 (32, M + 2), 264 (84, M^+), 192 (100, M − 72, C_2O_3), 157 (10.6, M − 107, C_2O_3Cl), and 132 (3, M − 132, C_4O_3ClH).

Thermal Rearrangement of 1,2-Dicarboxymethyl-5,6-benzo[3.0.2]bicyclo-7-thiaheptane-2,3 (I → XX) to Naphthalene-1,2-dicarboxylic Acid Dimethyl Ester.—I (3.56 g, 0.0128 mol) was dissolved in 5 ml of tetraethylene glycol dimethyl ether and heated for 15 min in a Woods metal bath thermostated at 240°.

(32) Samples for which high-resolution mass spectral molecular weights are reported were determined pure by vapor phase chromatography.

The dark-colored mixture was, after cooling, chromatographed over silica gel using CH_2Cl_2 as an eluting agent. By this procedure 2.6 g (0.016 mol, 82%) of XX was obtained, mp 77–79°. After five recrystallizations from CCl_4–hexane (3:5), we obtained 1.8 g of white crystals, mp 84° (lit.[32] mp 85°).

The thermal rearrangements of 1,2-dicarboxymethyl-4-methyl-5,6-benzo[3.0.2]bicyclo-7-thiaheptene-2,3 to 4-methylnaphthyl-1,2-dicarboxylic acid dimethyl ester (IV → XXI) and 1,2-dicarboxymethyl-3,4-dimethyl-5,6-benzo[3.0.2]bicyclo-7-thiaheptene-2,3 to 3,4-dimethylnaphthyl-1,2-dicarboxylic acid dimethyl ester (V → XXII) were carried out by the same procedure, yields 75%.

Thermal Rearrangement of 1-Carboxymethyl-5,6-benzo[3.0.2]-bicyclo-7-thiaheptene-2,3 (VI → XXIII) to α-Naphthylcarboxylic Acid Methyl Ester.—VI (1 g, 0.0045 mol) was in its pure form heated up in a Woods metal bath thermostated at 240° for 20 min. After 5–10 sec the mixture started to change color and the smell of sulfur was observable. The dark mixture was chromatographed over silica gel using CCl_4 as an eluting agent, yielding 0.65 g (77%) of pure methyl α-naphthoate: ir 1131 and 1276 (CO) and 1720 cm^{-1} (C=O); nmr δ 3.99 (s, OCH_3) and 7.3–8.1 (m, aromatic H).

The thermal rearrangement of 3-methyl-1-carboxymethyl-5,6-benzo[3.0.2]bicyclo-7-thiaheptene-2,3 (VII → XXIV) to 3-methylnaphthyl-1-carboxylic acid methyl ester was carried out in the same way: yields 70%; nmr δ 2.44 (s, CH_3), 3.93 (s, OCH_3), and 7.1–8.0 (m, aromatic H).

Thermal Rearrangement of 1-Phenyl-2-carboxymethyl-5,6-benzo[3.0.2]bicyclo-7-thiaheptene-2,3 (X → XXVI) to 1-Phenyl-2-naphthoic Acid Methyl Ester.—X (1 g, 0.0032 mol) was heated in a Woods metal bath thermostated at 240° for 10 min. After 5–10 sec the mixture became dark. The reaction was cooled and the mixture was chromatographed over silica gel using $HCCl_3$ as eluting agent to 0.72 g (81%) of pure 1-phenyl-2-naphthoic acid methyl ester. If very pure substance is required, one may purify this further by preparative vpc (column SE-30, oven temperature 260°), nmr δ 3.50 (s, OCH_3) and 7.0–7.9 (m, aromatic H).

The thermal rearrangement of 1-phenyl-2-carboxymethyl-3-methyl-5,6-benzo[3.0.2]bicyclo-7-thiaheptene-2-3 (XI → XXV) to 1-phenyl-3-methyl-2-naphthoic acid methyl ester was carried out in the same way: yields 80%; nmr δ 2.50 (s, CH_3), 3.5 (s, OCH_3), and 7.0–7.9 (aromatic H).

Registry No.—I, 31739-28-3; III, 24014-47-9; IV, 24014-46-8; V, 24014-48-0; VI, 31739-32-9; VII, 31739-33-0; X, 31739-34-1; XI, 31739-35-2; XIII, 31739-36-3; XV, 31739-37-4; XVI, 31739-38-5; XVII, 31739-39-6; XVIII, 31739-40-9; XXIX, 31739-41-0; XX, 10060-32-9; XXIII, 2459-24-7; XXIV, 31739-44-3; XXV, 31739-45-4; XXVI, 31790-95-1; dimethyl acetylenedicarboxylate, 762-42-5; benzo[*b*]-thiophene, 95-15-8; methyl propiolate, 922-67-8; 2-methylbenzo[*b*]thiophene, 1195-14-8; phenylpropiolic acid methyl ester, 4891-38-7; diphenylacetylene, 501-65-5; 2-phenylacetylene, 31739-46-5; dichloromaleic anhydride, 1122-17-4.

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Effects of Micelles on the Efficiency of Photoinduced Substitution Reactions and Fluorescence Quenching[1,2]

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The reactions of cyanide ion with photoexcited aromatic nitro compounds (4-nitrophenyl alkyl ethers, 1-nitronaphthalene, and 4-methoxy-1-nitronaphthalene) were examined in aqueous solutions containing micelles derived from hexadecyltrimethylammonium halide, sodium dodecyl sulfate, and mixtures of hexadecyltrimethylammonium halide and quaternary nitrogen detergents of the type $(CH_3)_3N^+(CH_2)_mOC_6H_4O(CH_2)_nCH_3$ (m = 4, 10; n = 0, 3, 7, 9). It was found that hexadecyltrimethylammonium chloride enhances the quantum yield of the reaction of 4-methoxy-1-nitronaphthalene by a factor of about 6800 and has little effect on the reaction of the 4-nitrophenyl alkyl ethers and that sodium dodecyl sulfate strongly inhibits the reactions of cyanide with nitroaromatics solubilized by the detergent. The results are rationalized on the basis of the effect of the micelles on both the local concentration of reactants and the character of the excited state of the nitroaromatic. Studies with the mixed micelles revealed that the efficiency of interaction of two organic groups (4-methoxy-1-nitronaphthalene and ROC_6H_4OR') can be altered by changing the relative position of these groups in the micelles. Thus, both the effectiveness of ROC_6H_4OR' as a quencher of the photoinduced reaction of the nitroaromatic with cyanide and the extent of quenching of fluorescence from ROC_6H_4OR' by the nitroaromatic were found to depend upon the position of the aromatic ring in the detergent (*i.e.*, on m and n) when the conditions favored micelle formation.

This paper reports results of a study of the effect of detergents on the course of some photochemical reactions of aromatic nitro compounds. The experiments were designed to test the extent to which rates of photoinduced bimolecular reactions might be influenced and controlled by exploiting local organizing and environmental effects of micelles.

That ionic detergents may appreciably alter rates of reaction of nucleophiles with organic substances in the ground state is well known.[3] For example, the rate of alkaline hydrolysis of 4-nitrophenyl esters of long-chain aliphatic acids is increased 8–18-fold by quaternary am-

(1) This research was supported by a grant from the National Science Foundation (GP-5 715).

(2) Part IX in the series on photoinduced substitution reactions. For part VIII, see K. E. Steller and R. L. Letsinger, *J. Org. Chem.*, **35**, 308 (1970).

(3) J. Baumrucker, M. Calzadilla, M. Centeno, G. Lehrmann, P. Lindquist, D. Dunham, M. Price, B. Sears, and E. H. Cordes, *J. Phys. Chem.*, **74**, 1152 (1970); C. A. Bunton and L. Robinson, *J. Org. Chem.*, **34**, 773, 780 (1969); **35**, 733 (1970); *J. Amer. Chem. Soc.*, **91**, 6072 (1969); **92**, 356 (1970); *J. Phys. Chem.*, **74**, 1062 (1970). For a review of the earlier literature, see E. H. Cordes, *Accounts Chem. Res.*, **2**, 329 (1969).

monium detergents[4] and is severely retarded by sodium dodecyl sulfate.[5] Utilization of detergent solutions as media for bimolecular photochemical reactions appeared attractive since micelle solutions transparent in the ultraviolet region could be prepared, the reactions could be initiated and terminated at will after the components have been thermally equilibrated, and micelles might in principle affect photochemical reactions by altering the properties of the excited states of the substrates as well as by changing the local concentration of the reactants.

Results

Reactions with Cyanide.—The reaction of cyanide ion with photoexcited nitroaromatics was selected to test the effect of detergents on a photochemical reaction involving an anion and a neutral organic species. Initial experiments were carried out with 4-nitroanisole which, on irradiation in aqueous solution in absence of detergents, reacts readily with cyanide ion and oxygen to give 2-cyano-4-nitroanisole and with hydroxide ion to give a mixture of 4-nitrophenoxide and 4-methoxyphenoxide.[6] The data in Table I show that

TABLE I

QUANTUM YIELDS FOR REACTIONS OF 4-$ROC_6H_5NO_2$ IN WATER

R	Detergent (0.01 *M*)	Nucleophile (0.01 *M*)	Φ
CH_3			0.0002
CH_3		OH^-	0.026
CH_3	HDTCl	OH^-	0.020
CH_3	SDS	OH^-	0.026
$C_{10}H_{21}$	HDTCl	OH^-	0.024
$C_{10}H_{21}$	SDS	OH^-	~0.0003
CH_3		CN^-	0.32
CH_3	HDTCl	CN^-	0.18
$C_{10}H_{21}$	HDTCl	CN^-	0.21

neither hexadecyltrimethylammonium chloride (HDTCl) nor sodium dodecyl sulfate (SDS) at 0.01 *M* concentration has an appreciable effect on the quantum yield for disappearance of 4-nitroanisole in these photoreactions, the value being within a factor of two of that in the detergent-free solution in each case. This result corresponds to the absence of a significant effect of detergents on the rate of alkaline hydrolysis of 4-nitrophenyl acetate[5] and may be rationalized by the assumption that 4-nitroanisole resides and reacts preponderantly in the aqueous medium outside the micelles.

Decyl 4-nitrophenyl ether was selected as a representative substrate possessing both the 4-nitrophenoxy chromophore and an apolar chain sufficiently long to ensure incorporation of the substrate in the micelles. It was prepared and found to be essentially insoluble in water (Table II) but readily solubilized by aqueous solutions of HDTCl and SDS. In contrast to 4-nitroanisole, no photoreaction was observed between decyl 4-nitrophenyl ether and cyanide ion in 0.01 *M* aqueous SDS (Table I). The inhibitory effect of the anionic detergent on the reaction of cyanide ion is in accord with expectations based on studies of effects of detergents on reactions of neutral molecules with hydroxide ion[5] and provides evidence that the substrate is indeed closely associated with the micelles in this sytem. On the other hand, the efficiency of the photoreaction of decyl 4-nitrophenyl ether with cyanide in the aqueous HDTCl medium was about the same as that of cyanide with 4-nitroanisole in either water or aqueous HDTCl (Table I); that is, incorporation of the nitrophenoxy chromophore in the positively charged micelles did not lead to enhancement in the efficiency of reaction with an anionic nucleophile.

TABLE II

PROPERTIES OF NITROAROMATICS

	Solubility[a] in $H_2O \times 10^4$ (*M*)	λ_{max}, nm		
		H_2O	Detergent[b]	CH_3CN[c]
4-Nitroanisole	6.5	316	315	308
Decyl 4-nitrophenyl ether	~0.024		315	309
1-Nitronaphthalene	2.3	343	338	334
4-Methoxy-1-nitronaphthalene	0.44	380	370	365

[a] Determined spectrometrically from uv absorption spectra of saturated solutions. [b] 0.01 *M* hexadecyltrimethylammonium chloride in H_2O. [c] 90% CH_3CN–10% H_2O.

Attention was then turned to the naphthalene derivatives, 1-nitronaphthalene and 4-methoxy-1-nitronaphthalene, which absorb at considerably longer wavelengths than the nitrophenyl ethers. Control experiments showed both compounds to be relatively stable when irradiated in water or aqueous organic or aqueous detergent solutions, the quantum yield for disappearance of the nitroaromatic being of the order of 2×10^{-3} for 1-nitronaphthalene and 2×10^{-4} for 5-methoxy-1-nitronaphthalene.

When 1-nitronaphthalene was irradiated in an aqueous solution containing cyanide ion, the maximum at 343 nm decreased and a new maximum developed at 300 nm, the position for λ_{max} for 1-cyanonaphthalene. That replacement of the nitro group by the cyano group occurred was confirmed by isolation of 1-cyanonaphthalene. Data for quantum yields for disappearance of 1-nitronaphthalene for reactions in water and in aqueous detergent solutions are presented in Table III. A

TABLE III

REACTION OF 1-NITRONAPHTHALENE WITH CYANIDE

Detergent (*M*)	KCN, mol/l.	Φ[a]
	0.004	0.06
	0.008	0.10
	0.020	0.17
	0.040	0.26
	0.010	0.10[b]
HDTCl (0.001)	0.004	0.06
HDTCl (0.008)	0.004	0.14
HDTCl (0.010)	0.004	0.11
HDTCl (0.020)	0.010	0.07
SDS (0.010)	0.004	0.035

[a] In H_2O. [b] In H_2O–CH_3CN (80:20).

plot of $1/\Phi$ *vs.* $1/[CN^-]$ for the reaction in water yields a straight line (intercept = 2.6); accordingly, this reaction, like that of cyanide with photoexcited 4-nitroanisole,[6] conforms to a scheme in which cyanide ion attacks the photoexcited nitroaromatic in a bimolecular process. Hexadecyltrimethylammonium chloride

(4) L. R. Romsted and E. H. Cordes, *J. Amer. Chem. Soc.*, **90**, 4404 (1968).

(5) M. T. A. Behm, J. G. Fullington, R. Noel, and E. H. Cordes, *ibid.*, **87**, 266 (1965).

(6) R. L. Letsinger and J. H. McCain, *ibid.*, **91**, 6425 (1969).

(0.01 M) increased the efficiency of the photochemical reaction by a factor of ~2-fold at $[CN^-] = 0.004$ M, whereas sodium dodecyl sulfate retarded the reaction.

Cyanide ion in aqueous solution also displaced nitrite from photoexcited 4-methoxy-1-nitronaphthalene, yielding 4-methoxy-1-napthonitrile; however, the reactivity of the photoexcited species was very low. Even at a cyanide concentration of 0.8 M the quantum yield for disappearance of 4-methoxy-1-nitronaphthalene was only 0.0017 (Table IV). When the photoreaction

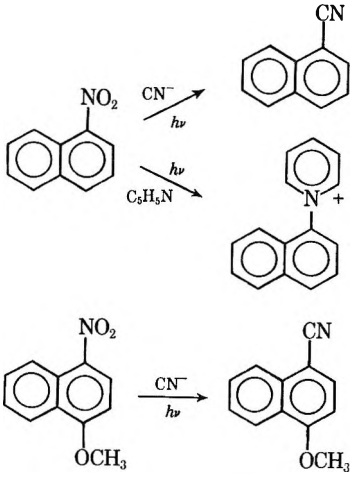
TABLE IV

REACTION OF 4-METHOXY-1-NITRONAPHTHALENE WITH CYANIDE

Detergent (0.01 M)	KCN, mol/l.	Φ[a]
	0	0.00015
	0.02	0.00020
	0.10	0.00035
	0.20	0.00048
	0.40	0.0009
	0.80	0.0017
HDTCl	0.004	0.068
HDTCl	0.006	0.091
HDTCl	0.010	0.130
HDTCl	0.020	0.168
SDS	0	0.00015
SDS	0.004	0.00015

[a] Quantum yield for disappearance of nitroaromatic at 375 nm. The solvent was water for solutions containing HDTCl and SDS and was water–*tert*-butyl alcohol (80:20) for detergent-free solutions.

was carried out in the presence of hexadecyltrimethylammonium chloride, a remarkable enhancement in quantum yield was observed. For reaction in an aqueous solution 0.01 M in KCN and 0.01 M in HDTCl, the quantum yield for disappearance of 4-methoxy-1-nitronaphthalene was 0.13, which corresponds to a 6800-fold enhancement relative to the quantum yield ($\Phi = 1.9 \times 10^{-5}$) for a reaction conducted in the absence of detergent.[7] From a preparative scale reaction conducted in the detergent medium, 4-methoxy-1-naphthonitrile was isolated as the sole material extractable with ether after



(7) The value for the homogeneous solution was interpolated from the data in Table IV after subtracting the quantum yield for decomposition of 4-methoxy-1-nitronaphthalene in the absence of cyanide. Because of the low solubility of 4-methoxy-1-nitronaphthalene in water, water–*tert*-butyl alcohol (80:20) was used as a solvent for the homogeneous solutions. Control experiments conducted with very low concentrations of the nitroaromatic in water showed that Φ for reaction in the mixed solvent represents an upper limit for the reaction in pure water.

precipitation of the detergent with a cation exchange resin. It may be noted that no photinduced reaction with cyanide was observed when the anionic detergent SDS, was used to solubilize the nitroaromatic.

Solvent Effects.—To assist in the interpretation of these results, an investigation of the effects of solvents on the efficiency of the photoinduced reactions of nitroaromatics with cyanide ion was undertaken. Preliminary studies, which have been published,[8] showed that a shift from 90% water–10% acetonitrile to 90% acetonitrile–10% water reduced the efficiency of reaction of potassium cyanide (0.01 M) with 4-nitroanisole by a factor of 50, had little effect on the reaction with 1-nitronaphthalene, and greatly enhanced the reaction with 4-methoxy-1-nitronaphthalene. Additional data on 4-methoxy-1-nitronaphthalene presented in Table V confirm the conclusion that solvents of low

TABLE V

EFFECTS OF SOLVENTS ON PHOTOREACTIONS OF 4-METHOXY-1-NITRONAPHTHALENE WITH CYANIDE

Organic component[a] of solvent (%)	[KCN], mol/l.	Φ
tert-Butyl alcohol (40)	0.01	0.0007
tert-Butyl alcohol (90)	0.01	0.038
Dioxane (80)	0.01	0.032
Dioxane (90)	0	0.002
	0.004	0.057
	0.006	0.074
	0.010	0.12
Acetonitrile (90)	0	0.0004
	0.004	0.0092
	0.010	0.021
	0.020	0.036
Acetonitrile (95)	0	0.0004
	0.0004	0.021
	0.006	0.029
	0.010	0.047

[a] The other component was water.

polarity favor the photochemical reaction of this nitroaromatic with cyanide ion. Indeed, the quantum yields in aqueous 90% acetonitrile, dioxane, or *tert*-butyl alcohol are comparable to those in the cationic detergent solution, and these organic solvents serve as good media for preparative scale reactions.

Aside from the influence of solvents on the character of the excited state of the nitroaromatic,[8] one would expect a shift to a less polar solvent to retard a reaction of a neutral organic substrate with an electrically neutral nucleophile as a consequence of the charge separation that develops in the transition state. In agreement with this expectation, photoexcited 1-nitronaphthalene was found to react readily with pyridine in a medium predominately water (80:20 water–*tert*-butyl alcohol) to give the 1-naphthylpyridinium ion, which was obtained in 89% yield as a picrate. When the solvent was 90:10 acetonitrile–water, the efficiency was only $^1/_{25}$th of that for the more polar medium.

Quenching by ROC_6H_4OR'.—Having found that the photoinduced reaction of 4-methoxy-1-nitronaphthalene with cyanide ion in aqueous media was greatly facilitated by the detergent HDTCl, we next inquired into the possibility of modifying the reactivity of the nitroaromatic by means of aromatic fragments

(8) R. L. Letsinger and R. R. Hautala, *Tetrahedron Lett.*, 4205 (1969).

aligned in the micelles. For this purpose detergents I–IV, possessing 1,4-dioxybenzene moieties four to ten carbon atoms removed from the quaternary nitrogen, were synthesized and were used to solubilize 4-methoxy-1-nitronaphthalene. It was of interest to see if the dioxybenzene fragments would inhibit the reaction of the nitroaromatic with cyanide and whether the extent of inhibition would depende upon the position of the inhibitory group in the micelles. The selection of this particular aromatic function was based on the previous observation that 1,4-dimethoxybenzene inhibits the photoreaction of 4-nitroanisole with cyanide, apparently *via* formation of a complex between the dimethoxybenzene and the excited nitroaromatic.[2]

I, $(CH_3)_3\overset{+}{N}(CH_2)_{10}OC_6H_4OCH_3\ Br^-$

II, $(CH_3)_3\overset{+}{N}(CH_2)_{10}OC_6H_4O(CH_2)_3CH_3\ Br^-$

III, $(CH_3)_3\overset{+}{N}(CH_2)_{10}OC_6H_4O(CH_2)_7CH_3\ Br^-$

IV, $(CH_3)_3\overset{+}{N}(CH_2)_4OC_6H_4O(CH_2)_9CH_3\ Br^-$

To minimize intrinsic differences in the ability of the modifier detergents to form micelles, hexadecyltrimethylammonium bromide was used as a support detergent to form mixed micelles.[9] Irradiation was carried out with the monochromator set at 375 nm in order to ensure that the light was absorbed by 4-methoxy-1-nitronaphthalene rather than by the dioxybenzene groups. The data in Table VI show that the detergents possessing dialkoxybenzene groups do function as inhibitors of the photochemical reaction and, further, that the extent of inhibition depends upon the position of the dialkoxybenzene moiety in the apolar chain of the detergent. Detergent IV is the most effective. At a concentration of 5×10^{-4} *M* it reduces the efficiency of the photoinduced substitution reaction of 4-methoxy-1-nitronaphthalene by a factor of 9.7. As the relative concentration of this detergent is increased the quenching factor increases, reaching 50 when the quencher detergent is present at 2×10^{-3} *M*. Detergent I is the least active and II and III are of intermediate activity. For comparison it may be noted that $\Phi_0/\Phi = 1.5$ for quenching of the reaction of 4-methoxy-1-nitronaphthalene with cyanide by 1,4-dimethoxybenzene at 5×10^{-4} *M* in homogeneous solution (95% acetonitrile–5% water).

TABLE VI

EFFECT OF QUENCHER DETERGENTS ON REACTION OF 4-METHOXY-1-NITRONAPHTHALENE (10^{-4} *M*) WITH CYANIDE (10^{-2} *M*)

Quencher detergent	Molarity × 10^3	HDTBr molarity × 10^3	Φ_0/Φ
None		2.0	1.0
I	0.5	1.5	1.5
II	0.5	1.5	5.3
III	0.5	1.5	5.6
IV	0.5	1.5	9.7
IV	1.0	1.0	24.0
IV	2.0	0	50.0

(9) That mixed micelles are formed when different detergents of like charge are mixed has been demonstrated by H. Inoue and T. Nakagawa, *J. Phys. Chem.*, **70**, 1108 (1966).

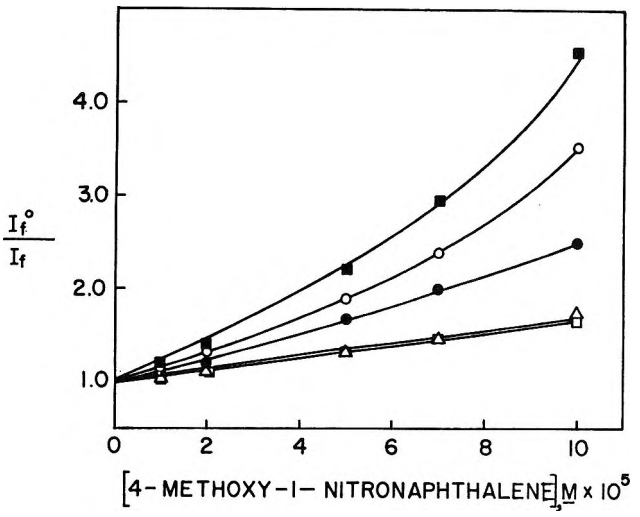


Figure 1.—Quenching of fluorescence from ROC_6H_4OR' in detergents I (□), II (●), III (■), and IV (○) by 4-methoxy-1-nitronaphthalene in 2×10^{-3} *M* hexadecyltrimethylammonium bromide in water and quenching of fluorescence from 1,4-dimethoxybenzene by 4-methoxy-1-nitronaphthalene in methanol (△).

Fluorescence Quenching.—Previous work has shown that a nitroaromatic will quench the fluorescence of a 1,4-dialkoxybenzene in homogeneous solution.[2] Accordingly, detergents I–IV may be used to study another question; namely, to what extent does micellar organization influence the interaction of organic fragments as measured by fluorescence quenching? For this study solutions were prepared that contained hexadecyltrimethylammonium bromide as the primary detergent (2×10^{-3} *M*), one of the quencher detergents (compounds I–IV, 1×10^{-4} *M*), and 4-methoxy-1-nitronaphthalene (at concentrations ranging from 0 to 10^{-4} *M*). The solutions were then irradiated at 290 nm to excite the dialkoxybenzene groups, and the fluorescence from these groups was measured.

As shown in Figure 1, the extent of quenching of fluorescence from the dialkoxybenzene groups does depend on the position of this group in the detergent molecules as well as on the concentration of the quencher, 4-methoxy-1-nitronaphthalene. Fluorescence quenching was most extensive in the case of III, in which the aromatic fragment is bounded by the longest apolar carbon chains, and was least in the case of I, in which the aromatic fragment resides at the end of the detergent molecule. Indeed, the extent of interaction of the nitroaromatic and dialkoxybenzene fragment measured by fluorescence quenching is no greater for the detergent system containing I than for solutions of 1,4-dimethoxybenzene and 4-methoxy-1-nitronaphthalene in homogeneous solution in methanol.

Organic solvents such as methanol are known to break up or "denature" micelles. Accordingly, if the variations in quenchability of fluorescence in the detergent solutions in fact stem from the micellar organization, the variations should disappear when sufficient methanol is added to afford solutions free of micelles. As a test of this point the experiments reported in Figure 1 were repeated with a solvent consisting of aqueous methanol (40% methanol) in place of water. For this set of experiments all detergents were found to behave identically and the plot of I_f^0/I_f *vs.* molarity of

4-methoxy-1-nitronaphthalene was superimposable on the curve for 1,4-dimethoxybenzene in Figure 1.

The ultraviolet spectra of dilute solutions of I–IV (1×10^{-4} *M*) in water exhibit a maximum at 287 nm. For comparable solutions that are also 4×10^{-3} *M* in HDTBr, λ_{max} shifts to longer wavelengths for II, III, and IV and is unchanged for I (see Table VII). These

TABLE VII

Detergent	Formula[a]	Mp, °C	λ_{max}, nm[b]
I	$C_{20}H_{36}NO_2Br$	151–152	287
II	$C_{23}H_{42}NO_2Br \cdot {}^1/_2H_2O$	196–197	289
III	$C_{27}H_{50}NO_2Br$	213–214	290, 350 (sh)
IV	$C_{23}H_{42}NO_2Br \cdot {}^3/_4H_2O$	132–134	290, 350 (sh)

[a] Satisfactory analytical data were reported for I, II, III, and IV (H for IV was a little low: calcd H, 9.57; found H, 9.20). [b] For solutions 1×10^{-4} *M* in specified detergent and 4×10^{-3} *M* in HDTBr. In absence of HDTBr λ_{max} was 287 nm (ϵ 2250 ± 100) in all cases. For comparison, 1,4-dimethoxybenzene shows maxima at 286 nm in water and at 289, 291, and 300 nm in hexane.

results suggest that I is not incorporated into the micelles of HDTBr, whereas the other detergents are. The low quenching efficiency for I can therefore be ascribed at least in part to the fact that most of this reagent resides in solution outside the micelles that contain the nitroaromatic. The difference in effectiveness of III and IV, however, appears to stem from differences in orientation of the dioxybenzene group within the micelles.

Discussion

Three systems were employed to examine the effects of micelles on photochemical processes in aqueous media. These utilized (a) the reaction of two components (cyanide and an aromatic nitro compound) "organized" by a simple anionic or cationic detergent, (b) competitive reactions involving three components (cyanide, 4-methoxy-1-nitronaphthalene, and ROC_6H_4OR' in compounds I–IV) organized within cationic micelles, and (c) fluorescence quenching involving two aromatic substances (ROC_6H_4OR' in compounds I–IV and 4-methoxy-1-nitronaphthalene) arranged in cationic micelles.

A wide range in the effects of simple ionic detergents was found. Of special interest are the magnitudes of the effects of hexadecyltrimethylammonium chloride on the photoreactions. Enhancements in the quantum yield in the detergent media relative to water ranged from 6800 for 4-methoxy-1-nitronaphthalene to 2 for 1-nitronaphthalene to zero for the nitrophenyl ethers. Previous discussions of effects of micelles on reaction rates have emphasized the effect of the detergent on the local concentration of reactants. Thus some enhancement in rate of reaction of cyanide with a neutral molecule solubilized by a quaternary nitrogen detergent would be expected since anions should be concentrated at the surface of the micelles containing the aromatic. The 6800-fold enhancement observed for the reaction of 4-methoxy-1-nitronaphthalene, however, is far out of the range characteristically observed for micellar effects on ground-state reactions and indicates that some other factor must be important. We believe the additional factor to be the change in the local environment (from water to the less polar water–hydrocarbon medium within the micelles), which can influence the reactivity of the excited state of the nitroaromatic. This conclusion is based on the strong dependence on solvent observed for quantum yields of photoinduced aromatic substitution reactions in the homogeneous solutions.[8] A decrease in solvent polarity greatly favors the reaction of photoexcited 4-methoxy-1-nitronaphthalene with cyanide, has little effect on the corresponding reaction of 1-nitronaphthalene, and strongly retards the reaction of a 4-nitrophenyl alkyl ether. Accordingly, the concentration and medium factors augment each other in the case of 4-methoxy-1-nitronaphthalene, with the result that an unusually large enhancement is observed, and they counteract each other in the case of a 4-nitrophenyl alkyl ether, with the result that little change in effective rate is apparent. The small enhancement for 1-nitronaphthalene is in accord with the expectation that only the concentration factor is important in this case; however, it should be noted that a large enhancement here would not be possible since the quantum yield for the reference reaction in water is relatively high.

That reactions of photoexcited 4-nitrophenyl decyl ether, 1-nitronaphthalene, and 4-methoxy-1-nitronaphthalene with cyanide are very inefficient in the presence of sodium dodecyl sulfate may be ascribed to the effect of the detergent on the concentration of reactants, cyanide ion being effectively screened from the nitroaromatic solubilized in the micelles. In view of the relatively high solubility of 4-nitroanisole in water and the fact that sodium dodecyl sulfate has no effect on the photoinduced reaction of 4-nitroanisole with cyanide, it seems highly probable that little of the 4-nitroanisole is incorporated in the micelles and that most of the photochemical reaction in this case occurs in the aqueous medium outside the micelles.

The experiments with the mixed micelles are of interest in that they demonstrate that three different types of reactants (an anion, a neutral molecule, and an aromatic fragment bearing a positive charge) can be assembled in a given micelle. Furthermore, the finding that the effectiveness of ROC_6H_4OR' in quenching the excited state of 4-methoxy-1-nitronaphthalene (as observed by inhibition of reaction of the nitroaromatic with cyanide) depends on the position of the dioxybenzene group in the hydrocarbon chain of the detergent indicates that photochemical reactions can be influenced or controlled by tailor-made molecules that affect the arrangement of groups within micelles. This conclusion is supported by the experiments that show that the quenching of fluorescence from ROC_6H_4OR' by interaction with 4-methoxy-1-nitronaphthalene is dependent on the position of the dioxybenzene group in the detergent molecule when micelles are present (*i.e.*, when the reaction is carried out in water) and is independent of the position of the dioxybenzene group in the detergent when the micellar structure is destroyed (*i.e.*, when the solution is "denatured" by addition of methanol). The differences in relative activity of III and IV as measured by quenching of the reaction of 4-methoxy-1-nitronaphthalene (Table VI) and by fluorescence quenching (Figure 1) probably reflect differences in the position of the functional groups in the micelles and differences in the geometrical requirements for the two types of interactions. Quenching of the photochemical

reaction probably involves intimate molecular contact between the two interacting species, whereas fluorescence quenching can occur over relatively large distances.

Experimental Section

Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill., or by Miss Hilda Beck, Northwestern University. Melting points were taken on a Thomas hot-stage apparatus and are corrected. Ultraviolet, infrared, and nmr spectra were recorded on a Cary 11, a Baird AB-2, and a Varian A-60 spectrometer, respectively.

Fluorescence spectra were recorded on a Hitachi Perkin-Elmer spectrometer (MPF-2A) with an excitation wavelength of 290 nm (excitation slit set at 4 and emission slit at 12). The observed intensities were corrected for absorption by 4-methoxy-1-nitronaphthalene by use of eq 1, where I_f^{cor} is the corrected intensity, I_f is the observed intensity, A is the absorbance of a reaction solution containing the methoxynitronaphthalene, and A' is the absorbance of the reaction solution without the methoxynitronaphthalene.

$$I_f^{cor} = I_f\left[\frac{A'(1 - 10^{-A})}{A(1 - 10^{-A'})}\right] \quad (1)$$

Quantum Yields.—Quantum yields were measured using a Bausch and Lomb monochromator (slits: 2 mm rear and 1 mm front) equipped with a 200-W Osram super pressure mercury arc. The wavelength of irradiation was near the absorption maximum of the nitroaromatic (Table II), a feature which minimizes any error in evaluating the quantity of light absorbed by the reactant. Quartz cuvettes equipped with Teflon microstirring bars were used as photolysis vessels. They were held in thermostated (25°) cell holders during irradiation and the extent of reaction was followed by the change in absorbance at the wavelength used for irradiation. In the course of the reaction, the absorbance fell to approximately one-third (for the nitrophenyl ethers) or one-fourth (for naphthalene derivatives) the initial value. The quantum yield, Φ, was evaluated by use of eq 2, where A and A_0 are absorbances at time t and t_0, respectively, ϵ is the molar extinction coefficient, and I is the incident intensity in einsteins/cm^{-2}/sec.[10] The incident intensity was determined before and after each photolysis by use of a ferrioxalate actinometer, and values for Φ were obtained from slopes of plots of the left hand portion of eq 2 against time. When the products of a reaction also absorbed at the wavelength of irradiation, it is necessary to correct the "raw" absorbance, A', which represents the sum of the absorbance of reactant and products. This correction was handled in the usual way by the relationship:[10] $A = A_0(A' - A_\infty)/(A_0 - A_\infty)$.

$$A_0 - A + \log\frac{1 - 10^{-A_0}}{1 + 10^{-A}} = \Phi\epsilon I(1000)(t - t_0) \quad (2)$$

Decyl 4-Nitrophenyl Ether.—Sodium 4-nitrophenoxide (6.0 g, 37 mmol) and 1-bromodecane (5.0 ml, 25 mmol) were heated in refluxing dimethylformamide (50 ml) for 19 hr, whereupon the solution was cooled and poured onto ice. Filtration and recrystallization of the precipitate from ethanol–water afforded 4.35 g (87%) of decyl 4-nitrophenyl ether, which on recrystallization melted at 42.5–43°: λ_{max} 309 nm (ϵ 10,900) (in acetonitrile); nmr ($CDCl_3$) τ 1.86 (2 H, d, J = 9.0 Hz), 3.07 (2 H, d, J = 9.0 Hz), 5.90 (2 H, t), 8.0–9.05 (19 H, m).

Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.99; H, 8.97; N, 5.00.

The other nitroaromatics were obtained from commercial sources and were recrystallized before use. Hexadecyltrimethylammonium chloride was purified by the method of Duynstee and Grunwald.[11]

Quencher Detergents.—The quencher detergents were all prepared in the same manner in a two-step sequence from the appropriate 4-alkoxyphenol. The procedure is represented by the synthesis of *N*,*N*,*N*-trimethyl-*N*-[4-(4′-decyloxyphenoxy)-butyl]ammonium bromide.

A methanolic solution of sodium methoxide, freshly prepared from 0.147 g (6.4 mmol) of sodium, was added to 1.60 g (6.4 mmol) of 4-(decyloxy)phenol (mp 71.5–72°) in anhydrous methanol. The solution was concentrated *in vacuo*, diluted with 50 ml of acetonitrile, and added dropwise over 2 hr to a refluxing solution of 1,4-dibromobutane (2.0 ml, 17 mmol) in 150 ml of acetonitrile. The solution was refluxed an additional 6 hr, cooled, and concentrated *in vacuo*. Ether and water were added to the mixture, and the resulting phases were extracted with 10% aqueous sodium hydroxide solution and ether. The ether layers were combined, dried over magnesium sulfate, and concentrated. Two recrystallizations from ethanol gave 1.37 g (57%) of the desired 1-bromo-4-(4′-decyloxyphenoxy) butane: mp 61–62°; nmr (CCl_4) τ 3.37 (4 H, s), 6.15 (4 H, t), 6.60 (2 H, t), 8.0–9.07 (23 H, m). To 0.70 g (18 mmol) of this ether in 30 ml of absolute ethanol was added through a Dry Ice–acetone condenser 7 ml (78 mmol) of trimethylamine. The solution was refluxed for 6 hr, concentrated *in vacuo*, and diluted with ether to precipitate the title compound (0.80 g, 99%). This material was dissolved in doubly distilled water, filtered through a fine-pore sintered-glass funnel, and lyophilized: mp 132–134°; nmr ($CDCl_3$) τ 3.16 (4 H, s), 6.11 (t) and 6.55 (s) (15 H total), 8.0–9.0 (m) with sharp signal at 8.7 and a distorted triplet at 9.09 (23 H total). The analyses for this compound and the related detergents in the series have been determined. All compounds in the series exhibited a maximum in the uv (water) at 287 nm with ϵ in the range of 2100–2360.

Preparative Photochemical Reactions. 4-Methoxy-1-naphthonitrile.—A Hanovia 450-W mercury lamp and immersion apparatus with a Pyrex filter sleeve were employed. The vessel, capacity 1100 ml, was equipped with a fritted-glass inlet for nitrogen and was cooled by a water condenser. For the reaction in aqueous acetronitrile, a solution containing 0.787 g of 4-methoxy-1-nitronaphthalene and 1.0 g of potassium cyanide in 740 ml of acetonitrile and 40 ml of water was irradiated for 90 min. The solution was then concentrated to 60 ml *in vacuo*, diluted to 160 ml with water, and extracted with three 200-ml portions of ether. The combined ether portions were dried, concentrated, and subjected to chromatography on a silica gel column (2.1 × 80 cm) with benzene–hexane (60:40) as solvent. In addition to 0.052 g of recovered 4-methoxy-1-nitronaphthalene there was obtained 0.458 g (70%) of 4-methoxy-1-naphthonitrile: mp 103–103.5° (lit.[12] mp 102.5, 104°); nmr τ 5.97 (3 H, s), 3.23 (1 H, d, J = 8.8 Hz), 2.23–2.53 (3 H, m), 2.19 (1 H, d, J = 8.8 Hz), 1.60–1.98 (2 H, m). This product also gave satisfactory analyses for C, H, and N.

For the reaction in the detergent solution, a solution was prepared from 0.203 g of 4-methoxy-1-nitronaphthalene, 0.651 g of potassium cyanide, and 3.96 g of hexadecyltrimethylammonium chloride in 1 l. of water. The mixture was photolyzed for 20 min in the immersion apparatus and then poured into a beaker and swirled with 60 g of Bio-Rex 70 resin (50–100 mesh, sodium form) to bind the detergent. The mixture was extracted with ether (500 ml) and worked up as before to give 0.098 g (54%) of 4-methoxy-1-naphthonitrile, mp 102.5–103° (mixture melting point undepressed).

Reaction of 1-Nitronaphthalene with Pyridine.—A solution containing 8.9 ml of pyridine and 47.6 mg (2.5×10^{-4} *M*) of 1-nitronaphthalene in 880 ml of water and 220 ml of *tert*-butyl alcohol was photolyzed in the Hanovia apparatus for 1 hr. It was then concentrated *in vacuo* at 40°, and a saturated aqueous solution of picric acid was added until no further precipitate appeared. The precipitate was collected and recrystallized from ethanol–acetone to give 82.1 mg (89%) of *N*-(1-naphthyl)-pyridinium picrate, mp 209–210°. A mixture melting point with a sample prepared independently from 1-napthylamine showed no depression.[13]

Anal. Calcd for $C_{21}H_{14}N_4O_7$: C, 58.07; H, 3.25; N, 12.90. Found: C, 58.02; H, 3.25; N, 12.84.

Reaction of 1-Nitronaphthalene with Cyanide.—A solution of 1-nitronaphthalene (50 ml, 5×10^{-4} *M*) and potassium cyanide

(10) R. R. Hautala, Doctoral Dissertation, Northwestern University, 1970. Other work in which descriptions of similar techniques for measuring quantum yields have appeared include A. Beckett and G. Porter, *Trans. Faraday Soc.*, **59**, 2038 (1963); R. O. de Jongh, Ph.D. Dissertation, University of Leyden, 1965; Y. Otsuji, T. Kuroda, and E. Imoto, *Bull. Chem. Soc. Jap.*, **41**, 2173 (1968).

(11) E. F. Duynstee and E. Grunwald, *J. Amer. Chem. Soc.*, **81**, 4540, 4542 (1959).

(12) A. Fischer, M. A. Riddolls, and J. Vaughy, *J. Chem. Soc. B*, 106 (1966); E. Lorz and R. Baltzly, *J. Amer. Chem. Soc.*, **73**, 93 (1951).

(13) Prepared by the general method of A. F. Vompe and N. F. Turitsyama, *Zh. Obshch. Khim.*, **28**, 2864 (1958).

(0.01 M) in acetonitrile–water (95:5) was irradiated in a Pyrex vessel with a General Electric 1000-W photochemical lamp for 425 sec. The solution was then shaken with a mixture of 150 ml of dichloromethane and 100 ml of aqueous 2 M sodium chloride solution. The organic layer was separated, washed with additional salt solution, dried, concentrated, and subjected to gas chromatography on a Hewlett-Packard Model 720 gas chromatograph equipped with dual 10 ft × 0.25 in. columns of 4.5% silicone gum rubber (GE-SE-52) on Chromosorb G. Only two substances were obtained from the reaction mixture: 1-cyanonaphthalene (51%) and unreacted 1-nitronaphthalene (31%). These compounds were characterized by their retention times, by infrared spectra, and by mixture melting point with authentic samples.

Registry No.—I, 31657-32-6; II, 31657-33-7; III, 31657-34-8; IV, 31657-35-9; 1-nitronaphthalene, 86-57-7; cyanide, 57-12-5; 4-methoxy-1-nitronaphthalene, 4900-63-4; decyl 4-nitrophenyl ether, 31657-37-1; 4-nitroanisole, 100-17-4; pyridine, 110-86-1; *N*-(1-naphthyl)pyridinium picrate, 31657-38-2; 1-bromo-4-(4′-decyloxyphenoxy)butane, 31657-39-3.

Photochemical [2 + 2] Cycloaddition Reactions at Low Temperatures. Synthesis of Bridgehead Substituted Bicyclo[*n*.2.0]dicarboxylates from Maleic Acid Derivatives and Ethylene

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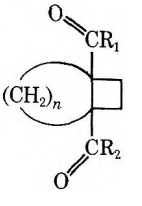
Irradiation through quartz at −65° or lower of ethylene saturated dichloromethane solutions of dimethyl cyclobutene-1,2-dicarboxylate, dimethyl cyclopentene-1,2-dicarboxylate, and cyclohexene-1,2-dicarboxylic anhydride produces the corresponding bicyclo [2.2.0], [3.2.0], and [4.2.0] derivatives in nearly quantitative yield in preparatively useful amounts with high quantum efficiency. Dimethyl cyclohexene-1,2-dicarboxylate does not add ethylene under a wide variety of experimental conditions. Maleic anhydride readily adds ethylene at low temperature in acetone to give a mixture of the maleic anhydride–acetone oxetane (21%) and cyclobutane-1,2-dicarboxylic anhydride (57%), while in an unreactive solvent the cyclobutane is the sole product (70%). Dimethyl acetylenedicarboxylate also reacts readily at low temperatures to add two molecules of ethylene to produce a 9:1 mixture (60–66% yield) of dimethyl bicyclo[2.2.0]hexane-1,4-dicarboxylate and dimethyl bicyclopropyl-1,1′-dicarboxylate. Dimethyl bicyclo[2.2.0]hexane-1,4-dicarboxylate is thermally converted to dimethyl α,α′-dimethyleneadipate with a half-life at 75° of about 53 min.

Photochemical [2 + 2] cycloaddition of olefins and/or acetylenes has provided an excellent route to a number of substituted cyclobutane and cyclobutene derivatives.[1-3] In most of the prior work, however, substituted olefins or acetylenes were the ground-state partners in the cycloadditions, giving substituted cyclobutanes or cyclobutenes. The use of ethylene[3] as the ground-state partner in [2 + 2] cycloadditions to give 1,2-disubstituted cyclobutanes has received much less attention. Furthermore, ethylene addition to a cyclic maleic acid derivative to give bridgehead dicarboxylate derivatives of bicyclo[*n*.2.0]alkanes has only recently been described.[4]

The use of low temperatures to carry out a variety of photochemical transformations can offer a number of distinct advantages. Among these are fewer undesirable side products which result from thermal reactions of the photoproduct, higher quantum yields, and greater solubility of gaseous reactants. We wish to report the results of some of our studies on the preparation of some 1,(*n* + 2)-bicyclo[*n*.2.0]alkanedicarboxylate derivatives **1**, where *n* = 2, 3, 4, by the photochemical cycloaddition of ethylene to the appropriate cyclic maleic acid derivatives, which show the advantages of low temperature preparative photochemistry.



1

where $R_1 = R_2 = OR', OH$; $R_1 =$

Results and Discussion

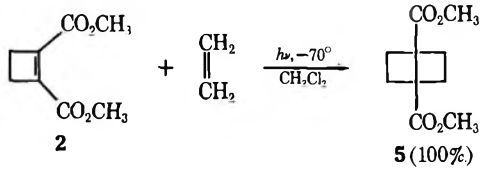
The additions of ethylene to dimethyl cyclobutene-1,2-dicarboxylate (**2**), dimethyl cyclopentene-1,2-dicarboxylate (**3**), and cyclohexene-1,2-dicarboxylic anhydride (**4**) were carried out by irradiation of solutions of each substrate at −70° in dichloromethane through quartz using a variable-temperature preparative photochemical reactor of our own design.[4a] Excellent yields of the bicyclo[*n*.2.0]alkane derivatives **5**–**7** were obtained in each case (eq 1–3). The use of low temperature and dichloromethane solvent to carry out these transformations is critical. For example, **2** gives a vari-

(1) Several reviews on these syntheses have appeared: (a) P. E. Eaton, *Accounts Chem. Res.*, **1**, 50 (1968); (b) W. L. Dilling, *Chem. Rev.*, **69**, 845 (1969); (c) P. G. Bauslaugh, *Syn.*, 287 (1970); (d) G. O. Schenck and R. Steinmetz, *Bull. Soc. Chim. Belg.*, **71**, 781 (1962).

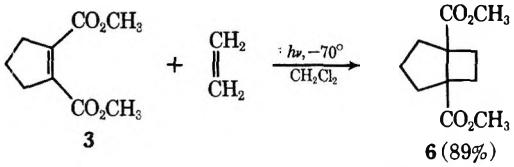
(2) For syntheses of cyclobutanes and cyclobutenes from substituted olefins and acetylenes, *cf.* (a) E. J. Corey, J. D. Bass, R. Lemathieu, and R. B. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964); (b) R. L. Cargill, J. R. Damewood, and M. M. Cooper, *ibid.*, **88**, 1330 (1966); (c) G. O. Schenck, W. Hartmann, and R. Steinmetz, *Chem. Ber.*, **96**, 498 (1963); (d) R. Steinmetz, W. Hartmann, and G. O. Schenck, *ibid.*, **98**, 3854 (1965); (e) G. R. Evanega and D. L. Fabiny, *Tetrahedron Lett.*, 2241 (1968); (f) H. Yamazaki and R. J. Cretanovi, *J. Amer. Chem. Soc.*, **91**, 521 (1969); (g) W. L. Dilling, T. E. Tabor, F. P. Boer, and P. P. North, *ibid.*, **92**, 1399 (1970).

(3) For cyclobutane synthesis with ethylene, *cf.* (a) H.-D. Scharf and F. Korte, *Chem. Ber.*, **98**, 764 (1965); (b) *Angew. Chem., Int. Ed. Engl.*, **4**, 429 (1965); (c) Y. Yamada, H. Uda, and K. Nakanishi, *Chem. Commun.*, 423 (1966); (d) P. H. Nelson, J. W. Murphy, J. A. Edwards, and J. H. Fried, *J. Amer. Chem. Soc.*, **90**, 1307 (1968); (e) P. E. Eaton, Abstracts of Papers, 156th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968; (f) P. E. Eaton and K. Nyi, *J. Amer. Chem. Soc.*, **93**, 2786 (1971); (g) W. C. Agosta and W. W. Lowrance, *Tetrahedron Lett.*, 3053 (1969).

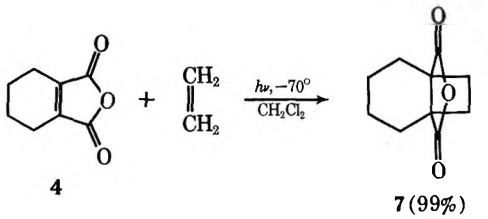
(4) (a) D. C. Owsley and J. J. Bloomfield, *Org. Prep. Proced., Int.*, **3**, 61 (1971); (b) *J. Amer. Chem. Soc.*, **93**, 782 (1971).



(1)



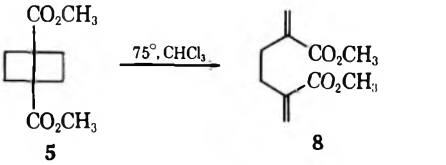
(2)



(3)

ety of products upon irradiation in ether at 0° in the presence of ethylene. The quantum efficiency of the photoreaction of **3** with ethylene drops off dramatically in dichloromethane at 10° (*vide infra*).

A structure proof of **5** is afforded by its facile rearrangement to the known dimethyl α,α'-dimethyleneadipate[5] (**8**) in quantitative yield (eq 4). Measure-

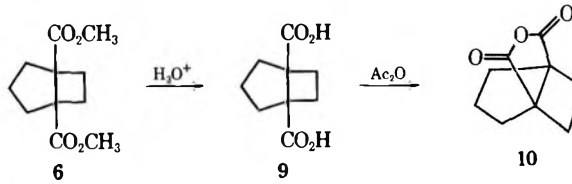


(4)

$k = 2.2 + 0.4 \times 10^{-4}$ sec^{-1}

ments of the isomerization rate at 75° gave a first-order rate constant of $2.2 \pm 0.4 \times 10^{-4}$ sec^{-1}.[4b,6] The rate of isomerization of **5** is approximately 10^8 times faster than that calculated for the rate of isomerization of unsubstituted bicyclo[2.2.0]hexane to 1,5-hexadiene ($k_{75°} = 4 \times 10^{-12}$ sec^{-1}).[7]

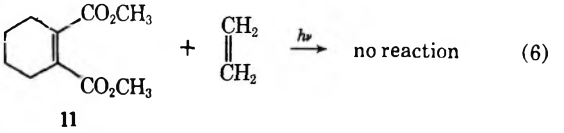
The structure and stereochemistry of the bicyclo[3.2.0]heptane derivative **6** was proved by hydrolysis to the diacid **9** and its subsequent conversion to the cyclic anhydride **10** (eq 5).



(5)

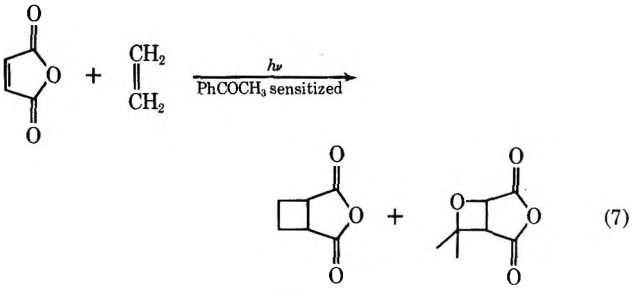
The structure of the bicyclo[4.2.0]octane derivative **7** was proved by comparison with an authentic sample.[8]

Strongly contrasting with the high reactivities of the cyclic maleic anhydride derivatives **2**, **3**, and **4** toward ethylene is dimethylcyclohexene-1,2-dicarboxylate (**11**) which could not be induced to react with ethylene under a variety of conditions (*vide infra*, eq 6).



(6)

The direct synthesis of cyclobutane-1,2-dicarboxylic anhydride **12** from ethylene and maleic anhydride has not previously been reported (eq 7), even though there

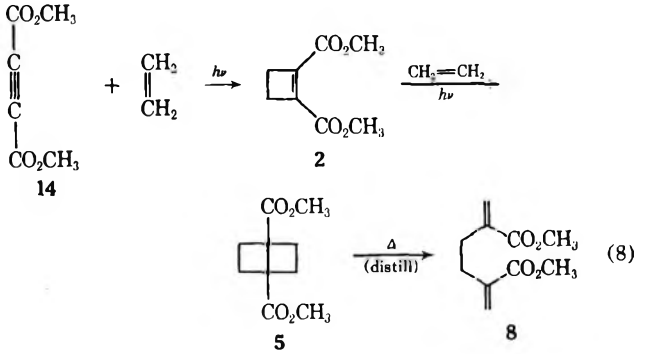


(7)

12, 50–71% **13** (in acetone solvent)

are numerous examples of either the reaction of substituted maleic anhydrides with ethylene or of substituted olefins with maleic anhydride.[1-3] For this reaction both the solvent and the reaction temperature are critical. At 5–10° reaction times are of the order of 1 week and the reactions are accompanied by polymer formation on the lamp housing. In acetone solvent, the formation of the oxetane[9] **13** represents an important side reaction. At or below −65°, the photolysis mixtures are quite clean and reaction times are on the order of 1–2 days. However, in acetone oxetane formation is still important, while in ethyl acetate **12** is produced in 71% yield as the sole product. None of the desired cycloaddition was observed in ether at 5–10°, but a white polymer was rapidly produced.

The cycloaddition of two molecules of ethylene to dimethyl acetylenedicarboxylate (**14**) offers an attractive, one-step synthesis of dimethyl α,α'-dimethyleneadipate (**8**) *via* a thermal rearrangement of the bicyclo[2.2.0]-hexane derivative **5** (eq 8). Thus, irradiation of a solu-



(8)

tion of **14** through quartz in dichloromethane at −80° and subsequent distillation afforded a 63% yield of a 9:1 mixture of **8** and an isomer **15** (eq 9). Monitoring

$$14 + 2CH_2{=}CH_2 \xrightarrow[CH_2Cl_2]{h\nu,\ -80°} 8 + 15\ (63\%) \quad (9)$$

9:1

(5) C. S. Marvel and S. D. Vest, *J. Amer. Chem. Soc.*, **81**, 984 (1959).

(6) The isomerization rate constant for **5** → **8** was incorrectly reported in our preliminary communication of this work (ref 4b). A complete study of the kinetics of this isomerization is now in progress in collaboration with J. Chickos of the University of Missouri, St. Louis.

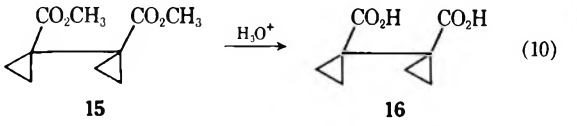
(7) (a) For a review of bicyclo[2.2.0]hexane chemistry, *cf.* K. B. Wiberg, *Advan. Alicycl. Chem.*, **2**, 230 (1968); (b) C. Steel, R. Zand, P. Hurwitz, and S. G. Cohen, *J. Amer. Chem. Soc.*, **86**, 679 (1964).

(8) (a) E. Vogel, D. Roos, and K. H. Disch, *Justus Liebigs Ann. Chem.*, **653**, 55 (1962); (b) R. A. Martin, Dissertation, University of Oklahoma, 1969.

(9) N. J. Turro and P. A. Wriede, *J. Org. Chem.*, **34**, 3562 (1969).

the reaction by glc showed that **2** was reacting very rapidly since it could not be detected.

That the minor product of the photolysis, **15**, was isomeric with both **5** and **8** was shown by its mass spectrum (see Experimental Section). The nmr and ir spectra of **15** are compatible with its formulation as dimethyl bicyclopropyl-1,1′-dicarboxylate.[10a] Final structure proof was afforded by its hydrolysis to the known bicyclopropyl-1,1′-dicarboxylic acid (**16**, eq 10).[10] The formation of **15** is not surprising in that



15 **16** (10)

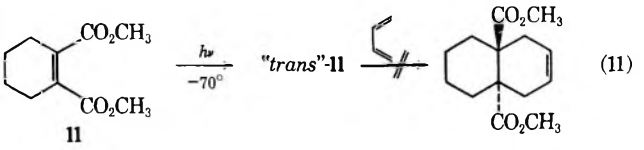
similar structures have been found in the photosensitized additions of maleic anhydride to acetylene and propyne,[11,12] of 3,6-dihydrophthalic anhydride to 2-butyne,[13] and of acetylenedicarboxylic acid to 1,4-cyclohexadiene.[14]

The solvent and temperature are again very important in the reaction of dimethyl acetylenedicarboxylate (**14**) with ethylene. Our experiments show that in ether solvent the primary reaction of **14** occurs with solvent rather than with ethylene. This type of behavior has previously been observed in cyclic ether solvents with both **14** and with diethyl fumarate,[15,16] in which the triplet states of these molecules are certainly involved.

The concerted cycloaddition of ground-state ethylene to an electronically excited π system to form a cyclobutane is a symmetry-allowed process.[17] However, it has been shown that the addition of substituted ethylenes to cyclic α,β-unsaturated ketones occurs through the triplet state of the ketones and that the products are derived from ring closures and intramolecular disproportionations of diradical intermediates.[1,2a] These data rule out a concerted reaction in these systems.

The nature of the excited state which is involved in the addition of ethylene to the cyclic maleic acid derivatives **2**–**4** cannot be ascertained on the basis of our data. The fact that one and only one product is formed in each case does not rule out the triplet states of **2**–**4** in the cycloadditions. This is supported by the fact that the same product is obtained in both the photosensitized[8] and unsensitized reaction of cyclohexene-1,2-dicarboxylic anhydride (**4**) with ethylene. Furthermore, no data have been obtained on the quantum yields of intersystem crossing from an excited singlet state to a triplet state of any cyclic or noncyclic maleic or fumaric acid derivative.[18]

The nonreactivity of dimethyl cyclohexene-1,2-dicarboxylate (**11**) toward ethylene was initially quite surprising. However, dimethyl cyclobutene-1,2-dicarboxylate (**2**), dimethyl cyclopentene-1,2-dicarboxylate (**3**), cyclohexene-1,2-dicarboxylic anhydride (**4**), and maleic anhydride all react with ethylene and make up a series of conformationally rigid molecules, while **11** may have some rotational freedom about the carbon–carbon double bond in the excited state. Therefore, it appears that the excited state of **11** may be conformationally different from those of **2**–**4** and maleic anhydride and may even be a *"trans"*-cyclohexene. 1-Acetylcyclohexene has been shown to undergo isomerization to a trans form.[1a] In an attempt to try to trap a hypothetical *"trans"*-**11**, a photolysis was performed in the presence of a large excess of butadiene at −70° (eq 11). No Diels–Alder product was formed (eq 11).



11 (11)

Baird[19] has noted that the equilibrium conformation of the lowest $^3\pi,\pi^*$ in a vibrationally relaxed, conjugated polyene has one of the double bonds twisted at an angle of 90°. Moreover, Lim, Li, and Li[20] have described the importance of out-of-plane vibrations in the vibronic coupling of n,π^* and π,π^* states of heteroaromatic and aromatic carbonyl compounds. Thus, the excited states of **11** may not only differ conformationally from those of **2**–**4** and maleic anhydride but also may differ electronically. Studies are presently under way to clarify this point.[18]

The formation of dimethyl bicyclopropyl-1,1′-dicarboxylate (**15**) in the photoaddition of ethylene to dimethyl acetylenedicarboxylate (**14**) needs to be discussed in some detail. Because similar products have been found in photoadditions which involve acetylenes as the ground-state partners,[11–14] the production of a product containing cyclopropane rings from an electronically excited acetylene must involve intermediates common to both types of reactions.

Hartmann[11] has proposed two types of intermediates to account for the formation of cyclopropyl compounds from triplet maleic anhydride and acetylene (eq 12, 13). Diradical intermediate **17** could give cyclobutene by spin relaxation and ring closure, while the carbene intermediate **18** could rearrange to cyclobutene.[21]

In Hartmann's case,[11] either intermediate can explain the results. However, the finding of bicyclopropyl compound **15** in the present case poses problems for an intermediate analogous to **17** and its reaction with ethylene (eq 14).

The site at which ethylene is required to attack **20** in order to ultimately give **15** is the site that is most sterically hindered and is the site at which the radical center is most highly stabilized. No products which would result from ethylene attack at the alternate site on **20** [*e.g.*, dimethyl cyclohexene-1,2-dicarboxylate (**11**)] have been found. Thus, because **11** is stable under these conditions (*vide supra*) an attack of ethylene on

(10) (a) J. M. Conia and J. M. Denis, *Tetrahedron Lett.*, 3445 (1969) (ir and nmr spectra of the diethyl ester); (b) L. Eberson, *Acta Chem. Scand.*, **13**, 46 (1959).

(11) W. Hartmann, *Chem. Ber.*, **102**, 3974 (1969).

(12) G. Klotzenberg, P. G. Fuss, and J. Leitch, *Tetrahedron Lett.*, 3409 (1966).

(13) R. Askani, *Chem. Ber.*, **98**, 3618 (1965).

(14) M. Takahashi, Y. Kitahara, I. Murata, T. Nitta, and M. C. Woods, *Tetrahedron Lett.*, 3409 (1966).

(15) P. Singh, *ibid.*, 2155 (1970).

(16) I. Rosenthal and D. Elad, *Tetrahedron*, **23**, 3193 (1967).

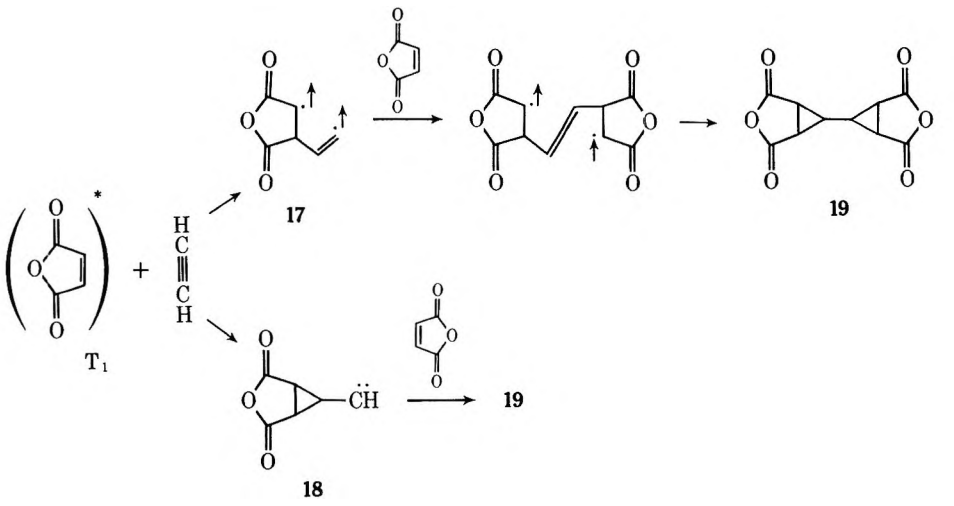
(17) *Cf.* R. B. Woodward and and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969), and references cited therein.

(18) We have obtained emission spectra of **2**–**4**, **14**, maleic anhydride, and maleic and fumaric esters. Quantum yields and lifetimes of fluorescence and phosphorescence are presently being studied in collaboration with D. R. Kearns of the University of California, Riverside.

(19) N. C. Baird, *Mol. Photochem.*, **2**, 153 (1970).

(20) E. C. Lim, Y. H. Li, and R. Li, *J. Chem. Phys.*, **53**, 2443 (1970).

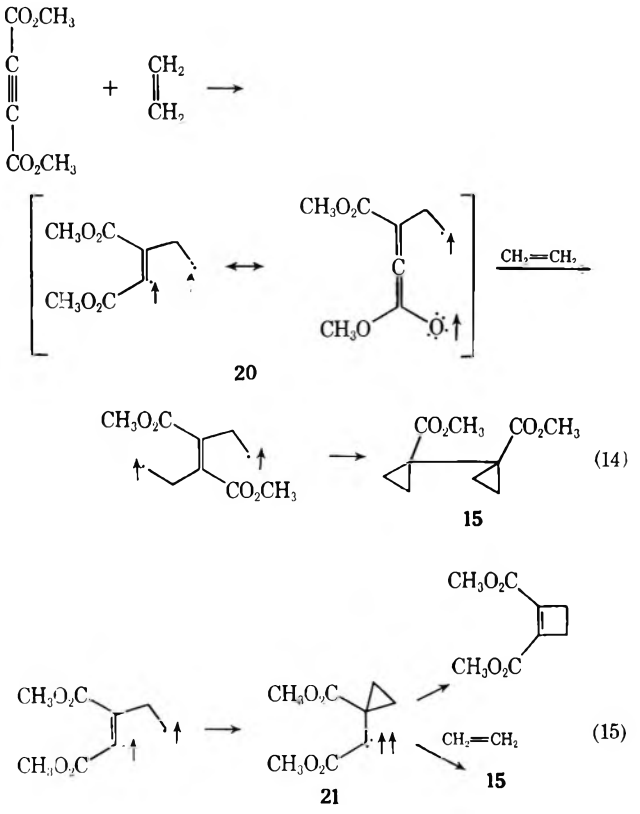
(21) L. Friedman and H. Schechter, *J. Amer. Chem. Soc.*, **82**, 1002 (1960).



(12)

(13)

20 is not very likely. An alternative pathway for decomposition of 20 is rearrangement to a triplet carbene 21 which is stabilized by an adjacent carbomethoxyl group (eq 15).[22] Askani's work[13] has a great deal of



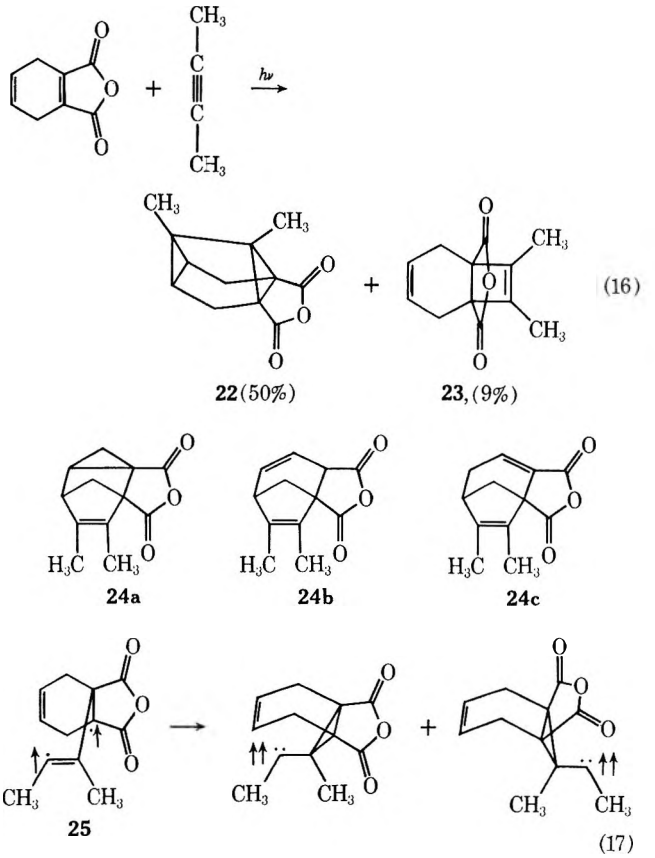
(14)

(15)

bearing on this point. The photosensitized addition of 2-butyne to 3,6-dihydrophthalic anhydride was found to give the products shown in eq 16, but 24a–c were not reported.

The formation of 22 and 23 in 50 and 9% yields, respectively, and the absence of products such as 24a–c strongly implies (1) formation of carbenes as intermediates and (2) their formation either directly or before spin–spin relaxation can occur in an intermediate such as 25 (eq 17).

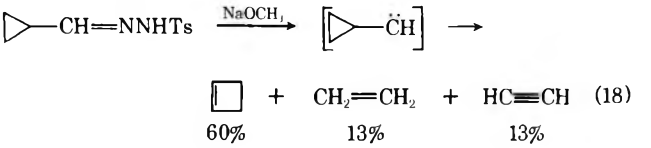
The work of Friedman[21] and others[23,24] shows that



(16)

(17)

cyclopropyl conjugated carbenes either rearrange to cyclobutenes or decompose to olefins and acetylenes (eq 18).



(18)

Application of the principle of microscopic reversibility to the previous results on cyclopropyl conjugated carbenes[21,23,24] implies that these species could be formed from acetylenes and olefins under photochemical conditions. The production of the cyclobutene (2) and bicyclo[2.2.0]hexane (5) derivatives from excited singlet dimethyl acetylenedicarboxylate and ethylene *via* a concerted process has not been discussed. Indeed, it may be the major pathway which produces 5.

(22) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, Chapter 6, p 95.
(23) W. Kirmse and K. H. Pook, *Chem. Ber.*, **98**, 4022 (1965).
(24) S. J. Cristol and J. K. Harrington, *J. Org. Chem.*, **28**, 1413 (1963).

However, this pathway does not explain the formation of the bicyclopropyl derivative **15**. Therefore, it may be likely that a multiplicity of pathways is necessary to account for the formation of both **5** and **15**.

Experimental Section

Microanalyses were carried out by Alfred Bernhardt Mikroanalytisches Laboratorium. Nmr spectra were recorded on either a Varian Associates T-60 or A-56/60 nmr spectrometer. Mass spectra were obtained on a Varian MAT CH-7 instrument.

Materials.—Dichloromethane (Mallinckrodt), tetrahydrofuran (THF) (Fisher), methanol (Mallinckrodt, anhydrous), and ethylene (Matheson, C. P. grade) were used without further purification. Pimelic acid (Eastman) was recrystallized from water. Thionyl chloride (Fisher reagent) and phosphorus pentachloride (J. T. Baker) were used directly from the bottle. Dimethyl acetylenedicarboxylate (Eastman White Label) was distilled before use. Dimethyl cyclobutene-1,2-dicarboxylate was prepared from 1,2-dicyanocyclobutane.[8,25] Cyclohexene-1,2-dicarboxylic anhydride was prepared by the phosphorus pentoxide catalyzed isomerization of 4-cyclohexene-1,2-dicarboxylic anhydride.[26] Dimethyl cyclopentene-1,2-dicarboxylate was prepared as previously described.[4a]

Reaction Kinetics.—The rate of the transformation **5** → **8** was followed at 75° in a Varian Associates A-56/60 nmr spectrometer with variable temperature probe. The probe temperature was calibrated by following the chemical shift of the hydroxyl protons of ethylene glycol as they varied with temperature. A solution of 50 μl of **5** in 0.5 ml of $CDCl_3$ with TMS and 20 μl of $CHCl_3$ as internal standards was prepared in an nmr tube. The reaction was followed by integrating the rise of the vinyl (at δ 6.06 and 5.47 ppm) and methoxy resonances (at δ 3.70 ppm) of **8** and the fall of the methoxy resonance of **5** (at δ 3.53 ppm). First-order plots were obtained which were linear to 3 half-lives. A first-order rate constant of 1.85×10^{-4} sec^{-1} was obtained for the rise of the vinyl protons of **8**, while a rate constant of 2.53×10^{-4} sec^{-1} was obtained for either the fall of the methoxy resonance of **5** or the rise of the methoxy resonance of **8**. We have no adequate explanation at present for these differences.[6]

Dimethyl Cyclohexene-1,2-dicarboxylate (11).—A solution of 100.0 g (0.66 mol) of cyclohexene-1,2-dicarboxylic anhydride[26] and 0.1 g of *p*-toluenesulfonic acid hydrate was prepared and stirred in 700 ml of methanol for 36 hr at room temperature. After the methanol had been stripped from the reaction mixture, the resulting clear oil was added to 156.8 g (0.75 mol) of phosphorus pentachloride in 500 ml of benzene. The mixture was stirred for 4 hr and was added to 1500 ml of absolute methanol. The methanol was chilled in a −8° cold bath and the rate of addition of the benzene solution was kept such that the temperature of the methanol never rose above −2°. The methanolic solution was concentrated *in vacuo* to yield an oil which was taken up in water (500 ml) and extracted four times with 400-ml portions of ether. The ether was washed four times with 200-ml portions of a 10% sodium bicarbonate solution and twice with 200-ml portions of water. It was then dried over magnesium sulfate and concentrated *in vacuo* to yield 86.1 g of a clear oil. The oil was fractionated through a 6-in. Vigreux column to yield 68.9 g (0.35 mol, 53%) of dimethyl cyclohexene-1,2-dicarboxylate, bp 84–85° (0.3 mm) [lit.[27] 75° (0.2 mm)].

Photochemical Cycloadditions. General Procedure.—All photochemical cycloadditions of ethylene were carried out using the variable temperature preparative reactor[4a] except where noted. Unless stated otherwise, the general procedure was as follows. The compound to be photolyzed was dissolved in 2800 ml of solvent in the reactor. Nitrogen was bubbled through the solution during cool down to −70 to −80°. Ethylene was then bubbled into the solution for 15–20 min at a flow rate of 6 l./min. Once the lamp was turned on, a flow rate of ethylene of 50–100 ml/min was maintained throughout the photolysis. All photolyses except for maleic anhydride reactions were carried out using unfiltered light from an Hanovia 450-W medium-pressure mercury arc.

Dimethyl Bicyclo[2.2.0]hexane-1,4-dicarboxylate (5).—Dimethyl cyclobutene-1,2-dicarboxylate[25] (**2**) (10 g, 0.058 mol) was irradiated in 2800 ml of dichloromethane for 2 hr at −70°. Then the −70° solution was sucked directly into a rotary film evaporator, the evaporation flask of which was held at −15° with an ice–acetone bath as the dichloromethane was stripped at 10-mm pressure. The flask was allowed to warm to 0° in order to remove the last traces of solvent. Dimethyl bicyclo[2.2.0]-hexane-1,4-dicarboxylate (**5**) was obtained in this manner in 100% yield (10.65 g, 0.0588 mol) as a low melting solid, liquid at room temperature. This material showed a single, sharp peak on glc (10 ft × 1/16 in. with 3% SE-30 on Aeropak 30, 125°) which had a retention time of 7.2 min, identical with its rearrangement product, dimethyl α,α′-dimethyleneadipate (**11**): nmr δ 3.53 (singlet, 6 H), 3.0–2.0 ppm (multiplet, 8 H); mass spectrum *m/e* (rel intensity) 198 (0.12), 107 (48), 79 (100), 77 (48), 59 (71), 39 (90).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.66; H, 7.22.

Attempted Photoaddition of Ethylene to 2 at 0°.—A mixture of 4.0 g (0.023 mol) of **2** in 800 ml of ether was prepared in a small reactor fitted with a quartz immersion well and gas dispersion tube. The ether solution was saturated with ethylene by bubbling the gas through it for 1 hr. The solution was then irradiated with an Hanovia 450-W medium-pressure mercury arc for 30 min at 0°. Glc examinations of the reaction mixture (SE-30, 125°) at the end of this time indicated that all of the starting diester had reacted. A complex mixture of products was produced which was shown to be the result of ether incorporation by nmr analysis.

Dimethyl Bicyclo[3.2.0]heptane-1,5-dicarboxylate (6).—Dimethyl cyclopentene-1,2-dicarboxylate (**3**) (27.6 g, 0.15 mol) was irradiated for 3 hr in 2800 ml of dichloromethane at −70°. After the reaction mixture had been concentrated *in vacuo*, the 30.6 g (96%) of crude product which remained was distilled through a short Vigreux column to yield 28.2 g (0.138 mol, 89%) of analytically pure dimethyl bicyclo[3.2.0]heptane-1,5-dicarboxylate (**6**): bp 75.5–76° (0.2 mm); nmr (CCl_4 solvent, TMS reference) δ 3.58 (singlet, 6 H), 2.57 (complex multiplet, 6 H), 1.6 ppm (complex multiplet, 4 H); $n^{25}D$ 1.4691.

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.04; H, 7.75.

Addition of Ethylene to Dimethyl Cyclopentene-1,2-dicarboxylate (3) at 10°.—In another experiment, 92.0 g (0.5 mol) of **3** was irradiated for 6 days at 10° in 4500 ml of methylene chloride saturated with ethylene. Glc (SE-30, 125°) showed that only approximately 40% of **3** had been consumed. The solution was concentrated to a volume of 2800 ml and irradiated in the variable temperature reactor at −70° in the presence of ethylene for 18 hr to complete the photolysis. A yield of 80.4 g (0.38 mol, 76%) of **6** was obtained.

Bicyclo[3.2.0]heptane-1,5-dicarboxylic Acid (9).—Dimethylbicyclo[3.2.0]heptane-1,5-dicarboxylate (**6**) (80.4 g, 0.38 mol) was refluxed for 24 hr in 400 ml of 6 *N* HCl. The product which crystallized from the solution was recrystallized from water to yield 43.0 g (0.24 mol, 63%) of **9**, mp 214–214.8°.

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.73; H, 6.42.

Bicyclo[3.2.0]heptane-1,5-dicarboxylic Anhydride (10).—A solution of 43.0 g (0.24 mol) of bicyclo[3.2.0]heptane-1,5-dicarboxylic acid (**9**) and 0.1 g of *p*-toluenesulfonic acid hydrate was prepared in 250 ml of acetic anhydride in a 500-ml round-bottomed flask equipped with reflux condenser and drying tube. The solution was heated on the steam bath for 24 hr. White crystals were deposited upon cooling of the solution. The product was isolated by suction filtration and was recrystallized from hot carbon tetrachloride to yield 31.4 g (0.195 mol, 81%) of **10**: mp 133–133.4°; ir 1865, 1935, 1780 cm^{-1} (cyclic anhydride).

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.89; H, 6.03.

Bicyclo[4.2.0]octane-1,6-dicarboxylic Anhydride (7).—A solution of 10.0 g (0.066 mol) of cyclohexene-1,2-dicarboxylic anhydride (**4**) in 2800 ml of methylene chloride was irradiated for 2 hr at −70°. When the reaction mixture was concentrated *in vacuo*, 11.80 g (0.066 mol, 99%) of **7** was obtained. It had melting point, mixture melting point (108–110°), and glc retention time identical with an authentic sample;[8] ir 1850 and 1790 cm^{-1} (cyclic anhydride); nmr (CCl_4 solvent, TMS reference)

(25) (a) W. H. Perkin, Jr., *J. Chem. Soc.*, **65**, 950 (1894); (b) D. Seebach, *Chem. Ber.*, **97**, 2953 (1964); (c) F. B. Kipping and J. J. Wren, *J. Chem. Soc.*, 1773 (1967).

(26) M. E. Bailey and E. D. Amstutz, *J. Amer. Chem. Soc.*, **78**, 3828 (1956).

(27) A. L. Barney and H. B. Stevenson, U.S. Patent 2,870,196 (Jan 20, 1959); *Chem. Abstr.*, **53**, 11237*g* (1959).

δ 2.34 (singlet, 4 H), 1.88 (multiplet, 4 H), and 1.5 ppm (multiplet, 4 H).

Attempted Photoaddition of Ethylene to Dimethyl Cyclohexene-1,2-dicarboxylate (11).—The photoaddition of ethylene to dimethyl cyclohexene-1,2-dicarboxylate (11) was attempted under a variety of conditions in the variable temperature apparatus. The procedures followed for the mechanical handling of the apparatus were as previously described. Table I gives

TABLE I

ATTEMPTED PHOTOADDITION OF ETHYLENE TO 11

Solvent[a]	Temp, °C	Filter	Sensitizer
Ether	−80	None	None
Dichloromethane	−73	None	None
Dichloromethane	−73	Pyrex	Acetophenone
Dichloromethane	27	Pyrex	Acetophenone
Acetone	−78	None	Acetone
Dichloromethane[b]	−70	None	None (400 g of butadiene added)

[a] All reactions were run with 29.7 g (0.15 mol) of 11 in 2800 ml of solvent. [b] 2400 ml of solvent.

the conditions used in these experiments. No cycloaddition product could be observed by glc.

Cyclobutane-1,2-dicarboxylic Anhydride (12).—The addition of ethylene to maleic anhydride in acetone, acetonitrile, ethyl acetate, and ether at 10 and −65° is summarized in Table II.

TABLE II

ADDITION OF ETHYLENE TO MALEIC ANHYDRIDE

Solvent	Temp, °C	Time	Yield,[a] %
Acetone (5 l.)	10	7 days	50[b]
Acetone (2800 ml)	−65	29 hr	57[c]
Acetonitrile (1300 ml)	10	7 days	68[d]
Ethyl acetate (2800 ml)	−65	44 hr	71[e]
Ether (5 l.)	10	7 days	0[f]

[a] Based on unrecovered maleic anhydride. [b] 196 g (2.0 mol) of maleic anhydride gave 72 g of product and 85 g of starting material. The crude reaction mixture showed oxetane by glc and nmr, but the distilled product contained only cyclobutanedicarboxylic anhydride. [c] 98 g (1.0 mol) of maleic anhydride gave 31.2 g of oxetane and after crystallization and distillation 72.2 g of cyclobutanedicarboxylic anhydride. [d] 98 g (1.0 mol) of maleic anhydride gave 65 g of the desired product and 23 g of starting material. [e] 98 g (1.0 mol) of maleic anhydride gave 71.6 g of desired product, 19.0 g of starting material, and 3.5 g of cyclobutane-1,2,3,4-tetracarboxylic dianhydride, mp 299–300° [G. W. Griffin, J. E. Basinski, and A. F. Vellturo, *Tetrahedron Lett.*, 13 (1960)]. [f] 98 g (1.0 mol) of maleic anhydride gave only a white polymer and none of the desired product.

The reactions carried out at 10° were conducted under nitrogen in a flask of appropriate volume with Pyrex-filtered light from a 450-W Hanovia medium-pressure mercury arc. Photolyses at low temperature were carried out in the low temperature reactor[4a] as described above except that a Pyrex filter was used. All reactions were photosensitized by addition of 5 g of acetophenone per mole of anhydride.

The reactions were worked up by concentrating the reaction mixture *in vacuo* and fractionally distilling the product. The structure of 12 was proved by comparison with an authentic sample prepared from 1,2-dicyanocyclobutane.[25a] The presence of the maleic anhydride–acetone oxetane 13 was inferred by its characteristic nmr frequencies at δ 5.25 (doublet), 1.67 (singlet), and 1.42 ppm (singlet).[9] Oxetane 13 tended to polymerize on attempted distillation or crystallization and was not isolated. Distillation of the reaction mixtures which contained oxetane 13 gave no oxetane in the distillate. Glc analyses were carried out on a 10 ft × 1/8 in. 1% OV-17 on Chromosorb G column programmed at 10°/min from 70 to 180°.

Dimethyl α,α′-Dimethyleneadipate (8) from Dimethyl Acetylenedicarboxylate (14).—Dimethyl acetylenedicarboxylate (14) (14.2 g, 0.1 mol) was irradiated for 18 hr at −80° in 2800 ml of dichloromethane. After the solvent had been distilled from the reaction mixture *in vacuo*, the resulting yellow oil was distilled at 71–74° (0.2 mm) through a short Vigreux column to yield 12.5 g (0.063 mol, 63%) of a 9:1 mixture of 8 and 15. The analysis was carried out at 125° on the 10 ft × 1/16 in. SE-30 column previously described. Retention times follow: 15, 6.2 min, and 8, 7.2 min. Dimethyl α,α′-dimethyleneadipate was crystallized from low boiling petroleum ether: mp 25–26° (lit.[5] 25–26°); nmr δ 6.18 (doublet, 2 H), 5.55 (broad singlet, 2 H), 3.70 (singlet, 6 H), 2.55 ppm (broad singlet, 4 H); mass spectrum *m/e* (relative intensity) 198 (0.4), 166 (32), 107 (100), 79 (58), 59 (35).

A sample of 15 was collected by preparative glc (10 ft × 0.25 in. 15% Apiezon L on Chromosorb W, 140°): ir 3090, 1725 cm^{-1}; nmr δ 3.5 (singlet, 6 H), 1.4–1.1 (complex multiplet, 4 H), 0.8–0.5 ppm (complex multiplet, 4 H); mass spectrum *m/e* (relative intensity) 198 (11), 183 (21), 167 (32), 166 (49), 151 (23), 139 (42), 107 (28), 106 (25), 79 (100), 77 (39), 59 (59), 28 (48).

The photoaddition may also be run on a larger scale. Thus, 50.0 g (0.325 mol) of 14 in 125 ml of dichloromethane was dripped from a Hershberg addition funnel into a photolyzing solution of ethylene in 2600 ml of dichloromethane in the variable temperature reactor at −80° over an 8-hr period. The solution was irradiated through quartz for a total of 52 hr with a 450-W medium-pressure mercury arc. The photolysis mixture was concentrated *in vacuo* and the residue was passed down a falling film molecular still at 110° (0.5 mm). A total of 49.1 g of a clear oil was collected. The oil was fractionated through a short Vigreux column. The first fraction, bp 28–30° (0.2 mm), contained 6.4 g (0.045 mol) of 14. The product mixture which weighed 36.9 g (0.186 mol, 66%) had bp 45–50° (0.05 mm).

Bicyclopropyl-1,1′-dicarboxylic Acid (16).—Dimethyl bicyclopropyl-1,1′-dicarboxylate (15) (100 mg, 0.5 mmol) was refluxed for 12 hr in 5 ml of 10% ethanolic KOH solution. The solution then was acidified with HCl and extracted three times with 15 ml of ether. The ether extracts were dried over magnesium sulfate and concentrated *in vacuo* to yield a tan solid. The tan solid was recrystallized from aqueous acetic acid to yield 52 mg (0.31 mmol, 63%) of bicyclopropyl-1,1′-dicarboxylic acid, mp 268–275° (sealed tube) (lit.[10b] 256–275°).

Attempted Photoaddition of Ethylene to Dimethyl Acetylenedicarboxylate (14) in Ether.—Using the dropping funnel technique discussed above, 50.0 g of 14 in 125 ml of ether was added over 6 hr to 2600 ml of ether saturated with ethylene at −80° in the variable temperature reactor. The solution was irradiated through quartz with the 450-W medium-pressure mercury arc for 18 hr. Work-up of the photolysis mixture yielded 71 g of an oil which showed at least seven components on glc (SE-30 column, 125°). The nmr spectrum of the oil showed that ether had participated in the reaction.

Registry No.—3, 13368-79-1; 5, 31947-22-5; 6, 31947-23-6; 7, 6537-91-3; 8, 31952-35-9; 9, 31952-36-0; 10, 31952-37-1; 12, 4462-96-8; 15, 29547-69-1; ethylene, 74-85-1; maleic anhydride, 108-31-6.

Investigations into Reaction Mechanisms of Peroxybenzoic Acid toward Diazodiphenylmethanes

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The reaction of diazodiphenylmethane Ph_2CN_2 with peroxybenzoic acid $PhCO_3H$ in benzene, Et_2O, or *i*-PrOH produces benzophenone in high yields along with benzoic acid and nitrogen, whereas no detectable amount of benzhydryl peroxybenzoate $PhC(=O)OOCHPh_2$ is formed. Reaction stoichiometry is 1 mol of peroxybenzoic acid (PBA) to 1 mol of diazodiphenylmethane (DDM) and a second-order-overall (order one in each of the reagents) kinetic law is obeyed. Kinetic data concerning reaction of DDM with PBA in nine solvents of varying characteristics show a parallelism with data for PBA oxidation of *p*-nitrodiphenyl sulfide and of cyclohexene. Substituents effects have been studied by measuring reaction rates for four substituted diazodiphenylmethanes [$XC_6H_4C(=N_2)C_6H_5$, with X = *p*-OCH_3, *p*-Cl,*m*-NO_2, *p*-NO_2] with PBA and for DDM with *p*-nitroperoxybenzoic acid. The effect of isotopic substitution (PBA-d_1) on rates was also determined. Reaction mechanisms which account for the results are discussed.

Diazoalkanes represent a class of useful intermediates in organic chemistry and the kinetics and mechanisms of many reactions of these molecules have been investigated.[2] It is known that a large variety of carboxylic acids reacts with diazodiphenylmethane and substituted diazodiphenylmethanes to form the corresponding benzhydryl esters in good yields.[2] Reaction rate data have been employed to evaluate Hammett σ constants, to establish ρ–ρ relationships, to determine structure–reactivity–temperature correlations, and to separate polar from steric effects.[2-6]

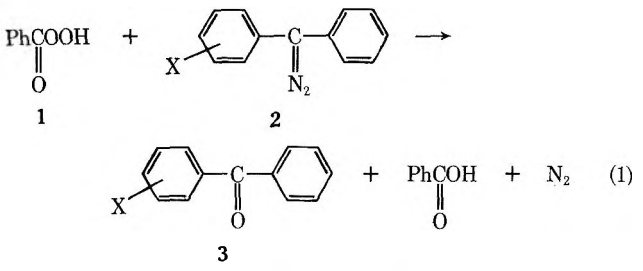
On the basis of much evidence, the accepted mechanism involves a rate-determining proton transfer to give an ion pair [RCO_2^- $^+N_2CHPh_2$] followed by rapid expulsion of N_2 to yield a second ion pair [RCO_2^- $^+CHPh_2$], which in turn collapses to form the ester or dissociates to give benzhydryl ethyl ether (in EtOH).[4,7]

Our interest in the field of peroxide reaction mechanisms[8] led us to investigate the reaction of peroxy acids with diaryldiazoalkanes, since it was believed these reactions might prove to be a convenient synthetic route to secondary and primary peroxy esters.[9] On the other hand, it had been reported that 9-diazofluorene yields 9-fluorenone upon reaction with peroxybenzoic acid.[10]

Using diphenyldiazomethane (DDM) and four other substituted diphenyldiazomethanes as substrates, we choose peroxybenzoic acid (PBA) as reaction partner because of the large body of kinetic data available for this representative peroxidic compound.[8,9] By determining reaction stoichiometry as well as by collecting kinetic data, we aimed to obtain information concerning the reaction course and the mechanisms.

Results and Discussion

We found that by reacting PBA (**1**) with DDM and four substituted diphenyldiazomethanes **2** in benzene Et_2O, or *i*-PrOH, the corresponding benzophenones **3** are obtained along with benzoic acid (BA) and nitrogen.



(1)

with X = H, *p*-OCH_3, *p*-Cl, *m*-NO_2, and *p*-NO_2

These reactions proceed smoothly at 25°. During the time that nitrogen is being evolved, the characteristic intense red or purple-red color of diazoalkane is discharged and PBA is consumed (iodometric titer). Experiments showed the stoichiometry to be 1 mol of PBA to 1 mol of diazoalkane and the yields of ketone to be in most cases greater than 90% (see Table I).

Reaction rates were measured by following diazoalkane disappearance by standard spectrophotometric techniques.[3a] Pseudo-first-order integrated plots were linear up to 80–90% reaction and kinetic experiments indicated that the overall kinetic order is two (order one in each of the reagents). Considering the first three entries on Table II, a plot of log k_1 *vs.* log $[PBA]_0$ gives a straight line of slope 1.03. The third and fourth entries show that, at constant $[PBA]_0$, the k_1 value practically does not change upon nearly doubling $[DDM]_0$; finally, k_2 values, obtained as $k_1/[PBA]_0$, are reproducible and agree within the limits of experimental errors (*ca.* ±3%).

For the reaction between PBA and DDM in dioxane and $ClCH_2CH_2Cl$, the presence of 0.1 *M* nitrobenzene, an effective radical trap, caused practically no change in k_2 values (see Table II); this makes the intervention of radical pathways unlikely. By measuring the rates for the reaction between $PhCO_3D$ (PBA-d_1) and DDM in dioxane (at 31.5°), a primary isotope effect k^H/k^D of

(1) To whom inquiries should be addressed: Department of Chemistry, Brown University, Providence, R. I. 02912.

(2) C. W. Cowell and A. Ledwith, *Quart. Rev., Chem. Soc.*, **24**, 119 (1970), and references cited therein.

(3) (a) J. D. Roberts, W. Watanabe, and R. E. Mc Mahon, *J. Amer. Chem. Soc.*, **73**, 760 (1951); (b) J. D. Roberts and C. M. Regan, *ibid.*, **74**, 3695 (1952); (c) J. D. Roberts and E. A. McElhill, *ibid.*, **72**, 628 (1950); (d) J. D. Roberts, E. A. McElhill, and R. Armstrong, *ibid.*, **71**, 2923 (1949).

(4) (a) R. A. More O'Ferral and S. I. Miller, *ibid.*, **85**, 2440 (1963); (b) J. D. Sharp Ritter and S. I. Miller, *ibid.*, **86**, 1507 (1964); (c) R. A. More O'Ferral, W. K. Kwok, and S. I. Miller, *ibid.*, **86**, 5553 (1964).

(5) C. K. Hancock and E. Foldwary, *J. Org. Chem.*, **30**, 1180 (1965); see also previous papers by Hancock, *et al.*, on the subject.

(6) N. B. Chapman, J. R. Lee, and J. Shorter, *J. Chem. Soc. B*, 769 (1969); see also previous papers of the series.

(7) A. F. Diaz and S. Winstein, *J. Amer. Chem. Soc.*, **88**, 1318 (1966).

(8) (a) R. Curci, R. A. Di Prete, J. O. Edwards, and G. Modena, *J. Org. Chem.*, **35**, 740 (1970); (d) R. Curci and J. O. Edwards in "Organic Peroxides," D. Swern, Ed., Wiley-Interscience, New York, N. Y., 1970, Chapter IV, pp 199–264; see also references cited therein.

(9) A. G. Davies, "Organic Peroxides," Butterworths, London, 1961, p 58 ff.

(10) A. Schonberg, W. I. Awad, and N. Latif, *J. Chem. Soc.*, 1368 (1951).

TABLE I

YIELDS OF CORRESPONDING KETONES IN THE REACTION OF DDM AND SUBSTITUTED DIAZODIPHENYLMETHANES WITH PBA[a]

Diazoalkane	% purity[b]	Reaction solvent	% yield of ketone
$C_6H_5C(=N_2)C_6H_5$	93.0	Benzene	92.0
	93.0	Benzene	94.0[c]
	93.0	Et_2O	94.0
	93.0	*i*-PrOH	87.0[d]
	93.0	*i*-PrOH	99.0[e]
$C_6H_5C(=N_2)C_6H_4$-*p*-OCH_3	94.0	Benzene	96.0
$C_6H_5C(=N_2)C_6H_4$-*p*-Cl	90.0	Benzene	96.0
$C_6H_5C(=N_2)C_6H_4$-*m*-NO_2	96.0	Benzene	90.0
$C_6H_5C(=N_2)C_6H_4$-*p*-NO_2	99.0	Benzene	99.0

[a] Unless otherwise noted, yields of ketones were determined (±4%) by glpc after reacting PBA and the diazo compound in equimolar amounts. [b] ±4%, as determined by following a titrimetric method (Experimental Section). [c] In this experiment, yields were determined by separating and weighing the reaction products (see Experimental Section). [d] In this solvent, other reaction products observed were $PhCO_2CHPh_2$ (6.8%) and *i*-$PrOCHPh_2$ (3.7%). [e] Reaction was carried out using an excess of PBA, *i.e.*, $([PBA]_0/[DDM]_0) \cong 20$.

1.33 ± 0.04 was estimated (Table II). Data concerning the effect of changing reaction solvent on rates are also collected on Table II along with activation enthalpies in two typical[8a] reaction media.

A few experiments aimed to evaluate the difference in reaction rates among PBA and BA toward DDM were also carried out. It was found that PBA reacts in dioxane at 31.5° about 60 times as fast as BA with DDM (for BA + DDM reaction, it is $k_2 = 0.102 \times 10^{-2}\ M^{-1}$ sec^{-1}); instead, in *i*-PrOH solvent at 25.0° the k_2 value found ($1.01 \times 10^{-1}\ M^{-1}\ sec^{-1}$) for the reaction of BA with diazodiphenylmethane indicates comparable rates for the acid and the peroxy acid (see also Table II).

In Table III kinetic data aimed to elucidate the substituent effect on rates are collected; for the reaction between PBA and substituted diazodiphenylmethanes in dioxane, a plot of log (k_2/k_2^0) *vs.* Hammett σ values gives a straight line (correlation coefficient 0.990) of slope (Hammett ρ) −0.96. Therefore, whereas electron-withdrawing groups in the phenyl ring of DDM decrease the reaction rate with PBA, the reaction of DDM with *p*-nitroperoxybenzoic acid in dioxane at 31.5° proceeds about 4.2 times as fast as with PBA (Table III). This suggests that the diazoalkanes act as nucelophiles, whereas the peroxy acid is the electrophilic partner in these reactions.

On the basis of stoichiometry and kinetic data, two main reaction mechanisms can be envisaged. Mechanism I involves direct attack by the diazoalkane nucleophilic carbon atom on the O–O bond of the peroxy acid molecule. Reactions of nucleophilic displacement on peroxidic oxygen by carbon compounds have been reviewed by Edwards;[11] diazoalkanes, because of the "anion-like" behavior of the carbon atom, would be expected to be effective nucleophiles.

In the scheme shown, the structure of **4** bears much similarity to the transition states proposed for the oxidation of olefins and sulfides by peroxy acids. The intramolecular H-bonded structure of peroxy acids in such solvents as CCl_4 or benzene is well documented, as is the importance of cyclic transition states similar to **4** in order to by-pass significant charge separation by an intramolecular hydrogen transfer.[8,9] Actually, a linear relationship (slope 1.06, cor coeff 0.974) is observed among the logs of rates of DDM reaction with PBA and the logs of rates for *p*-nitrodiphenylsulfide (PNDS) oxidation by PBA, in a variety of solvents (Figure 1). A similar linear relationship (with lower slope) can also be obtained by plotting log k_2 for DDM reaction *vs.* log k_2 for cyclohexene epoxidation by PBA.[8a] The factors influencing the observed trend of rates in the given solvent series could be ascribed mainly to differences among ground-state and transition-state specific solvation of PBA molecules, as it has already been discussed in detail.[8]

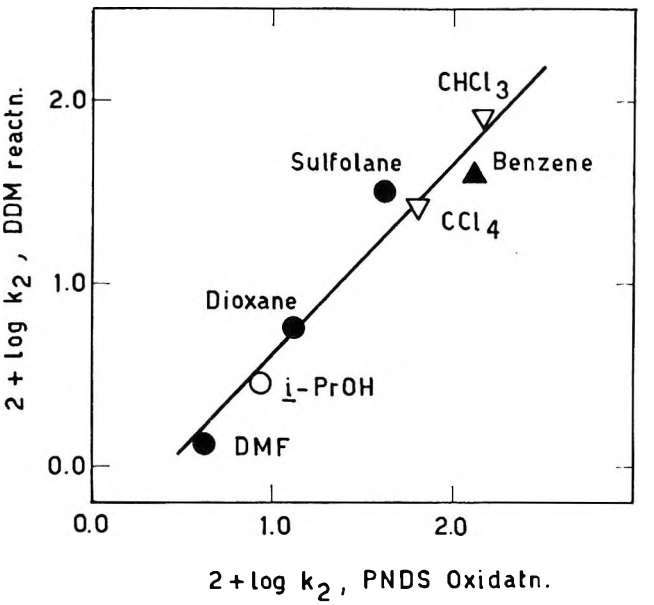
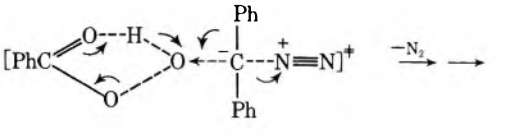


Figure 1.—Linear trend in the logarithmic plot of rate constants for the reaction of DDM with PBA *vs.* rate constants for the oxidation of *p*-nitrodiphenyl sulfide (PNDS) by PBA in various solvents.

Mechanism I

$$PhCO_3H + [Ph_2C{=}\overset{+}{N}{=}\overset{-}{N} \leftrightarrow Ph_2\overset{-}{C}{-}\overset{+}{N}{\equiv}N] \rightleftharpoons$$



4

$$PhCO_2H + O{=}CPh_2$$

The *ca.* 3.5 kcal mol^{-1} difference found in $\Delta H^{\ddagger}$ values for the reaction in dioxane and 1,2-dichloroetane (Table I) is in the expected direction, as is also the difference in $\Delta S^{\ddagger}$ values. The observed isotope effect (k^H/k^D = 1.33) is also consistent with a transition state structure such as **4**, being near to the values of 1.15 and 1.10 found respectively in the reaction of peroxyacetic acid with *p*-nitroaniline and of *m*-chloroperoxybenzoic acid with Schiff bases.[12,13]

Another mechanism resembling that accepted for the reaction of carboxylic acids with DDM could be drawn; this would imply the preliminary formation of peroxy

(11) J. O. Edwards in "Peroxide Reaction Mechanisms," J. O. Edwards, Ed., Wiley-Interscience, New York, N. Y., 1962, p 99.

(12) K. M. Ibne-Rasa and J. O. Edwards, *J. Amer. Chem. Soc.*, **84**, 763 (1962).

(13) V. Madan and L. B. Clapp, *ibid.*, **91**, 6078 (1969).

TABLE II

RATE CONSTANTS AND ACTIVATION PARAMETERS FOR THE REACTION OF DDM WITH PBA IN VARIOUS SOLVENTS

Solvent	$\epsilon^{25°}$	T, °C	10^2k_1,[a] sec^{-1}	10^2k_2,[a] M^{-1} sec^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, cal deg^{-1} mol^{-1}
Dioxane	2.21	31.5	0.152[b]	5.60	9.6[g]	−33.0[g]
			0.335[c]	6.00		
			0.640[d]	5.80		
			0.660[e]	6.00		
		20.0		2.87		
		25.0		3.23		
		25.0		3.16[f]		
		30.0		4.58		
		40.0		8.24		
Dioxane (PBA-d_1)		31.5		4.40		
1,2-Dichloroethane	10.4	31.5		56.8	5.8[g]	−40.0[g]
		10.0		24.8		
		20.0		40.5		
		20.0		38.0[f]		
		30.0		52.2		
$CHCl_3$	4.81	31.5		79.7		
CCl_4	2.24	31.5		25.8		
Benzene	2.28	31.5		39.0		
Sulfolane	41.4[h]	31.5		34.0		
THF	7.6	31.5		1.90		
i-PrOH	18.3	31.5		2.90		
		25.0		1.50		
DMF	36.7	31.5		1.44		

[a] k_1 values were obtained from pseudo-first-order integrated plots; in these runs usually $[DDM]_0$ ranged from 0.4×10^{-2} to 0.6×10^{-2} M, whereas $[PBA]_0$ was from 0.05 to 0.08 M (unless otherwise noted). Second-order rate constants were obtained as $k_2 = k_1/[PBA]_0$. [b] $10^2[DDM]_0 = 0.565$ M; $10^2[PBA]_0 = 2.72$ M. [c] $10^2[DDM]_0 = 0.565$ M; $10^2[PBA]_0 = 5.58$ M. [d] $10^2[DDM]_0 = 0.565$ M; $10^2[PBA]_0 = 11.0$ M. [e] 10^2 $[DDM]_0 = 1.09$ M; $10^2[PBA]_0 = 11.0$ M. [f] In the presence of 0.1 M $PhNO_2$. [g] At 25.0°. [h] At 30.0°.

TABLE III

SUBSTITUENT EFFECTS ON THE REACTION OF SOME SUBSTITUTED DIARYLDIAZOMETHANES $(XC_6H_4)C_6H_3CN_2$ WITH PEROXYBENZOIC ACIDS $YC_6H_4CO_3H$ IN DIOXANE AT 31.5°

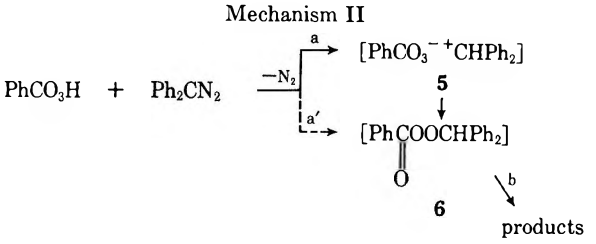
Substituent		10^2k_2[a]	(k_2/k_2^0)	σ[b]
For Y = H, X =	*p*-OCH_3	11.6	1.98	−0.268
	H	5.85	1.00	0.000
	p-Cl	4.04	0.691	+0.226
	m-NO_2	1.61	0.275	+0.710
	p-NO_2	0.95	0.162	+0.778
For X = H, Y =	H	5.85	1.00	0.000
	p-NO_2	24.7	4.22	+0.778

[a] From pseudo-first-order runs (see also footnote *a* of Table I). [b] σ values are from J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962.

ester **6**, which would in turn easily decompose to yield benzophenone and benzoic acid.

According to mechanism II, the separation of opposite charges which obtains upon formation of the intermediate ion pair **5** leads one to expect a significant increase in rate on increasing medium polarity.

Mechanism II



Indeed, Roberts, *et al.*, have shown that the logs of rates for reaction of BA with DDM increase linearly with the Kirkwood function $[(\epsilon - 1)/(2\epsilon + 1)]$ for various EtOH–water mixtures and that addition of nitrobenzene (ϵ 34.8) to EtOH (ϵ 24.3) also increases the rate.[3a] Inspection of kinetic data given on Table II, however, shows no clear dependence of rates on solvent dielectric constant. For example, the reaction rate in benzene (ϵ 2.28) is *ca.* 27 times as fast as in DMF (ϵ 36.7); within a series of similar solvents, the rate constant for solvent 1,2-dichloroethane (ϵ 10.4) is about 22 times higher than for CCl_4 (ϵ 2.24) but it is *lower* than that for $CHCl_3$ (ϵ 4.81).

Furthermore, in alcoholic solvents, as far as the out-of-cage reaction of benzhydryl cation with the nucleophilic solvent (to give Ph_2CHOR) can be competitive with recombination of $PhCH^+$ with $PhCO_3^-$ (to form **6**), a meaningful decrease in ketone yield might be expected. Instead, only a small decrease in the yield of $Ph_2C{=}O$ was observed when the reaction between PBA and DDM (in equimolar amounts) was performed in *i*-PrOH (see Table I); nevertheless, in this case, upon comparison with authentic samples, both benzhydryl isopropyl ether and benzhydryl benzoate were detected as reaction side products. This is not surprising since, as mentioned earlier, PBA and BA show similar rates in reacting with DDM in *i*-PrOH; therefore, as the reaction between PBA and DDM proceeds, the benzoic acid produced can itself react with the diazo compound in a consecutive reaction yielding the ether and the ester.[3-7] Indeed, when DDM was reacted with PBA excess in *i*-PrOH, benzophenone was produced in almost quantitative yield (Table I) and sizable amounts of *i*-$PrOCHPh_2$ and $PhCO_2CHPh$ could no longer be detected by glpc, tlc, or pmr.

All evidences so far collected, therefore, seem to point out that, should mechanism II hold for these reactions, it is unlikely that the reaction proceeds *via* the inter-

mediate formation of an ion pair such as **5**. However, the possibility remains that the intermediate peroxy ester **6** is formed directly from the reactants (path a'), perhaps *via* a cyclic transition state not too dissimilar to **4**.

It is apparent that more data need to be collected concerning the stability of secondary peroxy esters such as **6**; to our knowledge no benzhydryl peroxy ester **6** has yet been reported nor has any *sec*-diaryl peroxybenzoate. The difficulties arising in the syntheses of secondary peroxy esters are well recognized; these stem primarily from the easy decomposition of such compounds in the presence of bases as well as from the facile homolytic or heterolytic O–O bond cleavage, often accompanied by rearrangements.[14] Actually, our preliminary attempts to obtain **6** through the imidazolide route[14] have been so far unsuccessful; *sec*-butyl peroxyacetate has been reported by Mosher, *et al.*, to decompose (at 64.5°) much faster than the isomeric *tert*-butyl perester, yielding methyl ethyl ketone and acetic acid as major products *via* a cyclic transition state.[15]

It was reported that α-phenylethyl peroxyacetate $CH_3C(=O)OOCH(CH_3)Ph$ is sufficiently stable to be isolated upon reacting α-phenylethyl hydroperoxide with ketene.[9] Our preliminary experiments, however, indicate that on reacting PBA with $Ph(CH_3)C{=}N_2$ in CCl_4 solution again only acetophenone and benzoic acid are formed; furthermore, pmr spectra of the above said reaction solution at *ca.* −8° showed no evidence for intermediate formation of α-phenylethyl peroxybenzoate.

In conclusion, the results so far collected seem to point out that mechanism I should be preferred over mechanism II for the reactions studied; further work, presently in progress in these laboratories, is aimed to elucidate other aspects of the reactivity of diazoalkanes toward peroxy acids as well as toward other organic peroxides.

Experimental Section

Materials and Apparatus.—Melting points and boiling points are not corrected. Pmr spectra were recorded using a Varian A-60 or Perkin-Elmer R 12 spectrometer (both at 60 MHz) and a 90-MHz Bruker HFX-90 instrument. Ir spectra were obtained employing Perkin-Elmer 337 or 621 spectrophotometers; uv–visible spectra were recorded on a Cary 15 or Coleman-Hitachi 124 instrument.

The **diazoalkanes** listed below were prepared by oxidation of the corresponding hydrazones with Ag_2O or HgO in Et_2O.[16,17]

Diazodiphenylmethane: mp 29–31°; ir (liquid film) 2035 cm^{-1} (>C=$\overset{+}{N}$=$\overset{-}{N}$); vis max (dioxane) 525 nm (ϵ 94) [lit.[3a,17,18] mp 29–32°; ir (CH_2Cl_2) 2025 cm^{-1}; vis max (EtOH) 525 nm (ϵ 94)].

Diazo(*p*-chlorophenyl)phenylmethane: mp 27–28°; ir (liquid film) 2040 cm^{-1} (CNN); vis max (dioxane) 520 nm (ϵ 74) [lit.[19] mp 26–27°; vis max (MeCN) 526 nm (ϵ 85)].

Diazo(*m*-nitrophenyl)phenylmethane: thick oil; ir (liquid film) 2045 cm^{-1} (CNN); vis max (dioxane] 390 nm (ϵ 570) [lit.[19] oil; vis max (MeCN) 395 nm (ϵ 576)].

Diazo(*p*-nitrophenyl)phenylmethane: mp 80–83°; ir (Nujol) 2045 cm^{-1} (CNN); vis max (dioxane) 425 nm (ϵ 305) (lit.[20] mp 70–78°).

Diazo(*p*-methoxyphenyl)phenylmethane: mp 53–54°; ir (Fluorolube) 203 cm^{-1} (CNN); vis max (dioxane) 530 nm (ϵ 78).

1-Diazo-1-phenylethane: unstable oil; ir (liquid film) 2040 cm^{-1} (CNN); pmr (CCl_4) τ 7.53 (s, 3, $N_2{=}CCH_3$) and 3.0–2.0 ppm (m, 5, $C_6H_5CN_2$) (lit.[21] mp *ca.* −10°).

Purity of diazoalkanes samples was determined through the following procedure: A weighed amount of diazoalkane was dissolved in a suitable amount of dry dioxane in a volumetric flask; aliquots (2–3 ml) of this stock solution were allowed to react with a known excess of benzoic acid in MeCN (20–30 ml) and the unreacted excess acid was determined by titration with 0.1 *M* $Bu_4N^+OH^-$ in benzene–MeOH (thymol blue). Satisfactorily pure diazo compound samples were stored in a desiccator placed into a freezer (at *ca.* −20°) and used within a few days.

The hydrazones, starting materials for the synthesis of the listed diazoalkanes, have been prepared by the method of Szmant and McGinnis;[22] they were carefully purified by column (silica gel) chromatography (eluents: benzene, $CHCl_3$) and their purity was checked by comparison of their melting points with those reported in the literature,[19,22-24] as well as by recording their ir and pmr spectra.

Peroxybenzoic acid was prepared according to the method given by Swern, *et al.*,[25] using 98% H_2O_2 (FMC Corp.): mp 41–42°;[2] ir (CCl_4) 3260 (OH) and 1732 cm^{-1} (C=O); pmr (benzene-d_6) τ 3.3–2.1 (m, 5, $C_6H_5CO_3H$) and −1.35 ppm (broad s, 1, $-CO_3H$).

Peroxybenzoic acid-d_1 was obtained by shaking a benzene solution of the peracid-*h* in a separatory funnel with successive small portions of D_2O (Merck, ≥99.5%) deuterium label) until in the pmr spectrum the broad signal at τ −1.35 ppm (see above) had completely disappeared. Upon removal of the solvent *in vacuo*, a white solid residue was obtained which was handled in a drybox, mp 40–42°. The deuterium content of the sample was determined from its ir spectrum in CCl_4; the OH peak at 3260 cm^{-1} was used for analysis, after its extinction coefficient had been evaluated from spectra of the undeuterated acid. The proportion of peroxybenzoic acid-*h* in the deuterio peracid was found to be of *ca.* 4%.

***p*-Nitroperoxybenzoic acid** was also obtained and purified by the Swern's method, mp 136–137° dec (lit.[25] mp 138° dec. Iodometric analysis[26] indicated a purity of 97–99% for all peroxy acids listed above.

Benzhydryl isopropyl ether was synthetized by reacting benzhydryl chloride with *i*-PrONa in *i*-PrOH at reflux: bp 114–115° (0.5 mm); pmr (neat liquid) τ 8.92 [d, 6, J = 6.2 Hz, $CH(CH_3)_2$], 6.43 [heptuplet, 1, J = 6.2 Hz; $CH(CH_3)_2$], 4.62 [s, 1, $(C_6H_5)_2CH$], and 3.2–2.5 ppm [m, 10, $(C_6H_5)_2CH$]. *Anal.* Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 85.50; H, 8.02.

Benzhydryl benzoate was prepared by reacting benzhydryl alcohol with benzoyl chloride in pyridine; it was recrystallized from aqueous ethanol, mp 87–88° (lit.[3a] mp 87–88°).

Benzene, chloroform, 1,2-dichloroethane, carbon tetrachloride, 2-propanol, dioxane, tetrahydrofuran (THF), and acetonitrile solvents (C. Erba, high purity) were purified according to standard procedures[26] and fractionally distilled through an efficient column, ***N*,*N*-Dimethylformamide (DMF) and tetrahydrothiophene 1,1-dioxide (sulfolane)** were purified as already reported.[8a]

Reaction Stoichiometry.—The reaction studied was shown to have a stoichiometry of 1 mol of diazoalkane to 1 mol of peracid by the nearly quantitative isolaton of the products. In a typical experiment, DDM (1.0 g, 5.15 mmol) in dry benzene (30 ml) was added dropwise to a stirred solution of PBA (0.72 g, 5.2 mmol) of the same solvent (50 ml) at room temperature. The reaction solution was extracted with five 20-ml portions of 5%

(14) L. A. Singer in "Organic Peroxides," D. Swern, Ed., Wiley–Interscience, New York, N.Y., 1970, Chapter V, pp 265–312.

(15) L. J. Durham, L. Glover, and H. S. Mosher, *J. Amer. Chem. Soc.*, **82**, 1509 (1960).

(16) W. Schroeder and L. Katz, *J. Org. Chem.*, **19**, 6078 (1954).

(17) J. B. Miller, *ibid.*, **24**, 560 (1959).

(18) P. Yates, B. Shapiro, N. Yoda, and J. Fugger, *J. Amer. Chem. Soc.*, **79**, 5756 (1957).

(19) D. Bethell and J. D. Callister, *J. Chem. Soc.*, 3808 (1963).

(20) R. Huttel, J. Riedl, H. Martin, and K. Franke, *Chem. Ber.*, **93**, 1425 (1970).

(21) H. Staudinger and A. Gaule, *ibid.*, **49**, 1897 (1916).

(22) H. H. Szmant and C. McGinnis, *J. Amer. Chem. Soc.*, **72**, 2890 (1950).

(23) C. K. Hancock, R. F. Gibby, and J. S. Westmoreland, *ibid.*, **79**, 1918 (1957).

(24) D. E. Pearson, K. N. Carter, and C. M. Greer, *ibid.*, **75**, 5905 (1953).

(25) L. S. Gilbert, E. Siegel, and D. Swern, *J. Org. Chem.*, **27**, 1336 (1962); see also D. Swern, in "Organic Peroxides," D. Swern, Ed., Wiley–Interscience, New York, N. Y., 1970, Chapter VI.

(26) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath, Boston, Mass., 1957, p 281 ff.

aqueous $NaHCO_3$, the benzene layer dried ($MgSO_4$), and the solvent removed *in vacuo*, thus yielding 0.88 g (4.83 mmol, 94% yield) of benzophenone, mp 46–48°. The alkaline aqueous extracts were brought up to pH 1 (6 *N* HCl) and in turn extracted with benzene, and the benzene extract was dried ($MgSO_4$) and, after solvent removal, gave 0.61 g (5.0 mmol, 96% yield) of benzoic acid, mp 120–122°. To determine the ketone yields by glpc (Table I), stoichiometric amounts (usually *ca.* 2 mmol) of diazoalkane and peracid were allowed to react in the given solvent containing a known amount of a suitable internal standard, thereafter following the known analytical procedure;[27] glpc data were obtained on a Varian-Aerograph 1520 gas chromatograph using a 7 ft × 0.25 in. 5% SE-30 on Chromosorb W (60–80 mesh) column and a 6 ft × 1/8 in. 10% Carbowax 20M-TPA on Chromosorb W (60–80 mesh) column, tc detector, He carrier gas at *ca.* 30 ml/min.

Kinetics.—Kinetic data were obtained according to standard spectrophotometric techniques.[3a] The change of absorbance with time at the wavelength of maximum absorption in the visible for each diazoalkane (where PBA and reaction products are essentially transparent) was monitored by using a Gilford 2400 recording spectrophotometer equipped with a thermostatic cell holder. Temperature control was better than ±0.5°. Rate constants were obtained from pseudo-first-order integrated plots on the basis of the following equation.

$$-\log (A_t - A_\infty) = (k_1/2.3)t - \log (A_0 - A_\infty)$$

(27) H. M. McNair and E. J. Bonelli, "Basic Gas Chromatography," 5th ed, Varian-Aerograph, Walnut Creek, Calif., 1969, p 150.

Rate constants reported in Tables II and III are average values from at least two independent experiments whose results of which agree within the limits of experimental errors (±4%). The rate constants obeyed the Arrhenius equation and the activation parameters were evaluated by standard methods;[8a] precision in the estimation of $\Delta H^{\ddagger}$ is better than ±0.8 kcal mol^{-1} and better than ±3 cal deg^{-1} mol^{-1} for $\Delta S^{\ddagger}$.

Registry No.—$C_6H_5C(=N_2)C_6H_5$, 883-40-9; $C_6H_5C(=N_2)C_6H_4$-*p*-OCH_3, 20359-74-4; $C_6H_5C(=N_2)C_6H_4$-*p*-Cl, 1140-33-6; $C_6H_5C(=N_2)C_6H_4$-*m*-NO_2, 1218-71-9; $C_6H_5C(=N_2)C_6H_4$-*p*-NO_2, 13271-32-4; 1-diazo-1-phenylethane, 22293-10-3; *p*-nitroperoxybenzoic acid, 943-39-5; benzhydryl isopropyl ether, 5670-79-1; PBA, 93-59-4; PBA-d_1, 31657-65-5.

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Stereochemistry of the Addition of *N*-Arylmaleimides to the Acridizinium Ion[1]

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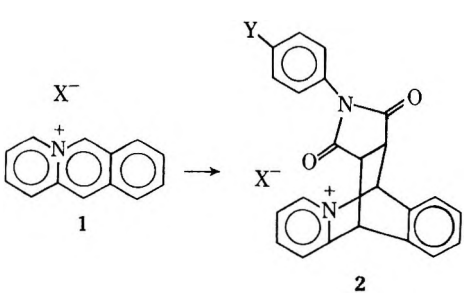
The cycloaddition of *N*-arylmaleimides to the acridizinium nucleus occurs stereospecifically anti with regard to the benzenoid nucleus. In strong acid *cis*-12,13-dicarboxy-6,11-dihydro-6,11-ethanoacridizinium salts undergo rearrangement affording a trans structure. Pyrolysis of the acridizinium arylmaleimide addition products affords derivatives of *N*-aryl-1-(2-pyridyl)naphthalene-2,3-dicarboximide.

The acridizinium ion (1) was the first positively charged alkenophile found to undergo a 4 + 2 cycloaddition reaction.[2] Although recently there has been a large increase in the number of examples of such cycloadditions,[3-6] for only five of the adducts is the *stereochemistry* known. It is already clear that despite the stereoselectivity shown in the cationic addition reaction the presence of the positive charge makes it impossible to apply without modification the rules[7] which have proved so useful in understanding the classical Diels–Alder reaction, and indeed, there exists some evidence that the cationic cycloaddition may not be concerted.[5,8]



The purpose of the present study was to determine whether the stereochemistry of the cycloaddition of *N*-arylmaleimides to the acridizinium ion was altered by changes in polarity of the *N*-aryl group and to learn something about the chemistry of the products. Two general procedures were used for the preparation of the adducts. Either the salt 1 was suspended in acetic acid and heated with the maleimide at 100°, or a melt was formed by heating the reactants at 160–170° without solvents. The high-temperature reaction had the advantage of being quite rapid and giving clean reaction products although the yields were slightly lower. Both reaction conditions led to the isolation of the same product, which seemed to consist of a single stereoisomer. As may be seen from Table I all adducts possessed carbonyl absorptions at 1704–1715 and 1783–1790 cm^{-1}. As would be expected from known imide spectra,[9] the lower frequency absorptions (asymmetric carbonyl stretch) were significantly the weaker of the two.

The nmr showed the expected doublets at approximately δ 5.7 for the bridgehead proton at C-11 and δ

(1) This research was supported by Public Health Service Grants No. HE-2170 of the National Heart Institute and No. CA-05509 of the National Cancer Institute.

(2) C. K. Bradsher and T. W. G. Solomons, *J. Amer. Chem. Soc.*, **80**, 933. (1958).

(3) D. L. Fields, T. N. Regan, and J. C. Dignan, *J. Org. Chem.*, **33**, 390 (1968).

(4) C. K. Bradsher and J. A. Stone, *ibid.*, **33**, 519 (1968).

(5) C. K. Bradsher and J. A. Stone, *ibid.*, **34**, 1700 (1969).

(6) D. L. Fields and J. B. Miller, *J. Heterocycl. Chem.*, **7**, 91 (1970).

(7) *E.g.*, J. A. Norton, *Chem. Rev.*, **31**, 319 (1942).

(8) C. K. Bradsher and I. J. Westerman, *J. Org. Chem.*, **36**, 969 (1971).

(9) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Boston, Mass., 1966.

TABLE I.—CYCLOADDITION PRODUCTS 2 OF ACRIDIZINIUM SALTS WITH *N*-ARYLMALEIMIDES

2

X	Y	Prepn method[a] (yield, %)	Registry no.	Mp,[b] °C	Formula[c]	Ir, carbonyl, cm^{-1}	Nmr (multiplicity)[d] C-6	C-11	C-12	C-16	Other
ClO_4	H	A (95)	32120-19-7	354–356	$C_{23}H_{17}ClN_2O_6$	1709, 1786	7.07 (d)	5.75 (d)	4.27 (q)	4.73 (q)	
Br	H	A (90), B (75)	32120-20-0	>380	$C_{23}H_{17}BrN_2O_2$						
ClO_4	Me	A (85)	32120-21-1	343–345	$C_{24}H_{19}ClN_2O_6$	1704, 1783	7.00 (d)	5.77 (d)	4.20 (q)	4.60 (q)	2.34 (s)
Br	Me	B (70)	32120-22-2	>380	$C_{24}H_{19}BrN_2O_2$						
ClO_4	Cl	A (90)	32120-86-8	311–313	$C_{23}H_{16}Cl_2N_2O_6$	1711, 1786	7.00 (d)	5.77 (d)	4.22 (q)	4.60 (q)	
Br	Cl	A (90), B (75)	32120-87-9	>380	$C_{23}H_{16}BrClN_2O_2$						
ClO_4	OMe	A (90)	32120-88-0	314–315	$C_{24}H_{19}ClN_2O_7$	1709, 1784	7.0[e]	5.74 (d)	4.18 (q)	4.55 (q)	3.88
Br	OMe	A (90), B (80)	32120-89-1	362–363	$C_{24}H_{19}BrN_2O_3$						
ClO_4[f]	$N(Me)_2$	A (60)	32120-90-4	327–329	$C_{25}H_{25}Cl_2N_3O_{10}$	1715, 1790	7.0[e]	5.70 (d)	4.20 (q)	4.60 (q)	3.66

[a] In method A the acridizinium salt was heated in acetic acid suspension at 100° with an excess of the maleimide, the time being about 20 hr for perchlorates and 2 hr for bromides. In method B the molten reactants were heated at 160–170° for ~15 min. See Experimental Section. [b] All occurred with decomposition. [c] Satisfactory analytical data was presented for all compounds in this table: Ed. [d] Signals due to aromatic protons have been omitted. Protons listed under *other* showed expected integration. [e] Overlapped signal. [f] Both counterions are perchlorate.

7.0 for the more strongly deshielded proton at C-6. Homonuclear spin decoupling studies with the *N*-(*p*-tolyl) derivative (Y = Me) showed that irradiation of the signal at δ 7.0 caused the quartet at δ 4.6 to collapse to a doublet, while irradiation of the signal at δ 5.7 caused the quartet at δ 4.2 to collapse to a doublet. This allowed assignment of the signal at δ 4.2 to be that of the proton at C-12 spin coupled to C-11 (J = 3.5 Hz) and to C-16 (J = 7 Hz). The signal at δ 4.6 must arise from the C-16 proton, spin coupled to the protons at C-6 and C-12.

It had been shown earlier[2] that the selective reduction of a cycloaddition product derived from an acridizinium salt could be effected in such a way that the pyridinium ring is saturated while the benzenoid ring is left intact. When hydrogenated under these conditions the *N*-phenylmaleimide adduct (2, Y = H) yielded **3**, which

3

had an nmr which was useful in making a tentative stereochemical assignment. Although the reduction produced dramatic changes in certain parts of the spectrum the signals due to the hydrogens at C-12 and C-16 remained virtually unchanged, suggesting that they were over the intact benzene ring as represented in **3** rather than over the reduced pyridine ring.

It had been hoped that unequivocal evidence for the stereochemical structure of maleimide adducts could be obtained by relating them to the known *anti,anti*- (**4b**) and *syn,syn*- (**5b**) 12,13-dicarbomethoxy-6,11-dihydro-6,11-ethanoacridizinium perchlorates. The imides **2** proved resistant to hydrolysis except in strong acid solutions and in 48% hydrobromic afforded neither of the known cis dicarboxylic acids (**4a** or **5a**) but a trans diacid (**6a**) characterized as its dimethyl ester (**6b**). In order to learn something more about this interesting rearrangement, the action of 48% hydro-

4

5

6

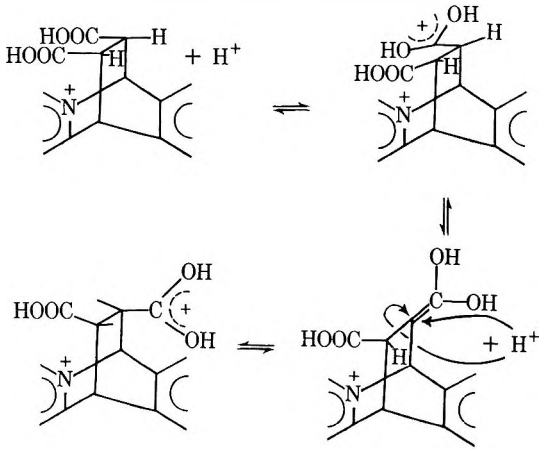
a, R = H
b, R = Me

bromic acid on the known cis dimethyl esters (**4b** and **5b**) was studied. Both were found to undergo hydrolysis and rearrangement to the same trans dicarboxylic

acid, making it clear that rearrangement involved the possibility of inversion of configuration at both of the ethano bridge carbon atoms (C-12 and C-13).

To explain this rearrangement it is postulated that the carboxyl groups are protonated followed by loss of the α hydrogen to give an enediol which may be protonated from either direction giving either inversion or retention of configuration. Scheme I shows the

SCHEME I
MECHANISM SHOWING INVERSION AT C-13



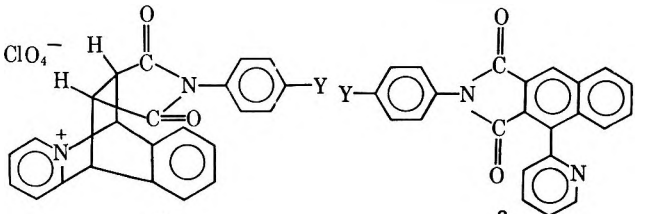
steps involved in the inversion at C-13, which is similar to what must happen at C-12. The structure of the trans product of the reaction is explicable in that the positively charged protonated carboxyl groups are at a maximum distance from each other without either group being in the immediate proximity of the positively charged nitrogen atom.

Support for this mechanism was obtained by carrying out the hydrolysis in 20% DCl in D_2O at reflux temperature. The diacid formed showed the C-6 and C-11 protons as singlets rather than doublets, while the signals for the C-12 and C-13 protons were very weak, together integrating for less than one-third of a proton, indicating almost complete exchange of the C-12 and C-13 hydrogens as would be predicted by the mechanism.

Proof of the stereochemistry of our maleimide cycloaddition products was obtained by synthesizing them from *anti,anti*-12,13-dicarboxy-6,11-dihydro-6,11-ethanoacridizinium perchlorate (**4a**) by refluxing it in acetonitrile with the appropriate arylamine. For the three imides synthesized (2, Y = H, Me, OMe) all physical properties were in complete agreement with those obtained from the cycloaddition products.

In order to compare the physical properties of some examples stereoisomeric with 2 but in which the imide ring was syn rather than anti with respect to the benzene ring, the syn,syn dicarboxylic acid (**5a**, available by an improved method) was heated with three arylamines, affording products (7) which were distinctly different from the anti isomers. It would be predicted that there might be an observable difference in the ir spectrum between the carbonyl absorptions of the stereoisomer with an imide ring over a quaternary nitrogen atom and the one in which the imide ring is over an uncharged benzenoid ring. All the maleimide cycloaddition products (2) in Table I show a pair of carbonyl absorption bands in the 1700–1800 region, the difference between them being 76 ± 3 cm^{-1}. It is probably significant that the corresponding difference observed for the three syn stereoisomers (7) synthesized was 63 ± 4 cm^{-1}. On the basis of the correlation it is probably safe to conclude that all of the maleimide addition products have the anti configuration.

The maleimide adducts (2) were found to lose hydrogen bromide on heating and although thin layer chromatography showed that several products were formed in each decomposition, only one type, an arylimide (7) derived from 1-(2-pyridyl)naphthalene-2,3-



7 8
Y = H, CH_3, Cl

dicarboxylic acid, was isolated. The structure is supported by spectroscopic evidence and by analogy to earlier work by Fields, *et al.*, on the ring opening of acridizinium cycloaddition products.[3,10] The uv absorption spectrum resembled that of 1-(2-pyridyl-naphthalene) and the ir showed the characteristic double carbonyl absorption of imides as well as an absorption at 910 cm^{-1} corresponding to the C–H out-of-plane vibrations for a pentasubstituted benzene ring. The nmr of the parent compound (**8**, Y = H) showed no aliphatic hydrogens. The mass spectrum suggested an aromatic structure in that there were only four ions of any significant abundance. These corresponded to the molecular ion, the M − 1 ion, the M − ArNCO ion, and the M − ArN − C_2O_2 ion. The formation of the wholly aromatic structure in the pyrolysis must arise from disproportionation or some other mode of dehydrogenation.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Ir spectra were determined with a Perkin-Elmer 137 spectrometer as potassium bromide pellets. All uv spectra were measured in 95% ethanol with a Beckman DBG spectrometer. The nmr spectra were determined with a Varian T-60 spectrometer and unless otherwise indicated trifluoroacetic was the solvent. Elemental analyses were by M-H-W Laboratories, Garden City, Mich.

***N*-(*p*-Trimethylammonium phenylperchlorate)maleimide.**—*N*-(*p*-Dimethylaminophenyl)maleimide[11] (3 g) was quaternized by refluxing for 3 hr with 12 g of methyl iodide in 50 ml of acetone. The product was crystallized from methanol–ethyl acetate and then dissolved in a minimum quantity of hot water, and 35% perchloric acid was added. The precipitate was crystallized from methanol–ethyl acetate, affording silvery plates, mp 275–277°, yield 46%.

Anal. Calcd for $C_{13}H_{15}ClN_2O_6$: C, 47.27; H, 4.54; N, 8.48. Found: C, 46.96; H, 4.54; N, 8.43.

Cycloaddition Reactions. Method A.—A suspension of 1.2 g of acridizinium perchlorate and 2–3.5 molar equiv of the *N*-arylmaleimide in 20 ml of glacial acetic acid was heated at 100° and stirred until there was a disappearance of the uv absorption at 399 mμ. This required 20 hr or more for the perchlorates and only about 2 hr for the more soluble bromides. The perchlorate salts were isolated by pouring the suspension into dry ether, collecting the precipitate, and crystallizing from acetonitrile–

(10) D. L. Fields and T. N. Regan, *J. Org. Chem.*, **35**, 1870 (1970).
(11) W. R. Roderick and P. L. Bhatia, *ibid.*, **28**, 2018 (1963).

ethyl acetate. The bromide salts were isolated simply by cooling the reaction mixture, collecting the product, and recrystallizing from methanol–ethyl acetate. Results of these reactions are reported in Table I.

Method B.—Acridizinium bromide was ground in a mortar with 2–3.5 molar equiv of the *N*-arylmaleimide. The mixture was heated in an oil bath at 160–170°. A clear melt was first formed, but after about 15 min a precipitate appeared. The hot suspension was poured into hot glacial acetic acid and the hot solution was filtered. The colorless product which crystallized on cooling was almost pure, but could be recrystallized from methanol–ethyl acetate.

***syn,syn*-12,13-Dicarbomethoxy-6,11-dihydro-6,11-ethanoacridizinium Perchlorate (4).**—The following procedure is superior to that described earlier.[4] Acridizinium perchlorate (3 g) and dimethyl maleate (8 g) were heated (safety shield!) at 150–160° for 15–20 min. The precipitate (2.0 g, 44%) which had formed during the heating was collected by filtering the hot solution. The solid was colorless, mp 299–300° (lit[4] 298–299°), and identical (ir, nmr) with an authentic sample. This material was hydrolyzed to the corresponding dicarboxylic acid by heating with 4% hydrobromic acid.[4]

Acid-Catalyzed Rearrangement of 12,13-Dicarboxy-6,11-dihydro-6,11-ethanoacridizinium Derivatives.—The following procedure for the hydrolysis-rearrangement of the *N*-phenylmaleimide adduct (**2**, Y = H), (as the perchlorate) will serve as an example of the general procedure used for all 12,13-dicarboxy derivatives. The adduct (1.0 g) in 35 ml of 48% hydrobromic acid was refluxed for about 20 hr. The volume of hydrobromic acid was reduced to 5 ml by vacuum evaporation and while the solution was still hot a small quantity of perchloric acid was added. Upon cooling colorless needles formed, mp 264–266°, which were probably the *anti,syn*-dicarboxylic acid although the melting point was higher than previously reported (lit.[4] 244–246°). The ir was identical with that found previously and the dimethyl ester formed by refluxing the diacid for 4 hr in a 5% methanolic solution of hydrogen chloride was identical in melting point, ir, and nmr with known *anti-syn*-12,13-dicarbomethoxy-6,11-dihydro-6,11-ethanoacridizinium perchlorate (**6a**).

Hydrogenation of the *N*-Phenylimide Adduct (2, X = ClO_4, Y = H).—The perchlorate salt of the named compound (2 g) was dissolved in 200 ml of 50% aqueous methanol. Platinum oxide (0.4 g) was added and the mixture was hydrogenated at atmospheric pressure and room temperature. After 2 hr, 3 molar equiv of hydrogen had been absorbed and absorption of hydrogen had virtually ceased. The solution was filtered and concentrated, and 35% perchloric acid added to precipitate the product. The analytical sample crystallized from methanol as off-white needles, mp 227–229°.

Anal. Calcd for $C_{23}H_{23}ClN_2O_6$: C, 60.21; H, 5.02; N, 6.11; Cl, 7.74. Found: C, 60.36; H, 5.24; N, 5.98; Cl, 7.70.

Synthesis of *N*-Aryl-13,15-dioxo-6,11,12,13,15,16-hexahydro-[6,11-*c*]pyrroloacridizinium Perchlorates.—The procedure is illustrated for the *syn*-*N*-*p*-tolyl derivative (**7**, Y = Me). The syn dicarboxylic acid perchlorate (**5a**, 0.75 g) was refluxed in 25 ml of acetonitrile for 2 hr with 1.5 g of *p*-toluidine. The solution was concentrated and ethyl acetate was added. Acetonitrile–ethyl acetate was used for recrystallization of the colorless product, mp 328–330° dec, ir 1724 and 1783 cm^{-1} (C=O).

Anal. Calcd for $C_{24}H_{19}ClN_2O_6$: C, 61.74; H, 4.07; N, 6.00. Found: C, 61.78; H, 4.12; N, 5.77.

The *syn*-*N*-phenyl analog (7, Y = H) was prepared by use of aniline in place of *p*-toluidine, mp 303–304° dec, ir 1715 and 1780 cm^{-1} (C=O).

Anal. Calcd for $C_{23}H_{17}ClN_2O_6$: C, 61.00; H, 3.76; N, 6.19. Found: C, 61.35; H, 3.80; N, 6.00.

The *syn*-*N*-(*p*-anisyl) analog (7, Y = OMe) was prepared by use of *p*-anisidine in place of *p*-toluidine, mp 325–327° dec, ir 1721 and 1786 cm^{-1} (C=O).

Anal. Calcd for $C_{24}H_{19}ClN_2O_7$: C, 59.69; H, 3.94; N, 5.80. Found: C, 60.01; H, 3.92; N, 5.73.

The anti analogs (2, X = ClO_4, Y = H, Me, OMe) were prepared in similar fashion except that the anti, anti dicarboxylic acid[4] (**4a**) was used in place of **5a**. In each case the product was identical (melting point, ir) with the cycloaddition product **2** obtained by reaction of the appropriate *N*-arylmaleimide with acridizinium perchlorate.

***N*-Aryl-1-(2-pyridyl)naphthalene-2,3-dicarboximides (8) by Pyrolysis of Adducts (2).**—This procedure was that used in pyrolysis of the *N*-phenylmaleimide adduct (**2**, X = Br, Y = H) to **8**, Y = H. The salt (2 g) was sublimed at 350° under a pressure of 0.2 mm. The sublimate was dissolved in ethanol and precipitated by addition of water, affording 0.5 g of an orange solid. The product was obtained as yellow needles: mp 229° from methanol; uv max 268 mμ (ε 11,200); ir 1704, and 1761 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 350 (80), 349 (100), 231 (10), 203 (10).

Anal. Calcd for $C_{23}H_{14}N_2O_4$: C, 78.86; H, 4.00; N, 8.00. Found: C, 78.97; H, 4.00; N, 7.97.

***N*-*p*-Tolyl Analog (8, Y = CH_3).**—This had mp 242–243°; uv max 262 mμ (ε 62,300); ir 1724 and 1773 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 364 (80), 363 (100), 231 (10), 203 (15).

Anal. Calcd for $C_{24}H_{16}N_2O_2$: C, 79.12; H, 4.40; N 7.69. Found: C, 79.44; H, 4.56; N, 7.79.

***N*-*p*-Chlorophenyl Analog (8, Y = Cl).**—This had mp 217–218°; uv max 263 mμ (ε 79,600); ir 1730 and 1775 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 384 (80), 383 (100), 231 (10), 203 (10).

Anal. Calcd for $C_{23}H_{13}ClN_2O_2$: C, 71.87; H, 3.38; N, 7.28. Found: C, 71.59; H, 3.52; N, 7.17.

Registry No.—**1**, 260-62-8; **3**, 32207-36-6; **4**, 15314-08-6; **7** (Y = H), 32207-37-7; **7** (Y = OMe), 32120-85-7; **7** (Y = Me), 32207-38-8; **8** (Y = H), 32111-05-0; **8** (Y = Cl), 32111-06-1; **8** (Y = Me), 32111-07-2; *N*-(*p*-trimethylammonium phenylperchlorate)maleimide, 32111-08-3.

The Vicinal Methyl–Methyl Eclipsing Interaction across a Carbon–Nitrogen Single Bond. Activation Parameters for *tert*-Butyl Rotation in *tert*-Butyldimethylaminoborane and *tert*-Butyldimethylaminotrideuterioborane

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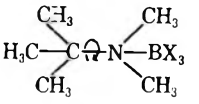
Nonequivalence in the *tert*-butyl group of *tert*-butyldimethylaminoborane (I) and *tert*-butyldimethylaminotrideuterioborane (II) made possible the determination of activation parameters for *tert*-butyl rotation in I (E_a = 11.6 ± 0.3 kcal/mol, $\Delta H^{\ddagger}$ = 11.2 ± 0.3 kcal/mol, $\Delta G^{\ddagger}$ = 10.0 ± 0.1 kcal/mol at −79°, $\Delta S^{\ddagger}$ = 6 ± 2 eu) and II (E_a = 11.5 ± 0.3 kcal/mol, $\Delta H^{\ddagger}$ = 11.1 ± 0.3 kcal/mol, $\Delta G^{\ddagger}$ = 10.1 ± 0.1 kcal/mol, $\Delta S^{\ddagger}$ = 5 ± 2 eu) using total nuclear magnetic resonance line-shape analysis. Available data from other systems indicating little difference in the steric requirements of CH_3 and BH_3 made possible the calculation of the methyl–methyl eclipsed repulsion (3.7 ± 0.3 kcal/mol) across the carbon–nitrogen single bond in I or II.

The availability of barriers to rotation about single bonds in simple acyclic systems is important for understanding the conformational dynamics of more complex structures[2] and for the development of a consistent theory for predicting such barriers.[3] Although a respectable amount of data is available regarding rotation about carbon–carbon and other single bonds,[3b,4] there is relatively little information concerning rotation about legitimate carbon–nitrogen single bonds, *e.g.*, CH_3NH_2 ($\Delta H^{\ddagger}$ = 2.0 kcal/mol),[5] $(CH_3)_3N$ ($\Delta H^{\ddagger}$ = 4.4 kcal/mol),[6] CH_3NO_2 ($\Delta H^{\ddagger}$ = 0.006 kcal/mol),[7] and (*tert*-C_4H_9)$(CH_3)_2N$ ($\Delta H^{\ddagger}$ = 6.2 kcal/mol).[8] However, many reports have been forthcoming concerning the detection of substantial rotational barriers about carbon–nitrogen bonds across which there is significant π bonding in the ground-state conformation[9] (*e.g.*, amides) or in which π bonding plays a role in the rotational process.[10]

There have been several reports of the detection of slowed rate processes in acyclic trialkylamines using dynamic nuclear magnetic resonance (dnmr) spectroscopy,[8,11] although the nature of the rate process observed, *i.e.*, rotation, inversion, or rotation–inversion, is controversial.[11] Some evidence is available supporting a common transition state for rotation and inversion in acyclic trialkylamines.[12]

This report concerns the determination of activation parameters for *rotation* about the central *tert*-butyl carbon–nitrogen single bond in *tert*-butyldimethylaminoborane (I)[13] and *tert*-butyldimethylaminotrideuterioborane (II) using the dnmr method and involves one of



I, X = H
II, X = D

relatively few examples of the observation of nonequivalence in *tert*-butyl.[8,14]

Results and Discussion

Examination of the pmr spectrum (60 MHz) of I in CH_2CHCl at −15° reveals two sharp singlet resonances due to *tert*-butyl (δ 1.32, 9 H) and $N(CH_3)_2$ (δ 2.56, 6H). The BH_3 resonance is not visible at amplitudes convenient for observing the *tert*-butyl and $N(CH_3)_2$ resonances due to large boron–hydrogen coupling constants[15] and broadening due to quadrupole-induced ^{10}B and ^{11}B spin relaxation.[16] Upon lowering the temperature, the $N(CH_3)_2$ peak remained unchanged to −110°, but the *tert*-butyl resonance broadened and separated into two sharp singlets at δ 1.34 and 1.16 with a respective area ratio of 2:1 (Figure 1). The width at half height ($W_{1/2}$) of the upfield *tert*-butyl peak (2.3 Hz) is slightly greater than the $W_{1/2}$ of the low field resonance (2.0 Hz) under slow exchange conditions (−100°, Figure 1). Over the temperature range from −95 to −125°, the chemical shift *difference* between the two *tert*-butyl resonances (10.9 ± 0.3 Hz) is independent of temperature, although the same slight downfield shift of both resonances is observed with increasing temperature (0.03 Hz/deg). From −95 to −125°, the $W_{1/2}$ of both *tert*-butyl resonances is independent of temperature.[8]

(1) Alfred P. Sloan Research Fellow, 1971–1973.

(2) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965; F. G. Riddell, *Quart. Rev., Chem. Soc.*, **21**, 364 (1967).

(3) (a) H. M. Pickett and H. L. Strauss, *J. Amer. Chem. Soc.*, **92**, 7281 (1970); (b) E. B. Wilson, Jr., *Advan. Chem. Phys.*, **2**, 367 (1959); J. P. Lowe, *J. Amer. Chem. Soc.*, **92**, 3799 (1970).

(4) D. J. Millen, *Progr. Stereochem.*, **3**, 138 (1962); R. A. Newmark and C. H. Sederholm, *J. Chem. Phys.*, **43**, 602 (1965); F. J. Weigart, M. B. Winstead, J. I. Garrels, and J. D. Roberts, *J. Amer. Chem. Soc.*, **92**, 7359 (1970).

(5) T. Nishikawa, T. Itoh, and K. Shimoda, *J. Chem. Phys.*, **23**, 1735 (1955).

(6) D. R. Lide, Jr., and D. E. Mann, *ibid.*, **28**, 572 (1958).

(7) E. Tannenbaum, R. J. Meyers, and W. D. Gwinn, *ibid.*, **25**, 42 (1956).

(8) C. H. Bushweller, J. W. O'Neil, and H. S. Bilofsky, *J. Amer. Chem. Soc.*, **92**, 6349 (1970).

(9) For a recent review, see W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **70**, 517 (1970).

(10) W. E. Bentz, L. D. Colebrook, and J. R. Fehlner, *Chem. Commun.*, 974 (1970); S. Brownstein, E. C. Horswill, and K. U. Ingold, *Can. J. Chem.*, **47**, 3243 (1969).

(11) C. H. Bushweller and J. W. O'Neil, *J. Amer. Chem. Soc.*, **92**, 2159 (1970); M. Saunders and F. Yamada, *ibid.*, **85**, 1882 (1963); W. R. Morgan and D. E. Leyden, *ibid.*, **92**, 4527 (1970); S. Brownstein, E. C. Horswill, and K. U. Ingold, *ibid.*, **92**, 7217 (1970); W. F. Reynolds and T. Schaefer, *Can. J. Chem.*, **42**, 2119 (1964).

(12) C. H. Bushweller, J. W. O'Neil, and H. S. Bilofsky, *J. Amer. Chem. Soc.*, **93**, 542 (1971); see also A. Rauk, L. C. Allen, and K. Mislow, *Angew. Chem., Int. Ed. Engl.*, **9**, 400 (1970).

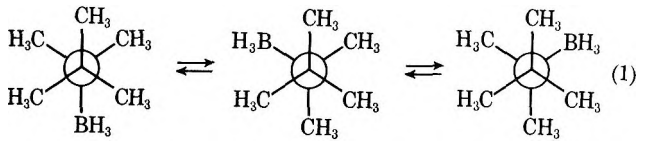
(13) C. H. Bushweller, H. Beall, W. J. Dewkett, and J. W. O'Neil, *Tetrahedron Lett.*, 4955 (1970).

(14) F. A. L. Anet, M. S. Jacques, and G. N. Chmurny, *J. Amer. Chem. Soc.*, **90**, 5243 (1968); W. E. Heyd and C. A. Cupas, *ibid.*, **91**, 1559 (1969); H. Kessler, *Angew. Chem., Int. Ed. Engl.*, **9**, 219 (1970).

(15) W. N. Lipscomb, "Boron Hydrides," W. A. Benjamin, New York, N. Y., 1963.

(16) M. Grace, H. Beall, and C. H. Bushweller, *Chem. Commun.*, 701 (1970); H. Beall, C. H. Bushweller, W. J. Dewkett, and M. Grace, *J. Amer. Chem. Soc.*, **92**, 3484 (1970); C. H. Bushweller, H. Beall, W. J. Dewkett, M. Grace, and H. S. Bilofsky, *ibid.*, **93**, 2145 (1971); D. Marynick and T. Onak, *J. Chem. Soc. A*, 1160 (1970).

The temperature dependence of the *tert*-butyl resonance in I is best rationalized by a slowing of *tert*-butyl rotation on the pmr time scale at low temperatures (eq 1). Since, as shown in eq 1, the N–CH_3 groups al-


(1)

ways experience equivalent environments, the shape of the $N(CH_3)_2$ resonance should be independent of any rate process except CH_3–N rotation. However, for the *tert*-butyl group in any of the three rotamers (eq 1), there are two equivalent methyls bisected by the BH_3 group and one other different methyl which bisects the $N(CH_3)_2$ group. Under conditions of slow rotation, the *tert*-butyl resonance should consist of two singlets of relative intensity 2:1 as observed.

Other possible rationalizations of the temperature dependence of the *tert*-butyl peak in I or II involve an inherently high barrier (>11 kcal/mol) to *tert*-butyl rotation with a rate-determining dissociation (eq 2) to free amine in which rotation is very rapid[8] or bimolecular displacement of one amine by another (eq 3) with both

$$\text{amine-BH}_3 \rightleftharpoons \text{amine} + \text{BH}_3 \quad (2)$$

$$\text{amine-BH}_3 + \text{amine}^* \rightleftharpoons \text{amine} + \text{amine}^*\text{-BH}_3 \quad (3)$$

processes effectively causing an exchange of the BH_3 moiety among the various amine molecules. If such processes were important on the time scale for the experiments reported above, such intermolecular exchange of BH_3 at higher temperatures should cause a coalescence of the respective *tert*-butyl and $N(CH_3)_2$ peaks of the complex and any added free amine. Addition of 1 molar equiv of *tert*-butyldimethylamine to a sample of I did not cause any change in the spectral behavior of I from room temperature to low temperatures. The *tert*-butyl resonance of the free amine (δ 1.00) remained sharp from room temperature to −110°, providing strong evidence against a dissociation or SN2 process. Thus, complexation by BH_3 has effectively stopped nitrogen inversion.

Because of the current interest in the relative steric size of hydrogen *vs.* deuterium, a dnmr study of *tert*-butyldimethylaminotrideuterioborane (II) was performed. The *tert*-butyl resonance of II displayed spectral changes at low temperature essentially the same as in I, although, under conditions of slow exchange, the chemical shifts of the two *tert*-butyl resonances (δ 1.32, 1.14) and the $N(CH_3)_2$ peak (δ 2.47) are slightly but consistently at higher field than in I.

A total nmr line shape analysis[17] of the *tert*-butyl resonances of I (Figure I) and II gave a series of rate constants as a function of temperature for *tert*-butyl rotation in I and II (Table I). A least-squares treatment of ln k_H (Table I) *vs.* $1/T$ (correlation coefficient 0.995) and ln k_D (Table I) *vs.* $1/T$ (correlation coefficient 0.998) gave activation parameters for *tert*-butyl rotation in I and II (Table II). The error assigned to E_a (Table II) is a maximum error obtained by drawing

(17) M. Saunders in "Magnetic Resonance in Biological Systems," A. Ehrenberg, Ed., Pergamon Press, New York, N. Y., 1967.

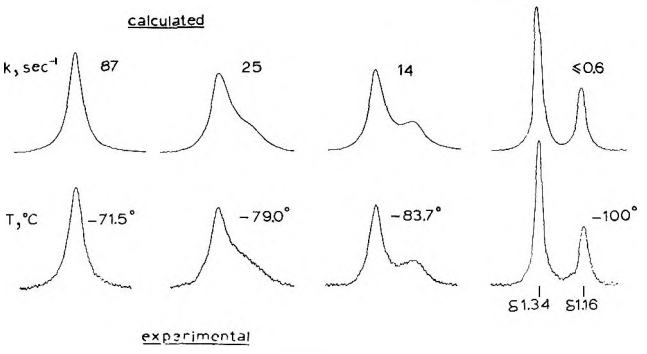


Figure 1.—The temperature dependence of the pmr spectrum (60 MHz) of the *tert*-butyl resonance of *tert*-butyldimethylaminoborane (I) and calculated spectra as a function of the rate of *tert*-butyl rotation.

TABLE I

RATE CONSTANTS FOR *tert*-BUTYL ROTATION IN I AND II AS A FUNCTION OF TEMPERATURE

I		II	
Temp, °C	k_H,[a] sec^{-1}	Temp, °C	k_D,[b] sec^{-1}
−67.9	140	−65.2	166
−71.5	87	−69.0	98
−75.8	45	−72.6	56
−79.0	25	−75.8	34
−83.7	14	−79.0	20
−87.0	7.0	−84.0	10
−90.0	5.0	−88.6	5.0

[a] k_H = first-order rate constant for disappearance of any methyl from any of the three sites on *tert*-butyl in I. [b] k_D = same for II.

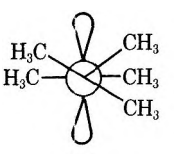
TABLE II

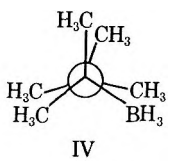
ACTIVATION PARAMETERS FOR *tert*-BUTYL ROTATION IN I AND II

	I	II
E_a, kcal/mol	11.6 ± 0.3	11.5 ± 0.3
$\Delta H^{\ddagger}$, kcal/mol	11.2 ± 0.3	11.1 ± 0.3
$\Delta G^{\ddagger}$, kcal/mol	10.0 ± 0.1	10.1 ± 0.1
$\Delta S^{\ddagger}$, eu	6 ± 2	5 ± 2

another line through the Arrhenius plot which gave a reasonable though worse fit than the line used.

The barriers to rotation of *tert*-butyl about a carbon–nitrogen single bond in I and II (Table II) are substantially higher than in the free *tert*-butyldimethylamine (E_a = 6.4 ± 0.3 kcal/mol, $\Delta H^{\ddagger}$ = 6.2 ± 0.3 kcal/mol, $\Delta G^{\ddagger}$ = 6.0 ± 0.1 kcal/mol, $\Delta S^{\ddagger}$ = 1.3 ± 2.0 eu)[8] and attest to significantly increased vicinal nonbonded repulsions in the transition state for I or II as compared to the free amine. Since nitrogen inversion is effectively locked *via* complexation by BH_3 in I and II and there exists in free *tert*-butyldimethylamine the definite possibility of nitrogen inversion, it would be naive to extract any trends regarding the relative magnitude of vicinal eclipsing interactions in these two systems. In the case of the free *tert*-butyldimethylamine, rotation and inversion most likely share a common transition state involving a planar (sp^2) configuration at nitrogen (III).[8,12] However, in I and II, complexation by BH_3 prevents any inversion process at nitrogen and the most


III


IV

reasonable transition state is the eclipsed form (IV) analogous to ethane. The positive $\Delta S^{\pm}$ for rotation in I and II may reflect in part a stretching of the nitrogen–boron bond in the transition state for rotation (IV) and slight concomitant rehybridization of nitrogen toward sp^2.

It is interesting to note that within experimental error the substitution of deuterium (II) for hydrogen (I) does not change the barrier to *tert*-butyl rotation (Table II) and that hydrogen and deuterium possess essentially the same conformational requirements in systems of this type.

The barrier to *tert*-butyl rotation in I and II is comparable to that for *tert*-butyl rotation in a series of halogenated methylbutanes (E_a = 10–12 kcal/mol).[18]

Recent evidence obtained for the 4-*tert*-butyl-1-methylpiperidine boranes indicates little preference for BH_3 axial (~53%) or equatorial (~47%);[19] *i.e.*, BH_3 has approximately the same conformational requirements as CH_3. Thus, the three vicinal eclipsing interactions in the transition state (IV) for *tert*-butyl rotation in I may be assumed to be approximately equal. The magnitude of one methyl–methyl eclipsed repulsion may be calculated to be one third of $\Delta H^{\pm}$ (Table II) for *tert*-butyl rotation or 3.7 ± 0.4 kcal/mol. The potential maximum for *n*-butane involving eclipsing of two methyl groups is estimated to be 4.4–6.1 kcal/mol.[20] Subtracting the two H–H eclipsing interactions (~2 kcal/mol), the methyl–methyl eclipsed repulsion in *n*-butane is estimated to be 2.4–4.1 kcal/mol.

(18) B. L. Hawkins, W. Bremser, S. Borcić, and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 4472 (1971).

(19) R. E. Lyle, J. J. Kaminski, and E. W. Southwick, Abstracts, 161st Meeting of the American Chemical Society, Los Angeles, Calif., March 29–April 2, 1971, abstract no. 146 (ORGN).

(20) W. G. Dauben and K. S. Pitzer, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956.

Experimental Section

The nmr spectra were obtained using a Varian HR-60A spectrometer equipped with a custom-built variable-temperature probe. Spectral calibrations were performed by the audio-modulation technique using a Hewlett-Packard 651-A audio-oscillator and 5221B electronic counter.

Temperature measurement was performed using a calibrated copper–constantan thermocouple permanently in place in the probe and is done simultaneously with the recording of the spectrum. Temperature measurement is accurate to ±0.3° at the sample.

The error (±5%) associated with the rate constants (Table I) obtained by matching theoretical to experimental spectra by superposition is a maximum error established by obviously poor fits at higher and lower values of the rate constant giving the best fit.

tert-**Butyldimethylaminoborane** (I) and *tert*-**butyldimethylaminotrideuterioborane** (II) were prepared by the method of Shore and Parry[21] using $LiBH_4$ and $LiBD_4$, respectively. The nmr, ir, and mass spectral data for I and II are entirely consistent with their respective structures.

Registry No.—I, 31121-07-0; II, 31819-36-0.

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(21) S. G. Shore and R. W. Parry, *J. Amer. Chem. Soc.*, **80**, 8 (1958).

The Thermal Decomposition of Bissilyl Peroxides and Triphenylsilyl Triphenylgermyl Peroxide[1]

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The thermal decomposition of bis(triphenylsilyl) peroxide gave an essentially quantitative yield of pentaphenylphenoxydisiloxane. Bis(*p*-tolyldiphenylsilyl) peroxide and bis(*p*-anisyldiphenylsilyl) peroxide were synthesized and analysis of the products of their thermal rearrangements gave a migratory aptitude series: *p*-anisyl, 6.0; *p*-tolyl, 1.1; phenyl, 1.0. These figures are consistent with a free-radical mechanism for the rearrangement. Triphenylsilyl triphenylgermyl peroxide was synthesized and its thermal decomposition occurs exclusively by phenyl–silicon bond cleavage to yield, ultimately, phenol, 0.62, triphenylgermyl moiety, 0.98, and polymeric diphenylsilyl oxide. Reproducible first-order kinetics were obtained with difficulty for 1 half-life for the thermal decomposition of the silylgermyl peroxide: k_{180}, 0.4; k_{190}, 1.0; k_{200}, 6.0 × 10^{-5} sec^{-1}.

In a previous paper the synthesis of several bissilyl peroxides was described. The present work was planned to study the decomposition of these bis peroxides and to attempt the synthesis of an unsymmetrical organometallic peroxide in which silicon and germanium would be joined by a peroxide link.

Results and Discussion

Bissilyl Peroxides.—Heating bis(triphenylsilyl) peroxide (I)[2] above its melting point (140–141°) gave an essentially quantitative yield (96%) of the rearrangement product II. The isolation of II was unexpected,

$$\underset{\text{I}}{(C_6H_5)_3SiOOSi(C_6H_5)_3} \xrightarrow{\text{heat}} \underset{\text{II}}{(C_6H_5)_3SiOSi(C_6H_5)_2(OC_6H_5)}$$

for from the thermal decomposition of the analogous bis(triphenylgermyl) peroxide it has been reported[3] that

(1) (a) Presented in part at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, ORGN 131. Taken in part from the Ph.D. thesis of A. K. Shubber, Case Western Reserve University, 1970. (b) Supported in part by the National Science Foundation through Grant GP-19018.

(2) R. L. Dannley and G. Jalics, *J. Org. Chem.*, **30**, 2417 (1965).

(3) R. L. Dannley and G. C. Farrant, *ibid.*, **34**, 2432 (1969).

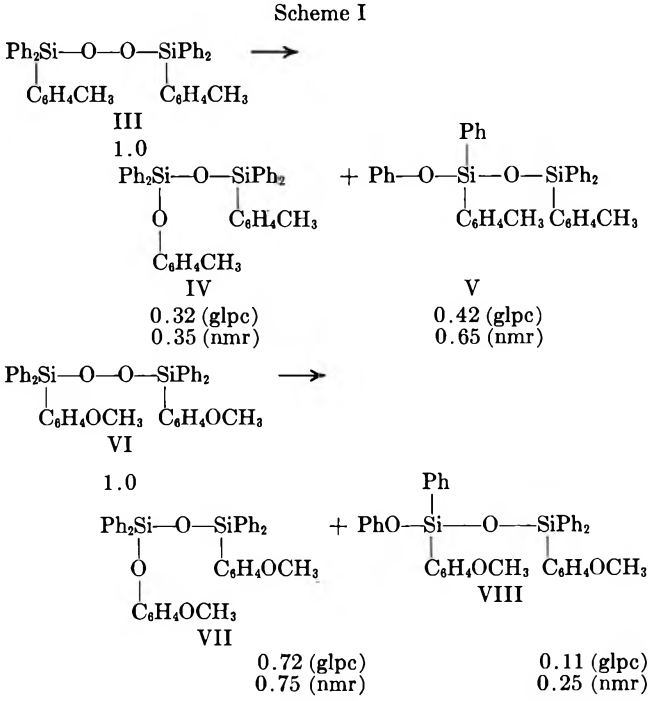
only hydrolysis products of the analogous phenoxydiphenylgermyl triphenylgermyl oxide could be recovered.

The structure of II was established from appropriate elemental analyses and a molecular weight determination as well as hydrolysis to a 90.6% yield of phenol. Also, the nmr spectrum of II consisted of one multiplet (τ 3.05–3.60) corresponding to phenoxy hydrogens and a second multiplet (τ 2.30–2.95) corresponding to phenyl hydrogens. The integrated areas under the peaks had the appropriate 1:5 ratio. The assignment of the peaks was confirmed by the nmr spectrum of I which consisted of a single multiplet (τ 2.30–2.90).

The rearrangement of I to II might proceed by either an ionic or homolytic mechanism. The migratory aptitudes of appropriate aryl groups in the reaction can be used to differentiate between these two alternative mechanisms. Therefore, two new peroxides (III and VI) were prepared in anticipation that the ratios of their isomeric rearrangement products (IV/V and VII/VIII) could be used to calculate the needed relative migratory aptitudes. III and VI were obtained in one-step syntheses from the corresponding triarylsilyl chlorides. In the course of the synthesis of III, *p*-tolyldiphenylsilyl hydroperoxide was obtained. This is the first triarylsilyl hydroperoxide reported containing unlike aryl groups.

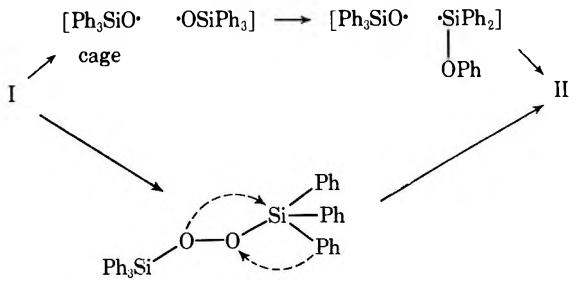
The isomeric rearrangement products of the bis peroxides could not be separated conveniently, but two analytical methods were available to determine the ratios of IV to V and VII to VIII. First, in each pair of isomers there were two types of methyl groups (*p*-tolyl *vs.* *p*-tolyloxy and *p*-anisyl *vs.* *p*-anisyloxy) which gave characteristic peaks in the nmr spectra permitting analysis. The assignment of the peaks was obtained by comparison to the nmr spectra of the corresponding peroxides. Second, alkaline hydrolysis of the isomer mixtures produced phenols which were analyzed by glpc. The results of the analysis are given in Scheme I. The nmr figures are the more accurate because the glpc analyses are based upon only a partial (74, 83%) recovery of the phenols, apparently due to some loss of the more volatile unsubstituted phenol. The glpc values serve to confirm the applicability of the nmr analysis, however.

Scheme I



The relative migratory aptitudes of the aryl groups are phenyl, 1.0; *p*-tolyl, 1.1; *p*-anisyl, 6.0. These low values are characteristic of a free radical but not an ionic rearrangement. For example, the analogous rearrangement of germanium hydroperoxides[3] led to the migratory aptitudes *p*-anisyl, 1.98; *p*-trifluoromethylphenyl, 1.36; phenyl, 1.0. Also, the rearrangement of bisgermanium peroxides gave the migratory aptitudes *p*-trifluoromethylphenyl, 1.25; phenyl, 1.0. A *p*-nitrophenyl/phenyl migratory ratio of 4.0–4.4:1 was reported for both the homolytic decomposition of diphenyl-*p*-nitrophenylmethyl hydroperoxide[4] and the oxidation of diphenyl-*p*-nitrophenylcarbinol with lead tetraacetate.[5,6] In contrast, for ionic processes such as the cleavage of aryltrimethylsilanes with mineral acid,[7] relative cleavage aptitudes are *p*-anisyl, 1500; *p*-tolyl, 21; phenyl, 1.0. Therefore, these data are consistent with a free-radical mechanism for the rearrangement of the bissilyl peroxides.

The quantitative formation of II from I must involve either a concerted process or a cage reaction to prevent the formation of some diphenoxytetraphenyldisilane as



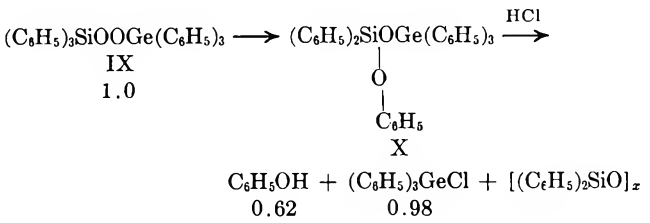
a coupling product. The high viscosity of the molten neat peroxide could be expected to give cage reactions, but a concerted process is not excluded. In a concerted reaction there could be a preferred conformation which would account for the migratory aptitudes.

The bissilyl peroxides do not respond to any of the conventional analysis for peroxide content and, in high boiling solvents, an overlap of the nmr peaks occurred. Therefore no kinetic measurements of the bissilyl peroxides decompositions were obtained.

Silylgermyl Peroxides.—When the present work was initiated, no covalent peroxides were known in which two metals were joined by a peroxide link. However, recently the synthesis of trimethylsilyltriphenylgermyl peroxide and triphenylsilyltriphenylgermyl peroxide (IX) have been reported.[8] These authors obtained IX from the silylamine and the germyl hydroperoxide in ether solution at 0–5°. The same procedure had been attempted in the present work without success. However, triphenylsilylamine and triphenylgermyl hydroperoxide were found to react slowly in refluxing methylene chloride to yield the desired peroxide IX.

(4) P. D. Bartlett and J. Cotman, *J. Amer. Chem. Soc.*, **72**, 3095 (1950).
(5) W. H. Starnes Jr., *ibid.*, **89**, 3368 (1967).
(6) W. H. Starnes Jr., *ibid.*, **90**, 1807 (1968).
(7) C. Eaborn and R. W. Bott, "The Bond to Carbon," Vol. 1, A. G. MacDiarmid, Ed., Marcel Dekker, New York, N. Y., 1968, p 410.
(8) A. P. Tarabarina, V. A. Yablokov, and N. V. Yablokova, *Zh. Obshch. Khim.*, **40** (5), 1094 (1970).

The thermal decomposition of IX either neat or in 1,2,4-trichlorobenzene yielded a new material (X) which, after treatment with anhydrous hydrogen chloride,[3] gave the following products. The essentially



quantitative recovery of triphenylchlorogermane proves that the migration of phenyl group occurs exclusively from the silicon atom. Although it has already been reported[3] that migration of a phenyl group from germanium to oxygen is possible, the rate of such a rearrangement may be too slow to compete here and the corresponding rearrangement of the silicon moiety is observed exclusively.

The thermal decomposition of IX in 1,2,4-trichlorobenzene was followed kinetically by iodometric titration. The unusual solvent was chosen because of its high boiling point as well as its solubility characteristics for the peroxide. The high stability of the peroxide necessitated temperatures of 180° or higher to give reasonable rates of decomposition. It was very difficult to get reproducible kinetics and reasonably good first-order plots were observed for only a single half-life. Therefore, the rate constants (Table I) should be considered initial rates and are not precise enough for an E_a calculation.

TABLE I

PSEUDO-FIRST-ORDER RATE CONSTANTS (SEC^{-1}) FOR THE FIRST HALF-LIFE DISAPPEARANCE OF TRIPHENYLSILYL TRIPHENYLGERMYL PEROXIDE (0.01 *M*) IN TRICHLOROBENZENE

T, °C	$k \times 10^5$, expt 1	$k \times 10^5$, expt 2	$k \times 10^5$, av
180	0.4 ± 0.05	0.4 ± 0.05	0.4
190	1.1 ± 0.1	0.9 ± 0.1	1.0
200	6 ± 1	7 ± 2	6

Experimental Section

***p*-Tolyldiphenylchlorosilane.**—The addition of *p*-bromotoluene (85.5 g, 0.5 mol) in anhydrous ether (500 ml) to magnesium (12 g, 0.5 g-atom) in ether (500 ml) produced the ethereal Grignard reagent which was filtered and the filtrate was added dropwise to a warm solution of diphenyldichlorosilane (252 g, 1 mol) in dry toluene (500 ml). The ether distilled during the addition and the residual toluene solution was refluxed (4 hr). The toluene was then removed under reduced pressure and the residue was vacuum distilled to give relatively pure *p*-tolyldiphenylchlorosilane [74 g, bp 150–160° (5 mm)] and *p*-tolyldiphenylbromosilane [44 g, bp 205–210° (5 mm), mp 61–62°]. The nmr and ir spectra corresponded to these assigned structures. Hydrolysis of the two fractions produced the same silanol.

***p*-Tolyldiphenylsilyl Hydroperoxide.**—Using the procedure previously described for silyl hydroperoxides,[2] *p*-tolyldiphenylchlorosilane (5.0 g, 0.016 mol) in ether (200 ml) with 98% hydrogen peroxide (5.0 ml, 0.2 mol) gave *p*-tolyldiphenylsilyl hydroperoxide (3.1 g, 62.5%) which melted at 75° after recrystallization from ether–petroleum ether (bp 30–60°). *Anal.* Calcd for $C_{19}H_{18}O_2Si$: C, 74.5; H, 5.93; Si, 9.15; active oxygen, 5.21. Found: C, 74.8; H, 6.04; Si, 9.07; active oxygen, 5.20.

Bis(*p*-tolydiphenylsilyl) Peroxide.—Anhydrous ammonia was bubbled (3 min) through a solution of *p*-tolyldiphenylchlorosilane (5 g) in anhydrous ether (150 ml), the solution stirred for 5 min, and 98% hydrogen peroxide (1.3 g) was added. After 3 min the precipitated ammonium chloride was removed by filtration, the ether solution washed three times with water, and the ether solution dried with magnesium sulfate. Evaporation of the ether solution gave an oily material which when recrystallized from petroleum ether at −20° gave bis(*p*-tolyldiphenylsilyl) peroxide (3.5 g, mp 135°). *Anal.* Calcd for $C_{38}H_{34}O_2Si_2$: C, 78.87; H, 5.92; Si, 9.68. Found: C, 78.95; H, 5.89; Si, 9.82. The nmr spectrum consisted of a multiplet (τ 2.4–3.0) and a singlet (τ 7.7).

***p*-Anisyldiphenylchlorosilane.**—*p*-Bromoanisole (47 g) in anhydrous tetrahydrofuran (50 ml) was added to magnesium (6 g) in tetrahydrofuran (250 ml). After refluxing, the Grignard reagent was filtered and added to diphenyldichlorosilane (73 g) in anhydrous benzene (300 ml) kept at a temperature high enough to distil the tetrahydrofuran. After all the tetrahydrofuran was distilled, the residue was refluxed (120 hr). After filtration to remove metallic salts, the solution was distilled to give 60 g of a mixture of *p*-anisyldiphenylchlorosilane [bp 180–195° (0.4 mm)] and *p*-anisyldiphenylbromosilane [bp 195–205° (0.4 mm)].

Bis(*p*-anisyldiphenylsilyl) Peroxide.—By a procedure identical with that for bis(*p*-tolyldiphenylsilyl) peroxide, *p*-anisyldiphenylchlorosilane (5g) in ether (150 ml) and 98% hydrogen peroxide (0.32 g) produced 2.8 g of bis(*p*-anisyldiphenylsilyl) peroxide (mp 112°). *Anal.* Calcd for $C_{38}H_{34}O_4Si_2$: C, 74.71; H, 5.62. Found: C, 74.59; H, 5.78. The nmr spectrum consists of a multiplet (τ 2.45–3.3) and a singlet (τ 6.4).

Thermal Decomposition of Bis(triphenylsilyl) Peroxide.—The peroxide (1 g, 0.0018 mol) in a sealed tube was heated (200°) for 4 hr. The cooled reaction mixture was extracted with petroleum ether and the extract was cooled to produce pentaphenylphenoxydisiloxane, mp 128–129° (0.96, g, 96% yield). *Anal.* Calcd for $C_{36}H_{30}O_2Si_2$: C, 78.50; H, 5.49; Si, 10.19; mol wt, 551. Found: C, 78.46; H, 5.64; Si, 10.45; mol wt, 575.

To prove the structure, the rearranged product (0.96 g) was refluxed with 20% potassium hydroxide in 50:50 aqueous methanol (25 ml) and benzene (10 ml) for 5 hr. The mixture was cooled and acidified with dilute hydrochloric acid, water was added, and the phenol was extracted with ether. The ether extract was dried and evaporated to dryness. Gas chromatographic analysis using a 15-ft column of 20% SE-30 on Chromosorb W AW/DMCS treated 80–100 mesh at 150° with *p*-cresol as an internal standard gave 0.906 mol of phenol produced per mole of rearrangement product. An identical hydrolysis procedure applied to the parent peroxide produced a negligible quantity of phenol.

Thermal Decomposition of Bis(*p*-tolyldiphenylsilyl) Peroxide.—After the peroxide (2.75 g) had been heated in an oil bath for 3 hr, it was transferred to a volumetric flask (25 ml) and benzene was added. Gas chromatographic analysis of an aliquot of the benzene solution showed no free phenol or *p*-cresol to be present, even after bubbling hydrogen chloride through the solution for 1 hr. Using the hydrolysis procedure previously described for pentaphenylphenoxydisiloxane, glpc analysis of an aliquot of the benzene solution with a 15-ft column of 20% SE-30 on 80–100 mesh Chromosorb W AW/DMSC at 145° and 2,5-xylenol as a internal standard showed 0.415 mol of phenol and 0.316 mol *p*-cresol per mole of peroxide or a *p*-tolyl/phenyl migratory aptitude of 1.52.

From the 4.7 ratio of the τ 7.35 singlet (*p*-tolyl-Si) to the τ 7.5 singlet (*p*-tolyloxy-Si) in the nmr, the tolyl/phenyl migratory aptitude is 1.1.

Thermal Decomposition of Bis(*p*-anisyldiphenylsilyl) Peroxide.—After heating the peroxide (250 mg) at 135° for 4 hr, the product exhibited two singlets (τ 6.3 and 6.4) in the nmr spectrum for the methoxy protons. The rearrangement product was refluxed with benzene (10 ml) and 20% methanolic potassium hydroxide (20 ml) for 4 hr. Water was added and the solution was acidified with dilute hydrochloric acid. The phenolic products were extracted with three portions (10 ml each) of ether. The ether extracts were dried, evaporated to dryness, and analyzed by glpc using the same conditions as for the cresol–phenol mixture except that *p*-cresol was used as an internal standard. In duplicate runs, the percentage yields were determined to be *p*-methoxyphenol, 78 and 65.5%, and phenol, 11.1 and 9.8%, for a migratory aptitude of *p*-anisyl/phenyl of 14. From the relative intensities of the τ 6.3/6.4 peaks in the nmr, the relative migratory aptitude of *p*-anisyl/phenyl is 6.

Triphenylsilyl Triphenylgermyl Peroxide.—A solution of triphenylsilylamine (2.1 g), triphenylgermyl hydroperoxide,[9] and methylene chloride (150 ml) was refluxed overnight, at the end of which time the evolution of ammonia had ceased. Removal of the solvent using a rotary evaporator and recrystallization of the residue from methylene chloride produced triphenylsilyl triphenylgermyl peroxide (4 g), mp 155° (lit.[8] mp 142–142.5°). *Anal.* Calcd for $C_{36}H_{30}SiGeO_2$: C, 72.7; H, 5.08. Found: C, 72.37; H, 5.04. Active oxygen titration showed a purity of 94%.

Thermal Decomposition of Triphenylsilyl Triphenylgermyl Peroxide.—After heating (165°) the asymmetric peroxide (0.2 g) for 16 hr, the product (mp 126°) had a different ir spectrum from that of the starting material. It was dissolved in methylene chloride and hydrogen chloride was bubbled through for 10 min. Triphenylmethane and *p*-cresol were added as internal standards and glpc analysis[3] showed a 98% yield of triphenylchlorogermane and a 62% yield of phenol.

Kinetics of the Decomposition of Triphenylsilyl Triphenylgermyl Peroxide.—The thermal decomposition of a trichlorobenzene solution of the peroxide (0.01 *M*) was followed iodometrically to give the first-order rates in $sec^{-1} \times 10^5$ in Table I.

Registry No.—I, 2319-39-3; II, 31952-39-3; III, 31952-40-6; VI, 31999-36-7; IX, 27526-19-8; *p*-tolyldiphenylchlorosilane, 13868-70-5; *p*-tolyldiphenylbromosilane, 31952-43-9; *p*-tolyldiphenylsilyl hydroperoxide, 31952-44-0; *p*-anisyldiphenylchlorosilane, 18670-55-8.

Acknowledgment.—We wish to thank Dr. George Jalics for the first isolation of pentaphenylphenoxydisiloxane from the rearrangement of bis(triphenylsilyl) peroxide.

(9) R. L. Dannley and G. C. Farrant, *J. Org. Chem.*, **34**, 2428 (1969).

A Thermal Two-Carbon Ring Expansion. 2-Cyclopentenones from 3-Cyclopropyl-3-oxopropanoates

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Received May 13, 1971

Pyrolysis of 3-cyclopropyl-3-oxopropanoates **1a–d** (**a**, $R_1 = R_2 = H$; **b**, $R_1 = CH_3$, $R_2 = H$; **c**, $R_1 = H$, $R_2 = CH_3$; **d**, $R_1 = R_2 = CH_3$) at 500–600° (1–3 mm) gave the corresponding 2-cyclopentenones **2a–d** in 50–80% yields. The resultant substitution patterns in **2a–d** led to the conclusion that the oxo group was extruded from **1a–d**. Pyrolysis of **1a** at 760 mm gave pyrandione **10b** (R = c-C_3H_5). Pyrolysis of **10b** at 1–3 mm gave 2-cyclopentenone (**2a**). This is presented as evidence for the existence of an acylketene intermediate **11b**. The rearrangement of **1** to **2** represents a novel two-carbon ring expansion reaction of cyclopropane derivatives.

Several two-carbon thermal ring expansion reactions of cyclopropanes are known.[1-11] Of these, only the vinylcyclopropane–cyclopentene rearrangement has received more than passing interest.[1-3,12] We wish to report[13] a new thermal rearrangement of 3-cyclopropyl-3-oxopropanoate esters **1a–d** to cyclopentenones **2a–d** in moderate yields (Table I) which may prove to be of synthetic interest.

Results and Discussion

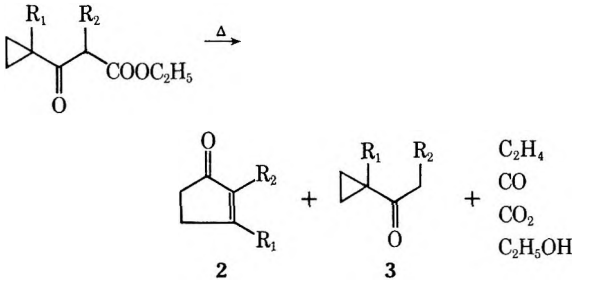
The products of pyrolysis of keto esters **1** near 500° at 1–3 mm included cyclopentenones **2**, ketones **3**, carbon monoxide, carbon dioxide, ethanol, and ethylene (eq 1).

TABLE I

PYROLYSIS OF KETO ESTERS 1a–d

Starting material	R_1	R_2	T, °C[a]	% yield of **2a–d**, glpc[b]	T, °C	% yield of **2a–d** isolated[c]
1a	H	H	565	51	540	47
1b	CH_3	H	500	65	500	60
1c	H	CH_3	585	65	585	58
1d	CH_3	CH_3	535	81	570	68

[a] Pyrolysis temperature affording greatest glpc yield. [b] Glpc yields based upon unrecovered starting material. [c] Isolated yields based upon weight of product recovered by distillation.



2 **3**

a, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = H$; $R_2 = CH_3$
d, $R_1 = R_2 = CH_3$

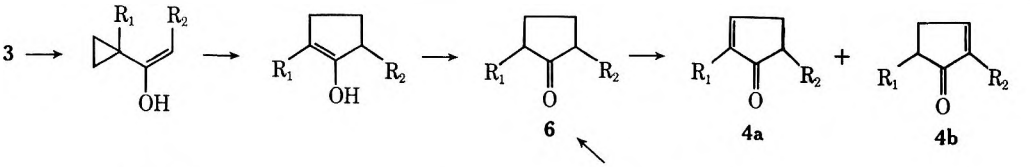
Table II presents evidence that the ratio of ketone **2a** and **3a** increased dramatically with an increase in the surface area of the pyrolysis packing material. This

(1) C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968, Chapters IX, X.
(2) R. Breslow, "Molecular Rearrangements, Part I," P. de Mayo, Ed., Interscience, New York, N. Y., 1963, Chapter 4.
(3) G. L. Closs, *Advan. Alicycl. Chem.*, **1**, 53 (1966).
(4) M. J. Goldstein and B. G. Odell, *J. Amer. Chem. Soc.*, **89**, 6356 (1967).
(5) O. L. Chapman and J. D. Lassila, *ibid.*, **90**, 2449 (1968).
(6) O. L. Chapman, M. Kane, J. D. Lassila, R. L. Loeschen, and H. E. Wright, *ibid.*, **91**, 6857 (1969).
(7) A. S. Kende, Z. Goldschmidt, and P. T. Izzo, *ibid.*, **91**, 6858 (1969).
(8) W. C. Agosta, A. B. Smith, III, A. S. Kende, R. G. Eilerman, and J. Benham, *Tetrahedron Lett.*, 4517 (1969).
(9) G. E. Cartier and S. C. Bunce, *J. Amer. Chem. Soc.*, **85**, 932 (1963).
(10) G. E. Cartier and S. C. Bunce, *Diss. Abstr.*, **25**, 826 (1964).
(11) J. W. Wilt, L. L. Maravetz, and J. F. Zawadski, *J. Org. Chem.*, **31**, 3018 (1966).
(12) There has been considerable interest, however, in the subject of homoconjugative participation of cyclopropyl systems in developing carbonium ion centers which does not usually result in ring expansion. See, *e.g.*, M. Hanack and H. M. Ensslin, *Tetrahedron Lett.*, 4445 (1965); M. J. S. Dewar and J. M. Harris, *J. Amer. Chem. Soc.*, **92**, 6557 (1970), and references cited therein.
(13) Preliminary report: W. F. Berkowitz and A. A. Ozorio, Abstracts, 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 22, 1970, ORGN 142.

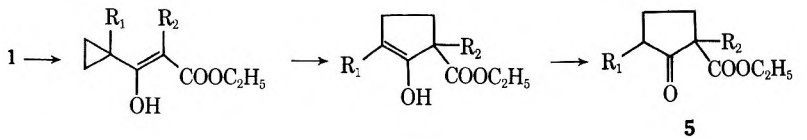
leads us to believe that the reaction affording **2** is catalyzed by glass surfaces[14] while that leading to **3** is not, and thus **2** and **3** are produced by competitive routes (see eq 4).

The substitution pattern of the cyclopentenones **2a–d** produced apparently requires the loss of the oxo group rather than the carbonyl of the carboxyl group. In the latter case the methyl groups of **1d** would appear in the 1 and 5 positions of the product (*e.g.*, **4a,b**) rather than in adjacent positions 2 and 3 as in **2d**.

This result precludes mechanisms involving the direct conversion of **3** to **2** (eq 2) or ones involving prior conversion of **1** to a cyclopentanone carboxylate (**5**), decarbethoxylation[15] to **6**, and subsequent formation of **4a,b**[16] (eq 3).



(2)

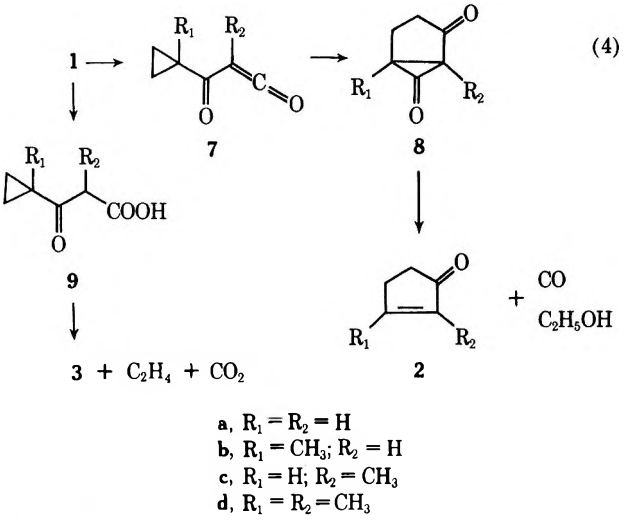


(3)

Furthermore, using conditions which would have converted **1** to **2**,[17] we found that cyclopropyl methyl ketone (**3a**) and cyclopentanone were recovered unchanged by pyrolysis (99 and 96% recovery, respectively) and α-carbethoxycyclopentanone (**5**, $R_1 = R_2 = H$) was converted to cyclopentanone (**6**, $R_1 = R_2 = H$) in 48% yield. In none of these reactions was 2-cyclopentenone detectable in the pyrolysate.[18]

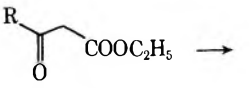
We suggest the shown in eq 4 mechanism for the conversion of **1** to **2** and **3**).

Formation of **3** from **1** (*via* **9**) is expected pyrolytic behavior of a β-keto ester.[15b,c] The mechanism is believed to consist of formation of a β-keto acid with subsequent decarboxylation, both steps proceeding by way of cyclic six-centered transition states.[19–21]

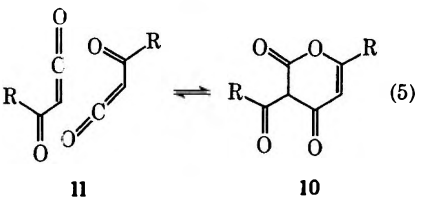


(4)

a, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = H$; $R_2 = CH_3$
d, $R_1 = R_2 = CH_3$



a, $R = CH_3$
b, $R = c\text{-}C_3H_5$



(5)

Formation of acylketenes (*e.g.*, **7**) from β-keto esters has never been observed; on the other hand, ketenes[25] have been obtained by pyrolysis of esters in competition with olefin formation.[26] It appears reasonable that the increased acidity of the α hydrogens of β-keto esters might enhance the rate of ketene formation. In addition, pyrolysis of acetoacetic ester has given dehydroacetic acid[27,28] (**10a**), which, it may be noted, can be considered as a Diels–Alder dimer of acylketene **11**[29] (eq 5).

Similarly, pyrolysis of β-keto ester **1a** at 760 mm (run 13) gave a white solid which we believe to be the analogous pyrandione **10b** (see Experimental Section). Thus, at low pressure (1–3 mm) formation of acylketene

(14) Acid or base washing, followed by thorough washing with distilled water, apparently had little effect on either the per cent conversion or the ratio of **2a** to **3a**.

(15) (a) Thermal decarbethoxylation, while not observed heretofore with α-carbethoxycyclopentanone, is a common reaction of β-keto esters,[15b,c] malonates,[15d] and α-cyano esters.[15e] (b) W. J. Bailey and J. J. Daly, Jr., *J. Org. Chem.*, **22**, 1189 (1957); (c) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 171; (d) W. J. Bailey and J. J. Daly, Jr., *J. Org. Chem.*, **29**, 1249 (1964); (e) W. J. Bailey and J. J. Daly, Jr., *J. Amer. Chem. Soc.*, **81**, 5397 (1959).

(16) Pyrolytic dehydrogenation of cyclopentanone to cyclopentenone was noted at 488–543° (99–314 mm) by E. R. Johnson and W. D. Walters, *ibid.*, **76**, 6266 (1954), and at 532–581° (11–30 mm) by F. M. Delles, *et al.*, *ibid.*, **91**, 7645 (1969). A static system was used in these investigations with much longer contact times than in our flow system.

(17) See Experimental Section.

(18) Glpc conditions used enabled easy detection of less than 1% of **2a** in a mixture of **2a**, **3a**, **4a**, and **5**.

(19) A. Maccoll and P. J. Thomas, *Progr. React. Kinet.*, **4**, 119 (1967).

(20) E. M. Hodnett and R. L. Rowton, *Radioisotop. Phys. Sci. Ind., Proc. Conf.*, **3**, 225 (1960); *Chem. Abstr.*, **58**, 4400*b* (1963).

(21) (a) D. B. Bigley and J. C. Thurman, *Tetrahedron Lett.*, 2377 (1967); (b) D. B. Bigley and J. C. Thurman, *J. Chem. Soc. B*, 941 (1967); (c) D. B. Bigley and J. C. Thurman, *ibid.*, 436 (1968). Whereas catalytic effects of glass surfaces have not been reported, it is reasonable to assume that they should be minimal since normal ester pyrolysis has been shown to be insensitive to changes in the (clean) surface area of silicaceous packing materials.[22–24]

(22) E. U. Emovon, *J. Chem. Soc.*, 1246 (1963).

(23) D. H. R. Barton, A. J. Head, and R. J. Williams, *ibid.*, 1715 (1953).

(24) M. Szwarc and J. Murawski, *Trans. Faraday Soc.*, **47**, 269 (1951).

(25) (a) H. M. Mackinnon and P. D. Ritchie, *J. Chem. Soc.*, 2564 (1957); (b) R. N. Bennett, A. A. Deans J. G. H. Harris, P. D. Ritchie, and J. S. Shim, *ibid.*, 4508 (1958); (c) A. L. Brown and P. D. Ritchie, *J. Chem. Soc. C*, 2007, 2013 (1968).

(26) C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).

(27) (a) S. Nakamura, S. Ishidoya, and U. Okubo, Japanese Patent 2375 (1955); *Chem. Abstr.*, **51**, 14826*b* (1957). (b) S. Nakamura and S. Ishidoya, Japanese Patent 1884 (1955). *Chem. Abstr.*, **51**, 4442*d* (1957).

(28) F. Arndt, *Org. Syn.*, **20**, 26 (1940).

(29) (a) H. Stetter and K. Kiehs, *Tetrahedron Lett.*, 3531 (1964); (b) H. Stetter and K. Kiehs, *Chem. Ber.*, **98**, 1181, 2099 (1965).

TABLE II

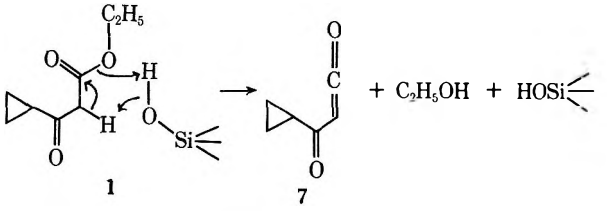
PYROLYSIS OF KETO ESTER 1a UNDER VARIOUS CONDITIONS[a]

Run	Packing material[b]	T, °C[c]	Product % yields[d] 2a	3a	C_2H_5OH	% unchanged 1a	Pyrolysate total wt, %[e]
1	A	470	14	36	56	48	68
2	A	575	5	18	37	80	88
3	A	625	8	30	58	78	84
4	B	600	20	16	42	19	69
5	C	460	27	31	65	21	70
6[f]	C	525	54	0	76	17	66
7[f]	C	540	52	0	85	8	79
8	C	565	51	7	74	0	73
9	C	625	46	5	75	0	63
10[g]	C	525	35	1	53 (CH_3OH)	0	78
11[g]	C	575	45	1	73 (CH_3OH)	0	70
12[h]	C	450	14	19	57	0	37[i]
13[j]	A	410	1	9	50	1	48[i]
14[k]	D	400				30	69

[a] Material entered the pyrolysis tube in the vapor state at 1–3 mm unless otherwise noted. [b] A, 6 × 6 mm Pyrex Rasching rings; B, 6-mm Pyrex helices; C, Pyrex glass wool; D, pumice stone. [c] Maximum temperature, ±10°, at the center of the tube oven prior to pyrolysis. [d] Glpc yields based on unrecovered 1a. For glpc conditions, see Experimental Section. [e] Weights of gases formed are not included. Quantitative conversion of 1a to 2a thus would afford only 83% by weight of pyrolysate. [f] Yields of isolated products based on unrecovered 1a. [g] The methyl ester of 1a was pyrolyzed. [h] Pyrolysis at 100 mm. [i] Low recoveries due to cooler tube ends which condensed and charred products. [j] Pyrolysis at 760 mm. A pyrandione (10b) was obtained in 20% yield. See Experimental Section. [k] Pyrolysis at 760 mm over pumice.[27] Pyrandione 10b was obtained in 79% yield (based on unrecovered 1a). See Experimental Section.

11b (= 7a) from 1a led to 2a, as in eq 4, while at high pressure (760 mm) the higher concentration of 11b permitted dimerization leading to 10b. Furthermore, pyrolysis of the dimer itself (10b) at low pressure gave 2-cyclopentenone-1 in 48% yield (run 22), presumably by way of a retro-Diels–Alder reaction leading to 11b, with subsequent rearrangement to 8 and extrusion of carbon monoxide as in eq 4.

We suggest that the loss of ethanol from 1 to give 7 is catalyzed by silanol groups of the glass surface (eq 6), mainly because we are unable otherwise to construct

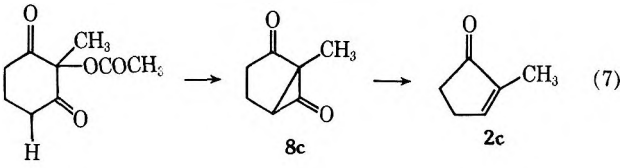


(6)

a reasonable six-centered cyclic transition state[25c] for dealcoholation.[30] We also think it less likely that the unimolecular rearrangement 7–8 or the decarbonylation 8–2 would be affected by a catalyst.

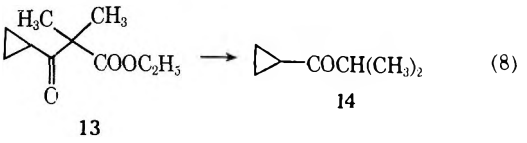
The rearrangement of 7 to 8 has, of course, no precedent as neither acylketenes nor cyclopropanones similar to 8 have ever been isolated. We can only indicate that it may be a thermally allowed[31] $\sigma_{2s} + \pi_{2a}$ electrocyclic reaction with subsequent (or, perhaps, simultaneous) nonlinear chelotropic elimination of carbon monoxide.

Intermediate 8c ($R_2 = CH_3$; $R_1 = H$) has been proposed[32] as the preliminary product of the pyrolytic loss of acetic acid from 12, giving, ultimately, 2c (eq 7). The formation of alkenes by the pyrolytic extrusion of a carbonyl adjacent to an acetoxy group has been noted in other instances, and preliminary formation of cyclopropanones was also proposed.[33]



(7)

Finally, β-keto ester 13, with no α hydrogens, afforded only ketone 14 in 77% yield upon pyrolysis (run 21). No cyclopentenones or ethanol were observed in the pyrolysate (eq 8).

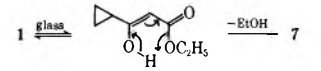


(8)

Experimental Section

All melting points were obtained on a Mel-Temp apparatus, and neither melting points nor boiling points are corrected. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Gas–liquid phase chromatography (glpc) was done with a Varian-Aerograph Model A-700, thermal conductivity apparatus. Areas of glpc records were integrated with a planimeter and adjusted for differing response factors by inclusion of an internal standard. Infrared spectra were determined with a Perkin-Elmer Model 237B or a Beckman Model IR-20 grating spectrophotometer. Ultraviolet spectra were determined with a Cary Model 14 or Bausch and Lomb Spectronic 505 recording spectrophotometer. Proton magnetic resonance spectra were obtained with a Varian Model A60-A spectrometer. Pyrolyses were done with a Hevi-Duty Electric Co. Type 77-T (600-W "Multi-Unit") tube oven.

(30) A reviewer suggested the highly plausible alternative of glass surface catalysis of the keto–enol shift with subsequent loss of ethanol, *e.g.*



(31) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970.

(32) T. A. Spencer, A. L. Hall, and C. F. von Reyn, *J. Org. Chem.*, **33**, 3369 (1968).

(33) (a) R. G. Carlson and J. H. Bateman, *ibid.*, **32**, 1608 (1967), and references cited therein; (b) see also A. S. Kende, *Chem. Ind. (London)*, 1053 (1956).

Materials.—Cyclopropyl methyl ketone, 3-methyl-2-cyclopentenone-1, dialkyl carbonates, methyl iodide, benzaldehyde, and 2-acetylbutyrolactone were obtained from Aldrich Chemical Co., Cedar Knolls, N. J., and were distilled prior to use. 2-Cyclopentenone was obtained from K and K Laboratories, Plainview, N. Y., and was distilled and then further purified by preparative glpc.[34] Ethyl 2-cyclopentanone-1-carboxylate (α-carbethoxycyclopentanone) was obtained from K and K and distilled prior to use.

Pyrex Raschig rings and helices were obtained from The Ace Glass Co., Vineland, N. J.; Pyrex glass wool (Corning No. 3950) was obtained from The Scientific Glass Apparatus Co., Bloomfield, N. J. Pumice stone (4–8 mesh) was obtained from Matheson Coleman and Bell. Catalytic activity of the glass surfaces appeared unaltered by either acid or base washing (followed by thorough rinsing with distilled water) and were only water washed and oven dried prior to use. The Vycor pyrolysis tubes (37 × 2.5 cm, 24/40 joints) were manufactured by Mr. Karl Schumann, Columbia University, New York, N. Y. The tubes were packed with fresh packing material for each run.

Thiouracil derivatives were prepared by the appropriate modification of the procedure of Spitzmiller;[35] 2,4-dinitrophenylhydrazone derivatives were prepared by the procedure of Shriner, Fuson, and Curtin.[36]

Ethyl 3-Cyclopropyl-3-oxopropanoate (1a).—Keto ester 1a was prepared by modification of the procedure of Johnson[37] using 25.0 g (0.30 mol) of cyclopropyl methyl ketone (3a) in 70 ml of anhydrous ether and 1 ml of absolute ethanol with a mixture of 55.2 g (1.15 mol) of sodium hydride (50% dispersion in mineral oil) and 260 g (2.2 mol) of diethyl carbonate in 300 ml of anhydrous ether. After the mixture was stirred at room temperature for 36 hr, work-up gave 35 g (75%) of keto ester 1a, bp 70° (2.8 mm) [lit.[38] bp 99–101° (11 mm)], which was 99.5% pure[34] after one distillation. A repeat of this procedure gave ester 1a in 82% yield after one distillation.

Methyl 3-Cyclopropyl-3-oxopropanoate (1a Methyl Ester).—Replacement of the diethyl carbonate by 200 g (2.2 mol) of dimethyl carbonate in the procedure used for 1a, gave, after 72 hr of stirring at room temperature and work-up, 32 g (75%) of 99.5% pure[34] 1a methyl ester after one distillation, bp 58° (1.5 mm). Stirring for 24 hr reduced the yield to 56%.

Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C 59.17; H, 7.03.

Ethyl ester 1a has ir (CCl_4) 5.75 (ester C=O), 5.88 (ketone C=O), and 3.24 μ (cyclopropyl CH). The methyl ester of 1 has ir (CCl_4) 5.72 (ester C=O), 5.87 (ketone C=O), and 3.24 μ (cyclopropyl CH). The nmr spectrum of 1a (ethyl ester) shows δ^{CCl_4} 0.74–1.09 (m, 4, cyclopropyl CH_2), 1.22 (t, 3, J = 7 Hz, CH_2CH_3), 1.78–2.24 (m, 1, cyclopropyl methine), 3.41 (s, 2, $COCH_2COO$), and 4.06 (q, 2, J = 7 Hz, CH_2CH_3). The nmr of 1a methyl ester shows δ^{CCl_4} 0.77–1.10 (m, 4, cyclopropyl CH_2), 1.84–2.32 (m, 1, cyclopropyl methine), 3.54 (s, 2, $COCH_2COO$), and 3.70 (s, 3, $COOCH_3$).

Both esters gave a positive ferric chloride test. Both esters were converted to 2-thio-6-cyclopropyluracil.[35,38] The identity of the derivatives was established by comparison of ir spectra and mixture melting point, mmp 239–41° (lit. mp 234–235°,[38] 239–240°[35]).

Ethyl 3-(1′-Methylcyclopropyl)-3-oxopropanoate (1b).—Keto ester 1b was prepared by Johnson's procedure[37] using 25.0 g (0.255 mol) of 1-methylcyclopropyl methyl ketone,[39] 260 g (2.2 mol) of diethyl carbonate, and 26.0 g (1.08 mol) of sodium hydride (50% dispersion in mineral oil) in 300 ml of absolute ether. Stirring for 24 hr at room temperature and work-up gave 31.2 g (73%) of keto ester 1b, bp 73–74° (0.25 mm). A second distillation through a spinning band column gave 29.68 g (70%) of 1b, bp 51.5–52° (0.025 mm).

Keto ester 1b gave a positive ferric chloride test: ir (CCl_4) 3.25 (cyclopropyl CH), 5.76 (ester C=O), 5.92 (ketone C=O), and 6.2 μ (enol C=C); nmr δ^{CCl_4} 0.53–0.93 (m, 4, cyclopropyl CH_2), 1.30 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 1.4 (s, 3, $CH_3C<$), 3.46 (s, 1.6, $COCH_2COO$), 4.31 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 5.21 (s, 0.16, HC=COH), and 12.8 (s, 0.24, HC=COH) (enol content = 20%).

2-Thio-6-(1′-methylcyclopropyl)uracil.—The thiouracil derivative was obtained in 18% yield: mp 212–213°; ir (KBr) 6.11 (C=O), 6.46 (C=S), 8.45 (CS), 13.25 μ (CS); nmr $\delta^{DMSO\text{-}d_6}$ 0.52–1.15 (m, 4, cyclopropyl CH_2), 1.31 (s, 3, CH_3C), 3.32 (s, 2, NH, disappears with addition of D_2O), 5.7 (s, 1, vinyl); uv $\lambda_{max}^{CH_3OH}$ 276 nm (ε 20,350), 219 (20,860); $\lambda_{max}^{CH_3OH,\ pH\ 12}$ 258 nm (ε 17,320), 316 (16,020).

Anal. Calcd for $C_8H_{10}N_2SO$: C, 52.60; H, 5.49; N, 15.36; S, 17.55. Found: C, 52.62; H, 5.45; N, 15.19; S, 17.49.

Ethyl 3-Cyclopropyl-3-oxo-2-methylpropanoate (1c).—Keto ester 1c was prepared from 20.7 g (0.211 mol) of cyclopropyl ethyl ketone,[40] 26 g (1.08 mol) of sodium hydride (50% dispersion in mineral oil), and 260 g (2.2 mol) of diethyl carbonate in 300 ml of anhydrous ether. The mixture was stirred at room temperature for 48 hr, and work-up gave 26.2 g (73%) of 1b, bp 72–74° (1.3–1.5 mm), after one distillation through a Teflon annular spinning band column.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.75; H, 8.31.

Keto ester 1c gave a positive ferric chloride test: ir (CCl_4) 3.25 (cyclopropyl CH), 5.75 (ester C=O), 5.86 μ (ketone C=O); nmr δ^{CCl_4} 0.73–1.10 (m, 4, cyclopropyl CH_2), 1.26 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 1.3 (d, 3, J = 7 Hz, $CHCH_3$), 1.80–2.28 (m, 1, cyclopropyl methine), 3.58 (q, 1, J = 7 Hz, $CHCH_3$), 4.2 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$).

2-Thio-5-methyl-6-cyclopropyluracil.—The thiouracil derivative was prepared in 17% yield: mp 238–239°; ir (KBr) 6.16 (C=O), 6.50 (C=S), 8.33 (CS), 12.68 μ (CS); uv $\lambda_{max}^{CH_3OH}$ 280 nm (ε 21,390), 223 (18,230); $\lambda_{max}^{CH_3OH,\ pH\ 12}$ 261 nm (ε 18,570), 318 (17,160); nmr $\delta^{DMSO\text{-}d_6}$ 0.75–1.17 (m, 4, cyclopropyl CH_2), 1.58–2.16 (m, 1, cyclopropyl methine), 1.90 (s, 3, $C=CCH_3$), 3.3 (s, 2, NH, disappears upon addition of D_2O).

Anal. Calcd for $C_8H_{10}N_2OS$: C, 52.72; H, 5.53; N, 15.37; S, 17.59. Found: C, 52.64; H, 5.54; N, 15.40; S, 17.67.

Ethyl 3-(1′-Methylcyclopropyl)-3-oxo-2-methylpropanoate (1d).—Keto ester 1b (90.28 g, 0.531 mol) was added dropwise to a stirred suspension of 14.0 g (0.584 mol) of sodium hydride (50% dispersion in mineral oil) in 1.5 l. of benzene at room temperature under nitrogen. When hydrogen evolution ceased, 141.9 g (1.00 mol) of methyl iodide was added rapidly and the resulting mixture was refluxed overnight under nitrogen and then poured into 1 l. of dilute aqueous acid. The aqueous layer was extracted twice with 100-ml portions of ether which were combined with the organic layer, dried over magnesium sulfate, and concentrated under reduced pressure to an oil which was distilled, affording 85.60 g (87%) of crude 1d, bp 69–70° (1 mm). Further distillation on a Teflon annular spinning band column did not separate a small amount of unmethylated 1b, and the crude keto ester 1d was therefore purified as follows.

A mixture of 25.17 g (*ca.* 0.137 mol) of crude 1d, 2.91 g (0.0275 mol) of benzaldehyde, 109 μl (1.1 mmol) of piperidine, and 300 μl (5.2 mmol) of glacial acetic acid in 200 ml of benzene was refluxed for 3 hr with removal of water (0.34 ml). The reaction mixture was washed with 5% hydrochloric acid, saturated aqueous sodium bicarbonate, and water, dried over magnesium sulfate, and concentrated *in vacuo* to an oil which, upon spinning band distillation, gave 20.4 g (81% recovery) of 1d, bp 67–67.5° (0.9 mm).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.30; H, 8.77.

Keto ester 1d gave a *negative* ferric chloride test: ir (CCl_4) 3.24 (cyclopropyl CH), 5.74 (ester C=O), 5.90 μ (ketone C=O); nmr δ^{CCl_4} 0.58–1.00 (m, 4, cyclopropyl CH_2), 1.24 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 1.24 (d, 3, J = 7 Hz, $>CHCH_3$), 1.36 (s, 3, $CH_3C<$), 3.67 (q, 1, J = 7 Hz, $>CHCH_3$), 4.13 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$).

2-Thio-5-methyl-6-(1′-methylcyclopropyl)uracil.—The thiouracil derivative was prepared in 20% yield: mp 225–226°; ir (KBr) 6.14 (C=O), 6.45 (C=S), 8.23 (CS), 12.94 μ (CS); uv $\lambda_{max}^{CH_3OH}$ 279 nm (ε 21,010), 219 (19,190); $\lambda_{max}^{CH_3OH,\ pH\ 12}$ 263 nm (ε 16,170), 320 (11,770); nmr $\delta^{DMSO\text{-}d_6}$ 0.65–0.94 (m, 4, cyclo-

(34) A 5 ft × 0.25 in. column packed with 60–80 Chromosorb W coated with 20% by weight of SE-30 silicone gum rubber was used for both analysis and isolation. The internal standard used was 4-methylcyclohexanone.

(35) E. R. Spitzmiller, *J. Amer. Chem. Soc.*, **69**, 2073 (1947).

(36) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed. Wiley, New York, N. Y., 1964.

(37) S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Amer. Chem. Soc.*, **90**, 2882 (1968).

(38) M. Jackman, A. J. Bergman, and S. Archer, *ibid.*, **70**, 497 (1948).

(39) N. L. Goldman, *Chem. Ind. (London)*, 1036 (1963).

(40) (a) P. Bruylants, *Bull. Soc. Chim. Belg.*, **36**, 519 (1927); *Chem. Abstr.*, **22**, 582 (1928); (b) M. Julia, S. Julia, and S.-Y. Tchen, *Bull. Soc. Chim. Fr.*, 1849 (1961).

TABLE III
PYROLYSIS OF KETO ESTERS 1a–d, 13, AND 10b[a]

Run	Starting material	T, °C[b]	Products, % yield 2a–d	3a–d	EtOH	Other	% recovery starting material	Total pyrolysate wt, %[c]
8	1a	565	51	7	74		0	73
7[d]	1a	540	47	0	78		8	79
15[e]	1b	500	65	9	86		0	67
16[d]	1b	500	60	0	82		0	68
17[e]	1c	585	65	2	87		0	66
18[d]	1c	585	60	0	83		0	70
19[e]	1d	535	81	2	61		9	71
20[d]	1d	570	68	0	75		0	75
21[e]	13	610				77 (14)	8	58
22[e]	10b	600	48	3			0	51

[a] Glass wool packing, 1–3 mm. [b] Maximum temperature, ±10°, at the center of the pyrolysis tube. [c] Weights of gases are not included in the total. Quantitative conversion of **1b** to **2b** would thus afford an 83.5% yield of pyrolysate by weight. [d] Yield based on weights of materials isolated by distillation and weight of keto ester committed to pyrolysis. [e] Glpc yield, based on unrecovered starting material. For individual glpc conditions, see Experimental Section.

propyl CH_2), 1.26 (s, 3, CH_3-c-C_3H_4), 1.90 (s, 3, C=CCH_3), 3.32 (s, 2, NH, disappears upon addition of D_2O).

Anal. Calcd for $C_9H_{12}N_2SO$: C, 55.08; H, 6.16; N, 14.29; S, 16.35. Found: C, 55.03; H, 6.20; N, 14.37; S, 16.41.

Ethyl 3-Cyclopropyl-3-oxo-2,2-dimethylpropanoate (13).—Keto ester **13** was prepared by the methylation procedure used for **1d** with 9.65 g (0.0567 mol) of keto ester **1c**, 2.86 g (0.059 mol) of sodium hydride (50% dispersion in mineral oil), and 24.2 g (0.17 mol) of methyl iodide in 500 ml of benzene, affording 8.38 g (84%) of keto ester **13** after one distillation, bp 55–57° (1.2 mm). Redistillation through a Teflon annular spinning band column using a reflux ratio of 50:1 gave 7.40 g (71%) of keto ester **13**, bp 52–53° (1.0 mm). (No difficulty was encountered in separating **13** from traces of **1c**.)

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.26; H, 8.76. Found: C, 65.15; H, 8.85.

Keto ester **13** gave a negative ferric chloride test: ir (CCl_4) 3.25 (cyclopropyl CH), 5.76 (ester C=O), 5.87 (ketone C=O), 7.23, 7.27 μ (*gem*-dimethyl); nmr δ^{CCl_4} 0.68–1.12 (m, 4, cyclopropyl CH_2), 1.25 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 1.32 (s, 6, >$C(CH_3)_2$), 1.7–2.16 (m, 1, cyclopropyl methine), 4.18 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$).

Pyrolysis Procedure.—The degassed material to be pyrolyzed was distilled at 1–3 g/hr, at 1–3 mm, into the top end of a 37 × 2.5 cm Vycor tube packed tightly with glass wool (16–18 g in 33 cm) or other packing (**1a**, runs 1–4, 14) and heated over 30 cm by a tube oven mounted horizontally at a 10–15° angle. The temperature was measured by a thermocouple at the center of the tube oven prior to insertion of the tube, which was temperature equilibrated for at least 30 min prior to use. Pressures were measured by a McLeod gauge on the line between the cold trap and a mechanical pump.

The hot product vapor was collected in a Dry Ice or liquid nitrogen cooled trap. On small runs (1–2 g) the pyrolysate was analyzed by glpc and yields were calculated using internal standards. On preparative runs (10–38 g) the trapped pyrolysate was distilled on a Teflon annular spinning band column and yields were based on isolated materials. Individual conditions and product yields are summarized in Table III.

Products.—Ketones **2a–d**, **3a–d**, **14**, and cyclopentanone were isolated for identification by preparative glpc of the pyrolysates of the corresponding keto esters (**1a–d**, **13**, **5**). In no case were isomeric ketones (*e.g.*, **2c** or **3c** from **1b**) noted.[41] Ethanol was isolated by preparative glpc and identified by comparison of glpc retention times and ir spectra with a commercial sample.

2-Cyclopentenone-1 (2a)[34,42] **and 3-Methyl-2-cyclopentenone-1 (2b).**[42]—Ketone **2a** was isolated from the pyrolysates of **1a** and **10b**. Ketone **2b** was isolated from the pyrolysate of **1b**. Both ketones were identified with commercial samples by comparison of glpc retention times, ir, uv, and nmr spectra and by the mixture melting points of the 2,4-dinitrophenylhydrazone derivatives.

2-Methyl-2-cyclopentenone-1 (2c).[42]—The ketone was obtained from the pyrolysates of **1c**, with bp 42–43° (0.25 mm) [lit. bp 46–48° (0.2 mm),[43] 59.1° (18.5 mm)[44]]: ir (CCl_4) 5.86 (C=O), 6.11 μ (C=C) [lit. 1705 (5.86), 1640 cm^{-1} (6.10 μ);[45] 1711 (5.84), 1642 cm^{-1} (6.09 μ)[43]]; uv $\lambda_{max}^{C_2H_5OH}$ 227 nm (ϵ 14,700) [lit. $\lambda_{max}^{95\%\ C_2H_5OH}$ 227 nm (ϵ 11,220);[45] 226 (8550)[43]]; nmr δ^{CCl_4} 1.70 (d, 3, J = 2 Hz, small side bands, CH=CCH_3, cis), 2.25–2.78 (m, 4, J = 2 Hz, $CH_2C'H_2$), 7.26–7.48 (m, 1, J = 1.5 Hz, CH=CCH_3, cis) (consistent with literature nmr values[43,45]). The 2,4-dinitrophenylhydrazone derivative had mp 223.5–224° (lit. mp 221–222°,[44] 219–220°[46]).

2,3-Dimethyl-2-cyclopentenone-1 (2d).[47]—The ketone was isolated from pyrolysates of **1d** with bp 50° (0.1 mm) [lit. bp 80° (10 mm);[48] 90–92° (25 mm);[49] 87–89° (20 mm)[50]]: ir (CCl_4) 5.86 (C=O), 6.05 μ (C=C) [lit. 1701 (5.87), 1656 cm^{-1} (6.04 μ)[43]]; uv $\lambda_{max}^{C_2H_5OH}$ 234 nm (ϵ 14,500) [lit. 235 nm (log ϵ 3.04);[49] 234 nm (ϵ 13,660);[48] 235 nm (ϵ 11,784);[51] 234 nm (ϵ 13,580)[43]]; nmr δ^{CCl_4} 1.63 (s, 3, CH_3), 2.04 (s, 3, CH_3), 2.10–2.67 (m, 4, $CH_2C'H_2$) (consistent with literature[43] nmr values). The 2,4-dinitrophenylhydrazone derivative had mp 231–232° (lit. mp 233°,[52] 230–231°[51]).

Cyclopropyl Methyl Ketone (3a).[34]—Ketone **3a** isolated from the pyrolysates of **1a** was identified with a commercial sample by comparison of glpc retention times, ir and nmr spectra, and mixture melting point of the 2,4-dinitrophenylhydrazone derivatives. Ketone **3a** was also recovered unchanged (99% recovery) when pyrolyzed at 575° (1–3 mm) with glass wool packing.

1-Methylcyclopropyl Methyl Ketone (3b).[42]—Ketone **3b** isolated from the pyrolysates of **1b** was identified with a sample prepared by the procedure of Goldman[39] by comparison of glpc retention times, ir and nmr spectra, and mixture melting point of the 2,4-dinitrophenylhydrazone derivatives.[53,54]

Cyclopropyl Ethyl Ketone (3c).—Ketone **3c** isolated from pyrolysates of **1c** was similarly identified with a sample prepared by the procedure of Julia[40b] (cadmium method). The 2,4-dinitrophenylhydrazone derivative had mp 167.5–168° (lit.[40b] mp 162–163°).

Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.80; H, 5.07; N, 20.13. Found: C, 51.51; H, 4.98; N, 20.13.

(41) However, a trace of what is probably 4-methyl-2-cyclopentenone-1 was isolated from a pyrolysate of **1b**.

(42) A 10 ft × 0.25 in. column packed with 69–80 Chromosorb W coated with 20% by weight of Apiezon L was used for analysis and collection. The internal standard was 4-methylcyclohexanone.

(43) H. N. A. Al-Jallo and E. S. Waight, *J. Chem. Soc. B*, 73 (1966).

(44) V. A. Mironov, E. V. Sobolev, and A. N. Elizarova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1607 (1963); *Bull. Acad. Sci. USSR*, 1467 (1963).

(45) O. E. Edwards and M. Lesage, *Can. J. Chem.*, **41**, 1592 (1963).

(46) I. N. Nazarov, L. A. Kazitsyna, and I. I. Zaretskaya, *Zh. Obshch. Khim.*, **27**, 606 (1957); *J. Gen. Chem. USSR*, **27**, 675 (1957).

(47) A 5 ft × 0.25 in. column packed with 60–80 Chromosorb W coated with 20% by weight of Apiezon L was used for both analysis and collection. The internal standard used was 4-methylcyclohexanone.

(48) S. Dev and C. Rai, *J. Indian Chem. Soc.*, **34**, 266 (1957).

(49) R. L. Frank, R. Armstrong, J. Kwiatek, and H. A. Price, *J. Amer. Chem. Soc.*, **70**, 1379 (1948).

(50) M. V. Mavrov and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 164 (1964); *Bull. Acad. Sci. USSR*, 145 (1964).

(51) M. Ansell, J. E. Emmett, and B. E. Grimwood, *J. Chem. Soc. C*, 141 (1969).

(52) H. Strickler, G. Ohloff, and E. sz Kovats, *Tetrahedron Lett.*, 649 (1964).

(53) M. Julia, S. Julia, and M. Y. Noel, *Bull. Soc. Chim. Fr.*, 1708 (1960).

(54) H. Monti, *C. R. Acad. Sci., Ser. C*, **265**, 522 (1967).

1-Methylcyclopropyl Ethyl Ketone (3d).[47]—Ketone **3d** was isolated from pyrolysates of **1d** and was identified by the following data: ir (CCl_4) 3.24 (cyclopropyl CH), 5.92 μ (C=O); nmr δ^{CCl_4} 0.48–0.73 (m, 2, cyclopropyl CH cis or trans to C=O), 0.81–1.28 (m, 2, cyclopropyl CH trans or cis to C=O), 0.98 (t, 3, J = 7.5 Hz, CH_2CH_3), 1.35 (s, 3, CH_3C), 2.43 (q, 2, J = 7.5 Hz, CH_2CH_3).

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 75.09; H, 10.87.

The 2,4-dinitrophenylhydrazone derivative had mp 120.5–121°.

Anal. Calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.17; H, 5.47; N, 19.23.

Cyclopropyl Isopropyl Ketone (14).[42]—Ketone **14** was isolated from the pyrolysates of **13** and was identified by the following data: ir (CCl_4) 3.24 (cyclopropyl CH), 5.88 (C=O), 7.20 7.33 μ (>$C(CH_3)_2$); nmr δ^{CCl_4} 0.56–1.02 (m, 4, cyclopropyl CH_2), 1.13 (d, 6, J = 7 Hz, $CH(CH_3)_2$), 1.68–21.6 (m, 1, cyclopropyl methine), 2.45–2.99 (q, 1, J = 7 Hz, degenerate $CH(CH_3)_2$).

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 74.85; H, 10.65.

The 2,4-dinitrophenylhydrazone derivative had mp 183° (sharply);

Anal. Calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.25; H, 5.51; N, 19.22.

Cyclopentanone (6).[34]—Cyclopentanone was recovered in 96% yield from the pyrolysate[55] of cyclopentanone and was produced in 48% yield by pyrolysis[55] of α-carbethoxycyclopentanone (**5**). The compound was identified with a commercial sample by comparison of glpc retention times, ir and nmr spectra, and mixture melting point of the 2,4-dinitrophenylhydrazone derivatives. No cyclopentenone was observed in either pyrolysate.[18]

3-Cyclopropanecarbonyl-6-cyclopropyl-2*H*-pyran-2,4(3*H*)-dione (10b).—This dehydroacetic acid analog was obtained by pyrolysis of **1a** at 760 mm. The keto ester was carried through the hot tube by stream of prepurified nitrogen (25 ml/min). Part of the pyrolysate solidified and, upon filtration and recrystallization (ethanol), afforded a white solid, mp 66–66.5°, in 20% yield. This material gave a positive ferric chloride test: ir (CCl_4) 3.24 (cyclopropyl CH), 5.82, 6.16, 6.52, 10.19 μ; uv $\lambda_{max}^{C_2H_5OH}$ 319 nm (ϵ 14,200), 233.5 (13,500); $\lambda_{max}^{C_2H_5OH,\ pH\ 12}$ 298 nm (ϵ 15,200), 232 (20,200);[56] nmr δ^{CDCl_3} 0.94–1.37 (m, 8, cyclopropyl CH_2), 1.56–2.05 (m, 2, cyclopropyl methine), 3.29–3.80 (dd, 1, J = 2.7 Hz, vinyl H), 5.99 (s, 1, enolic H).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.39; H, 5.43.

Pyrandione **10b** was also prepared in 80% yield by passing 39.2 g (0.25 mol) of keto ester **1a**, on a stream of prepurified nitrogen at 1 atm, over a 6-in. segment of pumice[27] at 400°. The pyrolysate was distilled under reduced pressure giving 11.7 g (29.8%) of unreacted **1a** and 15.2 g (55.5%) of **10b**, bp 125–126° (0.05 mm), which solidified upon cooling, mp 65–66°. This material was identified with the above sample by comparison of ir spectra.

Gases.—Carbon monoxide, carbon dioxide, and ethylene were identified in the untrapped pyrolysis product stream (1–3 mm) by comparison of glpc retention times with those of commercial samples. A 6 ft × 0.25 in. column packed with Porapak Q at room temperature was used for these analyses in a Gow-Mac, Model 69-100, thermal conductivity instrument. A gas sample volume of 7.5 ml was used.

Registry No.—**1a** methyl ester, 32249-35-7; **1a** ethyl ester, 24922-02-9; **1b**, 32249-37-9; **1b** thiouracil derivative, 32249-38-0; **1c**, 21741-37-7; **1c** thiouracil derivative, 32249-40-4; **1d**, 32249-41-5; **1d** thiouracil derivative, 32249-42-6; **2a**, 930-30-3; **2b**, 2758-18-1; **2c**, 1120-73-6; **2d**, 1121-05-7; **3d**, 25111-31-3; **3d** 2,4-DNPH, 32249-48-2; **10b**, 32249-49-3; **13**, 32249-50-6; **14**, 6704-20-7; **14** 2,4-DNPH, 32304-06-6.

Acknowledgments.—We gratefully acknowledge the support of Public Health Service Research Grant NIH ROI-AM11226 and of Queens College General Research Support Grant NIH 5-S05-FR-07064-03. The authors are also grateful to Professor N. L. Goldman of Queens College for useful discussions.

(55) The pyrolysis was done at 575° (1–3 mm) with glass wool packing.

(56) Dehydroacetic acid: $\lambda_{max}^{95\%\ C_2H_5OH}$ 310 nm (ϵ 11,200); $\lambda_{max}^{C_2H_5OH,\ pH\ 12}$ 294 nm (ϵ 8150) [J. A. Berson, W. M. Jones, and L. F. O'Callaghan, *J. Amer. Chem. Soc.*, **78**, 622 (1956)].

Nuclear Magnetic Resonance Spectroscopy. Proton Spectra of 2-Pyridones[1a]

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The proton magnetic resonance spectra of 2-pyridone, 1-methyl-2-pyridone, and 1-(2′-pyridyl)-2-pyridone in deuteriochloroform solution were recorded at 100 and 220 MHz. A computer-assisted analysis of these spectra yielded the chemical shifts and consistent sets of coupling constants. Some regularities in the effects of structure and concentration on the chemical shifts were observed. The spectra of 2-pyridone in deuterium oxide and benzene-d_6 were briefly explored.

The purpose of this study was to complete and refine the existing pmr data of 2-pyridone (**1**) and 1-methyl-2-pyridone (**2**) and to determine the spectral parameters of 1-(2′-pyridyl)-2-pyridone (**3**).[2] It is now commonly assumed[3] that the 2-pyridone, usually written as **1a**, is the predominant species in a tautomeric equilibrium with 2-hydroxypyridine (**1c**). Compounds **2** and **3** can only exist in the lactam form, represented as the resonance hybrid **1a** and **1b**. The numbering used in all tables and discussions is as shown in these structures.

The spectral analysis of **3** was of interest because it possesses both the 2-pyridone ring (A) and the pyridine ring (B) as an aromatic N substituent.

Assuming fast chemical exchange for the N–H proton, the ring protons of 2-pyridone represent an asymmetric four-spin system whose pmr spectrum is characterized by four chemical shifts and six coupling constants. The 60-MHz spectra of other 2-substituted pyridines have been analyzed rigorously as ABCD and, sometimes to a good approximation, as ABKL and AA′KL systems.[4]

The 100-MHz and 220-MHz spectra discussed in this paper approximate ABKX types but were treated as

(1) (a) Supported by the National Science Foundation. (b) On leave from Youngstown State University.

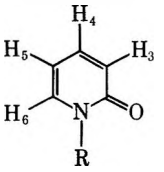
(2) (a) K. Takeda, K. Hamamoto, and H. Tone, *J. Pharm. Soc. Jap.*, **72**, 1427 (1952); *Chem. Abstr.*, **47**, 8071 (1953). (b) F. Ramirez and P. W. von Ostwalden, *J. Amer. Chem. Soc.*, **81**, 156 (1959).

(3) See, *e.g.*, A. Albert, "Heterocyclic Chemistry," 2nd ed, Athlone Press, London, 1968, p 92.

(4) V. J. Kowalewski and D. G. de Kowalewski, *J. Chem. Phys.*, **37**, 2603 (1962).

Table I

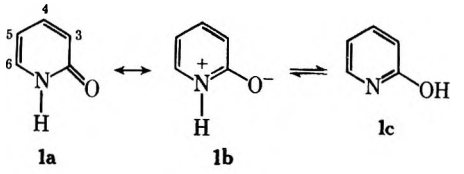
Spectral Parameters of 2-Pyridone and N-Substituted 2-Pyridones[a,b]



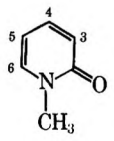
	2-Pyridone (R = H)		1-Methyl-2-pyridone (R = CH_3)		1-(2′-Pyridyl)-2-pyridone, ring A (R = C_5H_4N),
	c, d	e	f	g	h
ν_{H_3C-N}			3.59	3.59	
ν_5	6.30	6.4	6.17	6.15	6.29
ν_3	6.60	6.7	6.57	6.57	6.63
ν_4	7.49	7.7	7.34	7.26	7.38
ν_6	7.41	7.8	7.32	7.31	7.86
ν_{H-N}	13.65	11.43			
J_{34}	9.15 ± 0.05[i]	~10	9.12 ± 0.05		9.11 ± 0.05[i]
J_{35}	1.02	<1	1.38		1.29
J_{36}	0.70	0	0.70		0.71
J_{45}	6.64	~7	6.66		6.52
J_{46}	2.07	~2	2.07		2.03
J_{56}	6.46	~7	6.67		6.79

[a] Chemical shifts, in δ (parts per million). [b] Coupling constants, J (hertz). [c] 0.5 M in $CDCl_3$. [d] Chemical shifts of 2-pyridone, ν_6 = 7.53, ν_3 = 6.62, ν_5 = 6.59; shifts in C_6D_6 (0.2 M); ν_5 = 5.47. [e] Brügel,[10] 30% in DMSO. [f] 0.65 M in $CDCl_3$. [g] Elvidge and Jackman,[6] 5% in $CDCl_3$. [h] 1.2 M in $CDCl_3$. [i] In a few cases, analysis of the 100-MHz spectrum of the ±0.05 range: 2-pyridone, J_{35} = 1.16; 1-(2′-pyridyl)-2-pyridone, 8.15, $J_{4'5'}$ = 7.47 (*cf.* Table II).

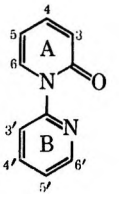
ABCD systems. Theory predicts for such systems 56 possible transitions,[5] 24 of which are combination bands of weak intensity, leaving 32 observable lines to be expected. Most of these lines (27 in the case of 2-pyridone) could be observed.



1a 1b 1c



2



3

The 56.4-MHz spectrum of 1-methyl-2-pyridone (2) as a 5% solution in deuteriochloroform had first been studied by Elvidge and Jackman[6] who, with the aid of an empirical equation and the proton line positions in pyridine and several lutidines, assigned the chemical shifts in Table I. The main features of the spectrum, aside from the high-field singlet due to the *N*-methyl protons, were a triplet at δ 6.15 ppm assigned to ring proton H-5, a doublet at 6.57 assigned to H-3, and a complex band at 7.3 due to H-4 and H-6. In this multiplet, the lowest field chemical shift (δ 7.31 ppm) was assigned to H-6, and the shift difference $\nu_6 - \nu_4$ amounted to 0.05 ppm. Other authors have confirmed these assignments,[7] studied the chemical shift of the *N*-methyl group in different solvents,[8] and calculated the ring-current contributions to the chemical shifts.[9] No coupling constants were reported.

The proton spectrum of 2-pyridone (1) as a 30% solution in dimethyl sulfoxide was reported by Brügel[10] who, with less detailed reasoning, made shift assignments for the ring protons in analogy to those proposed earlier by Elvidge and Jackman[6] for 1-methyl-2-pyridone. The N–H proton signal was found to be a broad peak at δ 11.4 ppm, and an approximate set of coupling constants, included in Table I, was reported.

Experimental Section

Practical grade 2(1*H*)-pyridone (Matheson Coleman and Bell) was recrystallized twice from benzene–cyclohexane using decolorizing carbon and dried *in vacuo*, mp 107–108°. 1-Methyl-2-pyridone (Aldrich) was dried over sodium hydroxide and distilled *in vacuo*, bp 60–62° (~1 torr). The clear distillate, when kept under nitrogen in the refrigerator, remained colorless for longer than a week. 1-(2′-Pyridyl-2-pyridone was prepared from 2-bromopyridine and pyridine *N*-oxide in toluene as solvent,[2b] and recrystallized twice from hexane–petroleum ether, mp 53–55°.

The pmr spectra were taken of solutions in deuteriochloroform containing 1% TMS ("Silanor C," Merck Sharp and Dohme). Those at 220 MHz were recorded on a Varian HR-220 spectrometer at a probe temperature of ~18°; all line positions were measured relative to TMS as internal standard. Similarly, the 100-MHz spectra[11] were obtained on a Varian HA-100 instrument at a probe temperature of ~28°.

Results and Discussion

Considering only the ring proton signals, both the 100-MHz and 220-MHz spectra of 2-pyridone (1) and 1-methyl-2-pyridone (2) as well as of 1-(2′-pyridyl)-

(5) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, Vol. 1, 1956, p 425.

(6) J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 859 (1961).

(7) D. W. Turner, *J. Chem. Soc.*, 847 (1962).

(8) J. S. N. Ma and E. W. Warnoff, *Can. J. Chem.*, **43**, 1849 (1965).

(9) G. G. Hall, A. Hardisson, and L. M. Jackman, *Tetrahedron*, **19**, Suppl. 2, 101 (1963).

(10) W. Brügel, *Z. Elektrochem.*, **66**, 159 (1962); the reported chemical-shift data refer to water as external standard with ν_{TMS} = 5.23 ppm.

(11) We are grateful for the help in recording these spectra from Dr. P. W. Sprague, California State College at San Bernardino.

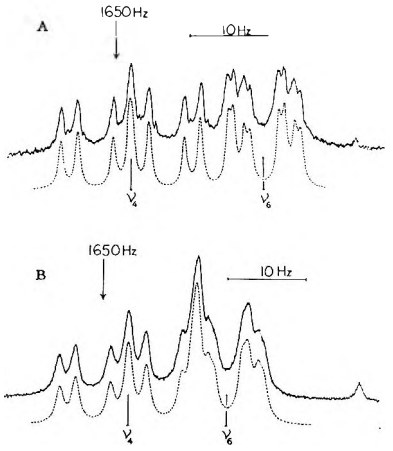


Figure 1.—Experimental and calculated 220-MHz spectra of 2-pyridone. Multiplet C: A, 0.5 *M*; B, 2.2 *M*. In this and the other figures, the solid lines are the experimental spectra recorded in $CDCl_3$ solution at 50-Hz sweep width; the dashed lines are calculated spectra based on the parameters given in Tables I and II. The reference point on each experimental spectrum is downfield from TMS.

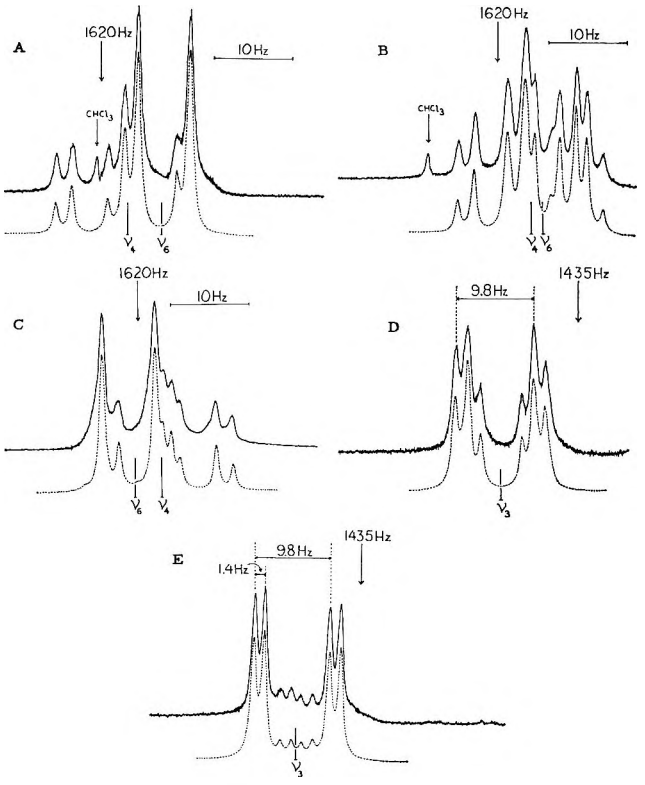


Figure 2.—Experimental and calculated 220-MHz spectra of 1-methyl-2-pyridone. Multiplet C: A, 0.65 *M*; B, 0.9 *M*; C, 1.3 *M*. Doublet B: D, 0.65 *M*; E, 0.9 *M*.

2-pyridone (**3**) show the distinctive features mentioned above, namely a low field multiplet (C) at δ ~7.5 ppm, a higher field doublet (B) at ~6.6, and a triplet (A) at ~6.3. These have different fine structures for each compound. In addition to these signals, the 1-(2′-pyridyl)-2-pyridone (**3**) spectrum shows a second multiplet (D) at δ ~7.9 ppm and another, lowest field doublet (E) at ~8.5. All parts of the 220-MHz spectrum of 1-(2′-pyridyl)-2-pyridone and representative examples of the spectra of 2-pyridone and 1-methyl-2-pyridone are shown in Figures 1–3. Also shown are the calculated spectra resulting from iterative fitting of the

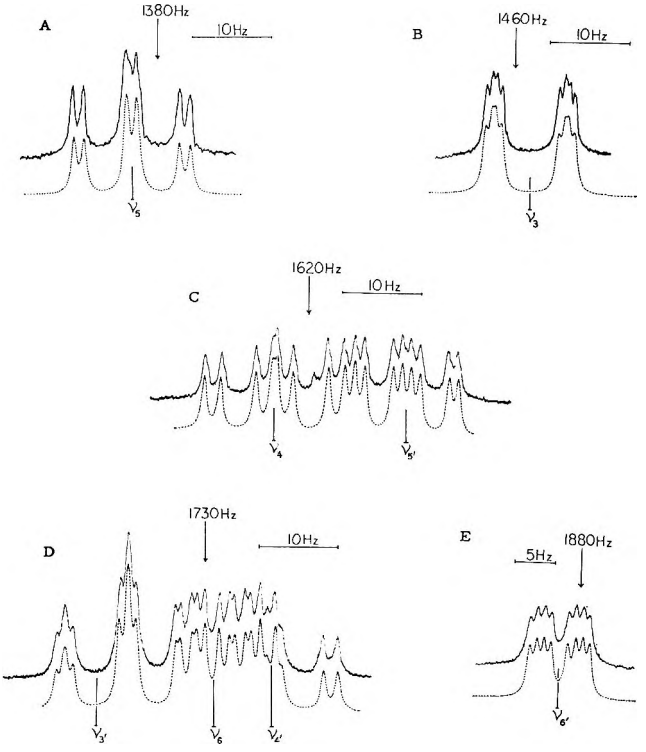


Figure 3.—Experimental and calculated 220-MHz spectra of 1-(2′-pyridyl)-2-pyridone (1.2 *M*): A, triplet A; B, doublet B; C, multiplet C; D, multiplet D; E, doublet E.

experimental line positions using the program LAOCN3,[12] modified to include CalComp plotting and plot accumulation. The root mean square errors in the overall fitting were in the range of 0.03–0.06 Hz.

In the interpretation of these spectra, the assumption was made that there is essentially no coupling between the ring protons of the 2-pyridone ring and the N–H, $N-CH_3$, or $N-C_5H_4N$ protons. Simple first-order analysis was partly applicable, but several of the spectral parameters could only be found by computer analysis. The coupling constants were estimated from the 220-MHz spectra, except for J_{34} and J_{36} in the case of 1-methyl-2-pyridone,[13] then refined in the iterative procedure, and finally confirmed by fitting the 100-MHz spectra. A summary of the parameters for **1**, **2**, and **3** is presented in Tables I and II.

As for the assignments of the chemical shifts of the pyridone ring protons, the doublet B and the triplet A were assigned to H-3 and H-5, respectively, in accord with the literature.[6,10] Inspection and computer simulation of multiplet C of 2-pyridone (Figure 1) revealed that the lowest field signal[14] pertains to H-4 and the slightly higher field doublet of quartets, featuring line spacings of 0.7 Hz, to H-6. This order of shifts is opposite to that reported by Brügel[10] for more concentrated solutions in dimethyl sulfoxide. However, a decrease in the shift difference $\nu_4 - \nu_6$ is observed with an increase in concentration from 0.5 to 2.2 *M* (Table III).

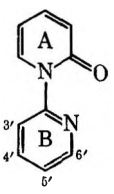
(12) A. A. Bothner-By and S. M. Castellano, "Computer Programs for Chemistry," Vol. 1, D. F. DeTar, Ed., New York, N. Y., W. A. Benjamin, Inc., 1968, p 10.

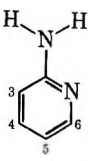
(13) In the doublet B (H-3 signal) of **2** (Figure 2D and 2E), there is a frequency (9.8 Hz) corresponding to the sum of J_{34} and J_{35}. This appears to be a case of "virtual coupling:" J. J. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1962).

(14) The center of this signal is the center of a quartet of doublets with the two centermost lines merged to produce an apparent triplet, and its upfield portion obscured by the H-6 signal in the more concentrated solutions.

Table II

Spectral Parameters of Ring B of 1-(2′-Pyridyl)-2-pyridone and of 2-Aminopyridine[a,b]





	1-(2′-Pyridyl)-2-pyridone (ring B)[c,d]		2-Aminopyridine[e]
ν_{NH_2}			6.21
$\nu_{5'}$	7.31	ν_5	6.60
$\nu_{4'}$	7.83	ν_4	7.44
$\nu_{3'}$	7.92	ν_3	6.70
$\nu_{6'}$	8.56	ν_6	8.11
$J_{3'4'}$	7.94 ± 0.05	J_{34}	8.3
$J_{3'5'}$	1.01	J_{35}	1.8
$J_{3'6'}$	0.88	J_{36}	1.0
$J_{4'5'}$	7.27	J_{45}	6.9
$J_{4'6'}$	1.86	J_{46}	1.7
$J_{5'6'}$	4.81	J_{56}	5.0

[a] Chemical shifts, in δ (parts per million). [b] Coupling constants, J (hertz). [c] 1.2 M in $CDCl_3$. [d] These shifts, except $\nu_{3'}$ and $\nu_{4'}$ which are at somewhat lower fields, and the coupling constants also fall within the usual range for the corresponding quantities in pyridine; see J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice Hall, Inc., Englewood Cliffs, N. J., 1965, pp 89, 99. [e] Brügel,[10] 30% in DMSO.

Table III

Effect of Structure and Concentration on the Chemical Shifts at 220 MHz of H-4 and H-6 in 2-Pyridones

Compound	Concn, mol/l.	ν_4[a]	ν_6[a]	$\nu_4 - \nu_6$, Hz
2-Pyridone	2.2	1646	1634	+12.3
	1.2	1648	1633	+14.5
	0.5	1648	1631	+16.8
1-Methyl-2-pyridone	1.3	1617	1620	−3.4
	0.9	1615	1614	+1.4
	0.65	1615	1611	+4.0
1-(2′-Pyridyl)-2-pyridone	1.2	1624	1729	−104.7

[a] Rounded values.

Computer simulation of the multiplet (C) of 1-methyl-2-pyridone (2) (Figure 2) showed that, in 0.65 M solution, the lower field signal again is to be attributed to H-4, contrary to what has been reported for the 56.4-MHz spectrum.[6] The shift difference is small ($\nu_4 - \nu_6 \sim 4$ Hz), however, and in more concentrated solutions (1.3 M) the order is inverted and the lowest field signal is due to H-6 (Figure 2C and Table III).[15]

The downfield half of multiplet C at 220 MHz of 1-(2′-pyridyl)-2-pyridone (**3**) (Figure 3C) resembled the corresponding portion of the 2-pyridone spectrum; hence, this was assumed to be the H-4 signal. The upfield portion of this multiplet was different in appearance and was attributed to H-5′ of ring B because (a) the analogously situated H-5 in 2-aminopyridine has the highest field chemical shift (Table II) and (b) there is a similarity in the chemical environments of H-5 ring A which has highest field chemical shift, and H-5′ of ring B (both are meta to their respective ring nitrogens and para to >C=O or >C—N<, respectively). The 22-line lower field multiplet (D) (Figure 3D) of **3**, known by integration to correspond to three protons, featured a prominent doublet of triplets on the downfield side. Because of the resemblance of this signal to the signal of H-3 (doublet B) of the 2-pyridones and, again, the analogous environment of H-3 and H-3′ in **3**, this signal was assigned to H-3′. Inspection of the remaining 16 peaks reveals that there is a quartet of doublets with a line spacing of 0.7 Hz in each doublet as expected for H-6 of ring A. The downfield shift of this signal, compared with that of 2-pyridone, is thought to be caused by the ring current of the neighboring pyridine ring B; H-6 is situated in the deshielding zone extending around ring B. Another quartet of doublets, interspaced with the H-6 signal, was assigned to H-4′ by exclusion. The lowest field doublet of quartets (E) in the spectrum of 1-(2′-pyridyl)-2-pyridone (Figure 3E) is a prominent feature in the 220-MHz as well as in the 100- and 60-MHz spectra of this compound. In analogy to the assignments for 2-aminopyridine[10,16] this lowest field signal is attributed to H-6′ of ring B. Table II summarizes the chemical shifts and coupling constants for the protons of ring B together with literature values of 2-aminopyridine for comparison.

The concentration effects on the shift difference $\nu_4 - \nu_6$, which have been mentioned above, are documented in more detail in Table III. Small changes in this shift difference produced pronounced changes in the appearance of the spectra, especially of multiplet C. It is likely that **1** is already so highly associated by hydrogen bonding at the concentration used, that ν_6 (which is most sensitive to concentration) is changed only by 3 Hz when the concentration is changed by a factor of more than four. In contrast, ν_6 for **2** changes by 9 Hz when the concentration is doubled, indicating that its degree of association (not, of course, involving hydrogen bonding) is changing more rapidly in the concentration range studied.

The spectra of 2-pyridone show pronounced solvent effects which were explored to some degree. The analysis of the deuteriochloroform solution 100-MHz spectrum led to a shift difference $\nu_4 - \nu_6$ of 5.9 Hz (0.06 ppm) and spectral parameters generally in good agreement with those listed in Table I. The iterative fitting of the acetone-d_6 solution spectrum, on the other hand, yielded a value of −0.6 Hz for $\nu_4 - \nu_6$, indicating that in this solvent the two chemical-shift positions have interchanged and the H-6 resonance is at the low field end. The chemical shifts observed, but not computer analyzed, in deuterium oxide and benzene-d_6, are presented in footnote d of Table I. Again, we fixed the H-6 resonance at the lowest field in the case of the benzene-d_6 solution.

Registry No.—**1**, 142-08-5; **2**, 694-85-9; **3**, 3480-65-7.

(15) A peak at δ 7.30–7.40 ppm often appeared in the multiplets (C) of 2-pyridone and 1-methyl-2-pyridone (*cf.* Figure 2) which arose from the ordinary chloroform present in the deuteriochloroform. In the solvent itself, this peak was found at δ 7.27 ppm.

(16) "High-Resolution NMR Spectra Catalogue," Varian Associates, Vol. 2, 1963, Spectrum No. 431.

Mass Spectrometry of Aryl Azides[1]

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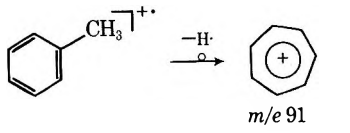
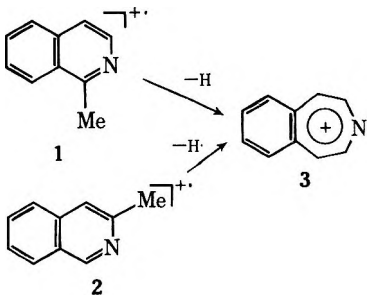
The mass spectra of 18 monosubstituted (Cl, CN, NO_2, MeO, Ph, Me) and two disubstituted phenyl azides are reported. The fragmentations of eight of the azides were found to fit a general or "normal" pattern, which is described. The fragmentation patterns of the other azides are described and discussed with respect to the "normal" fragmentations, supported in a number of cases with accurate mass determinations. The mass spectra of the three tolyl azides are discussed in particular, supported by accurate mass determinations and by a partial analysis of the low-resolution spectrum of *o*-tolyl azide-α-^{13}C.

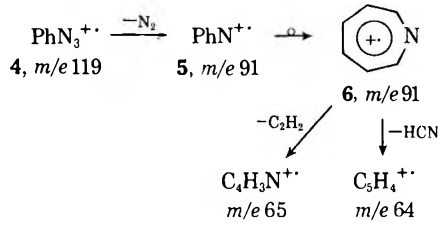
One of the more interesting areas of the mass spectrometry of organic molecules has been the study of the formation of the tropylium ion (*m/e* 91) from toluene, other C_7H_8 isomers, and from various benzylic compounds.[2-4] Similar ring-expansion pathways have been shown to best rationalize the mass spectral data from 1- and 2-methylisoquinolines **1** and **2**, respectively), in which a benzazatropylium (benzazepinium) ion **3** was postulated,[5] and for the even electron ion $C_6H_6N^+$ from aniline and derivatives thereof.[6,7]





Another route to a ring-expanded ion is *via* the nitrenium ion **5** [from phenyl azide (**4**)] which could give the H_5-azepinium ion **6**[8] (Scheme I). Loss of acetylene and hydrogen cyanide from **6** would give the fragment ions *m/e* 65 and 64, respectively. Evidence has been presented to show that **6** is indeed formed: measurement of the mass spectrum of phenyl azide-*1*-^{13}C showed that randomization of C-1 occurred prior to expulsion of HCN.[9] It was estimated that between one-half to five-sixths of **5** rearranged to **6**. It has also been found by deuterium labeling that the hydrogen atoms in **6** are completely randomized prior to any further fragmentation.[10] There is no other information concerning the mass spectrometry of aryl azides. It was felt that it would be of interest to study the electron impact induced decomposition of a series of ortho, meta, and para X-substituted aryl azides to determine the effect that these substituents might have on the fragmentation patterns. To this end 21 substituted aryl azides were synthesized and subjected to mass spectral analysis.

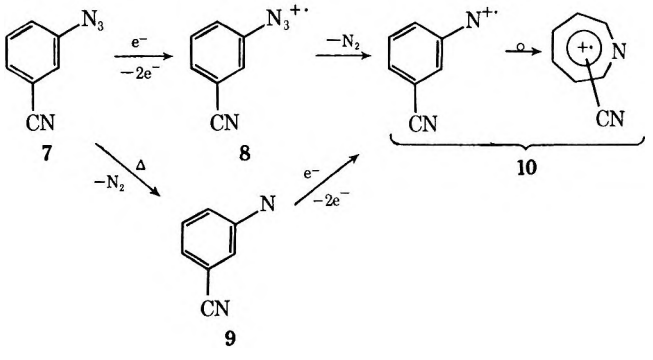
SCHEME I



Results and Discussion

Since aryl azides readily undergo thermolysis in the temperature range 140–170°,[11] the effect of variation of ion source temperature was studied for a model azide, *m*-cyanophenyl azide (**7**) (Scheme II).

SCHEME II



The spectra determined at various temperatures between 165 and 250° were identical except for a change in the ratio of the molecular ion **8** to $M^+ - N_2$ (**10**) peaks as illustrated in Figure 1. Since other than for this ratio the spectra were identical within experimental error, the most reasonable explanation for this behavior is that all of the fragmentation is derived from **10** and that it does not matter whether

(1) Presented in part at the Southeast-Southwest Combined Regional Meeting of the American Chemical Society, New Orleans, La., Dec 1970.

(2) (a) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden Day, San Francisco, Calif., 1967, pp 76–81. (b) H. M. Grubb and S. Meyerson, "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press, New York, N. Y., 1963, pp 516–519.

(3) A. S. Siegel, *J. Amer. Chem. Soc.*, **92**, 5277 (1970).

(4) I. Howe and F. W. McLafferty, *ibid.*, **93**, 99 (1971).

(5) M. Marx and C. Djerassi, *ibid.*, **90**, 678 (1968).

(6) K. L. Rinehart, Jr., A. C. Buchholz, and G. E. Van Lear, *ibid.*, **90**, 1073 (1963).

(7) A. V. Robertson and C. Djerassi, *ibid.*, **90**, 6992 (1968).

(8) W. D. Crow and C. Wentrup, *Tetrahedron Lett.*, 4379 (1967).

(9) P. D. Woodgate and C. Djerassi, *ibid.*, 1875 (1970).

(10) D. G. I. Kingston and J. D. Henion, *Org. Mass Spectrom.*, **3**, 413 (1970).

(11) R. A. Abramovitch and E. P. Kyba, "The Chemistry of the Azido Group," S. Patai, Ed., Interscience, London, 1971.

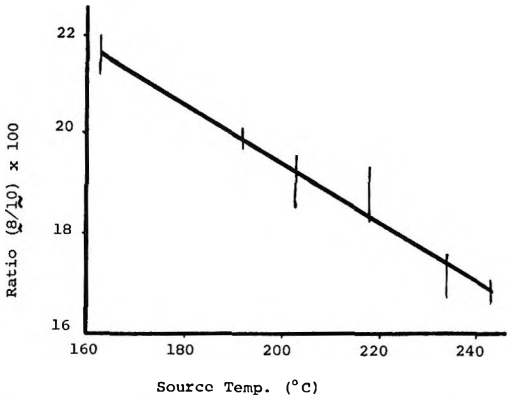


Figure 1.—Plot of the ratio of the relative abundance of 8/10 *vs.* source temperature. The uncertainties at each temperature are the average deviations in five scans.

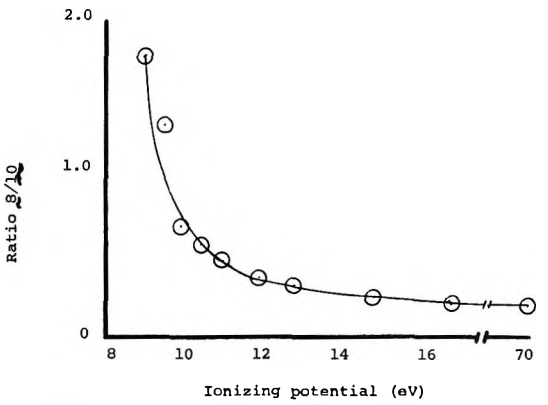


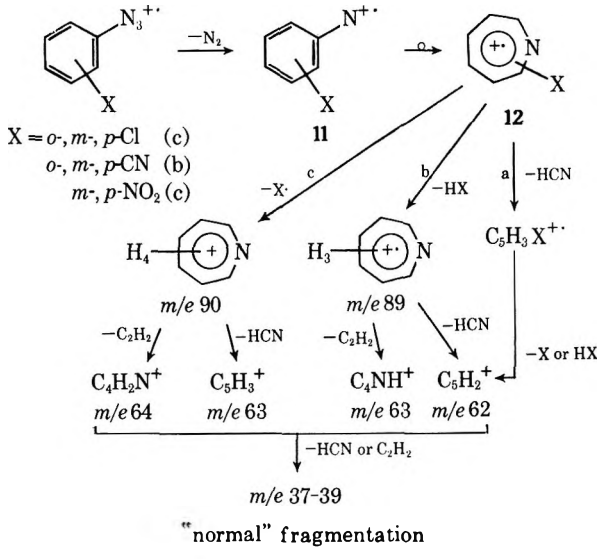
Figure 2.—Plot of the ratio of the relative abundance of 8/10 *vs.* ionizing voltage.

this arises from **8** or from the electron-impact ionization of the arylnitrene **9** formed by thermolysis of the azide **7**.

The effect of the variation of ionizing potential on the ratio **8/10** was studied also and the results are illustrated in Figure 2. As expected, the fragmentation pattern became simpler at lower ionizing voltages, but the ratio of **8/10** was not markedly affected until the ionizing voltage was taken below about 11 eV. The standard conditions used for the other azides unless otherwise stated were source temperature 250° and ionizing voltage 70 eV.

It has been found that eight of the aryl azides studied could be adequately described by a fragmentation pattern (Scheme III) quite analogous to that of phenyl

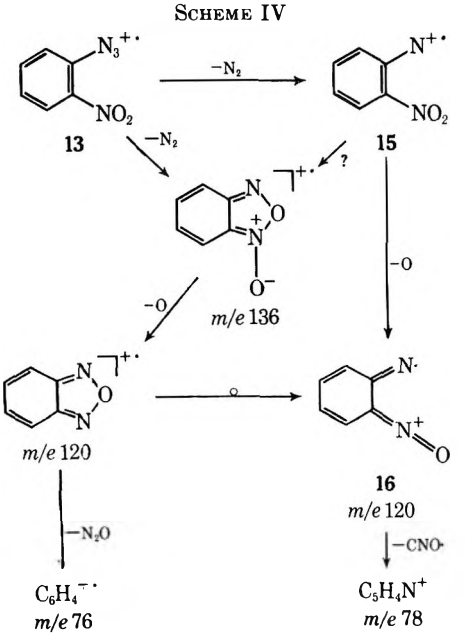
SCHEME III



azide (Scheme I), except that the unsubstituted azepinium ions were either one or two mass units lower than that from the unsubstituted azide. Table I presents the relative abundances of the major peaks for the three chloro-, three cyano-, and *m*- and *p*-nitrophenyl azides. These give rise to what will be referred to as "normal fragmentation," the chief characteristics of which are a relatively high ion current at *m/e* $M^+ - 28$, and/or 90 or 89, 63 and 62, and 39–37. In addition, there is only low ion current at *m/e* 77, 76, and 52–50 with these azides. The loss of hydrogen cyanide from the substituted azepinium ion **12** is usually negligible (path a, Scheme III), but a 10–13% relative abundance was observed with the chlorophenyl azides (*m/e* 98, Table I). (The fragmentation will be written as occurring *via* the azepinium ion **12**, instead of the nitrenium ion **11**, by analogy with phenyl azide. It is realized, of course, that only labeling experiments can establish whether the ring expansion does indeed occur with each azide.) Path b (loss of HX) is followed predominantly by the three cyano derivatives, path c (loss of X) mainly by the three chloro- and *m*-nitrophenyl azides, and an appreciable amount of path b was followed by *p*-nitrophenyl azide.

Exceptions to the "normal fragmentation" pattern will now be discussed. Figure 3 shows the mass spectrum of *o*-nitrophenyl azide (**13**), run at the source temperature of 170°. Although a part of the spectrum can be rationalized on the basis of a "normal fragmentation" (*m/e* 90, 63, and 39), there are major peaks at *m/e* 120, 78, 76, and 51. Scheme IV illus-

SCHEME IV



trates the proposed fragmentation pattern to give the *m/e* 76 and 78 peaks. The composition of these fragments as $C_5H_4N^+$ and $C_6H_4^{+\cdot}$ (and not $C_6H_6^{+\cdot}$ or $C_5H_2O^+$, and $C_5H_2N^+$, respectively) was established

TABLE I

RELATIVE ABUNDANCES OF THE MAJOR FRAGMENTS IN THE MASS SPECTRA OF EIGHT r-X-SUBSTITUTED PHENYL AZIDES

m/e	o-CN[a]	m-CN[b]	p-CN[c]	o-^{35}Cl[d]	m-^{35}Cl[e]	p-^{35}Cl[f]	m-NO_2[g]	p-NO_2[h]
M^+	21	15	17	18	22	22	12	24
$M^+ - 26$	20	16	15	*i*	*i*	*i*		4
$M^+ - 27$	12	10	11	8	8	8		6
$M^+ - 28$	100	100	100	89	100	100	19	52
98				11	13	10		
91	7	4	4	12	10	10	9	9
90	9	9	7	100	98	94	100	79
89	53	61	45	21	23	23		35
80								14
76	11	10	8					6
75	7	8	6	11	9	10		5
74				7	8	7		8
73				12	9	10		
65	24	17	13	10	9	10		8
64	19	16	16	32	30	32	36	54
63	25	23	24	82	88	85	83	100
62	37	44	39	29	35	32	13	49
61	9	8	7	14	16	16	7	13
52	14	12	13	10	8	6	6	27
51	13	12	10	12	10	7	12	14
50	13	12	9	19	22	22	18	32
41	9	9	7					
40				12	14	10	12	9
39	15	19	9	44	44	32	64	92
38	34	36	22	34	35	30	18	42
37	21	20	18	32	27	30	17	34

[a] Registry no. are given as follows: 31656-77-6; [b] 31656-78-7; [c] 18523-41-6; [d] 31656-80-1; [e] 31656-81-2; [f] 31656-82-3; [g] 1516-59-2; [h] 1516-60-5. [i] Same peak as the ^{37}Cl isotope $M^+ - 28$ peak.

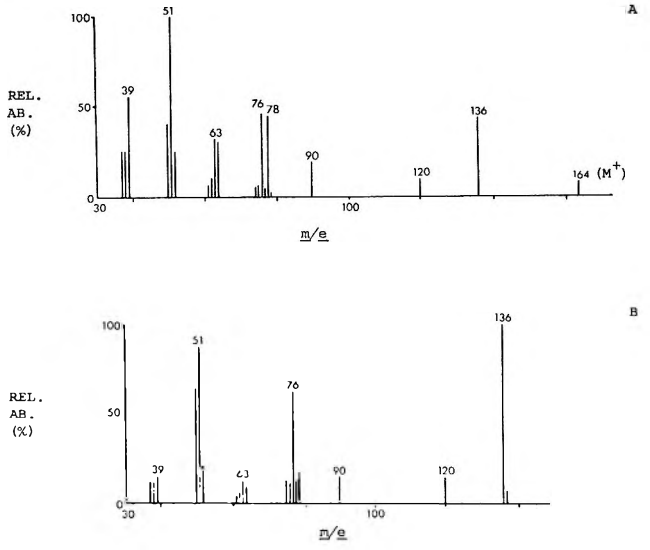


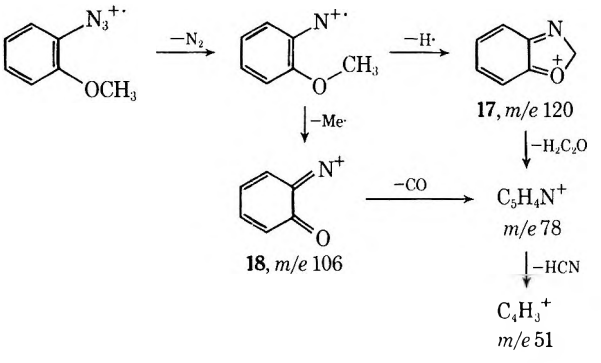
Figure 3.—Mass spectra of A, *o*-nitrophenyl azide (**13**); B, benzofuroxan (**14**).

by high-resolution mass spectrometry. The most likely source of the *m/e* 51 peak is the *m/e* 78 fragment which can lose HCN, although the *m/e* 76 fragment could presumably also yield it by loss of C_2H. Since it is known that benzofuroxan (**14**) is formed readily on thermolysis (>70°) of **13**, the mass spectrum of **14** was determined (Figure 3B). Although qualitatively the spectra are similar, there are some large quantitative differences, particularly in the fact that the molecular ion is the base peak with benzofuroxan and that the *m/e* 78 peak is considerably smaller than the *m/e* 76 peak. Thus, the azide must offer a pathway to *m/e* 78 that is not as readily available to **14**. It is suggested that this might be the sequence **13** → **15** → **16** (Scheme IV).

The three methoxyphenyl azides show pronounced "abnormal" fragmentation and exhibit major differences among themselves. The spectra of the three isomers are shown in Figure 4A–C. The spectrum of the meta isomer is relatively easy to rationalize *via* the methoxyazepinium ions (*m/e* 121), which may then lose a methyl radical to give the azepinone ions (*m/e* 106). Loss of CO and then HCN would give the other two major peaks in the spectrum, *m/e* 78 and 51, respectively. A small amount of normal fragmentation could be initiated by the loss of formaldehyde[12] from the methoxyazepinium ions to give the azepinium ion *m/e* 91.

The *o*-methoxy isomer has an additional mode of reaction, leading to the benzofurazan species **17** as shown in Scheme V. The elemental composition of

SCHEME V



(12) See ref 1b, pp 237–248.

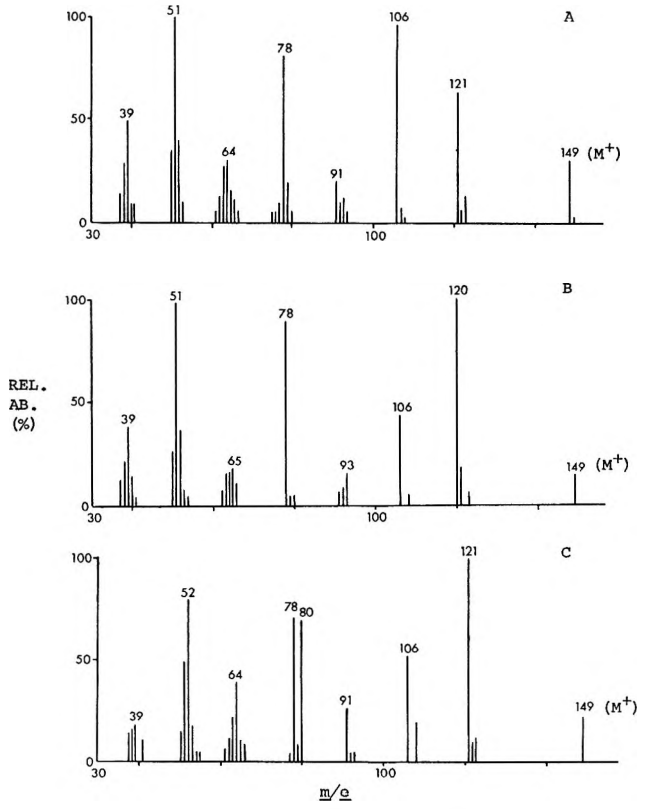
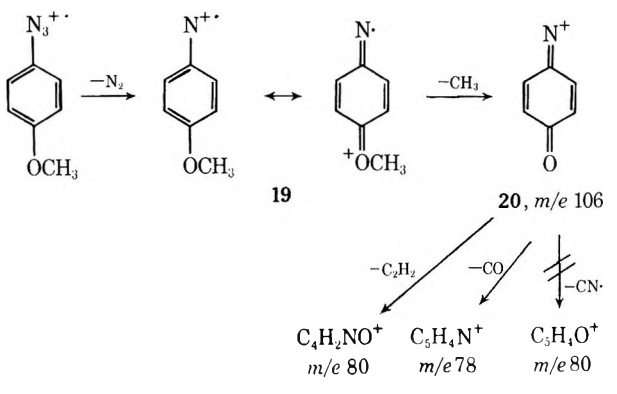


Figure 4.—Mass spectrum of A, *m*-methoxyphenyl azide; B, *o*-methoxyphenyl azide; and C, *p*-methoxyphenyl azide.

the ions shown in Scheme V were confirmed by accurate mass determination. The *m/e* 106 fragment ion might be **18** as shown in Scheme V or an azepinone ion. Loss of H· from $M^+ - 28$ appears very facile and still occurs at low ionization voltages. The peak at *m/e* 93 (Figure 4B) was found by high-resolution mass spectrometry to be composed of both $C_6H_7N^{+\cdot}$ and $C_6H_5O^+$, the latter perhaps arising *via* the loss of HCN from **17**. $C_6H_7N^{+\cdot}$ could arise from uncyclized nitrenium ion, with the ultimate expulsion of CO.

The most striking differences in the mass spectrum of *p*-methoxyphenyl azide (Figure 4C) and those of the ortho and meta isomers are the large peaks at *m/e* 80 and 52 in the spectrum of the former. The fragmentation pattern accounting for these differences is best rationalized on the basis of the resonance stabilized nitrenium ion **19** (Scheme VI), which can lose

SCHEME VI



a methyl radical to give the *p*-quinone–imino ion **20**. An analogous pathway has been described for the mass

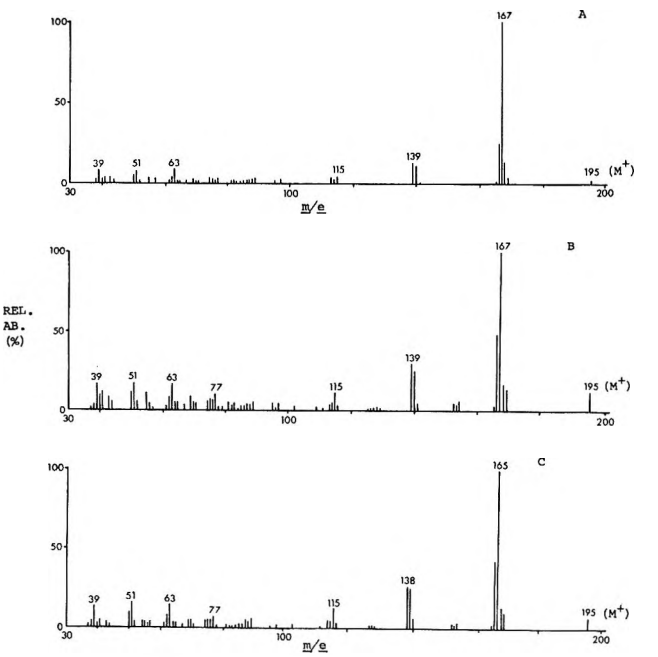
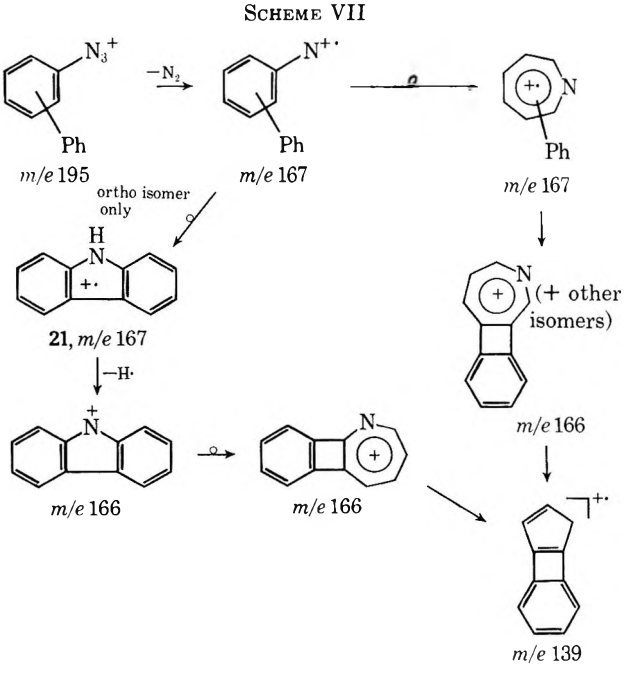


Figure 5.—Mass spectra of A, 2-azidobiphenyl; B, 3-azidobiphenyl; and C, 4-azidobiphenyl.

spectral fragmentation of *p*-anisidine.[13] Loss of carbon monoxide from **20** would give $C_5H_4N^+$, *m/e* 78. *A priori*, loss of CN· or C_2H_2 would give rise to the *m/e* 80 peak, but it was found by accurate mass determination that the peak was in fact monobaric, with the composition C_4H_2NO (loss of C_2H_2). Loss of carbon monoxide from this fragment would give the $C_3H_2N^+$ fragment at *m/e* 52.

The mass spectra of the three azidobiphenyls are given in Figure 5A–C. These are typical of biphenylyl types of fragmentations[14] in which very little ion current is observed at low *m/e* values. Scheme VII illustrates the proposed fragmentation pattern

SCHEME VII



(13) G. Spiteller and M. Spiteller-Friedmann, *Monatsh. Chem.*, **93**, 1395 (1962).

(14) See ref 1b, pp 86–88.

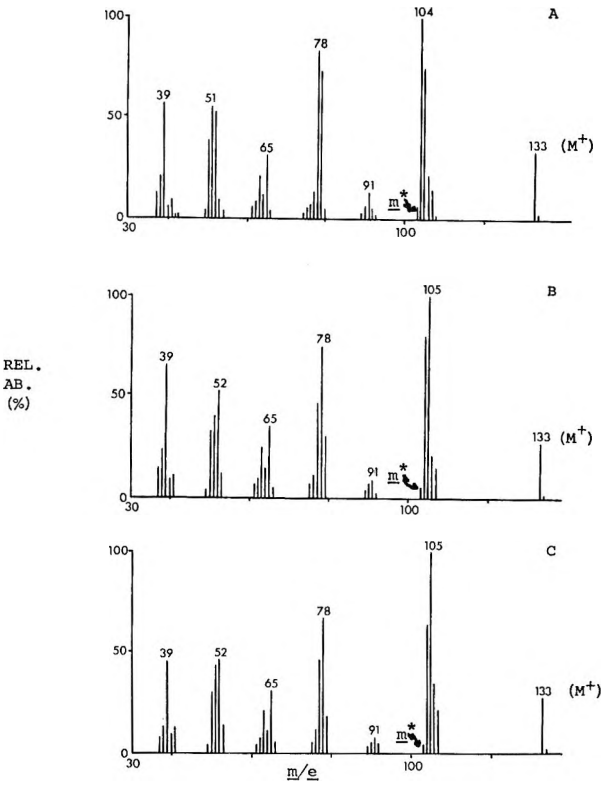
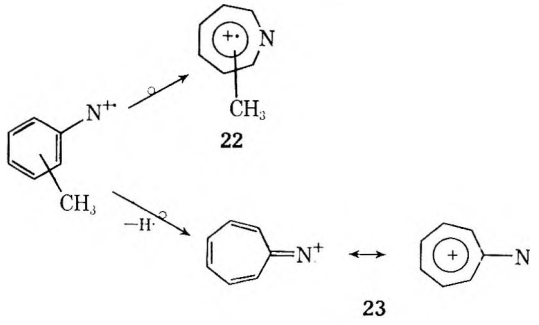


Figure 6.—Mass spectra of A, *o*-tolyl azide; B, *m*-tolyl azide; and C, *p*-tolyl azide.

for these molecules. It is possible that cyclization to the carbazole **21** is occurring with the ortho isomer, but there is no evidence in support of this.

The tolyl azides represent a very interesting class of compounds for mass spectral study in that they may lead to two different ring-expanded products, **22** and **23** (Scheme VIII). The mass spectra of the

SCHEME VIII



three isomeric tolyl azides are given in Figure 6A–C. Qualitatively, the spectra are similar and are all "abnormal" as defined above. They exhibit a metastable transition m* 103.1 corresponding to *m/e* 105 → 104 (calcd m* 103.0). Whereas the meta and para isomers give a base peak at *m/e* 105, the ortho isomer gives as the base peak *m/e* 104. In addition, the *m/e* 79 peak is much larger with the ortho isomer than from the other two (Table II). The ortho isomer also gives rise to a very weak diffuse metastable peak m* 76 (*m/e* 78 → 77) when the spectrum is determined on an MS-9 double focusing instrument; this was not observed in the low-resolution spectra determined on the CEC-21-104 using an accelerating potential of

TABLE II

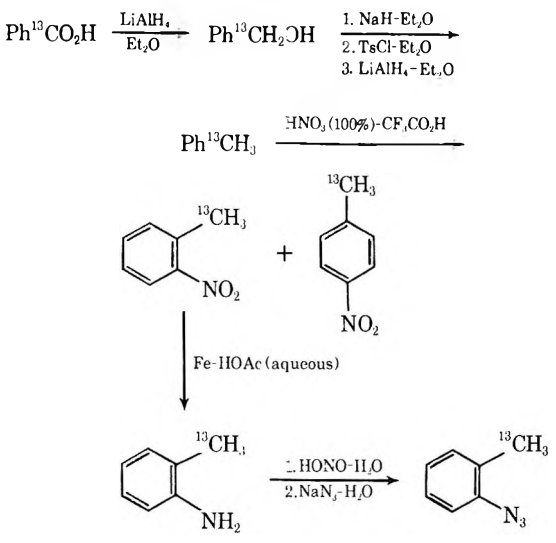
MASS SPECTRA OF TOLYL AZIDES. RELATIVE ABUNDANCE OF SELECTED IONS

	m/e									
Isomer	50	51	52	76	77	78	79	104	105	133
o-Me	39	57	54	14	47	84	74	100	76	25
m-Me	34	42	54	12	47	75	32	80	100	27
p-Me	30	44	47	12	47	68	19	64	100	27

1.2 kV. Again in the ortho isomer, an accurate mass determination indicates that *m/e* 107 is at least in part due to ($M^+ - C_2H_2$) (obsd, 107.0494; calcd for $C_5N_5N_3$, 107.0483). This process was not examined further here but, since all our azides show an $M^+ - 26$ peak (previously thought to be due exclusively to the primary amine cation), a more detailed study would appear to be warranted.

In order to investigate more fully the nature of the processes occurring in the electron impact induced decomposition of the tolyl azides, *o*-tolyl azide-α-^{13}C was synthesized starting from benzoic acid ^{13}C-carboxylate (61% enriched) as shown in Scheme IX.

SCHEME IX



The results of the mass spectral measurements on unlabeled and labeled *o*-tolyl azides are given in Table III. Slow scan rates and wide slit widths were used and for this reason the spectrum of the unlabeled azide (Table III) is not exactly the same as that presented in Table II in which a narrow slit width and fast scan rate was used. Since the conditions used for the determination of the spectra for the three isomeric tolyl azides were identical, the results given in Table II represent a valid comparison of the behavior of three isomers, but the spectrum given in Table III for *o*-tolyl azide is regarded as much more accurate.

It is easily calculated from the peak intensities at *m/e* 134 and 133 that the tolyl azide-α-^{13}C is 61% enriched in ^{13}C. One can obtain a calculated spectrum by taking 39% of the relative intensities of the unlabeled compound and adding to this 61% of the unlabeled compound *displaced upward by one mass unit.* The results are given in the sixth column in Table III. It can be seen that the agreement between the observed (column 5) and calculated abundances is good for the mass cluster *m/e* 103–108. On the other hand,

SCHEME X

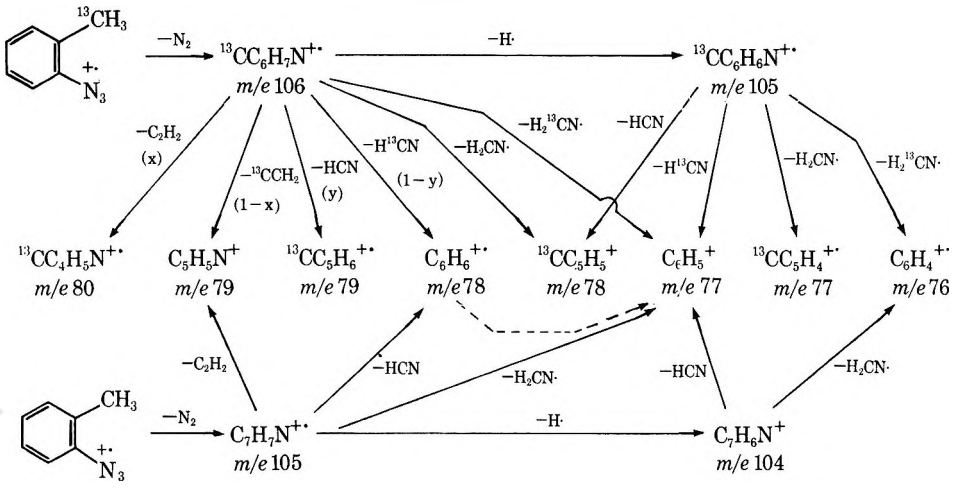


TABLE III
MASS SPECTRA OF UNLABELED AND $^{13}CH_3$-LABELED *o*-TOLYL AZIDE

m/e	Unlabeled azide[a]	Unlabeled azide cor for natural abundance of ^{13}C[b]	Labeled azide[c]	Labeled azide cor for natural abundance of ^{13}C[d]	Calcd spectrum[e]
135			1.3		
134	2.3		16.7	16.5	
133	25.6	25.7	10.1	10.5	
108			7.6	6.9	7.1
107	12.2	11.0	16.4	13.3	14.4
106	20.4	15.1	54.5	49.8	48.9
105	74.7	67.0	93.2	93.6	93.6
104	100.0	100.0	44.0	45.6	45.9
103	6.5	6.5	3.9	4.1	3.4
81	1.3	1.2	1.2	0.8	1.3
80	5.0	1.2	13.4	8.2	42.1
79	68.6	63.8	100.0	100.0	77.1
78	80.1	77.6	64.5	65.3	61.4
77	45.1	44.5	27.0	27.5	29.9
76	12.4	12.0	10.0	10.0	9.0
75	6.5	6.1	6.5	6.4	6.1
74	5.4	5.4	3.6	3.7	2.2

[a] See Experimental Section for conditions used. Average of five scans, average deviation, ±0.2. [b] See F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, New York, N. Y., 1967. [c] Average of seven scans, average deviation, ±0.2. [d] Weighted averages based on the fragments in Scheme IX were used. [e] See text for description of calculation. Spectrum is normalized so that *m/e* 105 peaks in observed ^{13}C and calculated spectra are of the same intensity.

there is very poor agreement between the observed and calculated spectra for the mass cluster *m/e* 74–81, particularly for *m/e* 79 and 80. This simple method of calculating the relative abundances also predicts that *m/e* 105 should be the base peak, whereas *m/e* 79 is observed to be the base peak in the spectrum of the labeled azide. Even if a statistical loss ($^1/_7$) of ^{13}C as $^{13}CCH_2$ is assumed to occur, the relative abundances of *m/e* 79 and 80 would become 84.4 and 36.2, respectively, still far from agreement with the observed spectrum.

To understand the processes that give rise to the mass cluster *m/e* 76–80, it is necessary to consider the possible fragmentations that can occur from the labeled and unlabeled azides, and this is outlined in Scheme X. The composition of the ions for the unlabeled azide in the *m/e* 76–80 range was confirmed by high-resolution mass spectrometry, and ions such as $C_6H_7^+$ for *m/e* 79, $C_5H_4N^{+\cdot}$ for *m/e* 78, and $C_5H_3N^+$ for *m/e* 77 were eliminated from consideration by the accurate mass determination. It appears that the most logical source of the fragments at *m/e* 79 and 78 for the unlabeled azide is $C_7H_7N^{+\cdot}$ (*m/e* 105), by loss of C_2H_2 and HCN, respectively, and that of *m/e* 76 is $C_7H_6N^+$ (*m/e* 104) by loss of H_2CN·. The *m/e* 77 fragment may arise either from $C_7H_7N^{+\cdot}$ by loss of H_2CN· or from $C_7H_4N^+$ by loss of HCN.

As can be seen from Scheme X, for the labeled azide there are a number of processes which occur to unknown extents as, for example, the amount of $^{13}CCH_2$ relative to C_2H_2 being lost from $^{13}CC_6H_7N^{+\cdot}$. If one assumes that loss of H_2CN· and $H_2{}^{13}CN$· from $^{13}CC_6N_7N^{+\cdot}$ and of N_2CN· from $CH_7N^{+\cdot}$ are unimportant, it is possible to calculate the extent to which the various other fragmentations are occurring to give *m/e* 76–80. Unfortunately, the results are not internally self-consistent, suggesting that the above assumption may not be valid. On the other hand, it can be seen that fragments *m/e* 80 and 79 (Scheme X) arise in a straightforward manner from *m/e* 106 and the proportions, *x* and *y*, in which $^{13}CC_6H_7N^+$ loses C_2H_2 and HCN, respectively [and hence $^{13}CCH_2$ (1 − x) and $H^{13}CN$ (1 − y)], can be readily determined from eq i and ii. In view of the relatively small size of the

$$m/e\ 80 \quad 0.61(63.8)x = 8.2 \qquad \text{(i)}$$
$$x = 0.21$$

$$m/e\ 79 \quad 0.39(63.8) + (0.61)(63.8)(1 - x) + (0.61)(77.6)y = 100 \qquad \text{(ii)}$$
$$y = 0.94$$

m/e 80 and 79 peaks, it is safer to estimate that *x* is in the range 0.1–0.2 and *y* in the range 0.8–0.9.

It can thus be seen that a large proportion (80–90%) of the acetylene lost from $^{13}CC_6H_7N^{+\cdot}$ contains the ^{13}C label and that only a small amount of the ^{13}C label is eliminated as $H^{13}CN$ (10–20%). This accounts qualitatively for the fact that the base peak in the mass spectrum of the labeled azide is *m/e* 79, whereas the base peak for the unlabeled azide spectrum is *m/e* 104. The preferential loss of the labeled methyl carbon atom in acetylene has the effect of decreasing the relative abundance at *m/e* 80 and increasing the relative abun-

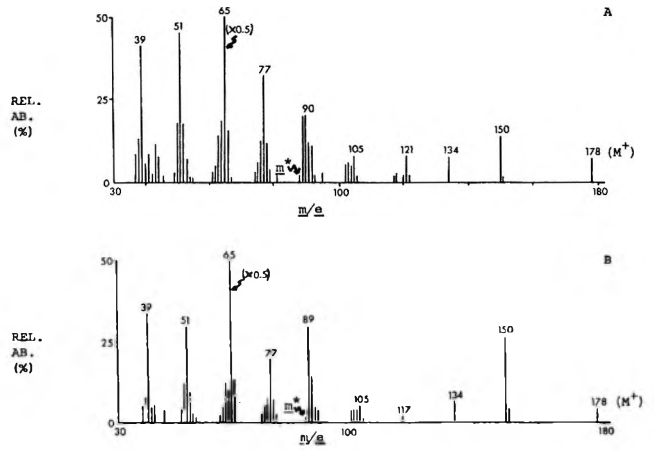
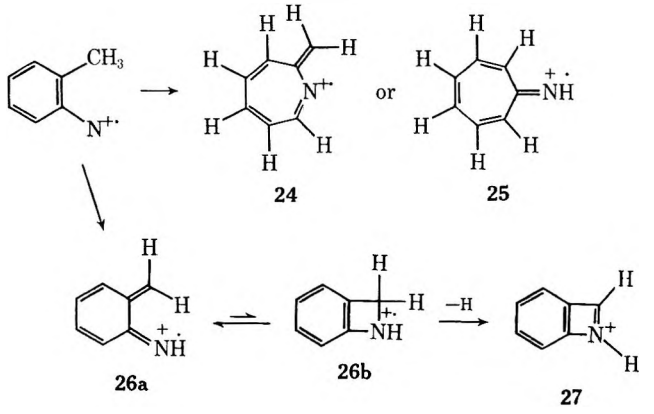


Figure 7.—Mass spectra of A, 2-azido-3-nitrotoluene; and B, 4-azido-3-nitrotoluene.

dance at *m/e* 79 to the point that the latter becomes the largest peak in the spectrum.

There are several possible structures for the $C_7N_7N^{+\cdot}$ fragment, and these are in Scheme XI. It is felt that,

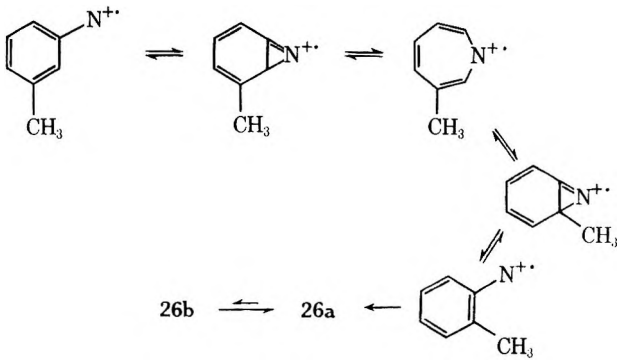
SCHEME XI



although structure **24** could account for the marked preferential loss of the methyl carbon atom as acetylene, there is no reason to expect loss of H· to give the *m/e* 104 fragment (known to occur by the observation of m* 103). Structure **25** could well give rise to the metastable transition m* 103, but it could not give the observed preferential loss of the methyl carbon atom as acetylene (at most, this would occur to the extent of 50%). Thus, neither **24** nor **25** represents a probable structure for the $C_7N_7N^{+\cdot}$ fragment. Structures **26a** ⇌ **26b** do account for the above observations. **26a** might be expected to lose the methyl group preferentially as acetylene and also to eliminate hydrogen cyanide not containing the methyl carbon. In addition, the equilibrium with **26b** could account for the small amount of methyl carbon lost as hydrogen cyanide and for the metastable transition *m/e* 105 → 104. This then leads to the suggestion that the structure for the *m/e* 104 fragment is **27**.

An examination of Table II indicates that the loss of acetylene from *m/e* 105 in the *o*-tolyl azide is much more facile than with the meta and para isomers, and a similar situation seems to exist for the metastable transition *m/e* 105 → 104. One possible explanation for these observations is that in all three azides elimination of C_2H_2 and HCN is occurring from the *o*-quinonoid type of structure **26a** (Scheme XI) and that the ring-expanded species **24**, **25** (Scheme XI), **22**, and **23** (Scheme VIII) are not important in the *fragmentation*. Ions such as **22** would be important, however, in interconverting positional nitrenium ion isomers. Thus, in order for the meta and para isomers to lose C_2H_2 and HCN by the same mechanism as does the ortho isomer, a nitrenium azepinium ion equilibrium (Scheme XII) would have to be established,

SCHEME XII



similar to that suggested for equilibration of tolyl carbenes at 420° in the gas phase.[15] This scheme would now account for the fact that the *o*-tolyl azide gives the largest of the *m/e* 104 and 79 peaks and the para isomer the smallest. Although ^{13}C labeling experiments were not carried out on *p*-tolyl azide, high-resolution mass spectrometry showed that the composition of the ions in the mass range *m/e* 76–80 derived from the para isomer was identical with that obtained from the *o*-tolyl azide.

The mass spectra of 2-azido-3-nitrotoluene and 4-azido-3-nitrotoluene are presented in Figure 7A, 7B. They contain features of both the nitrophenyl azides ($M^+ - N_2 - O$) and tolyl azides (m* 93 → 89). It is also interesting to note that the ratio of $(M^+):(M^+ - N_2)$ is much larger in the case of the *o*-methyl group than for the *p*-methyl group. This might mean that the *o*-methyl group is sterically hindering the usually very facile concerted cyclization–elimination of nitrogen to give the benzofuroxan. Dyall and Kemp[16] found virtually no evidence of an anchimerically assisted reaction in the thermolysis of 2-azido-3-nitrotoluene, as opposed to the case of *o*-nitrophenyl azide.

The mass spectrum of ferrocenyl azide has also been determined. This will be discussed, however, in a forthcoming paper on the mass spectra of some ferrocene derivatives.[17]

Experimental Section

Low-resolution mass spectra were recorded on a CEC 21-104 spectrometer, using as standard conditions (unless otherwise stated) the source temperature at 250°, ionizing potential of 70 eV, and an accelerating potential of 1200 V. Samples were introduced with a direct probe inlet. For all the spectra except

(15) W. T. Baron, M. Jones, Jr., and P. P. Gasper, *J. Amer. Chem. Soc.*, **92**, 4739 (1970).

(16) L. K. Dyall and J. E. Kemp, *J. Chem. Soc. B*, 976 (1968).

(17) R. A. Abramovitch, C. I. Azogu, E. P. Kyba, and R. G. Sutherland, unpublished results.

the quantitative work on the labeled and unlabeled *o*-tolyl azides, a slit width of 5 mils was used and the magnetic scan rate was such that the entire spectrum (from *m/e* 160 to *m/e* 28 in most cases) was determined in about 30 sec. For the quantitative work on *o*-tolyl azide, the slit width was set at 20 mils and the scan rate was such that a scan from *ca.* *m/e* 104 to 65 required about 30 sec, and flat-topped peaks were obtained. The high-resolution mass spectra were determined on a CEC-21-110B. All of the azides were known compounds, and their physical properties were in agreement with those reported in the literature. One representative synthesis (4-methyl-2-nitroazidobenzene) is reported here, as is the synthesis of *o*-tolyl azide-α-^{13}C in which the conditions were developed with unlabeled materials, such as to optimize the yields of the precious labeled product.

4-Methyl-2-nitroazidobenzene.—Sodium nitrite (2.8 g, 41 mmol) in water (25 ml) at 0–5° was added dropwise to a mixture of 4-methyl-2-nitroaniline (5.0 g, 33 mmol), concentrated sulfuric acid (6 ml), and water at 0–5°. Urea was added to remove the excess nitrous acid (starch–iodide paper) and the resulting solution was treated with activated charcoal for 30 min at 0°. Sodium azide (3.6 g, 55 mmol) in water (20 ml) at 5° was added slowly. The yellow precipitate which formed was filtered and dried. The solid was recrystallized from pentane to give 4-methyl-2-nitroazidobenzene (3.5 g, 60%), mp 36–38° (lit.[16] mp 35–36°).

Benzyl Alcohol-α-^{13}C.—Benzoic acid $^{13}CO_2H$ (*ca.* 62%) (3 g, 24.6 mmol) in dry ether (60 ml) was added to a 2 *M* solution of lithium aluminum hydride in ether (20 ml, 160 mmol) and the mixture was stirred and boiled under reflux for 24 hr. The cooled (0°) mixture was decomposed with 10% aqueous sodium hydroxide, filtered, dried, diluted with ether to 200 ml, and analyzed by gas chromatography using a 6 ft × $^3/_{16}$ in. column packed with SE-30 (20%) on Gas-Chrom Q (60–100 mesh) at 120° and a helium flow rate of 60 ml/min. *n*-Nonane was used as the internal standard. Yield of benzyl alcohol-α-^{13}C was 89%.

Toluene-α-^{13}C.—The above solution of benzyl alcohol (21.8 mmol) was boiled under reflux for 24 hr with sodium hydride (0.65 g, 27 mmol), cooled to −20°, and treated with *p*-toluenesulfonyl chloride (4.3 g, 22.6 mmol) in dry ether (70 ml, dried over molecular sieves) dropwise, with stirring at −20° for 2 hr and then at room temperature for 2 hr. A solution of 2 *M* lithium aluminum hydride (14 ml) in ether was added, and the mixture was stirred at room temperature for 3 hr and then boiled under reflux for 12 hr. Water (20 ml) and then 3 *N* HCl (100 ml) were added, and the ether layer was washed with water, dried, and evaporated to give toluene-α-^{13}C (67% yield).

***o*-Tolyl Azide-α-^{13}C.**—Toluene-α-^{13}C (1.0 g, 107 mmol) was added in one portion to 100% nitric acid (1 ml) in trifluoroacetic acid (25 ml) at 0°. The dark red-brown solution was allowed to stand for 1.5 hr by which time the color had almost totally disappeared. It was poured into water (250 ml) and the solution neutralized (Na_2CO_3 solid). The mixture was extracted with ether (two 150-ml portions), and the ethereal layer was washed (4% aqueous Na_2CO_3), dried, and evaporated to give a yellow oil (1.2 g) which was chromatographed on basic alumina (120 g). Elution with petroleum ether–benzene (97:3 v/v) gave pure (by glc) *o*-nitrotoluene-α-^{13}C (300 mg, 22% yield). Further elution gave a mixture of the ortho, meta, and para isomers (200 mg) and then the pure para isomer.

o-Nitrotoluene-α-^{13}C (300 mg, 2.2 mmol) was reduced with iron (3 g) in water (1.4 ml) and acetic acid (0.2 ml) to give the pure toluidine (glc) (180 mg, 76%). This was diazotized at 0°, the excess nitrous acid was destroyed with urea, and the solution was treated with ether (2 ml) and then NaN_3 (184 mg) in water (0.8 ml). Extraction with ether, washing the ethereal extract with 10% NaOH (2 × 5 ml), drying, and concentration gave the desired azide as a yellow liquid (67 mg, 30%), bp 28–30° (20 μ).

Registry No.—*o*-Nitrophenyl azide, 1516-58-1; benzofuroxan, 480-96-6; *m*-methoxyphenyl azide, 3866-16-8; *o*-methoxyphenyl azide, 20442-97-1; *p*-methoxyphenyl azide, 2101-87-3; 2-azidobiphenyl, 7599-23-7; 3-azidobiphenyl, 14213-01-5; 4-azidophenyl, 31656-91-4; *o*-tolyl azide, 31656-92-5; *m*-tolyl azide, 4113-72-8; *p*-tolyl azide, 2101-86-2.

Acknowledgments.—This work was supported by an NSF Grant, GP 18557. We thank Merck & Co. for a gift of 2 g of benzoic acid $^{13}CO_2H$.

Notes

The Mechanism of Acid Hydrolysis of Imidazolines

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Received April 13, 1971

Recently Haake and Watson[1] have proposed that amidines (and related strong bases) hydrolyze by nucleophilic attack by water on the diprotonated amidines. Their proposal was based on (1) the rate of hydrolysis of the strong base lysidine, 2-methylimidazoline (pK_a = 11),[2] being linearly dependent on acid concentration with a rate maximum at 10–12 *M* sulfuric acid which suggests a transition state consisting of a lysidinium ion, a proton, and water and (2) the large downfield shift in the nmr signals of lysidinium ion in sulfuric acid more concentrated than 102%, which suggests protonation of lysidinium ion to a dication. Because of its novelty, we undertook additional experiments to test the validity of the proposed mechanism. The results, which are reported in this paper, were all consistent with the proposed mechanism.

(1) P. Haake and J. W. Watson, *J. Org. Chem.*, **35**, 4063 (1970).
(2) R. B. Martin and A. Parcell, *J. Amer. Chem. Soc.*, **83**, 4830 (1961).

Experimental Section

Ultraviolet spectra were determined on a Cary Model 15 recording spectrometer. Nmr spectra were determined on a Varian T-60 spectrometer. Acid solutions were standardized as previously described.[1]

2-(*m*-Nitrophenyl)imidazoline.—To 7 ml of concentrated sulfuric acid cooled by an ice bath, 1.72 g of 2-phenylimidazoline was added; 7 ml of concentrated nitric acid was added dropwise to the cooled, stirred solution. The ice bath was removed and the solution was slowly heated to 60° and its temperature maintained at 60° for 10 min. The reaction mixture was then cooled by means of an ice bath and made alkaline with 50% potassium hydroxide. The precipitate was collected and purified by recrystallization from benzene. A yield of 1.2 g, mp 155–156°, was obtained: nmr (CCl_4) τ 1.4–2.8 (4.0 H, multiplet), 5.4 (1.2 H, singlet), τ 6.2 (4.0 H, singlet). Hydrolysis of this compound

gave *m*-nitrobenzoic acid (identified by melting point and nmr spectrum).

The procedure of Sawa, *et al.*,[3] was employed to prepare lysidine and the other 2-arylimidazolines in yields of 40–60%. Melting points and nmr spectra were consistent with the proposed structures: **lysidine**, recrystallized from benzene and vacuum sublimed, mp 101–102° (lit.[1] mp 103°); **2-(*p*-methylphenyl)-imidazoline**, recrystallized from benzene and vacuum sublimed, mp 182–183° (lit.[4] mp 183°); **2-(*p*-methoxyphenyl)imidazoline**, recrystallized from benzene, mp 138–139° (lit.[5] mp 140°); **2-(phenyl)imidazoline**, recrystallized from benzene and vacuum sublimed, mp 102–103° (lit.[5] mp 103°); **2-(*p*-chlorophenyl)-imidazoline**, recrystallized from benzene, mp 185–186° (lit.[5] mp 187°).

Kinetic Method.—The determination of the rates of lysidine hydrolysis by ultraviolet spectroscopy was as previously described.[1]

During the course of the hydrolysis of the 2-arylimidazoline in 9 *M* H_2SO_4 the methylene singlet at ~4.3 ppm upfield from the solvent peak progressively decreased in strength as a new signal arose at 0.5 ppm further upfield. The second signal was confirmed by nmr spectroscopy to be due to ethylene diammonium ion. The extent of hydrolysis was taken equal to $A_{4.3}/(A_{4.3} + A_{4.8})$, where $A_{4.3}$ and $A_{4.8}$ are the areas of the signals at 4.3 and 4.8 ppm from the solvent signal. Plots of ln $A_{4.3}/(A_{4.3} + A_{4.8})$ *vs.* time were linear for four to five points covering approximately two half-lives; the slopes were taken equal to the first-order rate constant. During the course of the hydrolysis of the 2-arylimidazolines, the arylcarboxylic acids (confirmed by melting points and nmr spectra) precipitated from solution and were removed by filtration before the extent of hydrolysis was determined by nmr. The initial concentration of the 2-arylimidazolines was approximately 0.2 *M*.

For the nmr determination of the rate of hydrolysis of lysidine in 4 *M* H_2SO_4, the method was the same as that for the arylimidazolines above. However, in 14 *M* H_2SO_4, because the signal due to ethylenediammonium ion is too broad to permit the accurate determination of its area and that of the methylene protons of lysidine separately, the areas of the methyl signlets of lysidine and the hydrolysis product acetic acid were employed to determine the extent of reaction. The initial concentration of lysidine was approximately 0.35 *M*.

Results and Discussion

The first-order rate constants listed in Tables I–III are the average of at least two determinations which agreed with one another to within 10%. The close similarities of the rates determined by the ultraviolet and nmr methods provides additional support for the view that the reaction which was followed is the hydrolysis of lysidine to acetic acid and ethylenediammonium ion.

TABLE I

OBSERVED FIRST-ORDER RATE CONSTANTS FOR HYDROLYSIS OF LYSIDINE IN SULFURIC ACID

Acid	Molarity	Temp, °C	10^5k_1, sec^{-1}
H_2SO_4	4	90.0	0.190[a]
H_2SO_4	4	90.0	0.210[b]
D_2SO_4	4	90.0	0.282[a]
D_2SO_4	4	90.0	0.284[b]
H_2SO_4	4	99.9	0.503[c]
H_2SO_4	4	108.0	0.899[b]
H_2SO_4	14	90.0	0.219[a]
H_2SO_4	14	90.0	0.227[b]
D_2SO_4	14	90.0	0.284[b]
H_2SO_4	14	99.9	0.55[c]
H_2SO_4	14	108.0	0.885[b]

[a] Rates determined by uv method. [b] Rates determined by nmr method. [c] Data from ref 1.

TABLE II

OBSERVED FIRST-ORDER RATE OF HYDROLYSIS OF LYSIDINE IN DIFFERENT ACIDS AT 90.0° [a]

Acid	H_0[b]	Log a_{H_2O}[c]	10^5k_1, sec^{-1}
3.5 *M* $HClO_4$	−1.47	−0.106	0.0663
3.5 *M* H_2SO_4	−1.52	−0.111	0.181
4 *M* HCl	−1.40	−0.107	0.207

[a] Rates determined by uv method. [b] M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957). [c] J. F. Bunnett, *J. Amer. Chem. Soc.*, **83**, 4956 (1961).

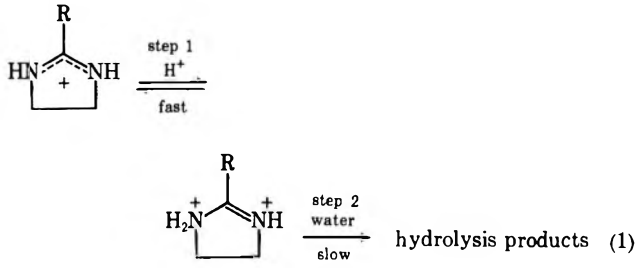
TABLE III

OBSERVED FIRST-ORDER RATE CONSTANTS FOR HYDROLYSIS OF 2-ARYLIMIDAZOLINES IN 9 *M* H_2SO_4 AT 138.5°

2-Aryl group	Registry no.	σ^+ value[a]	10^5k_1, sec^{-1}
p-Methoxyphenyl	6302-84-7	−0.764	1.26
p-Methylphenyl	13623-58-0	−0.306	1.40
Phenyl	936-49-2	0.00	1.45
p-Chlorophenyl	13623-52-4	0.112	1.40
m-Nitrophenyl	31659-42-4	0.662	1.37

[a] Of aryl substituent: K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, p 140.

The mechanism proposed in eq 1 for the acid hydrolysis of lysidine consists of the protonation of lysidinium ion[2] (pK_a = 11) in a preequilibrium step to a strongly acidic dication [half conversion of lysidinium ion to the dication occurs in >102% H_2SO_4 (H_0 < −13)] which undergoes rate-determining nucleophilic attack by water.



Because this proposed mechanism is in essence an A2 mechanism[6]—fast equilibrium protonation of the substrate followed by rate-determining nucleophilic attack by water—and consequently requires that the hydrolysis rates respond to reaction conditions and substituent effects in a manner similar to that of other A2 reactions, we have tested the proposed mechanism by determining catalyzing acid, temperature, solvent isotope, and substituent effects on the rate of hydrolysis.

Substituent Effect.—The mechanism of eq 1 predicts that the electronic effects of the substituent R on the rate of hydrolysis should be small if step 2 involves nucleophilic addition of water to the dication at the 2 position. The very similar rates of hydrolysis of the 2-arylimidazolines (Table III) yield a ρ value of essentially zero, which is consistent with the ρ values for related A2 mechanisms. For example, ρ values of 0.144 and −0.222 are observed for the acid hydrolysis of ethyl benzoates and benzamides, respectively, in

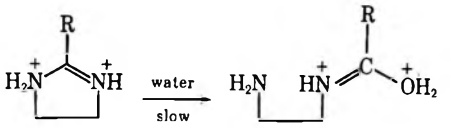
(3) N. Sawa, S. Kishizoe, K. Naga, M. Kuriyama, Y. Tsujino, and T. Shimamura, *Chem. Abstr.*, **63**, 11820c (1965).

(4) A. J. Hill and S. R. Aspinal, *J. Amer. Chem. Soc.*, **61**, 822 (1939).

(5) P. Oxley and W. F. Short, *J. Chem. Soc.*, 497 (1947).

(6) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, Chapter XIV.

60% aqueous ethanol at 100°.[7] It would seem quite unlikely that negligible electronic effects on the rate of hydrolysis would be obtained if step 2 consisted of a direct displacement reaction by water.



Because the protonation step should exhibit a negative ρ value (protonation of substituted acetophenones has a ρ^+ value of between −2.0 and −3.0[8]) and the direct displacement step should have a negligible ρ value,[9] the overall ρ value for the reaction should be significant and negative. For example, the acid-catalyzed hydrolysis of 2-aryl-1,3-oxathiolanes, which is considered to proceed by an A2 mechanism involving a rate-determining direct displacement by water step, has a ρ value of −1.66.[10]

Acid Effect.—It has been observed that for solutions of similar water activities (and acidity) that the rates of A2 reactions are faster in hydrochloric and sulfuric acids than in perchloric acid, while the reverse is observed for A1 reactions.[11] The data of Table II indicate that the relative rates of hydrolysis of lysidine in the indicated concentrations of perchloric, sulfuric, and hydrochloric acids are 1:2.7:3.1. This order is consistent with that observed for other A2 reactions—for both amides[11b] and esters[11c] the rates of hydrolysis are twice as fast in 4 *M* sulfuric acid as in 4 *M* perchloric acid.

Solvent Isotope Effect.—The solvent deuterium isotope effects, $k_{H_2SO_4}/k_{D_2SO_4}$, of 0.71 and 0.78 on the rates of hydrolysis of lysidine in 4 and 14 *M* sulfuric acid (Table I) are consistent with an A2 reaction in which the preequilibrium protonation of the substrate is fast and incomplete.[10,12] These isotope effects therefore confirm the previous proposal (based on nmr data which indicated that lysidinium ion is significantly protonated only in solutions more acidic that 102% sulfuric acid) that the inverse dependence of lysidine hydrolysis rate on acid concentration above 12 *M* sulfuric acid is not due to substantial conversion of the substrate to the reactive dication but to the retarding effect of decreasing water activity outweighing the accelerating effect of increasing medium acidity.[1]

In contrast to lysidine, the hydrolysis of acetamide exhibits a solvent isotope effect [k(H)/k(D)] of 0.7 in 0.1 *N* acid where acetamide is incompletely protonated and an isotope effect of 1.1 in 4 *N* acid where it is essentially completely protonated.[12]

Entropies of Activation.—Because of their large orientation and steric requirements, A2 reactions have entropies of activation of approximately −15 to −30 eu.[13] For example, the A2 hydrolyses of acetamide, ethyl acetate, and 2-phenyl-1,3-oxathiolane have entropies of activation of −37, −23, and −18 eu, respectively.[10,13]

From the second-order rate constants $k_1/[H_2SO_4]$ calculable from the data of Table I, entropies of activation of −26 and −31 (±4) eu may be calculated for the hydrolysis of lysidine in 4 and 14 *M* sulfuric acid (the corresponding enthalpies of activation are 22 and 21 kcal/mol, respectively). These entropy values, being similar to those for known A2 reactions, are consequently consistent with the mechanism of eq 1.

Thus the four mechanistic criteria which we have applied to the acid hydrolysis of the imidazolines have given results which, being consistent with the results expected for an A2 hydrolysis mechanism, provide evidence for the hydrolysis proceeding as outlined in eq 1. The negligible electronic effects on the rates of hydrolysis of the two arylimidazolines provide good evidence for the proposition that step 2 of eq 1 represents rate-determining nucleophilic addition of water to the dication at position 2 to form a tetrahedral addition intermediate which decomposes to the hydrolysis products (or reverts to reactants by loss of water from the dication).

Additional work in this laboratory has provided similar evidence in support of Haake and Watson's[1] proposal that guanidines also hydrolyze by an A2 mechanism analogous to that of eq 1.[14]

Registry No.—Lysidine, 534-26-9.

Acknowledgments.—We are grateful to the National Institutes of Health for support of this research.

(7) H. H. Jaffé, *Chem. Rev.*, **53**, 202 (1953).
(8) (a) G. C. Levy, J. D. Cargioli, and W. Racela, *J. Amer. Chem. Soc.*, **92**, 6238 (1970); (b) R. Stewart and K. Yates, *ibid.*, **80**, 6355 (1958).
(9) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 18.
(10) N. C. De and L. R. Fedor, *J. Amer. Chem. Soc.*, **99**, 7266 (1968).
(11) (a) V. C. Armstrong and R. B. Moodie, *J. Chem. Soc. B*, 934 (1969); (b) V. C. Armstrong, D. W. Farlow, and R. B. Moodie, *ibid.*, 1099 (1968); (c) C. A. Bunton, J. H. Carbtree, and L. Robinson, *J. Amer. Chem. Soc.*, **90**, 1258 (1968).
(12) M. L. Bender, *Chem. Rev.*, **60**, 67 (1960).
(13) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).
(14) S. Limatibul and J. W. Watson, *J. Org. Chem.*, **36**, 3805 (1971).

The Mechanism of Acid Hydrolysis of Guanidines

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On the basis of the nmr spectra of lysidine, 2-methylimidazoline, in concentrated sulfuric acid solutions and the curvilinear dependence of the rate of hydrolysis of lysidine on sulfuric acid concentration, Haake and Watson proposed that imidazolines and similar strong bases, such as guanidines, hydrolyze in acid solutions by rate-determining nucleophilic attack by water on the diprotonated substrate.[1] In a recent paper we have reported additional data which support their proposed mechanism for the acid hydrolysis of amidines.[2] We report in this communication experimental results which indicate that guanidines hydrolyze by an analogous mechanism as proposed by Haake and Watson[1] (eq 1).

The rates of hydrolysis of 1,1,3,3-tetramethylguanidine, TMG, and its expected hydrolysis products, 1,1-dimethyl- and tetramethylureas, were determined by nmr spectroscopy by following the disappearance of the substrate methyl singlet and the formation of the

(1) P. Haake and J. W. Watson, *J. Org. Chem.*, **35**, 4063 (1970).
(2) S. Limatibul and J. W. Watson, *ibid.*, **36**, 3803 (1971).

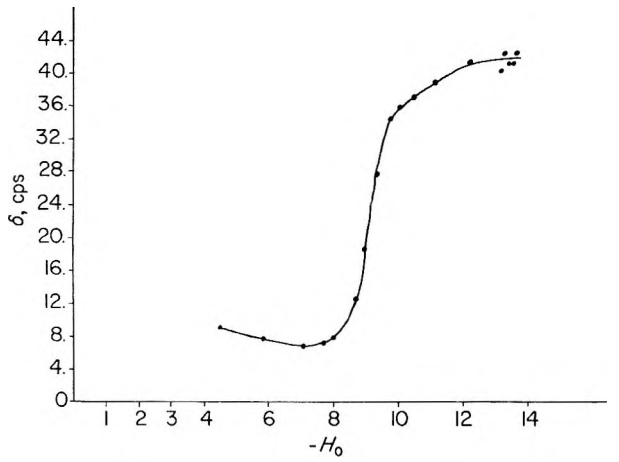
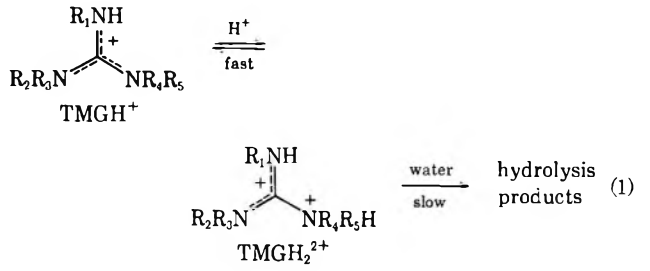


Figure 1.—Plot of the chemical shifts of the methyl protons of TMG relative to the methyl protons of dimethylammonium ion in sulfuric acid *vs.* H_0.

triplet of the hydrolysis product dimethylammonium ion.



The independence of the rate of hydrolysis of urea and ethylurea of acid concentration above 3 *M* H_2SO_4[3] and the observed first-order rate constants listed in Tables I and II indicate that dimethyl- and tetramethylureas

Table I

Observed First-Order Rates of Hydrolysis of 1,1-Dimethylurea and 1,1,3,3-Tetramethylurea in Sulfuric Acid[a]

Compd	H_2SO_4, *M*	Temp, °C	10^5k_1, sec^{-1}
1,1-Dimethylurea	4	108.1	1.8
1,1-Dimethylurea	4	138.5	42.7
1,1,3,3-Tetramethylurea	7.5	108.1	7.85
1,1,3,3-Tetramethylurea	7.5	138.5	89.0

[a] Rates determined by nmr with initial concentrations of ureas approximately 0.3 *M*.

hydrolyze considerably faster than TMG hydrolyzes in all the acid concentrations investigated. Therefore, there should be no complication of the determination of the rate of hydrolysis of TMG from a buildup of dimethyl- or tetramethylureas during the course of the TMG hydrolysis.

Because solvation effects on the chemical shifts are expected to be small and $TMGH^+$ has a pK_a of 13.6,[4] the large downfield shift in the methyl singlet of tetramethylguanidine above 84% H_2SO_4 (Table III) suggests protonation of $TMGH^+$ to a diprotonated tetramethylguanidine, $TMGH_2^{2+}$.[1] A plot of the chemical

(3) V. C. Armstrong, E. W. Farlow, and R. B. Moodie, *J. Chem. Soc. B*, 1099 (1968).

(4) I. M. Koltloff, M. K. Chantooni, and S. Blowmik, *J. Amer. Chem. Soc.*, **90**, 23 (1968); S. J. Angyal and W. K. Warburton, *J. Chem. Soc.*, 2492 (1968).

Table II

Observed First-Order Rate Constants for the Acid Hydrolysis of 1,1,3,3-Tetramethylguanidine[a]

H_2SO_4, *M*	Temp, °C	10^5k_1, sec^{-1}
1	138.5	0.056
2.3	138.5	0.130
3.5	138.5	0.211
4.0	108.1	0.0179
4[b]	108.1	0.0231
4.0	132.0	0.143
4.0	138.5	0.254
4[b]	138.5	0.302
5.0	138.5	0.30
6.0	138.5	0.35
7.5	138.5	0.42
9.0	138.5	0.44

[a] Initial concentration of TMG was approximately 0.3 *M*. [b] In D_2SO_4.

Table III

Chemical Shifts of the Methyl Protons of 1,1,3,3-Tetramethylguanidine in Sulfuric Acid[a]

% H_2SO_4	δ,[b] cps	$-H_0$[c]
59 (9.0 *M*)	9.2	4.46
70	7.8	5.80
78	6.8	7.03
82	7.2	7.66
84	8.0	7.97
88	12.4	8.61
90	18.4	8.92
92	27.6	9.29
94	34.4	9.68
96	35.6	10.03
98	36.8	10.41
99.5	38.4	11.12
100.0	41.2	12.20
102.0	40.	13.16
102.5	42.	13.29
103.0	40.8	13.38
103.5	40.8	13.47
105	42.	13.71

[a] Concentrations of dimethylamine hydrochloride and tetramethylguanidine were ~0.05 and ~0.03 *M*, respectively. [b] Chemical shifts are in cycles per second downfield from the central peak of the dimethylammonium ion triplet. [c] H_0 values below 60% H_2SO_4 are from (i) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957). H_0 values between 60 and 100% H_2SO_4 are from (ii) M. J. Jorgenson and D. R. Hartter, *J. Amer. Chem. Soc.*, **85**, 878 (1963). H_0 values for 100% and above H_2SO_4 are obtained by adding −1.10 H_0 units to the H_0 values of ref i as suggested in ref ii.

shift data, Figure 1, has the appearance of a titration curve with the $TMGH^+$ being half-protonated to the dication in approximately 91% H_2SO_4 (H_0 = −9.1).[5] Treatment of the data by the method of Bunnett and Olsen[6] yields an estimated pK_a of −11 for $TMGH_2^{2+}$ with a ϕ of −0.2. Nmr evidence for diprotonation of guanidines in FSO_3H-SbF_5 has been reported.[7]

The data of Tables II and IV are consistent with the A-2 type mechanism given in eq 1 and are very similar to the results observed for the acid hydrolysis of amidines[1,2] indicating that guanidines and amidines hydrolyze by similar mechanisms in acid solution.

Acid Concentration Effect.—The rate of hydrolysis of TMG increases linearly with acid concentration up

(5) G. C. Levy, J. D. Cargioli and W. Racela, *J. Amer. Chem. Soc.*, **92**, 6238 (1970).

(6) J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, **44**, 1899 (1966).

(7) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **90**, 6087 (1968).

TABLE IV
OBSERVED FIRST-ORDER RATE CONSTANTS FOR HYDROLYSIS OF 1,1,3,3-TETRAMETHYLGUANIDINE IN DIFFERENT ACIDS AT 138.5°

Acid	H_0[a]	Log a_{H_2O}[b]	$10^5 k_1$, sec^{-1}
3.5 *M* $HClO_4$	−1.47	−0.106	0.0289
4 *M* HCl	−1.40	−0.107	0.118
3.5 *M* H_2SO_4	−1.62	−0.111	0.211

[a] M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957). [b] J. F. Bunnett, *J. Amer. Chem. Soc.*, **83**, 4956 (1961).

to 6 *M* sulfuric acid suggesting that the transition state for acid hydrolysis consists of a proton, water, and the substrate which is $TMGH^+$ (pK_a = 13.6). In solutions more concentrated than 7.5 *M* H_2SO_4, the observed second-order rate constants decreased and the occurrence of a side reaction of undetermined nature was indicated by the nmr spectra of the reaction solutions.

Solvent Isotope Effect.—In 4 *M* sulfuric acid the solvent isotope effects, $k_{H_2SO_4}/k_{D_2SO_4}$, of 0.78 and 0.83 at 108.1 and 138.5°, respectively, are consistent with fast preequilibrium protonation of the substrate as indicated in eq 1. For the hydrolysis of lysidine in 4 *M* sulfuric acid at 90°, $k_{H_2SO_4}/k_{D_2SO_4}$ is 0.71.[2]

Entropies of Activation.—From the rates of hydrolysis of TMG in 4 *M* sulfuric acid at 108.1 and 138.5°, activation parameters of $\Delta S = -25$ eu and $\Delta H = 27$ kcal/mol may be calculated for the second-order rate constant $k_1/[H_2SO_4]$. The entropy of activation is very similar to that observed for the acid hydrolysis of lysidine, −26 eu, and other A2 reactions.[2]

Acid Effect.—It has been observed that A2 reactions are faster in sulfuric and hydrochloric acids than in perchloric acid solutions of comparable acidity and water activity.[8] The ratio of hydrolysis rates of TMG in perchloric, hydrochloric, and sulfuric acids of 1:4:7 (Table IV) is consequently consistent with the A2 mechanism of eq 1. The relative order observed for the hydrolysis of lysidine of 1:3.1:2.7 is slightly different.[2]

Thus our experimental results are consistent with the proposal that guanidines hydrolyze by an A2 mechanism as outlined in eq 1 and support the proposition that compounds, such as amidines and guanidines, which form highly resonance-stabilized conjugate acids undergo acid hydrolysis by nucleophilic attack by water on the diprotonated compounds.[1] The present experimental data are not considered sufficient to justify our speculating on whether the nucleophilic attack by water on the diprotonated guanidine consists of nucleophilic addition of water to form a tetrahedral intermediate (as favored for the amidine hydrolysis[2]) or a direct displacement (S$_N$2) reaction analogous to the mechanism proposed for the acid hydrolysis of carbamates.[8a]

Experimental Section

Nmr spectra were determined on a Varian T-60 spectrometer. Acid solutions were standardized as previously described.[1]

Dimethylurea was synthesized from dimethylamine and potassium cyanate[9a] and recrystallized from ethanol, mp 182–183° (lit.[9b] mp 182–183°). Aldrich 1,1,3,3-tetramethylurea was purified by distillation, bp 174–175° (lit.[10] bp 174–177°). Aldrich 1,1,3,3-tetramethylguanidine was purified by distillation, bp 164° [lit.[11] bp 159.5° (745 mm)]. The nmr spectra of the compounds were consistent with their structures.

In the acid solutions employed for the rate determinations, the ureas and 1,1,3,3-tetramethylguanidine absorbed at the same chemical shift and on hydrolysis gave rise to an upfield triplet which was confirmed to be due to dimethylammonium ion. For example, in 4 *M* H_2SO_4 the ureas and the tetramethylguanidine gave singlets at 3.3 ppm upfield from the solvent signal and dimethylammonium ion gave a triplet of 3.5 ppm upfield from the solvent signal. The rates of hydrolysis were determined from plots of ln $A_R/(A_R + A_P)$ *vs.* time, where A_R is the area of the reactant (urea or guanidine) singlet and A_P equals the area of the product dimethylammonium ion triplet. Linear plots consisting of four to five points and covering approximately 2 half-lives were obtained. The nmr determination of the protonation of tetramethylguanidinium ion was performed as previously described.[1,5]

Registry No.—1,1-Dimethylurea, 598-94-7; 1,1,3,3-tetramethylurea, 632-22-4; sulfuric acid, 7664-93-9; 1,1,3,3-tetramethylguanidine, 80-70-6.

(8) (a) V. C. Armstrong and R. B. Moodie, *J. Chem. Soc. B*, 934 (1969); (b) V. C. Armstrong, D. W. Farlow, and R. B. Moodie, *ibid.*, 1099 (1968); (c) C. A. Bunton, J. H. Crabtree, and L. Robinson, *J. Amer. Chem. Soc.*, **90**, 1258 (1968).

(9) (a) F. Arndt, *Org. Syn.*, **15**, 48 (1935); (b) F. Kurzer, *ibid.*, **32**, 61 (1952).

(10) H. Z. Lecler and K. Gubernator, *J. Amer. Chem. Soc.*, **75**, 1087 (1953).

(11) M. L. Anderson and R. N. Hammer, *J. Chem. Eng. Data*, **12**, 442 (1967).

Formation of 2-Alkyl-5-phenyltetrazoles from 1-Alkyl-5-phenyltetrazoles

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It is generally recognized that the reaction of a 1,5-disubstituted tetrazole with alkyl halide or alkyl benzenesulfonate gives a 1,4,5-trisubstituted tetrazolium salt.[2-9] We have found, however, that treatment of 1-alkyl-5-phenyltetrazole with alkyl iodide at 130° gave no tetrazolium salt but rather 2-alkyl-5-phenyltetrazole. To elucidate this novel isomerization process, some experiments were carried out at lower temperatures.

On heating 1-methyl-5-phenyltetrazole (1) with methyl iodide at 130° for 10 hr, 2-methyl-5-phenyltetrazole (2) was obtained in a quantitative yield. The presence of methyl iodide was essential to this reaction, since there was no conversion without methyl iodide.

Treatment of the 1-methyl isomer **1** with methyl iodide at 70° for 20 hr gave the 2-methyl isomer **2** together with the usual product, 1,4-dimethyl-5-phenyl-

(1) (a) To whom correspondence should be addressed: Department of Industrial Chemistry. (b) College of Liberal Arts and Sciences. (c) Department of Industrial Chemistry.

(2) R. A. Olofson, W. R. Thompson, and J. S. Michelman, *J. Amer. Chem. Soc.*, **86**, 1865 (1964).

(3) A. C. Rochat and R. A. Olofson, *Tetrahedron Lett.*, 3377 (1969).

(4) F. R. Benson, L. W. Hartzel, and W. L. Savell, *J. Amer. Chem. Soc.*, **73**, 4457 (1951).

(5) G. F. Duffin, J. D. Kendall, and H. R. J. Waddington, *Chem. Ind. (London)*, 1355 (1955).

(6) H. R. J. Waddington, G. F. Duffin, and J. D. Kendall, British Patent 785,334 (1957); *Chem. Abstr.*, **52**, 6030*i* (1958).

(7) S. Hunig and K.-H. Oette, *Justus Liebigs Ann. Chem.*, **641**, 94 (1961).

(8) E. K. Harville, C. W. Roberts, and R. M. Herbst, *J. Org. Chem.*, **15**, 58 (1950).

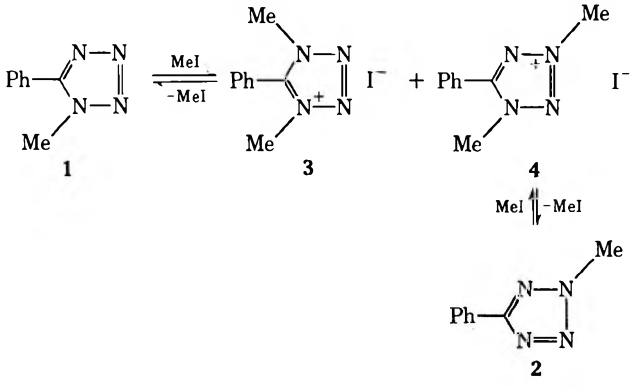
(9) R. Stolle, F. Pollecoff, and Fr. Henke-Stark, *Chem. Ber.*, **63**, 965 (1930).

tetrazolium iodide (**3**), in 27 and 35% yields, respectively. The structure of **3** was determined by the nmr spectrum, which had a singlet at δ 4.30 ppm indicating the equivalence of the two *N*-methyl protons. Thermal treatment of the 1,4-dimethyl salt **3** at 140° gave **1** in a quantitative yield.

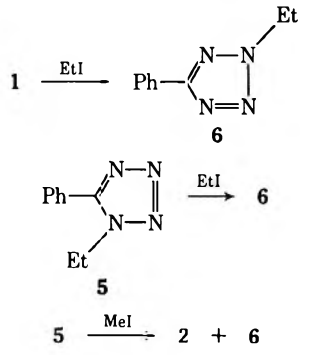
When a solution of the 1-methyl isomer **1** in methyl iodide was kept at room temperature for 90 days, there was obtained a small amount of the 2-methyl isomer **2** (6%) as well as a mixture (37%) of 1,4-dimethyl- (**3**) and 1,3-dimethyl-5-phenyltetrazolium iodide (**4**); 55% of **1** was recovered. Attempted separation of **4** from **3** was unsuccessful because of the thermal unstability of **4**. The nmr spectrum of the salts mixture showed three singlet peaks at δ 4.30, 4.54, and 4.76 ppm (78:11:11). The peak at δ 4.30 ppm was identified as the 1,4-dimethyl protons of **3**, and the other peaks at δ 4.54 and 4.76 ppm could be assigned to the 1-methyl and 3-methyl protons of **4**, respectively.[10-12] The ratio of **3** and **4** in the mixture was determined from the nmr spectrum (**3**:**4** = 78:22). Pyrolysis of the salt mixture (**3** and **4**) in refluxing toluene afforded the 1-methyl isomer **1** and the 2-methyl isomer **2** in a ratio of 76:24. This ratio is in accord with the ratio of **3** and **4** in the starting mixture, indicating the predominant formation of **2** from **4**, since the quantitative yield of **1** from the 1,4-dimethyl salt **3** was established.

These results suggest the following conclusions: (a) 1,3-dimethyl salt **4** is thermally less stable than 1,4-dimethyl salt **3** and decomposes at a temperature below 70°; (b) **4** is an intermediate in the formation of 2-methyl isomer **2** from 1-methyl isomer **1**: (c) on heating **4**, the 1-methyl group is preferentially eliminated to yield **2**.

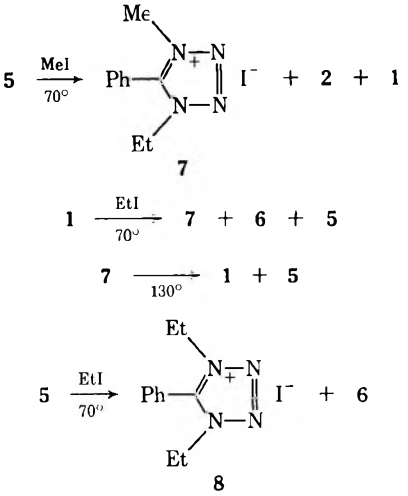
In the reaction of the 1-methyl isomer **1** with methyl iodide at 130°, the formation of **3** is reversible, and the net reaction leads to the 2-methyl isomer **2** by way of the 1,3-dimethyl salt **4**. The reaction of **2** with methyl iodide at 130° gives no **1**.



The same type of conversion was also studied on mixed alkyl systems. Treatment of 1-methyl- (**1**) or 1-ethyl-5-phenyltetrazole (**5**) with a large excess of ethyl iodide at 130° for 10 hr afforded the expected 2-ethyl-5-phenyltetrazole (**6**) quantitatively. Analogous treatment of the 1-ethyl isomer **5** with methyl iodide gave the 2-methyl isomer **2** (94%) together with a small amount of the 2-ethyl isomer **6** (6%).



When the reaction of the 1-ethyl isomer **5** with methyl iodide was carried out at 70° for 22 hr, 1-methyl-4-ethyl-5-phenyltetrazolium iodide (**7**) was obtained in 76% yield together with the 2-methyl isomer **2** (9.8%) and the 1-methyl isomer **1** (1.3%). The structure of **7** was elucidated by nmr and was also supported by the pyrolysis of **7**. On heating at 130°, **7** was decomposed completely within 40 min to give the 1-methyl isomer **1** and the 1-ethyl isomer **5** with a ratio of 16:84. The pyrolysis product contained no 2-alkyl isomer detected by nmr analysis. This indicated that both methyl and ethyl groups of **7** are attached to 1 and 4 nitrogen in the tetrazole ring, and methyl iodide was more easily eliminated than ethyl iodide. This tendency was consistent with the results in the thermal decomposition of pyrazolium[13] and indazolium halides.[14] Treatment of the 1-methyl isomer **1** with ethyl iodide at 70° afforded the 2-ethyl isomer **6** (52%) and the 1-ethyl isomer **5** (12.7%) together with a small amount of 1,4-dialkyl salt **7** (3.7%). The sharp contrast of the yields



of 1-methyl-4-ethyl salt **7** in the above alkylations of 1-alkyl-5-phenyltetrazole might be attributed to the different formation ratios of 1,4- *vs.* 1,3-dialkyl-5-phenyltetrazolium iodides. In the reaction of ethyl iodide with the 1-methyl isomer **1** or the 1-ethyl isomer **5**, the 1,3-diakyl salts might be formed in considerable yields and were decomposed to the 2-ethyl isomer **6**.

(10) The nmr assignments in the 1,3-dimethyl salt **4** are in accordance with those of the 1,3-dimethyltetrazolium salt[11] in which chemical shifts of 1- and 3-methyl protons were assigned to δ 4.60 and 4.80 ppm, respectively. As for the structure of the dimethyl salt assigned to **4**, a possibility of 1,2-dimethyl-5-phenyltetrazolium iodide could be excluded, since Henry, Finnegan, and Lieber reported no formation of 1,2-disubstituted derivative in the alkylation of 1- or 2-alkyl-5-aminotetrazole.[12]

(11) W. P. Norris and R. A. Henry, *Tetrahedron Lett.*, 1213 (1965).

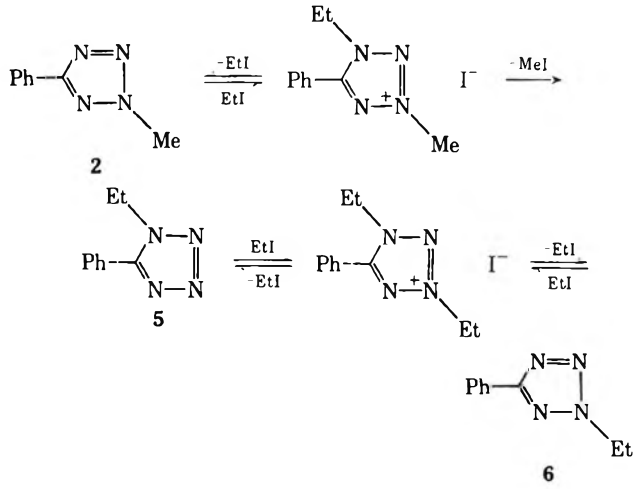
(12) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Amer. Chem. Soc.*, **76**, 2894 (1954).

(13) I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.*, **30**, 2942 (1960); *Chem. Abstr.*, **55**, 16519e (1961).

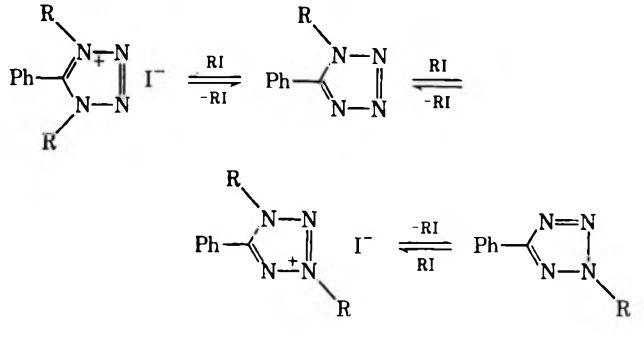
(14) K. V. Auwers and W. Pfuhl, *Chem. Ber.*, **58**, 1360 (1925); K. V. Auwers, H. Düsterdick, and H. Kleiner, *ibid.*, **61**, 100 (1928).

By contrast, in the reaction of **1** or **5** with methyl iodide at 70°, the 1,4-diakyl salt was formed in a greater proportion than the 1,3-dialkyl salt, which was suggested by the poorer yield of the 2-methyl isomer **2** and higher yield of the 1,4-dialkyl salt **3** or **7**.

Treatment of the 2-methyl isomer **2** with a large excess of ethyl iodide at 130° for 22 hr afforded the 2-ethyl isomer **6** in 16.8% yield. The converse reaction of **6** with methyl iodide at 130° for 13 hr gave **2** in 4.8% yield. These results suggest that 1,3-dialkyl-5-phenyltetrazolium iodide formed from the 2-alkyl isomer[11,12] decomposed under the reaction conditions to give a small amount of the 1-alkyl isomer as well as the 2-alkyl isomer, although thermal elimination of methyl iodide from 1,3-dimethyl-5-phenyltetrazolium iodide gives predominantly the 2-methyl isomer **2**. The 1-alkyl isomer formed *in situ* could be converted into another 2-alkyl isomer.



The overall isomerization processes from the 1-alkyl isomer into the 2-alkyl isomer have been shown to be reversible under the experimental condition at 130°, and the equilibria have favored the 2,5-disubstituted tetrazoles which are thermodynamically more stable than the 1,5 isomers.[15]



Experimental Section

Conversion of 1-Methyl-5-phenyltetrazole (1) into 2-Methyl-5-phenyltetrazole (2).—A solution of 1[16,17] (1.60 g) in methyl iodide (15 ml) was heated in a sealed glass tube at 130° for 10 hr. Evaporation of excess methyl iodide gave 1.59 g (100%) of crystalline **2**, mp 48.5° (lit.[18] mp 48–50°), identified by the nmr and mass spectra.[17]

Reaction of 1 with Methyl Iodide at 70°.—A solution of **1** (0.203 g) in methyl iodide (2 ml) was heated at 70° for 20 hr. The resultant mixture separated into two layers. The upper oily layer was washed with benzene and kept *in vacuo* to give 0.133 g (35%) of crystalline 1,4-dimethyl-5-phenyltetrazolium iodide (**3**): sintered at 128°, bubbled at 134°, and completely melted at 142°; nmr ($CDCl_3$) δ 4.30 (s, 6 H, 2 Me), 7.80 (m, 3 H, meta and para protons), 8.25 ppm (m, 2 H, ortho protons).

Anal. Calcd for $C_9H_{11}N_4I$: C, 35.78; H, 3.67; N, 18.54. Found: C, 35.64; H, 3.75; N, 18.23.

The lower layer and the benzene solution used for the washing of the oil were collected, and the solvents were removed *in vacuo* to give 0.115 g (57%) of crystals which consisted of 0.056 g (27%) of **2** and 0.059 g (30%) of **1** recovered. The ratio of **2** and **1** in the crystals was determined by integral ratio of the nmr spectrum at δ 4.38 and 4.18 ppm, respectively.[17]

Thermal Decomposition of 3.—The crystalline **3** (0.078 g) obtained in the above reaction was heated to reflux in xylene (5 ml). After 2 hr, all crystals of **3** were completely decomposed to be dissolved in xylene. Xylene was evaporated *in vacuo* to give 0.041 g (100%) of pale yellowish crystals identified as pure **1** by nmr spectrum.

Reaction of 1 with Methyl Iodide at Room Temperature.—A solution of **1** (0.127 g) in methyl iodide (10 ml) was allowed to stand at room temperature. After 90 days, a pale brownish oil was separated from the upper layer. The oil was washed with benzene, and the solvent was removed *in vacuo* at room temperature to give 0.088 g (37%) of crystals, whose nmr spectrum ($CDCl_3$) has three singlets at δ 4.30, 4.54, and 4.76 ppm (78:11:11). The distribution of **3** and **4** in the crystals was determined as 78:22. The upper layer and the benzene solution used for the washing of the oily product were collected, and the solvents were evaporated off *in vacuo* to give 0.077 g (61%) of crystals containing 0.008 g (6%) of **2** and 0.069 g (55%) of **1** recovered.

Thermal Decompositon of the Mixture of 3 and 4.—The mixture of **3** and **4** (0.100 g) obtained in the above reaction was heated in toluene for 18 hr. Insoluble solids, **3** and **4**, were completely decomposed to be dissolved in toluene. Evaporation of toluene *in vacuo* gave 0.053 g (100%) of pale yellowish crystals. The nmr spectrum showed that the product consisted of **1** and **2** in a ratio of 76:24.

Reaction of 1-Ethyl-5-phenyltetrazole (5) with Ethyl Iodide.—A solution of **5**[16,19] (0.2178 g) in ethyl iodide (3 ml) was heated at 130° for 10 hr. Evaporation of ethyl iodide gave 0.2316 g of brownish oil. To a methylene chloride solution of the product was added 0.001 g of charcoal. After filtration, methylene chloride was evaporated to give 0.2160 g (99%) of colorless liquid identified as 2-ethyl-5-phenyltetrazole (**6**). There was no detection of the starting ingredient **5** in the product by nmr analysis: bp 123° (5 mm); $n^{22}D$ 1.5536; nmr ($CDCl_3$) δ 1.68 (t, 3 H), 4.67 (q, 2 H), 7.50 (m, 3 H, meta and para protons), 8.15 ppm (m, 2 H, ortho protons); uv (EtOH) λ_{max} 239 nm (ϵ_{max} 15,800).

Anal. Calcd for $C_9H_{10}N_4$: C, 62.05; H, 5.79; N, 32.17. Found: C, 62.10; H, 5.66; N, 32.44.

Reaction of 5 with Ethyl Iodide at 70°.—A solution of **5** (0.0985 g) in ethyl iodide (3 ml) was heated at 70° for 24 hr. Evaporation of ethyl iodide gave 0.1043 g of crystals which were dissolved in 0.5 ml of acetone. To the acetone solution was added 10 ml of ether to precipitate the oily material which crystallized on standing. The ethereal solution was decanted and the residual colorless crystals (0.0146 g, 8.1%) were identified as 1,4-diethyl-5-phenyltetrazolium iodide (**8**): mp 154–155° (160° dec); nmr ($CDCl_3$) δ 1.73 (t, 6 H), 4.56 (q, 4 H), 7.76 (m, 3 H, meta and para protons), 8.25 ppm (m, 2 H ortho protons).

Anal. Calcd for $C_{11}H_{15}N_4I$: C, 40.02; H, 4.58; N, 16.97. Found: C, 40.20; H, 4.62; N, 17.14.

The ethereal solution was evaporated off to give 0.0898 g of pale yellowish crystals containing 0.0808 g (82.1%) of the starting ingredient **5** and 0.0090 g (9.1%) of isomerized **6**.

Reaction of 5 with Methyl Iodide.—A solution of **5** (0.1238 g) in methyl iodide (2 ml) was heated at 130° for 10 hr. Evaporation of methyl iodide gave 0.1172 g of long needles containing no ether-insoluble tetrazolium iodide. By nmr analysis, the composition of the product was found to be **2** (94%) and **6** (6%).

(15) W. S. McEwan and M. W. Rigg, *J. Amer. Chem. Soc.*, **73**, 4725 (1951); M. M. Williams, W. S. McEwan, and R. A. Henry, *J. Phys. Chem.*, **61**, 261 (1957).

(16) E. K. Harville, R. M. Herbst, and F. C. Sheiner, *J. Org. Chem.*, **15**, 662 (1950).

(17) R. R. Frazer and K. F. Haque, *Can. J. Chem.*, **46**, 2855 (1968).

(18) R. Huisgen, J. Sauer, and M. Seidel, *Chem. Ber.*, **94**, 2503 (1961).

(19) Mp 67–68° (lit.[16] mp 70–71°); nmr ($CDCl_3$) δ 1.55 (t, 3 H), 4.46 (q, 2 H), 7.64 and 7.67 ppm (d, 5 H); uv (EtOH) λ_{max} 231 nm (ϵ_{max} 10,900).

Reaction of 5 with Methyl Iodide at 70°.—A solution of **5** (0.1670 g) in methyl iodide (2 ml) was heated at 70°. When the reaction time was 3 hr, there was found a small amount of oily material as an upper layer, the amount of which increased as reaction time extended. After 22 hr of heating, methyl iodide was evaporated *in vacuo* to give an oily product which was dissolved in 0.5 ml of acetone. To the acetone solution was added 10 ml of ether to precipitate the oily material which crystallized on standing. The ethereal solution was decanted and the residual crystals (0.2308 g, 76.3%) were purified by the same additional procedure. The crystals were identified as 1-methyl-4-ethyl-5-phenyltetrazolium iodide (**7**): mp 118–119° (130° dec); nmr ($CDCl_3$) δ 1.83 (t, 3 H, CH_3CH_2), 4.29 (s, 3 H, CH_3), 4.58 (q, 2 H, CH_3CH_2), 7.70 (m, 3 H, meta and para protons), 8.24 ppm (m, 2 H, ortho protons).

Anal. Calcd for $C_{10}H_{13}N_4I$: C, 37.99; H, 4.15; N, 17.72. Found: C, 37.74; H, 4.07; N, 17.58.

The ethereal solutions were collected, and ether was evaporated off *in vacuo* to give 0.0393 g of liquid whose composition was determined by nmr analysis to be 0.0020 g (1.3%) of **1**, 0.0150 g (9.8%) of **2**, and 0.0173 g (10.3%) of **5**.

Thermal Decomposition of 7.—To 3 ml of benzene was added 0.0514 g of **7**, and the mixture in a sealed glass tube was kept at 130°. Upon heating for 40 min, the insoluble, molten **7** was decomposed completely to be dissolved in benzene. Evaporation of benzene gave 0.0277 g of liquid consisting of 0.0235 g (83%) of **5** and 0.0042 g (16%) of **1**.

Reaction of 1 with Ethyl Iodide.—A solution of **1** (0.0478 g) in ethyl iodide (2 ml) was heated at 130° for 10 hr. Evaporation of ethyl iodide gave 0.0520 g (100%) of pure **6**. Even a trace of **2** was not detected by nmr analysis.

Reaction of 1 with Ethyl Iodide at 70°.—A solution of **1** (0.1093 g) in ethyl iodide (2 ml) was heated in a sealed glass tube at 70°. Upon heating for 72 hr, a small amount of oily material was found in the reaction mixture. Evaporation of ethyl iodide gave 0.1201 g of yellowish liquid, which was dissolved in 0.5 ml of acetone. To the acetone solution was added 10 ml of ether to precipitate the oily material which crystallized on standing. The ethereal solution was decanted from the residual crystals (0.0079 g, 3.7%) which were identified as **7** by comparing the ir and nmr spectra with those of the authentic **7** prepared by the reaction of **5** with methyl iodide. The ethereal solution was evaporated *in vacuo* to give 0.1122 g of liquid which crystallized on standing. By nmr analysis, 0.0612 g (51.5%) of **6**, 0.0151 g (12.7%) of **5**, and 0.0359 g (30.5%) of **1** were found in the ether-soluble fraction.

Reaction of 2 with Ethyl Iodide.—A solution of **2** (0.1014 g) in ethyl iodide (2 ml) was heated at 130° for 22 hr. Evaporation of the solvent gave 0.1028 g of liquid containing 0.0834 g (83.1%) of **2** recovered and 0.0185 g (16.8%) of **6**.

Reaction of 6 with Methyl Iodide.—A solution of **6** (0.1080 g) in methyl iodide (2 ml) was heated at 130° for 13 hr. Evaporation of the solvent *in vacuo* gave 0.1101 g of liquid whose component was determined by nmr analysis to be **6** (95.2%) and **2** (4.8%).

Registry No.—**1**, 20743-50-4; **3**, 31818-92-5; **5**, 24433-71-4; **6**, 31818-94-7; **7**, 31818-95-8; **8**, 31818-96-9; methyl iodide, 74-88-4; ethyl iodide, 75-03-6.

Lactam Formation from the Condensation of Stilbenediamine with Glyoxal

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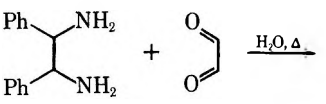
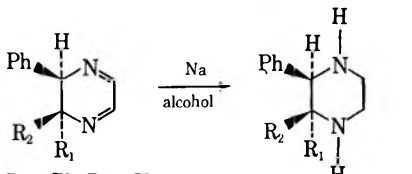
In 1941 Hayashi reported[1] that condensation of *dl*-stilbenediamine (**1**) with glyoxal yielded *trans*-2,3-diphenyl-2,3-dihydropyrazine (**2**) which on subsequent reduction with sodium and alcohol afforded *trans*-2,3-diphenylpiperazine (**3**). In a similar fashion *meso*-stilbenediamine (**4**) gave *cis*-2,3-diphenyl-2,3-dihydropyrazine (**5**) which in turn was readily reduced to *cis*-2,3-diphenylpiperazine (**6**).



1, *dl*
4, meso

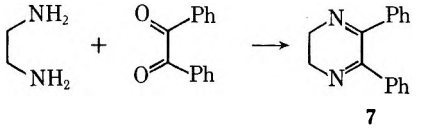


2, R_1 = Ph; R_2 = H
5, R_1 = H; R_2 = Ph

3, R_1 = Ph; R_2 = H
6, R_1 = H; R_2 = Ph

We now offer conclusive evidence that the original structural assignments for the condensation products **2** and **5** were incorrect and propose a plausible explanation for the formation of the observed products.

It has long been believed that 2,3-dihydropyrazines could be obtained by condensing α diketones with α,β-diamines;[2] for example, Mason[3] reported that heating benzil with ethylenediamine in alcoholic solution yielded 5,6-diphenyl-2,3-dihydropyrazine (**7**). Our experimental results confirmed the structure of this condensation product (**7**) as proposed by Mason. It was, therefore, of considerable interest to us to find that the product of the condensation of **1** with glyoxal di(sodium bisulfite) was *trans*-5,6-diphenylpiperazin-2-one (**8**) instead of the reported product **2**.



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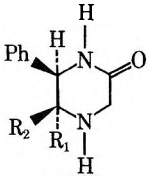


8, R_1 = Ph; R_2 = H
9, R_1 = H; R_2 = Ph

The presence of a lactam group in **8** was demonstrated by the ir spectrum, which displayed absorption bands at 1665 (C=O), 3180 (amide NH), and 3300 cm^{-1} (amine NH). The mass spectrum[4] showed a molecular ion at *m/e* 252 (rel intensity 30), indicating addition of glyoxal to stilbenediamine with the resulting loss of only 1 equiv mol of water. Fragment ions present at *m/e* (rel intensity) 147 (8), 146 (6), 118 (45), 106 (100), 104

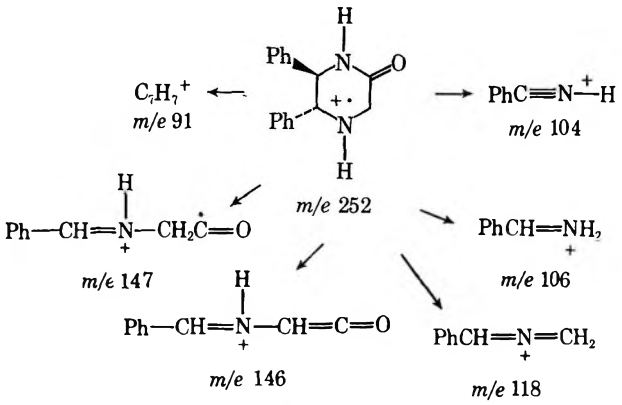
(1) T. Hayashi, *Sci. Pap. Inst. Phys. Chem. Res.*, **38**, 455 (1941); *Chem. Abstr.*, **41**, 5886 (1947).

(2) Y. T. Pratt, *Heterocycl. Compounds*, **6**, 412 (1957).

(3) A. T. Mason, *J. Chem. Soc.*, **55**, 97 (1889).

(4) Numbers following *m/e* values in the text refer to per cent relative abundance normalized to *m/e* 106 = 100%.

(13), and 91 (14) are compatible with structure **8** as shown in the following scheme.



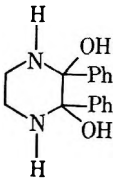
The nmr spectrum further substantiates the assigned structure **8**. The amine and amide protons appeared as broad singlets at 1.84 and 6.24 ppm, respectively, each integrating for one proton. A two-proton singlet at 3.77 ppm was assigned to the methylene group, while one-proton doublets at 3.78 and 4.54 ppm were ascribed to the methine protons adjacent to the amine and amide nitrogen atoms, respectively. The latter exhibited coupling constants of 9 cps, in agreement with axial–axial proton interactions[5] as required by structure **8**. The remaining ten aromatic protons resonate as a complex pattern between 6.8 and 7.4 ppm.

Condensation of **4** with glyoxal took the same unexpected route, yielding *cis*-5,6-diphenylpiperazin-2-one (**9**). Again, compound **9** had the same physical constants that Hayashi reported for *cis*-2,3-diphenyl-2,3-dihydropyrazine (**5**), but the spectral properties exhibited by **9** were similar to those of **8**. In the ir spectrum the lactam carbonyl appeared at 1675 cm^{-1}, the amine NH at 3290 cm^{-1}, and the amide NH at 3180 cm^{-1}. The mass spectral fragmentation pattern was identical with that obtained for **8**. The nmr spectrum displayed resonances at δ 1.79 (1 H, amine NH), 3.74 (2 H, $HNCH_2$), 4.51 (2 H, center of AB pattern,[6] J_{ax-eq} = 4 cps,[5] HCCH), 6.7–7.3 (10 H, HPh), 7.38 (1 H, amide NH).

(5) M. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 51.

(6) The low-field portion resonates as a triplet before D_2O exchange due to additional coupling (J = 4 cps) to the amide NH proton.

The product obtained (**7**) from the condensation of ethylenediamine and benzil could be formed either by sequential condensation and dehydration or by condensation to give **10**, followed by elimination of 2 mol of water. In the case of the condensation of **1** or **2**



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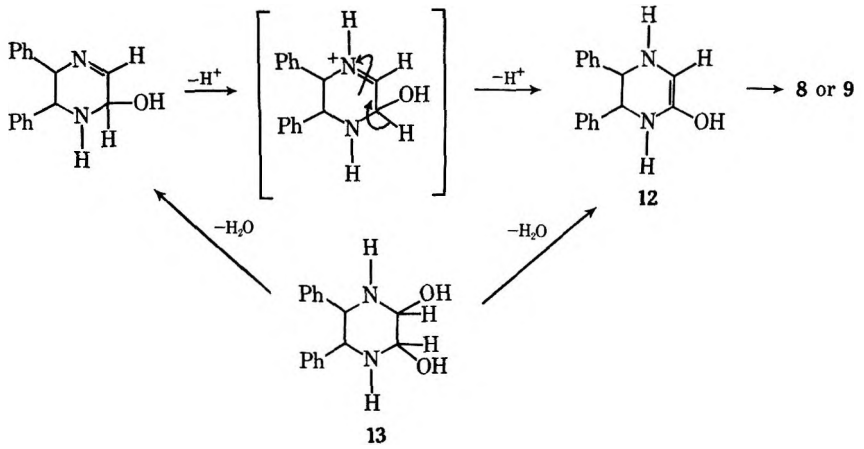
with glyoxal, the reaction may proceed through **11**, an imino alcohol intermediate, which by a protonation and deprotonation sequence could form **12**, the tautomeric form of the observed products **8** and **9**. The formation of the imino alcohol **11** could be envisioned by two different pathways. The first mechanism involves the self-condensation of the initially formed imino aldehyde, while the second pathway involves the formation of the dihydroxypiperazine **13** as an intermediate. Experimental data at hand does not exclude the possibility of direct dehydration of the latter to **12** instead of to **11**.



Experimental Section[7]

cis-5,6-Diphenylpiperazin-2-one.—To a warm solution of *meso*-stilbenediamine (5.0 g, 0.023 mol) in water (375 ml) was added glyoxal di(sodium bisulfite) (8.5 g, 0.032 mol) and the reaction mixture was kept at 70–80° on a water bath for 3 hr. The orange precipitate which formed was filtered, and the filtrate was treated with charcoal, filtered, and concentrated. The resulting solid was recrystallized from acetone–hexane, yielding 3.2 g (55%) of pure *cis*-5,6-diphenylpiperazin-2-one, mp 163.5–164.5° (reported for *cis*-2,3-diphenyl-2,3-dihydropyrazine, mp 163.5–164.5° [1]).

trans-5,6-Diphenylpiperazin-2-one.—To a hot solution of *dl*-stilbenediamine dihydrochloride (10.0 g, 0.035 mol) in water (350 ml) was added a hot solution of glyoxal di(sodium bisulfite) (10.0 g, 0.038 mol) in 2% aqueous HCl (250 ml). The reaction mixture was heated at 70–80° on a water bath for 3 hr, cooled, treated with charcoal, and filtered. The solvent was concentrated and the resulting solid was collected. The latter was treated with 30% aqueous potassium hydroxide to liberate the free base, which after recrystallization from benzene afforded

(7) Melting points were taken on a Thomas–Hoover apparatus and are uncorrected. Mass spectra were determined with a Model MS-902 mass spectrometer with a direct insertion probe and an ionizing current of 70 eV. Nmr spectra were determined in deuteriochloroform with a Varian A-60D spectrometer using tetramethylsilane as an internal standard. The ir scans were obtained with a Perkin-Elmer Model 225 spectrometer. No attempt was made to isolate or characterize the minor components in the reactions described.

5.3 g (60%) of the product, mp 202–203° (reported for *trans*-2,3-diphenyl-2,3-dihydropyrazine, mp 202–203° [1]).

Registry No.—1, 16635-95-3; 4, 951-87-1; 8, 31819-61-1; 9, 31819-62-2; glyoxal, 107-22-2.

Acknowledgments.—The authors wish to express their appreciation to Miss S. Swiatkowski for technical assistance and Dr. K. Doebel and Mr. R. Grulich for helpful discussions.

Pyridazines. XLII. Tetrazolo–Azido Isomerizations of Isomeric Pyridotetrazolo[1,5-*b*]pyridazines

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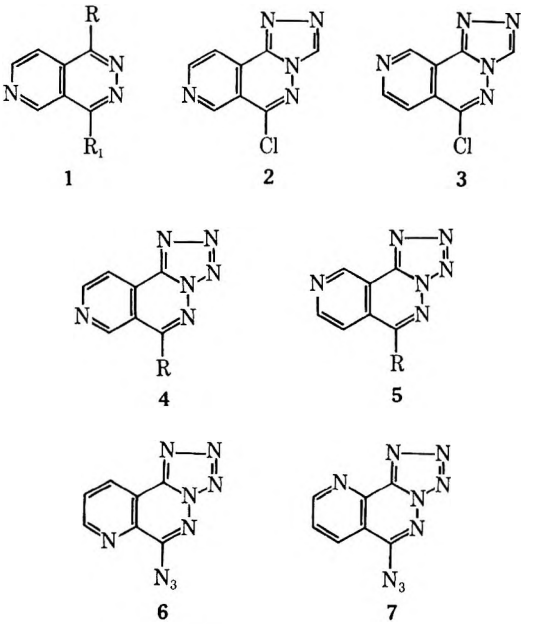
Our previous investigations on tetrazolo–azido isomerizations of several heterocyclic systems[1-3] prompted an investigation of this phenomenon on 6-azidopyrido[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**4**, R = N_3) and 6-azidopyrido[3,4-*d*]tetrazolo[1,5-*b*]pyridazine (**5**, R = N_3). The synthesis of both isomers was accomplished from the corresponding 1-chloro-4-hydrazinopyrido[3,4-*d*]pyridazine (**1**, R = Cl; R_1 = $NHNH_2$)[9] or its isomer (**1**, R = $NHNH_2$; R_1 = Cl) as starting compounds. These were converted either to the isomeric pyrido-*s*-triazolo[4,3-*b*]pyridazines (**2** and **3**) or into tetrazolo analogs **4** and **5** (R = Cl). Upon hydrazinolysis and subsequent nitrosation the isomeric azido compounds **4** and **5** (R = N_3) were obtained. Moreover, the isomer **4** (R = N_3) is obtainable in a direct synthetic approach from 1,4-dichloropyrido[3,4-*d*]pyridazine and sodium azide. The structures of both isomers were established by the nmr spectra. The singlet for H_{10} of compound **5** (R = N_3) appears at lower field than that for H_7 of compound **4** (R = N_3), as observed with similar polycyclic systems.[10,11] It was also observed that isomer **5** (R = N_3), when crystallized from ethanol, is transformed into the thermodynamically more stable isomer **4** (R = N_3).

In dimethyl sulfoxide-d_6 an equilibrium is established at 70°, consisting of about 33% of **5** (R = N_3) and 67% of **4** (R = N_3), whereas for the isomeric pair of 6-azidopyrido[3,2-*d*]tetrazolo[5,1-*b*]pyridazine (**6**) and 6-azidopyrido[2,3-*d*]tetrazolo[5,1-*b*]pyridazine (**7**)[1] the equilibrium mixture consisted of 42% of **6** and 58% of **7**. The determined enthalpy changes, ΔH, for these isomerizations, which follow first-order kinetics, were calculated as −2.2 kcal/mol for **5** → **4** (R = N_3) and −1.3 kcal/mol for **6** → **7**, respectively. The Arrhenius activation energies, E_a, calculated from the rate constants, are 25.2 kcal/mol (**5** → **4**, R = N_3) and 27.8 kcal/mol (**6** → **7**), respectively. As anticipated, they are somewhat higher than those observed with the corresponding azidotetrazolo[1,5-*b*]pyridazines,[1] whereas the enthalpy changes are lower. The calculated ΔS^* values were −2 eu for **5** → **4** (R = N_3) and −7 eu for **6** → **7**.



Experimental Section

Melting points were determined on a Kofler micro hot stage and are corrected. Infrared spectra were recorded on a Perkin-Elmer 137 Infracord as KBr disks, and nmr spectra were taken on a JEOL JNM-C-60HL spectrometer using tetramethylsilane as internal standard.

1-Chloro-4-hydrazinopyrido[3,4-*d*]pyridazine and 4-chloro-1-hydrazinopyrido[3,4-*d*]pyridazine were prepared according to Matsuura and Okui.[9] They formed the corresponding benzylidene derivatives: 1 (R = Cl; R_1 = NHN=CHPh), mp 283–284° (from EtOH and DMF, 3:1).

Anal. Calcd for $C_{14}H_{10}ClN_5$: C, 59.26; H, 3.55; N, 24.69. Found: C, 59.20; H, 3.46; N; 24.83.

The benzylidene derivative of the other isomer (**1**, R = NHN=CHPh; R_1 = Cl) had mp 252° (from EtOH and DMF, 3:1).

Anal. Calcd for $C_{14}H_{10}ClN_5$: C, 59.26; H, 3.55; N, 24.69. Found: C, 59.00; H, 3.41; N, 24.74.

6-Chloropyrido[3,4-*d*]-*s*-triazolo[4,3-*b*]pyridazine (3).—Compound 1 (R = Cl; R_1 = $NHNH_2$) (0.3 g) and diethoxymethyl acetate (1 ml) were gently heated until solution occurred and then boiled for 3 min. Upon cooling the separated product (0.26 g) was recrystallized from DMF and EtOH (1:3): mp 254° (it sublimes above 200°); nmr (DMSO-d_6) δ 9.52 (s, H_3), 8.28 (d, H_7), 9.25 (d, H_8), 9.88 (s, H_{10}), $J_{7,8}$ = 5.6 Hz.

Anal. Calcd for $C_8H_4ClN_5$: C, 46.73; H, 1.96; N, 34.07. Found: C, 46.45; H, 2.08; N, 34.33.

6-Chloropyrido[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (2).—The compound was prepared in the same way from compound 1 (R = $NHNH_2$; R_1 = Cl) (0.2 g) (yield 0.17 g): mp 260° (from EtOH and DMF, 1:3); nmr (DMSO-d_6) δ 9.50 (s, H_3), 9.40 (s, H_7), 9.25 (d, H_9), 8.45 (d, H_{10}), $J_{9,10}$ = 5.6 Hz.

Anal. Calcd for $C_8H_4ClN_5$: C, 46.73; H, 1.96; N, 34.07. Found: C, 47.10; H, 2.22; N, 34.26.

(1) B. Stanovnik and M. Tišler, *Tetrahedron*, **25**, 3313 (1969).
(2) A. Kovačič, B. Stanovnik, and M. Tišler, *J. Heterocycl. Chem.*, **5**, 351 (1968).
(3) B. Stanovnik, A. Krbavčič, and M. Tišler, *J. Org. Chem.*, **32**, 1139 (1967).
(4) A. Krbavčič, B. Stanovnik, and M. Tišler, *Croat. Chem. Acta*, **40**, 181 (1968).
(5) B. Stanovnik, M. Tišler, and P. Škufca, *J. Org. Chem.*, **33**, 2910 (1968).
(6) B. Stanovnik and M. Tišler, *Chimia*, **22**, 141 (1968).
(7) B. Stanovnik, M. Tišler, M. Ceglar, and V. Bah, *J. Org. Chem.*, **35**, 1138 (1970).
(8) A. Pollak, B. Stanovnik, and M. Tišler, *ibid.*, **35**, 2478 (1970).
(9) I. Matsuura and K. Okui, *Chem. Pharm. Bull. Jap.*, **17**, 2266 (1969).
(10) B. Stanovnik and M. Tišler, *Chimia*, **22**, 141 (1968).
(11) B. Stanovnik, M. Tišler, and P. Škufca, *J. Org. Chem.*, **33**, 2910 (1968).

6-Chloropyrido[3,4-*d*]tetrazolo[1,5-*b*]pyridazine (5, R = Cl).—An ice-cold solution of compound 1 (R = Cl; R_1 = $NHNH_2$) (0.5 g) in HCl (6 ml of 2 *N*) was treated under stirring with a cold aqueous solution of $NaNO_2$ (0.2 g in 3 ml of water). The product which separated was crystallized from EtOH (0.32 g): mp 177°; nmr ($CDCl_3$) δ 8.20 (d, H_7), 9.28 (d, H_8), 10.1 (s, H_{10}), $J_{7,8}$ = 6.0 Hz.

Anal. Calcd for $C_7H_3ClN_6$: C, 40.69; H, 1.46; N, 40.68. Found: C, 40.79; H, 1.83; N, 40.84.

6-Chloropyrido[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (4, R = Cl) was prepared as described above for 5 (R = Cl) in 75% yield: mp 184° (from EtOH); nmr ($CDCl_3$) δ 9.66 (s, H_7), 9.28 (d, H_9), 8.55 (d, H_{10}), $J_{9,10}$ = 5.7 Hz.

Anal. Calcd for $C_7H_3ClN_6$: C, 40.69; H, 1.46; N, 40.68. Found: C, 40.42; H, 1.62; N, 40.59.

6-Hydrazinopyrido[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (4, R = $NHNH_2$).—A mixture of 4 (R = Cl) (0.2 g), ethanol (5 ml), and hydrazine hydrate (1 ml of 80%) was heated under reflux for 15 min. The product was recrystallized from DMF and EtOH (3:1) (0.16 g), mp 290–293° dec.

Anal. Calcd for $C_7H_6N_8$: C, 41.58; H, 2.99; N, 55.43. Found: C, 41.90; H, 3.15; N, 55.49.

6-Hydrazinopyrido[3,4-*d*]tetrazolo[1,5-*b*]pyridazine (5, R = $NHNH_2$).—The compound was prepared as described above for the isomer 4 (R = $NHNH_2$) in 66% yield, mp 286–288° dec (from DMF and EtOH, 3:1).

Anal. Calcd for $C_7H_6N_8$: C, 41.58; H, 2.99; N, 55.43. Found: C, 41.35; H, 3.09; N, 55.09.

6-Azidopyrido[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (4, R = N_3).

A.—Compound 4 (R = $NHNH_2$) (0.2 g) was dissolved in HCl (4 ml of 2 *N*) and under stirring the ice-cold solution was treated with a cold solution of aqueous $NaNO_2$ (80 mg in 1 ml) dropwise, yield 0.16 g. For recrystallization the azide was dissolved in a minimum amount of EtOH at 40°, some charcoal was added, and, after stirring a few minutes at this temperature, the obtained filtrate was cooled to about −20° and the separated product was collected: mp 146–147°; ir 2155 cm^{-1} (N_3); nmr (DMSO-d_6) δ 9.46 (s, H_7), 9.37 (d, H_9), 8.53 (d, H_{10}), $J_{9,10}$ = 5.9 Hz.

Anal. Calcd for $C_7H_3N_9$: C, 39.44; H, 1.42; N, 59.14. Found: C, 39.31; H, 1.63; N, 59.24.

B.—A suspension of 1,4-dichloropyrido[3,4-*d*]pyridazine (1 g) and sodium azide (0.65 g) in ethanol (20 ml) was heated under reflux for 1 hr and evaporated then to half of the original volume. The residue was poured into ice (10 g) and the separated product (0.81 g) was collected. For analysis the compound was crystallized from ethanol, mp 146–147°. The compound was found to be identical in all respects with the product obtained as described under A.

6-Azidopyrido[3,4-*d*]tetrazolo[1,5-*b*]pyridazine (5, R = N_3).—This compound was prepared in a similar manner as described for the isomer 4 (R = N_3) under A, yield 83%, mp 163° (crystallization was performed as described above under A). If crystallization was attempted from boiling ethanol, the isomeric azide (4, R = N_3) was obtained. Also, when melted, upon solidification the isomer 4 (R = N_3) is formed: ir 2151 cm^{-1} (N_3); nmr (DMSO-d_6) δ 8.06 (d, H_7), 9.20 (d, H_8), 9.93 (s, H_{10}), $J_{7,8}$ = 5.7 Hz.

Anal. Calcd for $C_7H_3N_9$: C, 39.44; H, 1.42; N, 59.14. Found: C, 39.14; H, 1.68; N, 59.08.

Rate Constants and Equilibria.—For the determination of rate constants and equilibria measurements, nmr spectra of dimethyl sulfoxide-d_6 solutions were performed and the constants were calculated as described previously.[1]

For the system 5 → 4 (R = N_3) the values are as follows: ΔH = −2.2 ± 0.2 kcal/mol; rate constants, k_1 = 1.27 × 10^{-3} sec^{-1} (at 60°), k_2 = 3.45 × 10^{-3} sec^{-1} (at 80°); E_a = 25.2 ± 0.2 kcal/mol; ΔS = −2 eu.

For the system 6 → 7 the values are: ΔH = −1.3 ± 0.2 kcal/mol; rate constants, k_1 = 8.0 × 10^{-4} sec^{-1} (at 60°), k_2 = 1.39 × 10^{-3} sec^{-1} (at 70°), k_3 = 2.5 × 10^{-3} sec^{-1} (at 80°); E_a = 27.8 ± 0.2 kcal/mol; ΔS^* = +7 eu.

Registry No.—1 (R = Cl; R_1 = NHN=CHPh), 31767-04-1; 1 (R = NHN=CHPh; R_1 = Cl), 31767-05-2; 2, 31767-06-3; 3, 31767-07-4; 4 (R = Cl), 31767-08-5; 4 (R = $NHNH_2$), 31767-09-6; 4 (R = N_3), 31767-10-9; 5 (R = Cl), 31821-50-8; 5 (R = $NHNH_2$), 31767-11-0; 5 (R = N_3), 31767-12-1.

A New Synthesis of Alkyl Oximinoglyoxylates and the Corresponding Acid and Hydroximoyl Chlorides

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A number of syntheses of oximinoglyoxylate esters, $HON{=}CHCO_2R$, have been reported: the reaction of alkyl gloxylates[1] or the corresponding hemiacetal[2] or alkoxybromo esters[3] with hydroxylamine, the reaction of acetoacetic esters with nitrosylsulfuric acid,[4] and the alkylation of silver oximinoglyoxylate.[5] All these methods suffer from unavailability of starting materials or low overall yields.

Nitrile oxides, derived from hydroximoyl chlorides by treatment with base,[6] have been shown to be useful cross-linking agents for unsaturated polymers.[7] We have now discovered what appears to be a simple, direct synthesis of alkyl oximinoglyoxylates (I) and the corresponding hydroximoyl chlorides (II). The method involves the reaction of ketene with nitrosyl chloride, followed by treatment with excess alcohol to yield the oximino ester; chlorination then yields the hydroximoyl chloride. The conditions which ultimately

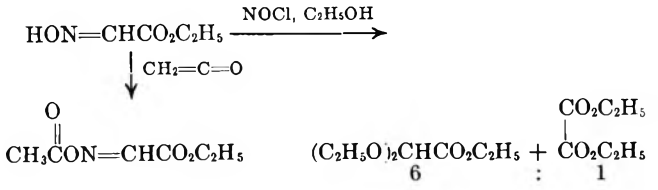
$$CH_2{=}C{=}O \xrightarrow[2.\ ROH]{1.\ NOCl} \underset{\mathbf{I}}{HON{=}CHCO_2R} \xrightarrow{Cl_2} \underset{\mathbf{II}}{\overset{Cl}{\overset{|}{HON{=}CCO_2R}}}$$

proved to be most successful for the preparation of oximinoglyoxylates consisted of first condensing a measured quantity of ketene in the desired solvent at −78°. One equivalent of nitrosyl chloride then was added slowly to the cold solution followed by an excess of alcohol. The reaction mixture was warmed to room temperature and stirred for several hours. Yields of 65–78% of methyl, ethyl, and *n*-butyl oximinoglyoxylates were obtained with this procedure. Both cis and trans isomers of the oximino esters were detected by gas chromatographic analysis. By-products in the ethyl system, which was studied most thoroughly, included diethyl oxalate, ethyl diethoxyacetate, hydrazine hydrochloride, and, probably, ethyl chloroacetate. All identifications except that of ethyl chloroacetate were firm and were made by comparison of purified samples with authentic materials, either commercially available or prepared by an independent route.

In order to obtain good yields of oximinoglyoxylates from the reaction of ketene, NOCl, and alcohols, several variables must be controlled carefully. First, the reaction temperature must be kept low, not only to prevent decomposition of the ketene–NOCl adduct but also to prevent ketene dimerization. Second, nitrosyl chloride

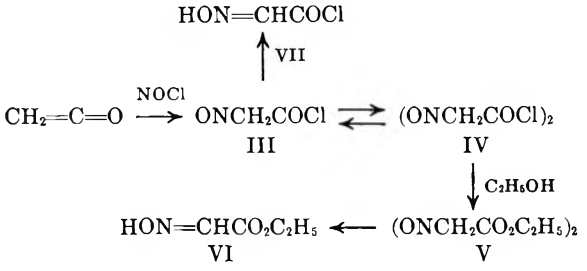
(1) L. J. Simon and G. Chavanne, *C. R. Acad. Sci.*, **143**, 904 (1906).
(2) L. W. Kissinger and H. E. Ungnade, *J. Org. Chem.*, **23**, 1517 (1958).
(3) L. A. Carpino, *ibid.*, **29**, 2820 (1964).
(4) L. Bouveault and A. Wahl, *Bull. Soc. Chim. Fr.*, **31** [3], 675 (1904).
(5) C. Cramer, *Ber.*, **25**, 713 (1892).
(6) H. Wieland, *ibid.*, **40**, 1667 (1907).
(7) D. S. Breslow, U. S. Patent 3,390,204 (1968).

must be added to ketene rather than *vice versa*. When addition was carried out in the reverse fashion, the yields of oximino esters decreased to less than 20% and the quantities of diethyl oxalate and ethyl diethoxyacetate increased markedly; several new by-products also appeared. Third, a 1:1 stoichiometry of ketene and nitrosyl chloride should be maintained as closely as possible, since both reactants have been demonstrated to react with the product. An excess of ketene is less harmful than an excess of NOCl, because it acylates the oxime rather slowly and will react with



the alcohol. Finally, an excess of alcohol is required; when a single equivalent was used, yields dropped to below 25%. Attempts to make the reaction stoichiometric in alcohol by the addition of an HCl acceptor (triethylamine, 2,6-lutidine, acrylonitrile,[8] Mg, Zn, or basic Al_2O_3) or to add the ketene–NOCl adduct to an equivalent of alcohol plus base did not improve the yields.

Evidence suggests that the reaction takes the following course.



Thus, when ketene and nitrosyl chloride are combined in methylene chloride at −80°, a blue solution, presumably due to monomeric nitrosoacetyl chloride (III), is first formed. The color fades rapidly and a white solid, postulated to be the dimeric nitrosoacetyl chloride (IV), precipitates.[9] Efforts to isolate IV failed owing to its instability at room temperature; an attempt at filtration resulted in ignition of the filter paper. Addition of ethanol to the solid, when formed in the absence of solvent, gave a second white solid which was relatively stable. Both the infrared and nmr spectra were consistent with the latter's formulation as the dimeric nitroso ester (V). The infrared spectrum showed neither –OH nor –C=N– absorption, but did exhibit carbonyl absorption at 5.68 μ. The nmr spectrum displayed resonances typical of an ethyl group and a sharp singlet (relative area 2.0) at δ 4.99 attributable to the methylene protons between the nitroso and carbonyl moieties. Even more significantly, when the solid was allowed to stand at temperatures above about −25°, it was slowly transformed into the oxime (VI). The half-life for this transformation was estimated to be several hours at 30° from an nmr experiment in which the rate of disappearance of the singlet at δ 4.99 and appearance of a singlet at δ 7.58, characteristic of the "vinylic" oxime C–H, was determined. Excess alcohol is necessary to favor esterification of nitrosoacetyl chloride (III or IV) over isomerization to oximinoglyoxylyl chloride (VII); VII never has been isolated, and probably polymerizes to $[-ON{=}CHCO-]_n$.[11]

Substitution of water for the alcohol gave oximinoglyoxylic acid in good yield. However, attempts to prepare the corresponding phenyl ester or di-*n*-butyl amide by substituting phenol or di-*n*-butylamine for the alcohol were unsuccessful.

Since aliphatic oximes can be converted into hydroximoyl chlorides by low-temperature chlorination in ether,[13] we attempted the one-step synthesis of ethyl 2-chlorooximinoglyoxylate (II, R = C_2H_5). Indeed, it was isolated in 60% yield when ketene, NOCl, ethanol, and chlorine were mixed at low temperature in the order given and in a ratio of 1:1:2:2. Although ethyl oximinoglyoxylate (I, R = C_2H_5) has been chlorinated with nitrosyl chloride in methylene chloride,[2] the excess alcohol required here interferes with the reaction, as already mentioned.

Experimental Section[14]

Ketene Generation and Measurement.—Ketene was generated by thermal cracking of acetone using a typical ketene lamp.[15] The resulting stream of ketene and by-product methane was passed through first a water condenser and then a cold trap maintained at −35° to remove entrained acetone. The amount of ketene produced per unit time was determined by passing the resulting gas stream into sodium hydroxide for 5.0 min and then titrating residual base. Above a ketene rate of *ca.* 1.5 mmol/min, significant quantities of ketene escaped from the sodium hydroxide solution.

In the experiments described below, the total amount of ketene used in a given experiment was determined by first measuring its rate of formation and then passing the gas stream into cold (−78°) solvent for a measured length of time. The ketene rate was usually redetermined after 0.5 or 1 hr; when it differed from the original rate, average values were used for the computation of the total amount of ketene. The gas stream exiting from the cold solvent was always conducted past a Dry Ice–acetone trap in an attempt to ensure that all of the ketene which passed into the flask would remain there. Measurements on the exit gas showed that no ketene escaped as long as the ketene input rate was less than *ca.* 1.5 mmol/min.

Preparation of Alkyl Oximinoglyoxylates (I) from Ketene, Nitrosyl Chloride, and Alcohol.—In a 250-ml, round-bottomed, three-necked flask equipped with a rubber septum, an adapter connected to a nitrogen manifold, and a Dry Ice–acetone condenser with a gas exit tube were placed a stir bar and 250 ml of methylene chloride. The flask was flushed with nitrogen and

(8) N. K. Bliznyuk, P. S. Khokhlov, R. V. Strel'tsov, Z. N. Kvasha, and A. F. Kolomiets, *J. Gen. Chem. USSR*, **37**, 1061 (1967).

(9) Monomeric nitroso compounds are reported to dimerize at −80° in preference to isomerization to oxime.[10]

(10) B. G. Gowenlock and W. Lüttke, *Quart. Rev. (London)*, **12**, 333 (1958).

(11) Oglobin and Kunovskaya[12] reacted ketene diethyl acetal with NOCl in ether and obtained a yellow solid without observing an intermediate blue solution. Although they postulated the formation of VI after hydrolysis, they isolated only the corresponding phenylhydrazone in low yield.

(12) K. A. Oglobin and D. M Kunovskaya, *J. Org. Chem. USSR*, **1**, 1741 (1965).

(13) G. Casnati and A. Ricca, *Tetrahedron Lett.*, 327 (1967).

(14) Infrared spectra were recorded using a Perkin-Elmer Model 137 Infracord. Proton nmr spectra were obtained using a Varian HA-60 spectrometer and were measured in deuteriochloroform solution using tetramethylsilane as an internal standard. Microanalyses were carried out by the Analytical Division of the Hercules Research Center.

(15) J. W. Williams and C. D. Hurd, *J. Org. Chem.*, **5**, 122 (1940).

cooled in a Dry Ice–acetone bath. The stopcock in the adapter was closed, and ketene gas was bubbled into the cold solvent for 90 min at a rate of 0.80 mmol/min using a needle inserted through the rubber septum. The total ketene input was 72 mmol. Nitrosyl chloride (1780 ml at 756 mm and 25°, 72 mmol, Matheson) was added to the cold solution in portions *via* a syringe during a 5-min interval; a green-blue color appeared, which gave way to a white solid. After a tenfold excess of anhydrous alcohol was added, the mixture was opened to nitrogen and stirred for 2 hr in the cold, then overnight at room temperature.

The methyl ester was isolated in 66% yield as a yellow solid by sublimation at 70° (0.2 mm). Resublimation gave a white solid, mp 53–55° (lit.[4] mp 55°), whose nmr spectrum agreed with the assigned structure (two singlets in a 3:1 ratio, the methyl protons at δ 3.87, and the oxime C–H at δ 7.58); it is rather surprising that only one of the two possible stereoisomers was observed.

The ethyl ester was isolated as a yellow oil by evaporation of the solvent. Analysis by gas chromatography on a 10-ft SE-30 column maintained at 130° (He flow 1.0 cc/sec, detector temperature 205°, injector temperature 220°) showed two peaks with retention times of 3.2 and 6.3 min; these were identical with those assigned to authentic cis and trans isomers, respectively, of ethyl oximinoglyoxylate. The material with the longer retention time was trapped; its infrared spectrum was identical with that of an authentic sample of ethyl oximinoglyoxylate prepared as described below. The yield was calculated to be 67% from the combined areas under the peaks of the two isomers. Two isomers of the *n*-butyl ester were isolated and identified in the same manner; the yield was calculated to be 70%.

Preparation of Authentic Samples of Ethyl and *n*-Butyl Oximinoglyoxylates.—A mixture of 5.0 g (54.4 mmol) of glyoxylic acid monohydrate (Aldrich), 25.0 ml of dry ethanol, and molecular sieves 4-A contained in a 100-ml round-bottomed flask equipped with a water condenser connected to a nitrogen manifold was refluxed under nitrogen for 16 hr. The mixture was cooled and, after 20 ml of additional ethanol was added, filtered. Evaporation of the filtrate gave 1.35 g of colorless liquid; this was redissolved in 30 ml of ethanol and treated with 920 mg (13.2 mmol) of hydroxylamine hydrochloride (Eastman) and 1.85 ml (13.2 mmol) of triethylamine (Eastman). The resulting mixture was stirred under nitrogen for 3 days at room temperature and filtered, and the fitrate was evaporated *in vacuo* to give a gummy solid. This was dissolved in 30 ml of water and the aqueous solution was extracted three times with 30-ml portions of ether. Evaporation of the combined, dried (Na_2SO_4) extracts gave a pale brown liquid which slowly crystallized. One recrystallization from an ether–hexane mixture gave 455 mg of white crystals, mp 34–35° (lit.[1] mp 35°). The nmr spectrum showed a singlet (relative area 1.00) at δ 7.58 assigned to the oxime C–H. A quartet (relative area 2.2) centered at δ 4.32 and a triplet (relative area 3.3) centered at δ 1.34 were attributed to the ethyl group protons.

n-Butyl glyoxylate[16] was reacted with hydroxylamine in a similar manner. Distillation gave a 56% yield of oximino ester, bp 77–82° (0.1 mm). The nmr spectrum showed a singlet (relative area 1.00) at δ 7.53 assigned to the oxime C–H. The remainder of the spectrum was comprised of a triplet (relative area 2.2) centered at δ 4.20, a multiplet (relative area 4.3) centered at *ca.* δ 1.5, and another triplet (relative area 3.2) centered at δ 0.87. These resonances were assigned to the methylene protons adjacent to oxygen, the internal methylene protons, and the methyl protons, respectively, of the butyl group.

Anal. Calcd for $C_6H_{11}NO_3$: C, 49.70; H, 7.64. Found: C, 49.86; H, 8.05.

Preparation of Oximinoglyoxylic Acid from Ketene, Nitrosyl Chloride, and Water.—Ketene (79.2 mmol) and nitrosyl chloride (79.2 mmol) were combined in 250 ml of dry tetrahydrofuran using a method similar to that described above. After water (1.0 mol) was added to the resulting black reaction mixture, it was stirred under nitrogen for 1 hr in the cold and then overnight at room temperature. Evaporation of the solvent using a rotary evaporator gave a black liquid which was placed on a watch glass and allowed to stand overnight while a nitrogen stream was directed onto it. The resulting orange solid was extracted four times with 100-ml portions of ether; evaporation of the combined, dried (Na_2SO_4) extracts gave 5.67 g of an orange solid. This was recrystallized once from an ether–hexane mixture to yield 4.73 g (67%) of light tan crystals, mp 137–140° (lit.[5] mp 140°). A mixture melting point of a sample prepared similarly and authentic HON=$CHCO_2H$ prepared using the procedure of Cramer[5] was undepressed. The X-ray powder diagrams of the two samples were identical.

Preparation of Ethyl Chlorooximinoglyoxylate from Ketene, Nitrosyl Chloride, Ethanol, and Chlorine.—In 120 ml of methylene chloride at −78° were combined 39.9 mmol of ketene and 38.0 mmol of nitrosyl chloride. After ethanol (76 mmol) was added and the resulting mixture was stirred for 15 min, chlorine gas [80 mmol = 1950 ml at 23° (760 mm)] was added *via* a syringe over a 10-min period. This mixture was stirred for 1 hr in the cold and then overnight at room temperature. Evaporation of the solvent gave 5.90 g of yellow solid which was recrystallized once from a 1:1 benzene–hexane mixture to give 2.94 g (52%) of while solid, mp 76–79° (lit.[17] mp 80°). The recrystallization filtrates yielded an additional 460 mg (8%) of ethyl chlorooximinoglyoxylate. The infrared spectrum of this material was identical with that of authentic ethyl chlorooximinoglyoxylate prepared by chlorination of ethyl oximinoglyoxylate. A mixture melting point of the two was undepressed.

Isolation of Ethyl Nitrosoacetate Dimer from Ketene, Nitrosyl Chloride, and Ethanol.—A 100-ml, round-bottomed, three-necked flask equipped with a rubber septum, an adapter connected to a nitrogen manifold, and a Dry Ice–acetone condenser with a gas exit tube was flushed with nitrogen and cooled in a Dry Ice–acetone bath. The stopcock on the adapter was closed, and ketene gas was bubbled into the empty flask for 45 min at a rate of 0.2 mmol/min using a needle inserted through the rubber septum. A small amount of ketene probably was not condensed, because its characteristic odor was noticed at the gas exit tube. Nitrosyl chloride [226 ml at 24° (754 mm)] was then added to the flask and a yellow solid deposited on the walls. After 10 min, 20 ml of dry ethanol was added, and a white solid rapidly replaced the yellow one. The resulting mixture was stored at −20° overnight and then filtered under nitrogen to give 401 mg of a white solid formulated as the dimeric nitroso ester (V). The infrared spectrum showed absorptions at 5.68, 6.99, 7.41, 8.01, 8.19, 8.60, 9.14, 9.70, 10.28, 11.27, 11.42, 12.60, and 13.30 μ.

The while solid was transformed into ethyl oximinoglyoxylate (identified by spectral comparison with an authentic sample) immediately upon addition of triethylamine and over a 3-day period upon standing at room temperature.

Reaction of Ethyl Oximinoglyoxylate with Nitrosyl Chloride in Ethanol.—In a 25-ml, round-bottomed, two-necked flask equipped with an adapter connected to a nitrogen manifold and a rubber septum were placed 154 mg (1.34 mmol) of ethyl oximinoglyoxylate and 10 ml of ethanol. To this solution cooled to *ca.* 0° in an ice–salt bath was added 1.34 mmol [33.0 ml at 26° (750 mm)] of nitrosyl chloride. The resulting mixture was stirred for 1 hr in the cold and then analyzed by gas chromatography on a 10-ft SE-30 column maintained at 124° (He flow 1 cc/sec, injector temperature 230°, detector temperature 250°). The peaks corresponding to the cis and trans isomers of ethyl oximinoglyoxylate had practically disappeared and were replaced by peaks in a 1:6 ratio with retention times of 5.4 and 9.4 min, respectively. The retention time of the former peak corresponded to that of authentic diethyl oxalate and that of the latter to ethyl diethoxyacetate. The latter identification was confirmed by trapping the material corresponding to this peak and comparing its infrared and nmr spectra with those of an authentic sample prepared as described by Bloch.[18] In another experiment, the material corresponding to the 5.4-min retention time peak was trapped and identified as ethyl oxalate by comparing its infrared and nmr spectra with those of a commercial sample.

Registry No.—I (R = Me), 31767-13-2; *cis*-I (R = Et), 31767-14-3; *trans*-I (R = Et), 31767-15-4; *cis*-I (R = Bu), 31767-16-5; *trans*-I (R = Bu), 31767-17-6; I (R = H), 3545-80-0; II (R = Et), 14337-43-0; V, 31760-16-4; ketene, 463-51-4; nitrosyl chloride, 2696-92-6.

(16) F. J. Wolf and J. Weijlard, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 124.

(17) G. S. Skinner, *J. Amer. Chem. Soc.*, **46**, 731 (1924).

(18) R. Bloch, *Ann. Chim. (Paris)*, [13] **10**, 583 (1965).

The Action of Hypochlorite on Sulfanilate

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The production of azobenzene-4,4′-disulfonate (**1**) by the action of chlorine on sulfanilate in aqueous sodium carbonate, observed by Tishchenko,[1] has been repeated with the use of commercial sodium hypochlorite solution. In this highly exothermic reaction a monochloroazobenzenedisulfonate (**2**) was formed as a by-product; when the temperature was held below 10° a phenazinedisulfonate (**3**) could also be isolated.

The sodium phenazinedisulfonate was readily extracted from the mixed azo salts (**1** with 10–15% of **2**) by 0.5 *M* sodium nitrate,[2] in which they are sparingly soluble, but the composition of this residual mixture was not appreciably changed by recrystallization or by chromatographic procedures. However, the triethylammonium salts proved to be separable; that of azobenzene-4,4′-disulfonic acid was isolated by repeated crystallization from methanol, that of its chloro analog **2** by taking advantage of its greater solubility in 1-butanol and acetone.

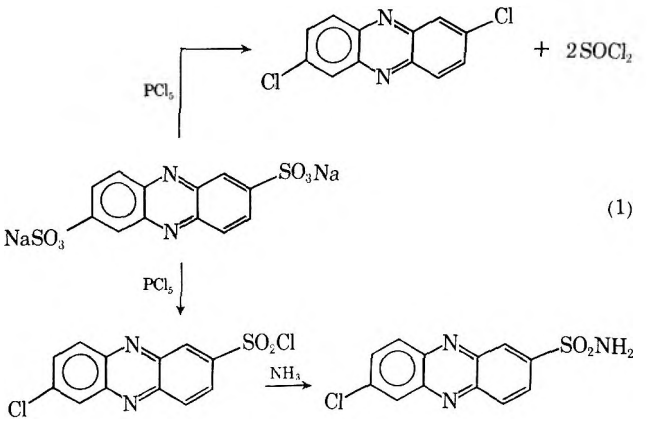
When samples of the mixed sodium azobenzenedisulfonates (**1** and **2**, freed of phenazinedisulfonate) were converted into disulfochlorides,[3,4] the products could be separated by crystallization from toluene, that from the monochloroazo compound being the more soluble.

As was to be expected, the chlorine atom in **2** was located in a position ortho to the azo group. This was supported by the infrared spectrum (in KCl) of the triethylammonium chloroazobenzenedisulfonate, which showed an absorption band at 730 cm^{-1}, not present in the corresponding chlorine-free salt; a strong band at the same wavelength was shown by 3-chloro-4-aminobenzene sulfonic acid and not by sulfanilic acid. The allocation was confirmed by synthetic evidence: oxidation of a mixture of potassium sulfanilate with 75% of an equimolar quantity of potassium 3-chloro-4-aminobenzenesulfonate with permanganate by the procedure of Laar[3] afforded a small yield of azodisulfonates containing 70% of the theoretical amount of chlorine; the disulfonanilide from this product, after purification, was shown by mixture melting point to be identical with a sample derived from the reaction of hypochlorite with sulfanilate alone.

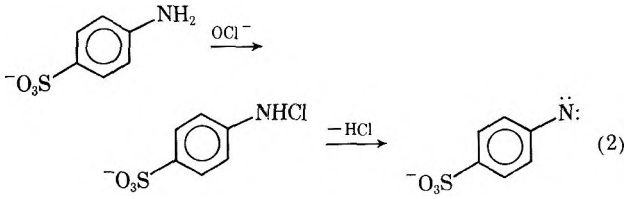
Introduction of chlorine from the hypochlorite into the carbon structure must have taken place prior to the formation of the azobenzenedisulfonic ion, for no reaction between sodium azobenzene-4,4′-disulfonate and hypochlorite could be detected, even at 25°.

The replacement of a sulfonic group by chlorine, reported in the case of benzenesulfonic acid by Meyer and Schlegel,[5] was observed to take place to a slight extent in the preparation of azobenzene-4,4′-disulfochloride, when 4-chloroazobenzene-4′-sulfochloride appeared as a more soluble by-product. The position entered by the chlorine atom was confirmed by reduction of the azo group in the corresponding sulfonanilide by stannous chloride, whereby *p*-chloroaniline, characterized as its acetyl derivative,[6] mp 178°, was obtained as the sole steam-volatile base.

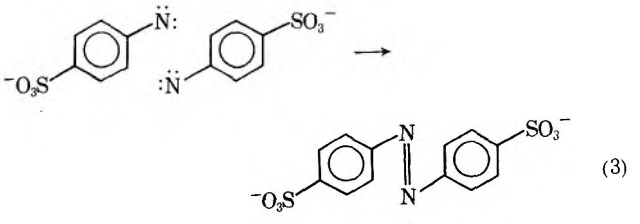
The sulfonate groups in the phenazine product **3** are in positions 2 and 7 as evidenced by the formation of the well-known 2,7-dichlorophenazine[7,8] upon treatment of the sodium salt of **3** with thionyl chloride and dimethyl formamide.[9] With phosphorus pentachloride, reaction takes place less rapidly; there is formed not only some dichlorophenazine, but also another toluene-soluble product, 2-chlorophenazine-7-sulfochloride, which on treatment with ammonia yields 2-chlorophenazine-7-sulfonamide (eq 1). Thionyl chloride was detected among the volatile components of the reaction mixture.



The reactions of sulfanilate with hypochlorite are attributable to transitory formation of nitrenes (eq 2).



The formation of azobenzenedisulfonate is pictured as a simple combination of two nitrene molecules (eq 3).



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(1) D. V. Tishchenko, *J. Russ. Phys. Chem. Soc.*, **60**, 153 (1928).

(2) 0.5 *M* sodium acetate extracts the phenazine derivative equally well, but is less readily removable by methanol.

(3) C. Laar, *J. Prakt. Chem.*, **20**, 242 (1879).

(4) C. Laar, *Ber.*, **14**, 1928 (1881).

(5) H. Meyer and K. Schlegl, *Monatsh. Chem.*, **34**, 56 (1913); H. Meyer, *ibid.*, **36**, 719 (1915).

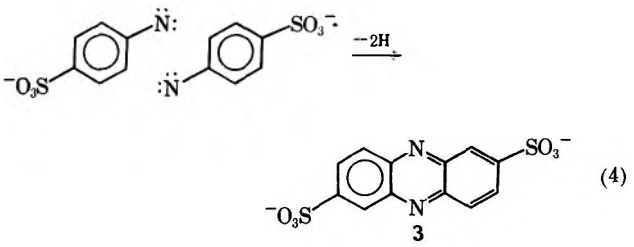
(6) N. V. Sidgwick and H. E. Rubie, *J. Chem. Soc.*, **119**, 1013 (1921).

(7) R. A. Abramovitch and B. A. Davis, *J. Chem. Soc. C*, 119 (1968); *J. Heterocycl. Chem.*, **5**, 793 (1968).

(8) The author is deeply indebted to Dr. Abramovitch for confirming the identity of this product, by means of its infrared spectrum, with a sample prepared in his laboratory by a different method.

(9) H. H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, **42**, 1653 (1959).

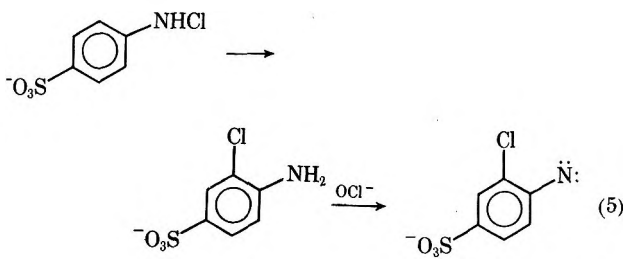
In the formation of phenazinedisulfonate, dehydrogenation is involved (eq 4). To account for the formation



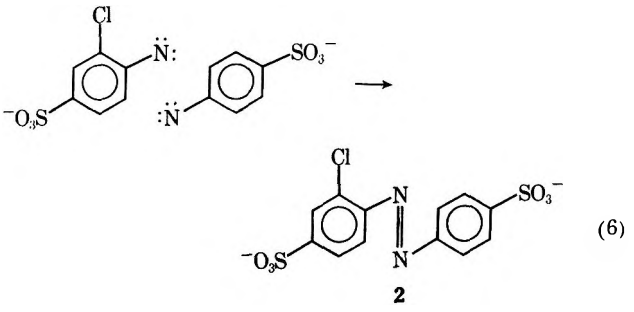
(4)

3

of the chloroazobenzenedisulfonate, migration of a chlorine atom from nitrogen to carbon (eq 5) would be followed by the coupling of the chlorinated nitrene with the chlorine-free species (eq 6).



(5)



(6)

2

Intermediary formation of nitrenes has recently been invoked to explain the mechanism of the deoxygenation of nitrosobenzene by ethyl phosphite.[10] Although reactions of this kind have not hitherto been postulated to take place in alkaline aqueous solution, their occurrence therein would be consistent with the experimental observations here reported.

Experimental Section

All melting points were observed in capillary tubes and with calibrated thermometers. In the early stages of the work the microanalyses were performed under the direction of Dr. S. M. Nagy at the Massachusetts Institute of Technology, later by the Scandinavian Microanalytical Laboratory and by the Galbraith Laboratories of Knoxville, Tenn.

Oxidation of Sulfanilate.—In a typical preparation a solution of 48 g (0.25 mol) of sulfanilic acid in 450 ml of water and enough sodium carbonate to bring the pH to 9 was chilled in an ice–salt bath. When the temperature had fallen to below 5°, 600 ml of commercial sodium hypochlorite solution (0.7 *M*, pH 12) was added dropwise, with mechanical stirring, during 2 hr, the reaction mixture being held at about 0°. The mixture was then left to stand at 3–5° for 20 hr and the orange-yellow crystals which had separated were collected, washed with small quantities of water and then with methanol, and dried (crop A, 5.9 g). The combined filtrates were concentrated under reduced pressure to 256 ml; the resulting suspension was chilled overnight at 3° and filtered. The pale brown, crystalline product was washed with 2 *M* $NaNO_3$ and then with methanol, and dried (crop B, 12.2 g). The mother liquor was concentrated to 150 ml, when NaCl had begun to separate. The solids were washed with 2 *M* $NaNO_3$ to remove NaCl, with 0.5 *M* $NaNO_3$, and then with methanol, and dried. The light red powder (25.6 g) was recrystallized from 300 ml of water, from which crop C (18.2 g) was obtained.

Silver Phenazine-2,7-disulfonate.—The first crystals collected (crop A) were washed with 0.5 *M* $NaNO_3$, but the washings yielded no phenazinedisulfonate. Crops B and C, washed with 0.5 *M* $NaNO_3$, yielded a dark solution which was concentrated to one-quarter volume and the resulting solid was washed with 2 *M* $NaNO_3$ and then with methanol, and dried (7.1 g). This product was almost completely soluble in 90 ml of 0.5 *M* $NaNO_3$; after treatment with decolorizing carbon the filtrate was acidified with 2 ml of 2 *M* HNO_3 and treated with an excess of silver nitrate solution. The canary-yellow precipitate of silver phenazinedisulfonate was washed with 0.05 *M* $AgNO_3$, then with 1:1 CH_3OH–H_2O, and dried *in vacuo* at 110°, yield 6.75 g (9.8%).

Anal. Calcd for $C_{12}H_6N_2O_6S_2Ag_2$: C, 26.0; H, 1.1; N, 5.1; S, 11.6; Ag, 39.0. Found: C, 26.1; H, 1.6; N, 5.0; S, 11.8; Ag, 38.8.

In pure water this salt forms a colloidal suspension which peptizes silver halides and passes through filter paper.

Triethylammonium Azobenzene-4,4′-disulfonate.—A portion of crop C, after being washed with $NaNO_3$ and methanol, was recrystallized from water and dried.

Anal. Found: C, 36.95; H, 2.15; Cl, 1.1; N, 7.1; S, 16.4. Calcd for $C_{12}H_7ClN_2O_6S_2Na_2$ + $8C_{12}H_8N_2O_6S_2Na_2$: C, 37.05; H, 2.08; Cl, 1.0; N, 7.2; S, 16.4. Calcd for $C_{12}H_7ClN_2O_6S_2Na_2$ + $7C_{12}H_8N_2O_6S_2Na_2$: C, 36.93; H, 2.02; Cl, 1.1; N, 7.2; S, 16.4.

The washed mixture of sodium salts crops A, B, and C was converted into the sparingly soluble calcium salts, which were then decomposed with aqueous triethylammonium carbonate. The filtrate was evaporated to dryness and the residue was repeatedly recrystallized from methanol until it melted sharply, without decomposition, at 242°. The pure salt forms flat orange-yellow prisms, readily soluble in cold methanol, markedly less so in ethanol, sparingly in propanols and butanols, and almost insoluble in acetone: uv $\lambda_{max}^{H_2O}$ 320 and 435 nm (E_{mol} 17,600 and 907, respectively).

Anal. Calcd for $C_{24}H_{40}N_4O_6S_2$: $(C_2H_5)_3N$, 37.2. Found: 36.6.

Stability of Sodium Azobenzene-4,4′-disulfonate toward Hypochlorite.—A solution of 6.5 g of the pure triethylammonium azobenzene-4,4′-disulfonate in water was decomposed with sodium carbonate and the liberated amine was volatilized under reduced pressure. The residue was diluted to 450 ml and treated with 50 ml of 0.7 *M* sodium hypochlorite at 25°. After 2 hr ammonia was added (to reduce hypochlorite). The solution was evaporated under reduced pressure at 30–35°, diluted to 500 ml, and acidified with acetic acid; to the clear solution 100 ml of 1 *M* calcium acetate was added. When cold, the crystalline calcium salt was washed with cold water and dried. The yield (4.5 g) was almost quantitative.

Anal. Calcd for $C_{12}H_8N_2O_6S_2Ca$: Ca, 10.5. Found: Ca, 10.4; Cl, 0.0.

Triethylammonium 2-Chloroazobenzene-4,4′-disulfonate.—The methanolic mother liquor from the triethylammonium azobenzene-4,4′-disulfonate was evaporated to dryness and the residue was washed with cold 1-butanol until the solvent extracted very little yellow color. The extract was evaporated to dryness under reduced pressure and the solids were washed with cold acetone until the washings were no deeper in color than a saturated solution of the pure triethylammonium azobenzene-4,4′-disulfonate in acetone. This filtrate was chilled overnight at 5°, decanted from a small amount of crystalline product, treated with charcoal, and allowed to evaporate spontaneously for 2 weeks at 5°, when fine yellow-orange needles (of the chlorine-free salt) and large, red rhombic prisms had deposited. The former were removed mechanically by gentle agitation with the mother liquor, decantation and filtration, the process being frequently repeated with the filtrates. The rhombs, which remained undisturbed, were selected manually and dried at 90°. They melted at 191° and were slightly more soluble than the chlorine-free salt in alcohols and acetone: uv $\lambda_{max}^{H_2O}$ 323 and 439 nm (E_{mol} 17,500 and 867, respectively).

(10) R. J. Sundberg, *J. Amer. Chem. Soc.*, **88**, 3781 (1966); R. J. Sundberg, R. H. Smith, Jr., and J. E. Bloor, *ibid.*, **91**, 3392 (1969); R. J. Sundberg and R. H. Smith, Jr., *J. Org. Chem.*, **36**, 295 (1971); R. J. Sundberg and C.-C. Lang, *ibid.*, **36**, 300 (1971).

Anal. Calcd for $C_{24}H_{39}ClN_4O_6S_2$: Cl, 6.1; N, 9.7; S, 11.1. Found: Cl, 6.1; N, 9.9; S, 10.9.

2-Chloroazobenzene-4,4′-disulfochloride.—Another preparation of sodium salts, similar to crop C, was converted into disulfochlorides by treatment with thionyl chloride and dimethylformamide[9] and the products were fractionally crystallized from toluene. The least soluble component was the expected azobenzene-4,4′-disulfochloride, mp 224°; on concentration the mother liquor yielded the 2-chloro derivative, slender needles from toluene, mp 174°, almost insoluble in cyclohexane.

Anal. Calcd for $C_{12}H_7Cl_3N_2O_4S_2$: Cl, 25.7; S, 15.5. Found: Cl, 25.6; S, 15.4.

4-Chloroazobenzene-4′-sulfochloride.—The mother liquor from the foregoing fraction was evaporated to dryness and the residue was washed with cyclohexane, which extracted a pale red product, fine needles, mp 127°.

Anal. Calcd for $C_{12}H_8Cl_2N_2O_2S$: C, 45.7; H, 2.5; Cl, 22.5; N, 8.9; S, 10.2. Found: C, 45.7; H, 2.5; Cl, 22.8; N, 8.8; S, 10.2.

4-Chloroazobenzene-4′-sulfonanilide.—Treatment of the above sulfochloride with aniline yielded the anilide, red-orange leaflets from methanol, mp 171°, readily soluble in acetone.

Anal. Calcd for $C_{18}H_{14}ClN_3O_2S$: C, 58.2; H, 3.8; Cl, 9.6; N, 11.3; S, 8.6. Found: C, 57.5; H, 3.7; Cl, 9.6; N, 11.4; S, 8.3.

The sodium derivative forms filamentous needles, almost insoluble in 0.05 *M* NaOH.

Replacement of One Sulfo Group in Azobenzene-4,4′-disulfochloride by Chlorine.—Pure azobenzene-4,4′-disulfochloride (3.8 g) in toluene (7 ml) was subjected under the usual conditions[9] to the action of thionyl chloride and dimethylformamide for 2 hr on the steam bath. When cool, the recovered crude starting material (3.36 g, mp 200–212°) was recrystallized from toluene, 2.65 g, mp 223°. The mother liquor was washed with water and treated with aniline; the product, purified through the sodium derivative and recrystallized, consisted of red-gold leaflets, mp 171°, 0.25 g.

Replacement of One Sulfo Group in Sodium Phenazine-2,7-disulfonate.—An intimate mixture of 6.7 g of sodium phenazinedisulfonate and 9.2 g of phosphorus pentachloride was heated in 15 ml of toluene under reflux on the steam bath for 23 hr. No gas was evolved in the reaction. The suspended solids were washed with 50 ml of toluene to extract yellow products and the combined filtrate was distilled at 25–30° under slightly reduced pressure. The presence of thionyl chloride in the distillate was demonstrated by mixing it with ice–water and aspirating the resulting sulfur dioxide into dilute permanganate, which was reduced with the formation of sulfate.

The residue from the distillation of the toluene washings was treated with concentrated aqueous ammonia; after 24 hr the mixture was shaken with dilute NaOH and the yellow washings were concentrated and acidified with acetic acid. The resulting colorless, amorphous precipitate of 2-chlorophenazine-7-sulfonamide, mp 303° with darkening, weighed 1.5 g after being washed with water and methanol. It was insoluble in water, 1-butanol, toluene, and acetic acid.

Anal. Calcd for $C_{12}H_8ClN_3O_2S$: N, 14.3; S, 10.9. Found: N, 14.3; S, 10.9.

The alkali-washed toluene solution was concentrated; the residue on recrystallization from toluene yielded 1.9 g of 2,7-dichlorophenazine, long, pale yellow needles, mp 266°, identical with the sole product (67% yield) obtained by treatment of sodium phenazinedisulfonate with thionyl chloride and dimethylformamide.

During the course of this study, many derivatives were prepared by standard methods, largely in a search for compounds which might be of aid in effecting the separation of chlorinated from unsubstituted azobenzenedisulfonates. Analyses and characterizations of these are outlined below.

Trimethylammonium azobenzene-4,4′-disulfonate was obtained as red-orange needles from ethanol, mp 267°.

Anal. Calcd for $C_{18}H_{28}N_4O_6S_2$: $(CH_3)_3N$, 25.7. Found: N, 26.1.

Pyridinium azobenzene-4,4′-disulfonate was obtained as orange needles from ethanol, mp 225°.

Anal. Calcd for $C_{22}H_{20}N_4O_6S_2$: N, 11.2. Found: N, 11.1.

Azobenzene-4,4′-disulfonamide was obtained as fine yellow needles or leaflets, appreciably soluble in acetone, almost insoluble in ethanol, insoluble in water, mp 322°, darkening only at the melting point. This compound is described in the literature as fairly readily soluble in alcohol, still solid at 300°,[11] also as charring above 250° without melting.[4]

Azobenzene-4,4′-di(sulfonyl-*N*-dimethylamine) was obtained as red-orange leaflets from dimethylformamide, mp 312°.

Anal. Calcd for $C_{16}H_{20}N_4O_4S_2$: N, 14.1. Found: N, 14.1.

Azobenzene-4,4′-di(sulfonyl-*N*-diethylamine) was obtained as long, flat, red-gold needles, mp 187° from acetone–ethanol.

Anal. Calcd for $C_{20}H_{28}N_4O_4S_2$: N, 12.4. Found: N, 12.9.

Azobenzene-4,4′-disulfonanilide was obtained as heavy red prisms from hot acetone, mp 264°, sparingly soluble in most organic liquids, insoluble in water, readily soluble in dilute alkali.

Anal. Calcd for $C_{24}H_{20}N_4O_4S_2$: N, 11.4; S, 13.0. Found: N, 11.2; S, 13.0.

Azobenzene-4,4′-di(sulfonyl-*N*-methylaniline) was obtained as long, pink needles from toluene, mp 221°.

Anal. Calcd for $C_{26}H_{24}N_4O_4S_2$: N, 10.8; Found: N, 10.7.

Barium 2-chloroazobenzene-4,4′-disulfonate was sparingly soluble in water.

Anal. Calcd for $C_{12}H_7ClN_2O_6S_2Ba$: C, 28.2; H, 1.4; Cl, 6.9; N, 5.5; S, 12.5; Ba, 26.9. Found: C, 28.2; H, 1.9; Cl, 7.1; N, 5.7; S, 11.9; Ba, 27.7.

2-Chloroazobenzene-4,4′-disulfonanilide was obtained as red needles from toluene, mp 216°, readily soluble in acetone.

Anal. Calcd for $C_{24}H_{19}ClN_4O_4S_2$: C, 54.8; H, 3.6; Cl, 6.7; N, 10.6; S, 12.2. Found: C, 55.4; H, 3.8; Cl, 6.5; N, 10.6; S, 12.2.

4-Chloroazobenzene-4′-sulfonyl-*N*-diethylamine was obtained as pale pink, slender needles from ethanol, mp 152°.

Anal. Calcd for $C_{16}H_{18}ClN_3O_2S$: C, 55.0; H, 4.6; Cl, 10.1; N, 12.0; S, 9.2. Found: C, 54.5; H, 5.2; Cl, 10.5; N, 11.9; S, 8.3.

4-Chloroazobenzene-4′-sulfonyl-*N*-methylaniline was obtained as pink prisms from acetone–methanol, mp 166°, sparingly soluble in methanol.

Anal. Calcd for $C_{19}H_{16}ClN_3O_2S$: C, 59.2; H, 4.2; Cl, 9.2; N, 10.9; S, 8.3. Found: C, 58.8; H, 4.2; Cl, 9.4; N, 10.8; S, 8.5.

Sodium Phenazine-2,7-disulfonate.—To aqueous suspensions of the silver salt, aqueous sodium chloride was added dropwise; at the equivalence point the suspended solids coagulated. Sodium carbonate solution was also effective. The filtrates, on concentration, yielded fine, pale yellow needles, readily soluble in water, sparingly in 2 *M* sodium acetate or nitrate, insoluble in methanol: uv $\lambda_{max}^{H_2O}$ (pH 1, 7, 14) 257 and 370 nm (E_{mol} 70,000 and 820, respectively).

Anal. Calcd for $C_{12}H_6N_2O_6S_2Na_2$: C, 37.6; H, 1.6; N, 7.3; S, 16.7; Na, 12.0. Found: C, 37.5; H, 1.6; N, 7.3; S, 16.8; Na, 12.0.

Potassium phenazine-2,7-disulfonate was obtained as stout prisms, containing $4H_2O$ (15%) lost at 110°.

Anal. Calcd for $C_{12}H_6N_2O_6S_2K_2$: N, 6.7; K, 18.8. Found: N, 6.7; K, 18.6.

Barium phenazine-2,7-disulfonate was a pale yellow compound whose solubility in water was 0.03% at 28°, 0.066% at 100°.

Anal. Calcd for $C_{12}H_6N_2O_6S_2Ba$: Ba, 28.8. Found: Ba, 28.4.

Triethylammonium phenazine-2,7-disulfonate was obtained as fine, pale yellow needles, mp 213°, readily soluble in methanol, less so in ethanol and 2-propanol.

Anal. Calcd for $C_{24}H_{38}N_4O_6S_2$: N, 10.3; S, 11.8. Found: N, 10.4; S, 11.8.

2-Chlorophenazine-7-sulfonanilide was obtained as light yellow leaflets from acetone, mp 215°; solution in dilute NaOH is deep orange.

Anal. Calcd for $C_{18}H_{12}ClN_3O_2S$: C, 58.6; H, 3.3; Cl, 9.6; N, 11.4; S, 8.7. Found: C, 58.4; H, 3.3; Cl, 9.5; N, 11.5; S, 8.7.

Registry No.—Hypochlorite, 14380-61-1; sulfanilate, 2906-34-5; silver phenazine-2,7-disulfonate, 31819-69-9; triethylammonium azobenzene-4,4′-disulfonate, 31819-70-2; calcium azobenzene-4,4′-disulfonate, 31819-71-3; triethylammonium 2-chloroazobenzene-4,4′-disulfonate, 31819-72-4; 2-chloroazobenzene-4,4′-disulfochloride, 31819-73-5; 4-chloroazobenzene-4′-sulfochloride, 31819-74-6; 4-chloroazobenzene-4′-sulfon-

(11) H. Limpricht, *Ber.*, **14**, 1356 (1881).

anilide, 31819-75-7; 2-chlorophenazine-7-sulfonamide, 31819-76-8; 2,7-dichlorophenazine, 3372-79-0; trimethylammonium azobenzene-4,4′-disulfonate, 3819-78-0; pyridinium azobenzene-4,4′-disulfonate, 31819-79-1; azobenzene-4,4′-di(sulfonyl-*N*-dimethylamine), 31819-80-4; azobenzene-4,4′-di(sulfonyl-*N*-diethylamine), 31819-81-5; azobenzene-4,4′-disulfonanilide, 31819-82-6; azobenzene-4,4′-di(sulfonyl-*N*-methylaniline), 31819-83-7; barium 2-chlorobenzene-4,4′-disulfonate, 31819-84-8; 2-chloroazobenzene-4,4′-disulfonanilide, 31815-05-1; 4-chloroazobenzene-4′-sulfonyl-*N*-diethylamine, 31815-06-2; 4-chloroazobenzene-4′-sulfonyl-*N*-methylaniline, 31815-07-3; sodium phenazine-2,7-disulfonate, 31815-08-4; potassium phenazine-2,7-disulfonate, 31815-09-5; barium phenazine-2,7-disulfonate, 31815-10-8; triethylammonium phenazine-2,7-disulfonate, 31815-11-9; 2-chlorophenazine-7-sulfonanilide, 31815-12-0.

Acknowledgment.—The author is grateful to Dr. J. S. Fruton for according him laboratory facilities in the Department of Biochemistry of Yale University during the early stages of this work and to the National Institutes of Health for a grant in support of the laboratory; to Dr. Sidney Farber for making it possible for this investigation to be completed in the Children's Cancer Research Foundation at the Children's Hospital Medical Center in Boston; to Dr. Johannes Meienhofer for the hospitality of his large Sephadex column and for advice in the interpretation of infrared spectra; to Mr. Roger Cavallo and Miss Kathleen Gould for uv and ir data; to Dr. Mervyn Israel for helpful advice relative to the organization of this report.

Photodifluoramination of Fluoromethane

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Photodifluoramination of alkanes with N_2F_4 at 253.7 nm involves the steps[1] shown in eq 1–5. When methane is subjected to this reaction, HCN is produced by unimolecular elimination of HF from chemically activated CH_3NF_2,[2] a system that has been used as an elimination chemical laser.[3] We report now the photodifluoramination of fluoromethane, a case which contrasts dramatically with that of methane.

$$N_2F_4 \longrightarrow 2NF_2 \quad (1)$$

$$NF_2 \xrightarrow{h\nu} NF + F \quad (2)$$

$$R\text{-}H + F \longrightarrow HF + R \quad (3)$$

$$R + NF_2(N_2F_4) \longrightarrow R - NF_2 \quad (4)$$

$$NF + NF_2 \longrightarrow N_2F_2 + F \quad (5)$$

Irradiation of an equimolar mixture of CH_3F and N_2F_4 in a Pyrex vessel for 30 min at a total initial pressure of 108 Torr gave the results summarized in eq 6.

$$\begin{array}{lll} & CH_3F + N_2F_4 \xrightarrow{253.7\ nm} & \\ \text{mmoles} & 2.18 \quad 2.23 & \\ & CH_3F + FCH_2NF_2 + (FCH_2)_2 + & \\ & 0.02 \quad 2.02 \quad 0.05 & \\ & N_2F_2 + SiF_4 + N_2O + N_2 & (6) \\ & 0.99 \quad 0.55 \quad 0.27 \quad 0.10 & \end{array}$$

The reaction was monitored by quantitative mass spectrometry. Products were separated by trap-to-trap distillation and the contents of each trap were examined by mass and infrared spectrometry and by gas chromatography.

During photodifluoramination of CH_4 under these reaction conditions, significant unimolecular elimination of HF occurs from CH_3NF_2 which is vibrationally excited. However, if the FCH_2NF_2 formed as described suffers any loss of HF at all, the amount of elimination must be several orders of magnitude lower than elimination from CH_3NF_2. Mass balances indicate that 94% of the carbon introduced as CH_3F is accounted for by FCH_2NF_2 and recovered CH_3F. We conclude therefore that $(k_2/k_1)_{FCH_2NF_2} \gg (k_2/k_1)_{CH_3NF_2}$.

$$CH_3 + NF_2(N_2F_4) \longrightarrow CH_3{}^*NF_2 \begin{cases} \xrightarrow[k_2]{M} CH_3NF_2 \\ \xrightarrow[k_1]{} HCN + 2HF \end{cases}$$

The remarkable effect produced by replacing one of the C–H bonds in the above system with a C–F bond may be due to the greater capacity of a C–F bond to store excess vibrational energy.[4,5] The presence of a C–F linkage also may increase the activation energy for HF elimination across the C–N bond of a difluoramine.[6]

Formation of FCH_2CH_2F is undoubtedly due to some coupling of the FCH_2 radical intermediates, the first time this process has been observed in the photodifluoramination reaction. The higher concentration of NF_2 and N_2F_4 relative to that of the alkyl radical (R) generated in step 3 generally makes step 4 much more important than dimerization of R.

Experimental Section[7]

Caution: Tetrafluorohydrazine and derivatives should be handled with care. Operations were conducted routinely behind shields.

Photodifluoramination of Fluoromethane.—In an apparatus described previously for the photodifluoramination of methane,[1] 2.18 mmol of fluoromethane (99.0%, Matheson) and 2.23 mmol

(1) C. L. Bumgardner, E. L. Lawton, K. M. McDaniel, and H. H. Carmichael, *J. Amer. Chem. Soc.*, **92**, 1311 (1970).

(2) C. L. Bumgardner, E. L. Lawton, and H. Carmichael, *Chem. Commun.*, 1079 (1968).

(3) T. D. Padrick and G. C. Pimentel, *J. Chem. Phys.*, **54**, 720 (1971).

(4) J. T. Bryant, B. Kirtman, and G. O. Pritchard, *J. Phys. Chem.*, **71**, 3439 (1967); D. Sianesi, G. Nelli, and R. Fontanelli, *Chem. Ind. (Milan)*, **40**, 619 (1968).

(5) J. A. Kerr, D. C. Phillips, and A. F. Trotman-Dickenson, *J. Chem. Soc.*, 1086 (1968).

(6) A. Maccoll, *Chem. Rev.*, **69**, 33 (1969).

(7) Proton nuclear magnetic resonance, fluorine nuclear magnetic resonance, infrared, and mass spectra were obtained using the following instruments, respectively: Varian HA-100 high-resolution spectrometer, Varian DA 60 high-resolution spectrometer, Beckman IR-5A spectrophotometer, and Consolidated Model 620 and Associated Electronics Model MS902 mass spectrometers. Nmr spectra were run as approximately 5% by volume solutions in deuteriochloroform with the probe temperature at 25°. Fluorine (^{19}F) chemical shifts (ϕ) are in parts per million relative to fluorotrichloromethane as an external reference. Proton (^1H) chemical shifts (δ) are in parts per million downfield relative to tetramethylsilane as an internal reference.

of N_2F_4 (99.3%)[8] were irradiated for 30 min at a total initial pressure of 108 Torr. The reaction mixture was then distilled in a vacuum line equipped with stopcocks and joints lubricated with Kel-F90 fluorocarbon grease. Further purification was achieved by gas phase chromatography using a 10 ft × 0.375 in. copper column containing 30% by weight of QF-1 on 60–80 mesh Chromosorb P, helium as carrier gas, and a thermal conductivity cell as detector. 1,2-Difluoroethane, N_2F_2,[9] N_2O, N_2, and SiF_4 were identified by comparison of infrared and mass spectra with those of authentic samples. The ^{19}F nmr spectrum of $F^aCH_2NF_2^b$ showed a triplet at ϕ 202.8 (F^a) and a signal at ϕ −27.6 (F^b) in the ratio of 1:2, respectively. In the ^1H nmr spectrum absorption occurred at δ 5.15 (doublet in triplet). The coupling constants, J_{F^aH} = 48 and J_{F^bH} = 22 Hz, agree with data on similar compounds.[1] Bands (cm^{-1}) in the infrared spectrum of FCH_2NF_2 were observed at 2950 (CH), 1130, 1125 (CF), and at 940, 935, 929, 860, 845 (NF_2). The mass spectrum showed peaks at m/e corresponding to 85 (parent), 46 (FCHN), 33 (FCH_2), 28 (CH_2N), and 27 (CHN). The results shown in eq 6 were obtained by quantitative mass spectral analyses using pure samples for calibration. The reaction was repeated twice at a total initial pressure of 108 Torr and twice at 216 Torr with similar product yields.

Registry No.—Fluoromethane, 593-53-3; N_2F_4, 10036-47-2.

Acknowledgment.—We are grateful to the National Science Foundation for generous support of this work and to the National Aeronautics and Space Agency for a fellowship for E. L. L.

(8) Kindly supplied by the Gorgas Laboratory, Rohm and Haas Co., Huntsville, Ala.

(9) Both *cis* and *trans* forms obtained: R. Ettinger, F. A. Johnson, and C. B. Colburn, *J. Chem. Phys.*, **34**, 2187 (1961); R. H. Sanborn, *ibid.*, **33**, 1855 (1969); S. King and J. Overend, *Spectrochim. Acta*, **22**, 689 (1966).

Side-Chain Amination during the Reaction of Methylbromothiophenes with Potassium Amide[1]

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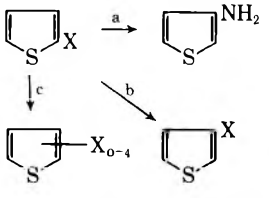
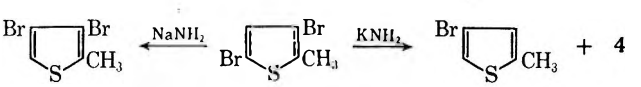
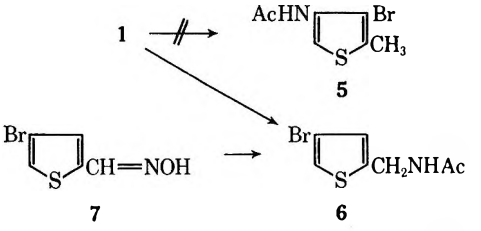
The reaction of α-bromo- and α-iodothiophenes with metal amides leads to cine amination (path a), halogen rearrangement (path b), and/or halogen disproportionation (path c) depending on the reaction conditions and the specific compounds involved.[2] This paper reports a fourth possible reaction of this system.



Although 2-methyl-3,5-dibromothiophene (**1**) reacts[3] with sodium amide according to path b (**1** → **2**), with potassium amide 2-methyl-4-bromothiophene (**3**) and an amine **4** (isolated as its acetamide **6**) are the only products obtained. Surprisingly, the spectral properties of this amide are inconsistent with those expected for a thienylacetamide such as **5** produced *via* path a and instead suggests the thenylacetamide structure **6**. This hypothesis was substantiated by the independent

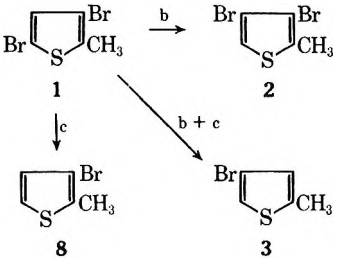




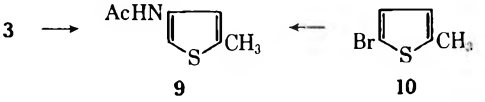
preparation of **6** from the oxime **7** of 4-bromothiophene-2-carboxaldehyde.[4]

The conversion of **1** to **4** probably involves paths b and c, side-chain bromination, and subsequent displacement of the resulting reactive[5] thenyl bromine by amide ion. In order to specify the sequence of the first three of these steps an attempt was made to intercept and/or test possible reaction intermediates.

At −60° the reaction of **1** with potassium amide gives as the major product **2** (path b) with minor amounts of **3** (paths b and c) and **8** (path c). Both **2** and **3** were treated with potassium amide at −33° followed by acetic anhydride to determine if any thenylamide **6** was formed. In the first case it was, while in the second



case it was not (85% recovery of **3**). The only amide found in this last reaction was the thienylacetamide **9**, formed by normal substitution. This same amide is the



only one obtained from the reaction of **10**[6] with potassium amide.[3]

(1) Abstracted in part from the Ph.D. dissertation of H. W. A., Texas Christian University, 1968.

(2) (a) M. G. Reinecke and H. W. Adickes, *J. Amer. Chem. Soc.*, **90**, 511 (1968); (b) M. G. Reinecke, *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, **14** (2), C68 (1968).

(3) M. G. Reinecke, H. W. Adickes, and C. Pyun, *J. Org. Chem.*, **36**, 2690 (1971).

(4) S. Gronowitz, P. Moses, A. Hornfeldt and R. Hakansson, *Ark. Kemi*, **17**, 165 (1961).

(5) S. Gronowitz, *Advan. Heterocycl. Chem.*, **1**, 88 (1963).

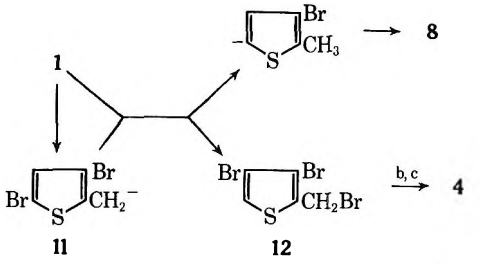
(6) The reported[7] preparation of **10** by the reaction of 2-methylthiophene with *N*-bromosuccinimide (NBS) has on occasion[3] proceeded well in our hands. On other occasions,[1] however, this procedure has led to extensive or even complete formation of 2-thenylbromide. This fickle nature of NBS is well known[8] and understood[9] but nevertheless difficult to control, at least in our hands. For this reason a reliable, alternative synthesis of **10** is described in the Experimental Section.

(7) K. D. Dittmer, R. P. Martin, W. Herz, and S. J. Cristol, *J. Amer. Chem. Soc.*, **71**, 1201 (1949).

(8) N. B. Chapman and J. F. A. Williams, *J. Chem. Soc.*, 5044 (1952).

(9) H. J. Dauben, Jr., and L. L. McCoy, *J. Amer. Chem. Soc.*, **81**, 4863 (1959).

These results suggest that side-chain bromination requires that more than one bromine atom be attached to the thiophene ring. A possible mechanism for this reaction which is consistent with this observation as well as our previous investigations[2] involves initial formation of a thenyl carbanion **11** in which the negative charge is partially stabilized by the cumulative inductive effects of the bromine atoms. This carbanion attacks a labile[10] α-bromine atom of a bromothiophene



such as **1** to generate thenyl bromide **12** and the dehalogenated thiophene **8**.

Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra were taken as films or KBr disks on a Beckman IR-10 or a Perkin-Elmer 237 instrument and were calibrated with a polystyrene film. Nmr spectra were obtained with a Varian A-60A instrument and calibrated with TMS as an internal reference. A Finnegan 1015SL quadrupole mass spectrometer was used for the mass spectrum determination. Gas chromatographic analysis was carried out on an Aerograph Autoprep A-700 using a 14 ft × 0.25 in. column of 20% DC QF-1 on Chromosorb W. Analyses were performed at M-H-W Laboratories, Garden City, Mich.

Reaction of 2-Methyl-3,5-dibromothiophene (1) with Potassium Amide.—Following the previously described procedure,[3] 5.2 g (0.02 mol) of **1** was treated with 0.12 mol of KNH_2 in 150 ml of liquid NH_3 for 15 min. After the usual work-up procedure,[3] the neutral fraction consisted of 0.5 g (14%) of 4-bromo-2-methylthiophene (**3**) identified by a comparison of its infrared spectrum with that of an authentic sample.[3] The basic fraction was acetylated and worked up as previously described[3] to give 0.71 g (15%) of the thenylacetamide **6**, mp 89–89.5°, whose infrared and nmr spectra were identical with those of a synthetic sample prepared as described below.

A vpc analysis of the neutral fraction from a similar reaction carried out at −60° showed the presence of starting material **1** (27%), 3,4-dibromo-2-methylthiophene (**2**) (24%), 4-bromo-2-methylthiophene (**3**) (5%), and 3-bromo-2-methylthiophene (**8**) (3%). Each of these products was identified by a comparison of its vpc retention time and spectral properties with those of authentic samples.[3]

4-Bromo-2-thiophenealdehyde Oxime (7).—The crude 4-bromo-2-thiophenealdehyde obtained from the reaction of 2.42 g (0.01 mol) of 2,4-dibromothiophene, 0.01 mol of BuLi in hexane, and 0.1 mol of DMF by the procedure of Gronowitz[4] was converted to 0.7 g (34%) of the oxime **7**: mp 150–151.5° (recrystallized from H_2O with the aid of Norit); ir 3200, 2870, 1645, 935, 900, 875, 830, 755 cm^{-1}.[11]

Anal. Calcd for C_5H_4BrNOS (**7**): C, 29.14; H, 1.96; N, 6.80. Found: C, 28.91; H, 1.90; N, 6.59.

2-Acetamidomethyl-4-bromothiophene (6).—A mixture of 0.21 g (0.001 mol) of **7**, 25 ml of ether, and 3 g (0.1 mol) of $LiAlH_4$ was heated under reflux for 2 hr. After destruction of the excess $LiAlH_4$ with wet ether the filtered solution was treated with 5 ml of acetic anhydride. Removal of the solvents on a rotary evaporator left a residue which was recrystallized from H_2O to give 0.11 g (47%) of **7**: mp 88.5–89°; nmr (CF_3COOH) τ 7.62 (s, 3, CH_3), 5.28 (d,[13] J = 5 Hz, 2, CH_2), 3.03 (m, 1, 5 H),[15] 2.86 (d, J = 1.8 Hz, 1, 3 H),[15] 1.50 (s, 1, NH); ir 3305, 1648, 1548, 825, 735 cm^{-1}.[11]

Anal. Calcd for C_7H_8BrNOS (**6**): C, 35.91; H, 3.44; N, 5.98. Found: C, 36.14; H, 3.60; N, 5.87.

Reaction of 3,4-Dibromo-2-methylthiophene (2) with Potassium Amide.—Following the previously described procedure,[3] 5.08 g (0.0197 mol) of **2** was treated with 0.039 mol of KNH_2 in liquid NH_3 at −33° for 15 min. The neutral fraction after work-up contained 2.8 g (55%) of recovered starting material, **2**, identified by its infrared spectrum. The acetylated basic fraction yielded 0.15 g (6%) of **6**, mp 88–89°, whose nmr and infrared spectrum were identical with those of authentic **6**.

Reaction of 4-Bromo-2-methylthiophene (3) with Potassium Amide.—One gram (0.00565 mol) of **3**[3] and 0.017 mol of KNH_2 were treated as above to give 0.85 g (85%) of recovered **3** in the neutral fraction. The acetylated basic fraction yielded a few milligrams of a white solid whose infrared spectrum was identical with that of **9** obtained as described below.

4-Acetamido-2-methylthiophene (9).—The acetylated basic fraction from the reaction of 2-bromo-5-methylthiophene (**10**) with potassium amide (reaction **1b** → **2b** in ref 3) contained a small amount (7%) of a tan, amorphous solid which after sublimation and crystallization from methanol–water gave white plates of **9**: mp 118–120°; nmr ($DCCl_3$) τ 7.90 (s, 3, CH_3CO), 7.60 (d, J = 1 Hz, 3, CH_3), 3.30 (m, 1, 5 H), 2.80 (d, J = 1 Hz, 1, 3 H); ir 3260, 1650, 820, 735 cm^{-1};[12] mass spectrum (70 eV) m/e (rel intensity) 155 (21), 113 (52), 112 (23), 80 (40), 45 (63), 43 (100), 39 (36), 28 (40), 15 (39).

Anal. Calcd for C_7H_9NOS (**9**): C, 54.16; H, 5.84; N, 9.03. Found: C, 54.38; H, 5.58; N, 8.82.

2-Bromo-5-methylthiophene (10).—To a solution of 7.3 g (0.075 mol) of 2-methylthiophene in 35 ml of dioxane was added 12 g (0.075 g-atom) of Br_2 in 75 ml of dioxane over a period of 1.5 hr. The reaction mixture was stirred at room temperature for an additional 5 hr and then treated with 400 ml of 10% $NaHCO_3$. The oily layer which separated was removed and the water layer was extracted with three 100-ml portions of ether. The combined oil and ether extracts were washed with two 50-ml portions of H_2O and dried (Na_2SO_4), and the ether was removed by distillation through a 40-cm Vigreux column. The residue was analyzed by vpc and the major product (84% yield) was identified as 2-bromo-5-methylthiophene (**10**), bp 68–69° (17 mm), by a comparison of its spectral properties with those of an authentic sample.[3,7]

Registry No.—**1**, 29421-73-6; **2**, 30319-01-8; **3**, 29421-92-9; **6**, 31767-00-7; **7**, 31767-01-8; **9**, 31767-02-9; **10**, 765-58-2; potassium amide, 17242-52-3.

Acknowledgment.—This research was generously supported by The Robert A. Welch Foundation and the Texas Christian University Research Foundation.

(10) P. Moses and S. Gronowitz, *Ark. Kemi*, **18**, 119 (1961).

(11) Although the region from 806–826 cm^{-1} is usually cited[12] as being characteristic of 2,4-disubstituted thiophenes, many such compounds also appear to have strong absorptions from 720 to 760 cm^{-1}.[1,3,12]

(12) S. Gronowitz, P. Moses, and A. Hornfeldt, *Ark. Kemi*, **71**, 237 (1961).

(13) This apparent doublet is also found in the nmr of the acetamide of the benzylamine (4.17 τ, J = 6 Hz in CCl_4) and is probably due to restricted rotation around the amide bond.[14]

(14) L. A. LaPlanche and M. T. Rogers, *J. Amer. Chem. Soc.*, **85**, 3728 (1963).

(15) A. R. Katritzky, "Physical Methods in Heterocyclic Chemistry," Vol. II, Academic Press, New York, N. Y., 1963, pp 117–121.

Boron Photochemistry. VIII. Oxidative Photocyclization of Anilinoboranes

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Received June 15, 1971

In a recent publication[1] we presented a novel photochemical synthetic route to the B-phenyl derivatives of

(1) P. J. Grisdale and J. L. R. Williams, *J. Org. Chem.*, **34**, 1675 (1969).

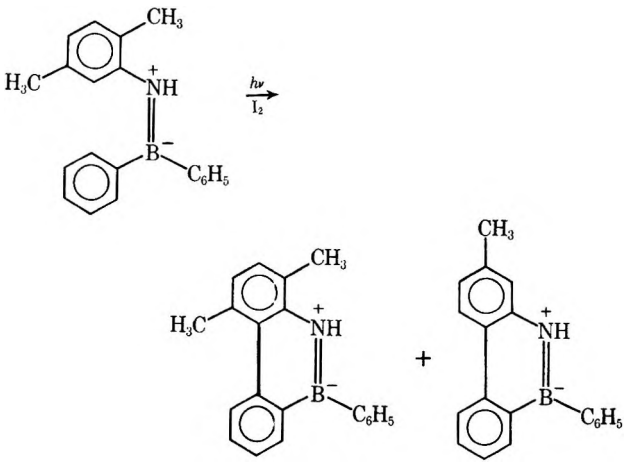
the borazaro-, boroxaro-, and borathiarophenanthrenes (**3**). The route for the photochemical and normal[2,3] syntheses of these heterocyclic phenanthrene systems is shown in Scheme I.

For simple unsubstituted boroxaro- and borazarophenanthrenes the photochemical route offers little advantage over the normal syntheses since the corresponding 2-hydroxy- and 2-aminobiphenyls (**4a**, **4b**) are readily available. For the borathiaro compound the photochemical route is preferable in that high yields of the desired compound **3c** are obtained. However, the great potential for the photochemical route to these systems is in its application to the synthesis of substituted derivatives. To date very few substituted derivatives of these systems have been reported, perhaps because of the experimental difficulties involved. As an example we can consider the borazarophenanthrene system. Two methods are available for the preparation of substituted derivatives: (a) electrophilic substitution in the nonheterocyclic rings[4,5] and (b) synthesis from a substituted 2-aminobiphenyl.[6] The former process yields a mixture of 6- and 8-substituted isomers together with some 6,8-disubstituted derivatives; the separation of these products is tedious and time-consuming. The latter process involves the synthesis of the corresponding substituted 2-aminobiphenyls which, in most cases, is very laborious. The photochemical approach outlined in Scheme II largely overcomes these problems.

The conversion of the R-substituted 2-iodoaniline (**5a**) to the R-substituted 10-phenyl-10,9-borazarophenanthrene (**7**) represents an extension of our previous findings. Since many 2-iodoanilines are easily prepared, this procedure offers an attractive route to the substituted heterocyclic compounds **7**. We have now discovered that the substituted anilines **5b**, when converted to the aminoboranes **6b**, can be oxidatively photocyclized in the presence of elemental iodine to furnish the derivatives **7** in moderate yield. This is analogous to the oxidative photocyclization of stilbene and other ethylenes,[7] but the ready availability of the aminoboranes **6b** makes this a very desirable procedure to obtain the borazarophenanthrene system substituted in the nitrogen-bearing ring.

Table I indicates the scope of the reaction. Included are yields determined from spectral data and of isolated analytical samples. The reaction can be applied to a large number of anilines substituted with either electron-donating or electron-withdrawing substituents. The reaction failed completely only in the case of *m*-nitro- and *p*-nitroanilines. The mass spectrum of the end product resulting from acetanilide indicated the presence of the unsubstituted compound which would result from aniline itself. This could result from deacetylation before or after the photocyclization step. Attempts to substitute strongly electron-withdrawing groups on nitrogen in borazarophenanthrenes have failed previously also.[8]

The position of a single substituent in the aniline has little effect on the yield. In the case of the meta-substituted anilines, two isomeric borazarophenanthrenes could be formed (the 5- and 7-substituted derivatives). We observed only one product in such cases, and steric effects would very much favor cyclization to yield the 7 isomer. In addition, we have good evidence from the cyclization of the dimethylanilines to indicate that this is so. Photocyclization of the aminoborane derived from 2,5-dimethylaniline and diphenylboron chloride yields a mixture of mono- and dimethyl heterocyclic compounds in approximately equal amounts. The



cleavage of a C–C bond leading to demethylation competes favorably with the formation of the sterically hindered 5,8-dimethyl derivative. In the case of 3,5-dimethylaniline we were unable to isolate a sample of the heterocycle for analysis, but mass spectral data on the crude mixture indicated the presence of the dimethylborazarophenanthrene. The positioning of a substituent in the 5 position is very unfavorable sterically, hence the reduced yield. The reaction involving 2,6-dimethylaniline yields the 8-methylborazarophenanthrene with elimination of a methyl group, although in this case there is no alternative route. Such eliminations have been observed in other oxidative photocyclization reactions.[9]

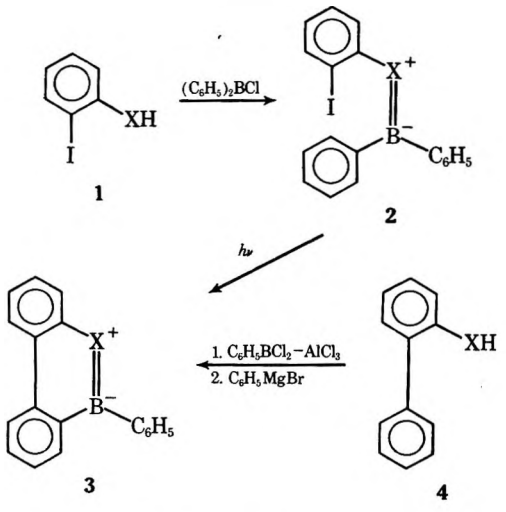
The *o*-bromoaniline also yields a mixture of borazarophenanthrenes, the unsubstituted derivative, and the 8-bromo compound. These probably result from competition between an oxidative photocyclization and one involving elimination of HBr, analogous to the case of *o*-iodoaniline.[1] In other radical reactions of halo-substituted benzenes, similar reactivity is observed for chloro, bromo, and iodo compounds.[10]

The amines which presented problems are listed in Table II with supporting data and comments.

All of the compounds listed in Table I had satisfactory mass spectral and nmr data. Their solutions all showed the typical ultraviolet spectrum of the borazarophenanthrene system with the two long-wavelength bands separated by about 15 nm. The majority had the long-wavelength band between 330 and 336 nm, but, for the 6-methoxy and 8-carbethoxy compounds, the band occurred at 345 and 347 nm, respectively.

(2) M. J. S. Dewar, V. P. Kubba and R. Pettit, *J. Chem. Soc.*, 3073 (1958).
(3) M. J. S. Dewar and V. P. Kubba, *J. Org. Chem.*, **25**, 1722 (1960).
(4) M. J. S. Dewar and V. P. Kubba, *Tetrahedron*, **7**, 213 (1959).
(5) M. J. S. Dewar and V. P. Kubba, *J. Org. Chem.*, **25**, 1722 (1960).
(6) M. J. S. Dewar and P. J. Grisdale, *ibid.*, **28**, 1759 (1963).
(7) E. V. Blackburn and C. J. Timmons, *Quart. Rev. (London)*, **23**, 482 (1969).
(8) M. J. S. Dewar and P. M. Maitlis, *Tetrahedron*, **15**, 35 (1961).
(9) K. L. Servis and K. N. Fang, *Tetrahedron Lett.*, No. 8, 967 (1968).
(10) J. T. Pinhey and R. D. G. Rigby, *ibid.*, **16**, 1267 (1969).

SCHEME I



SCHEME II

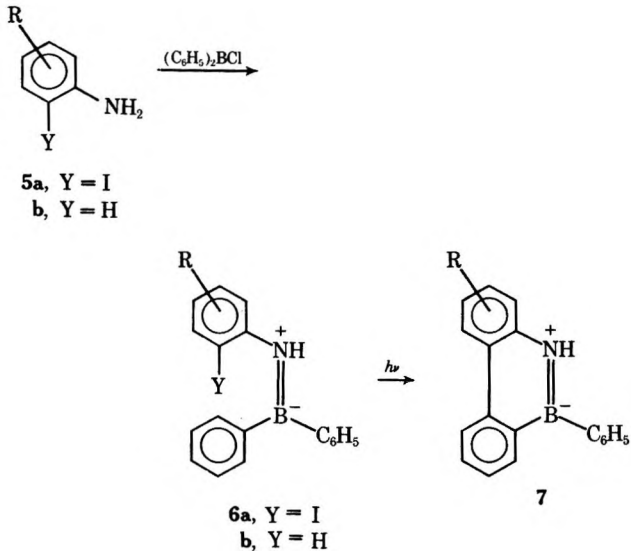
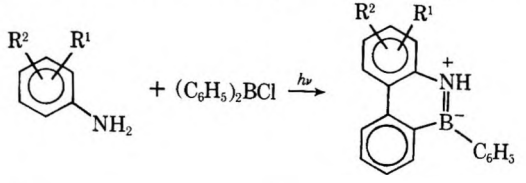


TABLE I.—DATA FOR THE SUBSTITUTED 10-PHENYL-10,9-BORAZAROPHENANTHRENES FROM THE REACTION



Substitution in aniline	Substitution in product	Registry no.	Yield, % (spectral)	Yield, % (isolated)	λ_{max}, nm	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % B	Calcd, % N	Calcd, % Hal	Found, % C	Found, % H	Found, % B	Found, % N	Found, % Hal
2-Methoxy	8-Methoxy	31899-13-5	21	20	330	119–120	$C_{19}H_{16}BNO$	80.1	5.6	3.8	4.9		79.8	5.9	3.7	4.8	
3-Methoxy	7-Methoxy	31896-40-9	20	14	334	165–166	$C_{19}H_{16}BNO$						79.6	5.6	3.7	4.8	
4-Methoxy	6-Methoxy	31896-41-0	18	10	345	92–94	$C_{19}H_{16}BNO$						80.0	5.7	3.6	5.1	
2,3-Dimethyl	7,8-Dimethyl	31899-16-8	20	18	332	130–131	$C_{20}H_{18}BN$	84.9	6.3	3.8	4.9						
2,4-Dimethyl	6,8-Dimethyl	31899-17-9	29	27	336	136–138	$C_{20}H_{18}BN$						84.6	6.5	3.7	5.2	
N-Methyl	*N*-Methyl	31899-18-0	20	18	329	123–125	$C_{19}H_{16}BN$	84.8	6.0	4.0	5.2		84.5	6.1	3.9	5.1	
2-Methyl	8-Methyl	31899-19-1	55	33	331	94–96	$C_{19}H_{16}BN$						84.6	6.3	3.8	5.1	
3-Methyl	7-Methyl	31896-46-5	52	33	332	114–117	$C_{19}H_{16}BN$						84.6	6.3	3.8	4.8	
4-Methyl	6-Methyl	31899-20-4	38	30	337	117–119	$C_{19}H_{16}BN$						84.6	6.4	4.0	5.1	
None	None	19091-94-2	40	30	329	107–110	$C_{18}H_{14}BN$										
2-Chloro	8-Chloro	31896-49-8	29	20	329	109–111	$C_{18}H_{13}BClN$	74.7	4.5	3.7	4.8	12.3	74.8	4.7	3.6	5.0	11.8
3-Chloro	7-Chloro	31896-50-1	26	17	330	123–126	$C_{18}H_{13}BClN$						74.7	4.8		5.0	12.0
4-Chloro	6-Chloro	31896-51-2	29	15	336	104–106	$C_{18}H_{13}BClN$						74.5	4.8		4.9	12.3
4-Bromo	6-Bromo	31899-25-9		4	337	91–93	$C_{18}H_{13}BBrN$	64.7	3.9	3.2	4.2	23.9	64.9	3.1	3.1	4.4	23.9
2-Carbethoxy	8-Carbethoxy	31899-26-0		24	357	136–138	$C_{21}H_{18}BNO_2$	77.1	5.5	3.3	4.3		77.4	5.8	3.3	4.4	
4-Cyano	6-Cyano	31896-54-5	18	16	331	191–192	$C_{19}H_{13}BN_2$	81.5	4.6	3.9	10.0			5.0	3.9	9.6	

TABLE II

GLC/MASS SPECTRAL ANALYSES FOR PRODUCTS FROM THE PHOTOCYCLIZATION

Substitution in aniline	10-Phenyl-10,9-borazarophenanthrenes (*m/e* values)
N-Acetyl	Unsubstituted[a] (255)
2-Bromo	Unsubstituted[a] (255) + 8-bromo (333)
2,5-Dimethyl	7-Methyl[a] (269) + 5,8-dimethyl (283)
2,6-Dimethyl	8-Methyl[b,c] (269)
3,5-Dimethyl	5,7-Dimethyl (283)

[a] These compounds had identical uv spectra and glc retention times with those listed in Table I. [b] Reference 2. [c] This derivative was isolated in 35% yield, mp 94–96°.

The procedure described here provides a simple, novel route to substituted borazarophenanthrenes. In addition it may well prove convenient for the facile ortho phenylation of amines to yield various 2-aminobiphenyl derivatives, since the heterocyclic compounds readily deboronate in cold sulfuric acid.[3] As mentioned earlier, the synthesis of substituted 2-aminobiphenyls is a very laborious procedure. This type of synthesis also offers an attractive route to other condensed borazarohydrocarbons through suitable choice of diaryl boron halide and aromatic amine. These areas are under investigation and will be reported later.

Experimental Section

General.—All melting points are corrected. Spectra were determined with Cary Model 15 (uv) and Varian A-60 (nmr) instruments. Mass spectra were determined with a CEC 21-110B instrument, equipped with a heated inlet system as described by Caldecourt[11] but constructed of glass.

Analytical glpc was performed using an F & M Model 720 gas chromatograph equipped with a 0.25 in. × 10 ft column packed with 10% UCW 98 on Chromosorb W.

Materials.—Eastman grade amines were used without further purification but were thoroughly dried in the photoreactor. Chlorodiphenylborane was prepared by the method of Niedenzu, Beyer, and Dawson.[12]

Photocyclizations.—The horizontal thin-film photochemical reactor described earlier was used in these experiments.[13] A second side arm was added to facilitate the addition of solid elemental iodine to the reactor. The amines (10 mmol) were placed in the flask, which was then pumped out with gentle warming (infrared lamp) for 1 hr. It was filled with dry nitrogen and reevacuated, and the process was repeated. Finally 600 ml of dry cyclohexane was distilled off sodium hydride into the reactor. Chlorodiphenylborane (5 mmol) was then injected into the flask and the mixture was rotated for 0.5 hr at room temperature. Iodine (11 mmol) was introduced while a generous flow of dry nitrogen was passing through the flask. The solutions were irradiated using a Hanovia 100-W 608A-36 lamp in a quartz insert. The progress of the reaction was followed by withdrawing 100-μl samples, diluting them in methanol (3 ml) containing a trace of sodium sulfite, and examining the uv spectra. After 15–20 hr the concentration of the desired species usually reached a maximum and the cyclohexane solution was washed with three 200-ml portions of water, three 100-ml portions of dilute HCl, two 50-ml portions of sodium sulfite solution, three 100-ml portions of dilute sodium hydroxide solution, and finally two 100-ml portions of water. The cyclohexane was then dried and evaporated. The crude product was either passed through a short pad of silica and recrystallized from ligroin (bp 63–75°) or recrystallized immediately from ligroin (bp 63–75°). Physical data are listed in Table I.

(11) V. J. Caldecourt, *Anal. Chem.*, **27**, 1670 (1955).

(12) K. Niedenzu, H. Beyer, and J. W. Dawson, *Inorg. Chem.*, **1**, 738 (1962).

(13) J. L. R. Williams and P. J. Grisdale, *Chem. Ind. (London)*, 1477 (1968).

Synthesis of the Zinc(II) Chelate of 6-(α-Hydroxy-β-carbomethoxyethyl)pyrroporphyrin Methyl Ester

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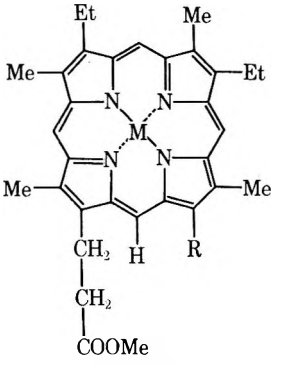
A porphyrin model compound with a β-ketopropionic acid side chain in the 6 position should be of interest since ring closure might take place between this side chain and the adjacent meso position forming a five-membered isocyclic ring. If such a ring closure takes place readily, a hypothesis concerning the biosynthesis of the isocyclic ring of the structurally similar chlorophyll may be advanced.

A β-hydroxypropionic acid derivative would be a convenient intermediate for this purpose and could be obtained from the corresponding formyl compound, using the Reformatsky reaction.

$$\text{porphyrin—CHO} + \text{BrCH}_2\text{COOCH}_3 + \text{Zn} \longrightarrow [\text{porphyrin—CH(CZnBr)CH}_2\text{COOCH}_3] \longrightarrow \text{porphyrin—CH(OH)CH}_2\text{COOCH}_3$$

Accordingly, 6-formylpyrroporphyrin methyl ester (**5**) was prepared from pheophytin (**1**). The conditions used were essentially those of Fischer[1] and Vida.[2] Compound **1** was degraded to pyrroporphyrin methyl ester (**2**). Compound **2** was converted to its Zn(II)



2, R = H; M = 2H
3, R = H; M = Zn
4, R = H; M = Fe
5, R = CHO; M = 2H
6, R = CHO; M = Zn
7, R = CH[OH]CH_2COOMe; M = Zn
8, R = CH=CHCOOMe; M = Zn

chelate **3** with zinc diacetate in acetic anhydride. Attempts to formylate the Zn(II) chelate were unsuccessful; therefore compound **3** was converted into the Fe(II) chelate **4** with ferrous acetate.

Compound **4** was formylated with dichloroethoxyethane in the presence of stannic chloride to yield the 6-formyl compound which in turn was converted to the Zn(II) chelate of 6-formylpyrroporphyrin methyl ester (**6**) with zinc diacetate.

In the Reformatsky reaction, compound **6** was treated with bromoacetic methyl ester to yield the Zn(II) chelate of 6-(α-hydroxy-β-carbomethoxyethyl)pyrropor-

(1) H. Fischer and H. Orth, "Die Chemie des Pyrrols," Leipzig, 1937.

(2) J. Vida, Research Report, Harvard University, Cambridge, Mass., 1962.

phyrin methyl ester (7) as the major product. In the course of this reaction relatively mild conditions were used to avoid further reaction or hydrolysis of the relatively unstable allylic alcohol produced in the reaction.

Experimental Section

Pyrroporphyrin Methyl Ester (2).—Pheophytin (5-g portions) was heated in an autoclave for 16 hr with 40.0 g of potassium hydroxide in 50 ml of methanol. The temperature was carefully maintained at 145–150°. The reaction mixture was cooled and transferred to a 500-ml flask using methanol and water. The solution was evaporated; the residue was dissolved in 40 ml of methanol and 60 ml of water and acidified, with cooling to pH 6 with 10% aqueous hydrochloric acid (*ca.* 240 ml was needed). A precipitate separated. It was filtered, dried at room temperature, dissolved in 30 ml of pyridine, and further diluted with 800 ml of ether. The organic layer was extracted thoroughly first with *ca.* 1 l. of 1% and then with *ca.* 2 l. of 2% aqueous hydrochloric acid. Since some material precipitated during the acid extraction, it was important to filter the acid extracts. They were neutralized with concentrated ammonium hydroxide to pH 4 and extracted thoroughly with chloroform. The chloroform extracts were washed with water and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to yield a solid. The solid residue (1.2–1.5 g) was dissolved in 100 ml of chloroform and treated with a 5 *M* excess of ethereal diazomethane at 0° for 1 hr. The solvents were then removed under reduced pressure, and the residue was dissolved in 20 ml of warm dichloromethane and 40 ml of methanol. The solution was cooled overnight. On filtration, 1 g of **2** was obtained. The mother liquors gave an additional 150–200 mg. From 18 g of pheophytin, 4 g (22%) of crystalline **2** was obtained: λ_{max} (chloroform) 498, 531, 566, 618 mμ. This material showed several spots on tlc and was purified as its Zn(II) chelate.

Zn(II) Chelate of Pyrroporphyrin Methyl Ester (3).—The crude pyrroporphyrin methyl ester (350 mg) and $Zn(OAc)_2 \cdot 2H_2O$ (350 mg) were dissolved in a mixture of 100 ml of acetic acid and 10 drops of acetic anhydride. The solution was refluxed for 30 min under nitrogen. The solvents were distilled off under reduced pressure, and the residue was dissolved in 50 ml of chloroform. The chloroform solution was washed with saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, and concentrated. This solution was chromatographed on a 10-g silica gel column (prepared in chloroform) and eluted with chloroform. The middle fractions gave the purest material: mp 235–237° (dichloromethane–methanol); λ_{max} (chloroform) 532 and 568 mμ; ir (KBr pellet) 5.74 μ (ester C=O).

Fe(II) Chelate of Pyrroporphyrin Methyl Ester (4).—The Zn(II) chelate of pyrroporphyrin methyl ester (1.2 g) was dissolved in 70 ml of acetic acid. To this solution was added a hot solution of ferrous acetate prepared by refluxing 1.2 g of ferrous chloride ($FeCl_2 \cdot 4H_2O$), 1.0 g of sodium acetate, and 100 mg of *ferrum reductum* in 140 ml of acetic acid under nitrogen for 20 min followed by filtration. The reaction solution was refluxed 10 min under nitrogen and then 20 min exposed to dry air. The cooled solution was poured into water; the resulting precipitate was filtered off, washed with a large volume of water, and dried. The crude yield was 1.33 g (100%).

Dichloroethoxymethane.—Phosphorus pentachloride (120.0 g) was placed in a round-bottom flask equipped with a reflux condenser and a funnel. Freshly distilled ethyl formate (80 ml) was added dropwise to the phosphorus pentachloride, allowed to stand until solution was complete, and then refluxed for 1 hr. The mixture was distilled and the fraction boiling at 105–108° (760 mm) was collected (105 g) and used.

6-Formylpyrroporphyrin Methyl Ester (5).—Compound **4** (500 mg) was dissolved in 70 g of dichloroethoxymethane, bp 105–108°. The solution was warmed to 55° in a water bath, and 250 mg of stannic chloride was added dropwise and stirred at 55° for 10 min. An additional 250 mg of stannic chloride was added dropwise and stirring was continued for an additional 10 min. The reaction mixture was poured on 600–800 g of ice while stirring vigorously. After 30–60 min a flocculent precipitate separated which was filtered and dried. The crude yield was *ca.* 550 mg. The dry residue was dissolved in 25 ml of concentrated sulfuric acid at room temperature, stirred for 10 min, and poured onto 200 g of ice. *Ca.* 40 ml of concentrated ammonium hydroxide was added with cooling, and the mixture was extracted with chloroform. The extracts were washed with water, dried over anhydrous sodium sulfate, and concentrated to *ca.* 10 ml. Ether (600 ml) was added. The ether–chloroform solution was washed with 1 l. of 1.5% aqueous hydrochloric acid and the aqueous layer was discarded. The ether–chloroform solution containing compound **5** was repeatedly extracted with 7% aqueous hydrochloric acid.

To the hydrochloric acid extracts containing compound **5** concentrated ammonium hydroxide was added to adjust the pH to 4. Compound **5** was extracted to chloroform and the chloroform solution was washed with water and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in 15 ml of chloroform and 25 ml of methanol and cooled overnight to give 200 mg (40%) of **5**: mp 240°; ir (KBr pellet) 5.74 (ester C=O), 6.02 μ (aldehyde C=O); λ_{max} (chloroform) 515, 556, 578, 636 mμ. The tlc of compound **5** showed traces of two to three other substances.

Zn(II) Chelate of 6-Formylpyrroporphyrin Methyl Ester (6).—Compound **5** (300 mg) was dissolved in 50 ml of acetic acid. $Zn(OAc)_2 \cdot 2H_2O$ (300 mg) was added, followed by 10 drops of acetic anhydride. The mixture was stirred with reflux under nitrogen for 30 min and concentrated. The solution was diluted with chloroform and then washed thoroughly with saturated sodium bicarbonate and water. The chloroform solution was dried and the solvent was evaporated under reduced pressure. The residue was dissolved in 2 ml of methanol and 2 ml of dichloromethane and cooled. The yield was 240 mg (70%): mp 221–223°; λ_{max} (chloroform) 554 and 600 mμ. Chromatography of the mother liquors using Florisil gave an additional small amount of crystalline material.

Zn(II) Chelate of 6-(α-Hydroxy-β-carbomethoxyethyl)pyrroporphyrin Methyl Ester (7). The Reformatsky Reaction.[3]—Activated zinc[4] (300 mg) was placed in a three-neck flask, equipped with a magnetic stirrer and a reflux condenser. The zinc was heated for 1 hr at 110° under a stream of nitrogen. The flask was then cooled to room temperature; 15 ml of absolute tetrahydrofuran was added, followed by 0.8 ml of freshly distilled bromomethyl acetate. After the dissolution of zinc was completed (*ca.* 10–15 min), 130 mg of **6**, predried at 80° (0.1 mm) for 1 hr, was added in one portion. After 10 min the reaction was essentially complete. Chloroform (50 ml) was added to the reaction mixture and the reaction was cooled to 0°. At this temperature 5 ml of 10% sulfuric acid was added, and the reaction mixture was stirred vigorously for 30 min.

Then the chloroform layer containing compound **7** was washed with a 6% sodium bicarbonate solution and then water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was dissolved in a small volume of chloroform and chromatographed on a preparative silica gel tlc plate (0.75-mm thickness) using chloroform. After 5–8 hr, three main zones were separated, which were scraped off separately and extracted with chloroform–methanol (1:1). Three major products were thus obtained.

Compound **8**: red-brown rhombic plates; mp 232–233° (dichloromethane–chloroform); on tlc largest R_f, a green zone; ir (KBr pellet) 6.2 μ; λ_{max} (chloroform) 548 and 593 mμ; Zn-free material, λ_{max} (chloroform) 508, 550, 570, 638 mμ; yield 27.0 mg.

Compound **7**: micro red needles; mp 225–227° (chloroform–ether); on tlc very small R_f, a red zone; ir (KBr pellet) 2.8 (OH stretching), 5.74 (ester C=O), 7.0 μ; λ_{max} (THF) 500 mμ (ε 1930), 535 (11,750), 573 (12,710); yield 39.0 mg (26.7%).

Anal. Calcd for $C_{36}H_{40}O_5N_4Zn$: C, 64.14; H, 5.98; N, 8.31. Found: C, 63.71; H, 5.97; N, 7.89.

Unidentified compound: red-brown plates; mp 250–253° (chloroform–methanol); on tlc intermediate R_f, a green zone; ir (KBr pellet) 6.05 μ; λ_{max} (chloroform) 548 and 593 mμ; yield 25.0 mg.

Registry No.—**2**, 5174-83-4; **3**, 31635-80-0; **4**, 31635-81-1; **5**, 31635-82-2; **6**, 31705-56-3; **7**, 31635-83-3; **8**, 31635-84-4.

Acknowledgment.—I wish to express my thanks to Professor R. B. Woodward for his generous invitation and support.

(3) F. Bohlmann, *Ber.*, **90**, 1519 (1957).
(4) L. Fieser and W. Johnson, *J. Amer. Chem. Soc.*, **62**, 575 (1940).

Dehydration of Secondary Alcohols by Hexamethylphosphoric Triamide

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The dehydration of secondary alcohols in refluxing hexamethylphosphoric triamide (HMPT) without added catalysts proceeds in good yield (70–98%) to afford unrearranged olefins.[1] We now report stereochemical studies which partly elucidate the mechanism of the reaction.

The following compounds were prepared by standard synthetic procedures (see Experimental Section): *cis*- and *trans*-2-phenylcyclohexanol, 1-phenylcyclohexanol, *cis*- and *trans*-2-*tert*-butylcyclohexanol, *trans*-1(e)-decalol, and *trans*-1(a)-decalol. The products of the HMPT-catalyzed dehydration of these compounds, as well as those of some commercially available alcohols, are shown in Table I.

TABLE I
PRODUCTS OF THE HMPT-CATALYZED DEHYDRATION OF ALCOHOLS AT 215–230°

Alcohol	Reflux period, min	Relative amounts of volatile products: Products	%
trans-2-Phenylcyclohexanol	60	1-Phenylcyclohexene	54
		3-Phenylcyclohexene	46
cis-2-Phenylcyclohexanol[a]	65	1-Phenylcyclohexene	59
		3-Phenylcyclohexene	42
1-Phenylcyclohexanol	50	1-Phenylcyclohexene	100
trans-2-*tert*-Butylcyclohexanol	90	1-*tert*-Butylcyclohexene	56
		3-*tert*-Butylcyclohexene	44
cis-2-*tert*-Butylcyclohexanol	55	1-*tert*-Butylcyclohexene	95
		3-*tert*-Butylcyclohexene	5
trans-1(e)-Decalol	60	$\Delta^{1(9)}$-Octalin	61
		trans-Δ^{1}-Octalin	36
		Δ^{9}-Octalin	3
trans-1(a)-Decalol	55	$\Delta^{1(9)}$-Octalin	77
		trans-Δ^{1}-Octalin	14
		Δ^{9}-Octalin	9
2-Decalol (mixture of isomers)	*b*	Δ^{1}- and Δ^{2}-octalins (mixture of isomers) (98% yield)	100
1-Phenylethanol	*b*	Styrene (47% yield)	99
		1-Phenylethyldimethylamine	1

[a] Corrected for the presence of 28% trans isomer. [b] By distillation from the reaction mixture.

In all cases, olefin formation was accompanied by copious and rapid evolution of dimethylamine, and, in those cases in which the olefin was collected by distillation from the reaction mixture, the dimethylamine was observed to form prior to the distillation of the olefin. Moreover, the refluxing solvent, in the absence of a hydroxylic substrate, produces dimethylamine only very slowly and in small quantity. These observations, when considered in the light of the known chemistry of HMPT,[2,3] suggest prior formation of an alkyl tetramethylphosphorodiamidate (eq 1). Such compounds, which have been examined as flame retardants,[4] are heat sensitive, and distillation of ethyl tetraethylphosphorodiamidate at 150–160° may have given octaethylpyrophosphoramide.[5] The following discussion, then, will deal with the decomposition of this presumed intermediate under the reaction conditions.[6]

$$ROH + (Me_2N)_3P{=}O \longrightarrow ROP(NMe_2) + Me_2NH\uparrow \quad (1)$$
$$\qquad\qquad\qquad\qquad\quad \| \quad O$$

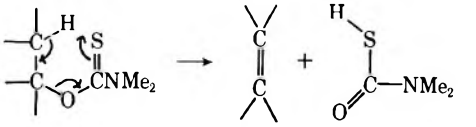
The three likely reaction pathways for the elimination are E1, E2, or Ei, requiring respectively the presence of carbonium ions, of trans elimination, or of cis elimination. The absence of carbonium ions in the reaction has definitely been established by the observation that 1- and 2-decalols undergo the elimination without the accompanying substantial rearrangement to Δ^{9}-octalin (see Table I). By contrast, phosphoric acid catalyzed dehydration of mixed 2-decalols gives mainly Δ^{9}-octalin,[7] and a similar dehydration of *trans*-1(a)-decalol in the present study gave 75% Δ^{9}-octalin, 20% $\Delta^{1(9)}$-octalin, and 4% *trans*-Δ^{1}-octalin.

Rearrangement of the products, once formed, apparently does not occur. HMPT dehydration of *trans*-2-phenlcyclohexanol over a conversion range of 65 to 100% shows virtually the same product distribution (see Table II). In addition, 1-phenylcyclohexanol gives only 1-phenylcyclohexene under the reaction conditions.

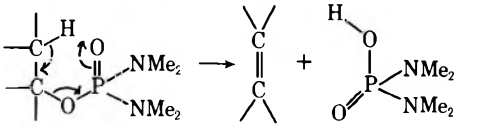
TABLE II
HMPT DEHYDRATION OF *trans*-2-PHENYLCYCLOHEXANOL

Reflux time, min	Conversion, %	Product distribution, %: 3-Phenylcyclohexene	1-Phenylcyclohexene
15	65.5	43	57
30	99	46	54
60	100	46	54
600	100	43	57

An Ei pathway has been proposed by Newman and Hetzel[8] for the pyrolysis of *O*-alkyl dimethylthiocarbamates (eq 2), and this reaction appears to be analogous to the decomposition of alkyl tetramethylphosphorodiamidates (eq 3). Cis elimination on *cis*-2-



(2)



(3)

(1) R. S. Monson, *Tetrahedron Lett.*, 567 (1971).

(2) H. Normant, *Angew. Chem., Int. Ed. Engl.*, **6**, 1046 (1967).

(3) H. Normant, *Colloq. Int. Cent. Nat. Rech. Sci.*, No. 182, 207 (1970).

(4) Y. L. Gefter, "Organophosphorous Monomers and Polymers," Pergamon Press, New York, N. Y., 1962.

(5) B. Loev and J. T. Massengale, *J. Org. Chem.*, **22**, 1186 (1957).

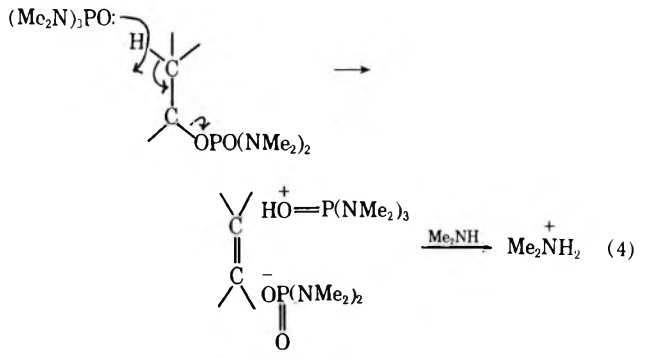
(6) Our original postulate (*cf.* ref 1) that the reactive intermediate was an alcohol–HMPT complex has been abandoned in the light of the experimental evidence presented herein.

(7) A. S. Hussey, J.-F. Sauvage, and R. H. Baker, *J. Org. Chem.*, **26**, 256 (1961).

(8) M. S. Newman and F. W. Hetzel, *ibid.*, **34**, 3604 (1969).

phenylcyclohexanol, *cis*-2-*tert*-butylcyclohexanol, and *trans*-1(a)-decalol would be expected to give as the primary products 3-phenylcyclohexene, 3-*tert*-butycyclohexene, and *trans*-Δ^1-octalin, respectively. However, the observed major products from these three alcohols on treatment with HMPT were 1-phenylcyclohexene, 1-*tert*-butylcyclohexene, and $\Delta^{1(9)}$-octalin, results which exclude an Ei mechanism.

All of the product ratios are consistent with an E2 mechanism (eq 4). (The apparent selectivity in the



(4)

dehydration of *cis*-2-*tert*-butylcyclohexanol has been discussed in the literature and appears to be the result of special factors.[9]) An E2 pathway is also consistent with our earlier observation[10] that primary alkyl halides undergo HMPT-initiated dehydrohalogenation, a reaction which certainly proceeds by an E2 pathway. It thus appears reasonable that the solvent is capable of catalyzing E2 eliminations once a suitable leaving group has been formed.

The fate of the tetramethylphosphorodiamidate fragment has not been the subject of a thorough investigation. However, in those cases in which the molar excess of HMPT is not great (for example, a 3:1 ratio of HMPT to alcohol), a gummy, crystalline precipitate formed during the reaction. Spectral examination of the precipitate suggested the presence of pyrophosphate derivatives. After suitable purification, the mixture yielded bis(dimethylammonium) dihydrogen pyrophosphate, $(Me_2NH_2)_2H_2P_2O_7$. The formation of this substance can be explained by subsequent reactions of the phosphorus containing by-products of reaction 4. Moreover, the generation of the pyrophosphate linkage under related conditions[5] has been discussed above.

Experimental Section

Hexamethylphosphoric triamide and all other reagents not specifically described below were commercially available and were used without further purification. Melting points were determined on a Fisher–Johns apparatus and are uncorrected; boiling points are uncorrected. Gas chromatographic analyses were carried out on an Aerograph Model 600 HyFi with flame ionization detector, column FFAP on acid-washed Chromosorb, 80–100 mesh, 20 ft × 0.125 in. stainless steel with nitrogen as the carrier gas, flow rate 20 ml/min. The oven was operated at constant temperatures varying from 120 to 180 ± 2°. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. Nmr spectra were taken on a Jeolco Model C-60 spectrometer with TMS as internal standard. Analyses were by Chemical Analytical Services, University of California, Berkeley, Calif.

Starting Materials.—The following compounds were prepared as described: *trans*-2-phenylcyclohexanol,[11] 1-phenylcyclohexanol,[12] *cis*-2-*tert*-butylcyclohexanol,[9] *trans*-2-*tert*-butylcyclohexanol,[9] *trans*-1(e)-decalol,[13] and *trans*-1(a)-decalol.[14,15] The fraction, bp 78–79° (0.05 mm), of a commerical mixture of *cis*- and *trans*-2-phenylcyclohexanol was taken up in pentane, cooled in a Dry Ice bath and seeded with the pure trans isomer. After crystallization, the supernatant liquid was decanted. Two more repetitions of this procedure, followed by evaporation of the pentane, resulted in an oil which consisted of 72% cis isomer and 28% trans isomer by glpc analysis. The products obtained from HMPT dehydration of this mixture were corrected for the known product distribution obtained from the pure trans isomer.

Comparison Compounds.—Styrene and 1-phenylcyclohexene were the commercially available materials. 1-*tert*-Butylcyclohexene was prepared by dehydration of *cis*-2-*tert*-butylcyclohexanol in 85% phosphoric acid.[9] Δ^9-Octalin and $\Delta^{1(9)}$-octalin were prepared as a 4:1 mixture by the lithium–ethylenediamine reduction of tetralin.[16] The identities of other products were inferred from their relative retention times and infrared and nmr spectra.

Dehydrations in HMPT. A. Reflux Method.—The alcohol was dissolved in 5 to 30 times its weight of HMPT to give a convenient volume. The solution was refluxed (215–230°) for the indicated period. The evolution of dimethylamine could easily be followed by the formation of its deep blue amine complex with indicating Drierite. After cooling, the solution was taken up in pentane, washed three times with brine, dried, and subjected to glpc analysis.

B. Distillation Method.—The distillation technique of HMPT dehydration on a synthetic scale (0.1 mol of alcohol) has been described.[1]

Dehydration of *trans*-1(a)-Decalol in Phosphoric Acid.—The alcohol (0.1 g) was mixed with 4 ml of 85% phosphoric acid and heated at 130–155° for 100 min. The cooled reaction mixture was diluted with water and extracted with pentane. The pentane solution was washed once with 10% sodium carbonate solution, twice with brine, and dried. The resulting solution was subjected directly to glpc analysis.

Isolation of 1-Phenylethyldimethylamine.—The execution of HMPT dehydration on 0.1 mol of 1-phenylethanol resulted in a 47% yield of distilled styrene. The cooled reaction mixture was diluted with water and extracted with ether. The ethereal solution was washed three times with brine and then extracted with 3 *N* hydrochloric acid. The aqueous acid extract was washed with ether and then made distinctly basic with 3 *N* sodium hydroxide solution. This aqueous mixture was now extracted with ether, the ethereal solution dried over potassium hydroxide pellets, and the ether vaporated affording the crude product in less than 1% yield. It was identified by conversion[17] to the picrate, which was recrystallized from methanol, mp 133–134° (lit.[18] mp 138–139°).

Isolation of Bis(dimethylammonium) Dihydrogen Pyrophosphate.—The reaction of 150 ml of HMPT with 0.3 mol of 1-phenylethanol gave, after a 60-min reflux period, a gummy, light yellow precipitate weighing 17.2 g. After decantation of the reaction mixture, the precipitate was transferred to a Soxhlet extractor and extracted overnight with isopropyl alcohol affording white crystals in the extraction flask. This material was further purified by dissolving in hot absolute ethanol and dilution with cold isopropyl alcohol. Repetition of this procedure gave 4.1 g of hygroscopic crystalline material, mp 178–180° dec. The presence of the pyrophosphate group was verified by treating an aqueous solution of the material with zinc acetate solution, which treatment afforded an immediate copious precipitate in-

(9) H. L. Goering, R. L. Reeves, and H. H. Espy, *J. Amer. Chem. Soc.*, **78**, 4926 (1956).

(10) R. S. Monson, *Chem. Commun.*, 113 (1971).

(11) C. H. DePuy, G. F. Morris, J. S. Smith, and R. J. Sinay, *J. Amer. Chem. Soc.*, **87**, 2421 (1965).

(12) L. F. Fieser and J. Szmuszkovicz, *ibid.*, **70**, 3352 (1948).

(13) R. S. Monson, D. Przybycien, and A. Baraze, *J. Org. Chem.*, **35**, 1700 (1970).

(14) W. Huckel, *et al.*, *Justus Liebigs Ann. Chem.*, **645**, 115 (1961).

(15) W. G. Dauben, R. C. Tweit, and C. Mannerskautz, *J. Amer. Chem. Soc.*, **76**, 4420 (1954).

(16) W. G. Dauben, E. C. Martin, and G. J. Fonken, *J. Org. Chem.*, **23**, 1205 (1958).

(17) R. L. Shriner, R. C. Fuson, and D. Y. Curten, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964.

(18) G. Wittig and D. Krauss, *Justus Liebigs Ann. Chem.*, **679**, 34 (1964).

dicative of the pyrophosphate group.[19] When the purified material was heated to its melting point, decomposition occurred, and dimethylamine could be detected by its characteristic odor: ir (film) 2.94 (NH), 7.83 (P=O), and 10.32 μ (POP).

Anal. Calcd for $C_4H_{18}N_2O_7P_2$: C, 18.0; H, 6.7; N, 10.5; P, 23.1. Found: C, 18.3; H, 6.5; N, 10.5; P, 23.4.

Registry No.—HMPT, 680-31-9; *trans*-2-phenylcyclohexanol, 2362-61-0; *trans*-1(a)-decalol, 31729-83-6; bis(dimethylammonium) dihydrogen pyrophosphate, 31729-84-7.

Ackowledgment.—The authors express their appreciation to the Research Foundation of California State College at Hayward for financial support.

(19) W. M. Latimer and J. H. Hildebrand, "Reference Book of Inorganic Chemistry," 3rd ed, Macmillan, New York, N. Y., 1951, p 232.

The Synthesis of Some New Cysteine-Containing Unsymmetrical Disulfides[1]

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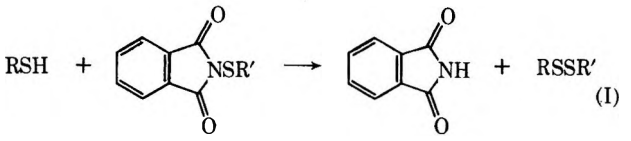
It was recently found[2] that a convenient route for the synthesis of dialkyl and aralkyl unsymmetrical disulfides is the thiolysis of the corresponding thiophthalimide as shown in eq I. Excellent yields, stable precursors, and minimal disulfide interchange are among the advantages offered by this method. Some of the disulfides prepared in this manner were the simple peptides, *S*-benzylthioglutathione and *S*-benzylthio-L-cysteine hydrochloride (R′ = benzyl in eq I).

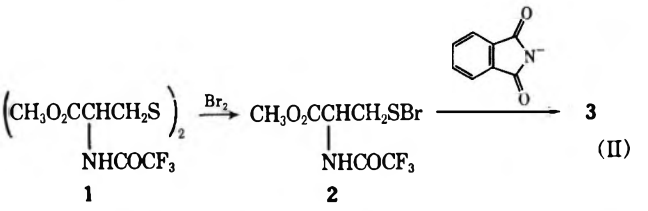


(I)

We now wish to report the synthesis of a cysteine-containing thiophthalimide, which has provided us with an excellent synthetic route *via* eq I to some new unsymmetrical disulfides, in two of which both R and R′ are cysteine or glutathione residues.

A 65% yield of *N*-trifluoroacetyl-*S*-phthalimido-L-cysteine methyl ester (**3**) (Table I) was obtained (eq II) by first brominating[3] disulfide[4] **1** at 0°, and then treating the resulting sulfenyl bromide **2** with the phthalimide anion.

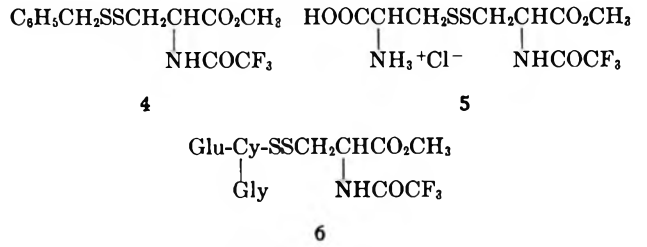
Although **2** was used directly without isolation, evidence for its formation derives from nmr data. The methylene absorption of **2** in trifluoroacetic acid solution is shifted 0.3 ppm downfield relative to that of **1**. This appears reasonable, since the methylene absorption of the chlorine analog of **2** is found[5] 0.5 ppm downfield from that of **1**.



(II)

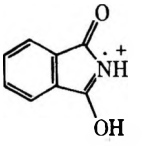
1 2

Thiolysis of **3** with benzyl mercaptan, cysteine hydrochloride monohydrate, and glutathione, according to eq I, gave excellent yields (92–99%) of the corresponding disulfides **4**, **5**, and **6**, respectively. Absence of the corresponding symmetrical disulfides in the products



4 5 6

was established by tlc, except in the case of **6** where traces were found. The structures of compounds **3**–**6** were consistent with infrared, nmr, mass spectral, and elemental analyses. The mass spectrum of **3** shows an intense peak at *m/e* 148, likely due to formation of fragment a.



a

Major peaks reported[6] in the mass spectra of other thiophthalimides (at *m/e* 147, 130, 104, and 76) were also observed.

Disulfides **4**–**6** showed fragmentation similar to **1** as previously reported.[4] Cleavage of both the disulfide bond and the C–S bond on the side of the blocked cysteine residue was evident from intense peaks at *m/e* 230 and 198, respectively.

Attempts to selectively remove the trifluoroacetyl and methyl ester protective groups by mild alkaline hydrolysis of thiophthalimide **3** and disulfide **4** were unsuccessful, as both the S–N[7a] and S–S[7b] linkages proved too labile to withstand even the mild basic conditions[8] required to remove the trifluoroacetyl group. Treatment of **3** with 0.01 *N* NaOH at 5° for 0.5 hr gave 69% of phthalimide.[9] Reaction of **4** with 1 *N* NaOH under similar conditions gave 27% of benzyl disulfide.[9]

Thus it is clear that thiolysis of a cysteine thiophthalimide with an alkyl thiol, cysteine, or glutathione, provides a rapid, clean, and almost quantitative syn-

(1) Organic Sulfur Chemistry. XII. For part XI, see D. N. Harpp and D. K. Ash, *Int. J. Sulfur Chem.*, in press.

(2) (a) K. S. Boustany and A. B. Sullivan, *Tetrahedron Lett.*, 3547 (1970); (b) D. N. Harpp, D. K. Ash, T. G. Back, J. G. Gleason, B. A. Orwig, W. F. Van Horn, and J. P. Snyder, *ibid.*, 3551 (1970).

(3) The yield of sulfenyl bromide was considered to be quantitative; treatment of the corresponding sulfenyl chloride with the phthalimide anion resulted in the formation of significant amounts of phthalimide, thus indicating proton abstraction. No other identifiable products resulted.

(4) The yield of disulfide was 95%: D. N. Harpp and J. G. Gleason, *J. Org. Chem.*, **36**, 73 (1971).

(5) P. Mathiaparanam, Ph.D. Thesis, McGill University, 1971.

(6) B. A. Orwig, M.Sc. Thesis, McGill University, 1971.

(7) (a) J. E. Kerwood and M. Behforouz, *J. Org. Chem.*, **34**, 51 (1969); (b) A. Parker, and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).

(8) It has been reported that the trifluoroacylamide bond is labile at pH greater than 10: E. Schallenberg and M. Calvin, *J. Amer. Chem. Soc.*, **77**, 2779 (1955).

(9) The remaining reaction mixture was not further investigated.

TABLE I

$RSCH_2CHCO_2CH_3$
|
$NHCOCF_3$

No.	R	Yield, %	Calcd, % C	H	N	S	Found, % C	H	N	S
3	Phthalimido-	65	44.68	2.95	7.45	8.52	44.66	2.99	7.54	8.57
4	$C_6H_5CH_2S$-	97	44.18	3.99	3.96	18.15	43.78	4.21	4.13	17.92
5	$HOOCCHCH_2S$- | $NH_3^+Cl^-$	99	27.94	3.65	7.24	16.58	28.24	4.17	7.33	16.89
6	Glu-Cy- | Gly	92	35.82	4.32	10.44	11.95	35.81	4.43	10.34	12.23

thetic route to unsymmetrical cysteine disulfides. The possibility of using thiophthalimides in peptide synthesis with selectively removable amino and carboxylic acid protective groups is being further explored.

Experimental Section

Melting points were taken on a Gallenkamp block and are uncorrected. Optical rotations were measured on a Perkin-Elmer Model 141 automatic polarimeter. Elemental analyses were performed by Organic Micro-analyses, Montreal. Infrared spectra were recorded on a Perkin-Elmer 257 grating spectrometer. Mass spectra were obtained on an AEI-MS-902 instrument. Nmr spectra were recorded on a Varian T-60 spectrometer.

***N*-Trifluoroacetyl-*S*-phthalimido-L-cysteine Methyl Ester (3).**—To a suspension of 4.60 g (0.01 mol) of disulfide **1** in 30 ml of 1,2-dichloroethane (DCE) at 0° was added 4.80 g (0.03 mol) of bromine in 15 ml of DCE. After stirring for 2–3 min, the cloudy, red solution was rapidly added to a similarly cooled suspension of 3.70 g (0.02 mol) of the potassium derivative of phthalimide in 45 ml of DCE. Anhydrous conditions were maintained throughout the experiment. After stirring at 0° for 10 min., the suspension was stirred for an additional 90 min at ambient temperature. Insoluble material was then filtered, giving 2.39 g (100%) of KBr. The filtrate was evaporated *in vacuo*, giving an orange solid, which on recrystallization from methanol–water gave 4.87 g (65%) of white needles mp 121–123°. A second recrystallization gave a sample of analytical purity: mp 125–126°; $[\alpha]^{22}D$ +54.4° (*c* 0.226, CCl_4); ir (KBr) 3260, 1730, 1690, 1540, 1270, 1180, 1150, 1040, cm^{-1}.

***N*-Trifluoroacetyl-*S*-benzylthio-L-cysteine Methyl Ester (4).**—A solution of 1.00 g (2.7 mmol) of **3** and 0.33 g (2.7 mmol) of benzyl mercaptan in 10 ml of ethyl acetate was refluxed for 24 hr. On subsequent cooling, phthalimide crystallized and was filtered. The solvent was removed *in vacuo* and the residue was taken up in 5 ml of carbon tetrachloride; additional phthalimide was obtained, total yield 0.38 g (96%), mp 234–235° (lit.[10] mp 238°). The filtrate was again evaporated *in vacuo*, giving a clear oil which crystallized on cooling to give 0.92 g (97%) of a pale yellow solid: mp 38–40°; $[\alpha]^{22}D$ +39.7° (*c* 0.363, $CHCl_3$); ir (KBr) 3300, 1740, 1700, 1540, 1300, 1200, 1180, 1160 cm^{-1}.

***N*-Trifluoroacetyl-*S*-cysteinyl-L-cysteine Methyl Ester Hydrochloride (5).**—A solution of 0.233 g (1.33 mmol) of L(+)-cysteine hydrochloride monohydrate[11] and 0.500 g (1.33 mmol) of **3** in 10 ml of ethanol was refluxed for 2 hr. On cooling, phthalimide crystallized and was filtered. The filtrate was evaporated to ~2–3 ml and 20 ml of water was added, giving an additional 0.006 g of phthalimide on cooling, total yield 0.179 g (91%), mp 234–237°. The filtrate was then evaporated *in vacuo* to give a white, solid foam, which was dried to constant weight under vacuum: yield 0.512 g (99%); mp 151–153° dec; $[\alpha]^{22}D$ −142.4° (*c* 0.433, 1 *N* HCl); ir (KBr) 3700–2400 (broad), 1800–1680, 1570, 1200 cm^{-1} (broad).

***N*-Trifluoroacetyl-*S*-glutathionyl-L-cysteine Methyl Ester (6).**—A solution of 0.408 g (1.33 mmol) of glutathione and 0.500 g (1.33 mmol) of **3** in 20 ml of ethanol–water (50:50 v/v) was refluxed for 2 hr. After cooling to room temperature and standing for 8 hr, 0.187 g (95%) of phthalimide crystallized and was filtered, mp 228–232°. The solvent was evaporated *in vacuo* to 10 ml and 10 ml of water were added. On cooling overnight, an additional 0.049 g of precipitate formed. Tlc [silica gel, C_6H_6–Et_2O (5:2)] showed this second crop to be composed of phthalimide and the symmetrical disulfide **1**. The filtrate was evaporated *in vacuo* and dried to constant weight, giving 0.659 g (92%) of a white, solid foam: mp 173° dec; $[\alpha]^{22}D$ −103.0° (*c* 0.463, 1 *N* HCl); ir (KBr) 3700–2400 (broad), 1720, 1650, 1540, 1200 cm^{-1} (broad). Tlc [cellulose, BuOH–HOAc–H_2O (12:3:5)] showed the presence of a trace impurity of lower mobility than **6** attributable to a small quantity of the symmetrical glutathione disulfide.

Hydrolysis of 3.—To 500 ml of 0.01 *N* NaOH at 5° was added a solution of 0.376 g (1 mmol) of **3** in 5 ml of dioxane. After stirring for 0.5 hr at 5°, the solution was acidified to pH ~6 by the addition of 1 *N* HCl. A precipitate of phthalimide formed [0.101 g (69%), mp 225–231° (lit.[10] mp 238°)]. Tlc [silica gel, C_6H_6–Et_2O (5:2)] showed a major component having the same mobility as phthalimide and two minor components of lower mobility.

Hydrolysis of 4.—To a solution of 0.117 g (0.331 mmol) of **4** in a few drops of methanol was added 3 ml of 1 *N* NaOH previously cooled to 5°. After stirring at this temperature for 0.5 hr, the milky solution was acidified to pH ~6 by the addition of 1 *N* HCl. The resulting precipitate was filtered, washed with water, dried, and washed well with ether. Evaporation of the ether washings gave 0.011 g (27%) of benzyl disulfide, mp 65–67° (lit.[10] mp 69°). Tlc showed the ether-insoluble residue to be a mixture of at least four components.

Registry No.—**3**, 31892-91-8; **4**, 31862-24-5; **5**, 31862-25-6; **6**, 31892-92-9.

Acknowledgment.—We thank the Defense Research Board of Canada (Grant No. 9530-97) for financial support of this work.

(10) Handbook of Chemistry and Physics, 47th ed, Chemical Rubber Publishing Co., Cleveland, Ohio.

(11) Two small impurities revealed by tlc in the precursor thiol were also discovered in the product.

Pilloin, a New Flavone from *Ovidia Pillo-Pillo*

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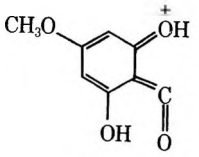
Received April 26, 1971

In connection with a general phytochemical investigation of the native vegetation of southern Chile, we report here the structure determination of a new flavone, pilloin ($C_{17}H_{14}O_6$, mp 236.5–237.5°), which was isolated from *Ovidia pillo-pillo* Meisner (formerly designated as *Dafne pillo-pillo* Gay), family *Thymelaeaceae*.

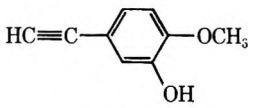
The nmr spectra of pilloin in pyridine-d_5 and its diacetyl and diethyl derivatives in $CDCl_3$ established that the natural product was a dimethyl ether of luteolin, and the mass spectrum of pilloin showed peaks at *m/e* 167 and 148 for fragments A and B, respectively,[1]

(1) H. Budzikiewicz, C. Djerassi, and D. H. Williams in "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. II, Holden-Day, San Francisco, Calif., 1964, p 262.

indicating that each aromatic ring contained one methoxyl group.



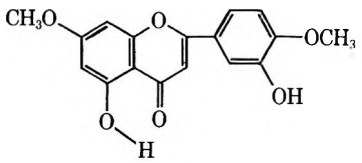
A



B

These spectral findings were supported by converting pilloin to both luteolin and luteolin tetramethyl ether.

Pilloin was shown to be different by direct comparison (ir, tlc, melting point, and mixture melting point) with velutin, luteolin 3′,7-dimethyl ether,[2] and, since the ultraviolet spectral curve with $AlCl_3$ (a bathochronic shift of 24 mμ of band I)[3] and ir (band at 3300 cm^{-1} for a hydrogen-bonded C-5 hydroxyl group) data established the presence of a C-5 hydroxyl group, pilloin must be the previously undescribed luteolin 4′-7-dimethyl ether (I). The ultraviolet spectrum in sodium acetate–ethanol confirmed that the 4′ position was blocked.[3]



I

Experimental Section[4]

Pilloin (3′,5-Dihydroxy-5′,7-dimethoxyflavone).—Leaves and branches of *Ovidia pillo-pillo* were collected in December 1968, in Los Ulmos, about 10 km south of Valdivia, Chile. Dried and ground material (2 kg) was extracted three times with 6 l. of ethanol at 50° for 12 hr. The ethanolic extract was concentrated under vacuum to give a syrup, which was poured into water (2 l.). The precipitate was discarded and the aqueous solution was then extracted with chloroform. On concentration a dark yellow precipitate was obtained, which was recrystallized from a methanol–chloroform mixture (2:1); with a yield of 0.2 g of pilloin: mp 235.5–236.5°; uv max 250, 270, and 330 mμ (log ε 4.13, 4.15, and 4.21); ir (KBr) 3300 (OH), 1660 (C=O), 1605, 1506, and 1455 (C=C), 813 cm^{-1} (two adjacent free hydrogen atoms); nmr (pyridine-d_5) 3.77 (s, OCH_3), 3.81 (s, OCH_3), 4.94 (s, 3′-OH), 6.61 (s, 2, 6 H and 8 H), 7.00 (s, 3 H), 7.08 (d, J = 8 Hz, 5′ H), 7.59 (q, J = 8, 2 Hz, 6′ H), and 7.89 (d, J = 2 Hz, 2′ H); mass spectrum 314 (parent), 285 (M − 29), 271 (M − 43), 167 ($C_8H_7O_4$), 148 ($C_9H_8O_2$), 138 ($C_7H_6O_3$), 133 ($C_8H_5O_2$), and 123 ($C_7H_7O_2$).

Anal. Calcd for $C_{17}H_{14}O_6$: C, 64.96; H, 4.49. Found: C, 64.60; H, 4.76.

3′,5-Diacetoxy-4′,7-dimethoxyflavone.—Treatment of pilloin with acetic anhydride–pyridine formed the diacetate: uv max 232, 260, and 321 mμ (log ε 4.37, 4.17, and 4.46); nmr ($CDCl_3$) 2.35 (s, $OOCCH_3$), 2.42 (s, $OOCH_3$), 3.78 (s, $2OCH_3$), 6.47 (s, 3 H), 6.58 and 6.83 (each d, J = 2 Hz, 6 H and 8 H), 7.02 (d, J = 8.5 Hz, 5′ H), 7.54 (d, J = 2 Hz, 2′ H), 7.69 (q, J = 8.5, 2 Hz, 6′ H).

3′,5-Diethoxy-4′,7-dimethoxyflavone.—Ethylation of pilloin with diethyl sulfate–potassium carbonate gave the diethoxy derivative: mol wt 370 (mass spectrum); nmr ($CDCl_3$) 1.53 (2 t, 6, CH_2CH_3), 4.16 (2 q, 4, CH_2CH_3), 3.88 and 3.93 (each s, OCH_3), 6.33 and 6.51 (each d, J = 2 Hz, 6 H and 8 H), 6.52 (s, 3 H), 6.93 (d, J = 8 Hz, 5′ H), 7.30 (d, J = 2 Hz, 2′ H), 7.46 (q, J = 8, 2 Hz, 6′ H).

3′,4′,5,7-Tetramethoxyflavone.—Methylation of pilloin with dimethyl sulfate–potassium carbonate formed the tetramethoxy derivative, which was crystallized from benzene: mp 190–191° (lit.[5] mp 192–193°); mass spectrum 342 (parent), 341 (M − 1), 313 (M − 29), 312 (M − 30), 162 ($C_{10}H_{10}O_2$), 152 ($C_8H_8O_3$), 147 ($C_9H_7O_2$), 137 ($C_8H_9O_2$).

3′,4′,5,7-Tetrahydroxyflavone, Luteolin.—Demethylation of pilloin with hydrogen iodine gave luteolin. The ultraviolet spectra in ethanol was identical with an authentic sample of luteolin.[6] The ultraviolet shifts with sodium acetate–ethanol were almost identical with those reported for luteolin.[7]

Registry No.—1, 32174-62-2; 1 deacetate, 32174-63-3; 1 diethyl ether, 32174-64-4; 1 tetramethyl ether, 855-97-0.

Acknowledgments.—I wish to express my thanks to Dr. Juan Garbarino, Universidad Católica de Chile, for helpful discussions, and to Mr. Aurelio Reyes for his participation in early phases of this work. Thanks are also due to Professor F. Marcus for his help with the preparation of the manuscript.

(2) K. C. Das, W. J. Farmer, and B. Weinstein, *J. Org. Chem.*, **35**, 3989 (1970). The author thanks Professor B. Weinstein, University of Washington, for a sample of velutin.

(3) L. Jurd in "The Chemistry of Flavonoid Compounds," T. A. Geissman, Ed., Macmillan, New York, N. Y., 1962, p 107.

(4) Melting points are uncorrected. Mass spectrum, nuclear magnetic resonance (internal tetramethylsilane, 100 MHz) and mycroanalysis were generously provided by the University of Zurich, through Dr. Jorge Naranjo, whose cooperation I gratefully thank. Thin layer chromatography employed silica gel G as a support, chloroform as the developer, and iodine for detection.

(5) J. Grinpenberg in "The Chemistry of Flavonoid Compounds," T. A. Geissman, Ed., Macmillan, New York, N. Y., 1962, p 406.

(6) The author thanks Professor C. Galeffi, Instituto Chimico dell'Universitá, Torino, and Professor S. Tira, Instituto Superiore di Sanitá, Roma, for samples of luteolin.

(7) B. Valdes, *Phytochemistry*, **9**, 1253 (1970).

A Directing Effect of Oxygen in Perhydrophthalans

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Received March 11, 1971

Pasto's recent evaluation of the directive effects caused by a 3-alkyl group in substituted cyclohexenes[2] prompts us to report our work related to this problem. As part of an investigation directed toward the synthesis of guaianolide sesquiterpenes, we chose as one of our models 7-methyl-*cis*-3a,4,7,7a-tetrahydrophthalan-5-one (2), presumably to be prepared by a sequence as delineated in eq 1.[3] It became apparent during the early phases of our research, however, that we might be able to observe some directive effects caused by the phthalan oxygen during hydration of **1**, and we accordingly attempted an analysis of regiospecific[7] directive effects. Of the several methods available for hydration we chose to investigate hydroboration with diborane and disiamylborane and oxymercuration. In all cases studied, the alcohols resulting from the hy-

(1) NDEA Predoctoral Fellow, 1968–1971.

(2) D. J. Pasto and J. A. Gontarz, *J. Amer. Chem. Soc.*, **92**, 7480 (1970).

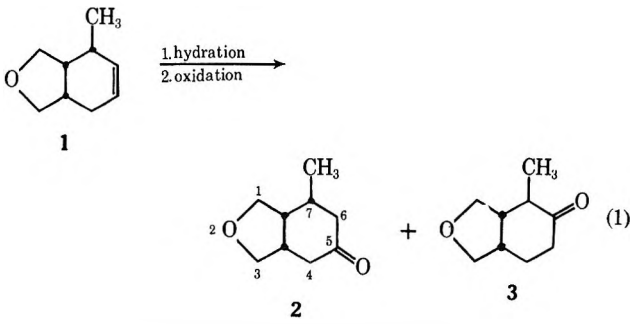
(3) The ease of preparation of phthalan derivatives has resulted in their occasional use as models for the corresponding carbocyclic systems. The various oxygen-containing models have been useful for mechanism studies[4] and synthetic work.[5] The question of whether there are electronic and directive effects associated with the heteroatom has been raised.[6]

(4) E. L. Eliel and C. Pillar, *J. Amer. Chem. Soc.*, **77**, 3600 (1955).

(5) A. P. Krapcho and B. P. Mundy, *J. Org. Chem.*, **32**, 2041 (1967).

(6) B. Rickborn and S. Y. Lwo, *ibid.*, **30**, 2212 (1965).

(7) A. Hassner, *Accounts Chem. Res.*, **4**, 9 (1971).



drations were immediately subjected to Jones oxidation, and the ketones were analyzed.[8]

The results of several experiments are summarized in Table I, along with a parallel study on the conforma-

TABLE I

HYDRATIONS OF 1 AND 3-METHYLCYCLOHEXENE

Expt no.	Hydration method	Ketone ratio 2	Ketone ratio 3
	1 → (1. hydration; 2. Jones oxidation) 2 + 3		
1	B_2H_6/H_2O_2, OH^-	40	60
2	R_2BH/H_2O_2, OH^-	62	38
3	$Hg(OAc)_2/OH^-$, NaBH	82	18
	3-methylcyclohexene → 3-methylcyclohexanone (A) + 2-methylcyclohexanone (B)		
		A	B
1[a]	B_2H_6/H_2O_2, OH^-	46	54
2[b]	R_2BH/H_2O_2, OH^-	33	67
3	$Hg(OAc)_2/OH^-$, $NaBH_4$	88	12
4	$Hg(O_2CPh)_2/OH^-$, $NaBH_4$	87	13

R_2BH designates disiamylborane

[a] See ref 9 and H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **83**, 2544 (1961). [b] Brown (footnote *a*) has reported that disiamylborane attacks equally at C-2 and C-3. We have repeated our experiments several times and consistently get the results reported in Table I. It is not easy to reconcile these differences, however; a reasonable explanation invoking allylic strain[10] accounts for our results.

tionally less homogeneous 3-methylcyclohexene. The ketones **2** and **3** could be separated by glc for quantitative analysis; however, column chromatography was the method of choice for separation and purification on a preparative scale. Identification and structure assignment of **2** and **3** was accomplished after deuterium exchange of the α hydrogens by examining, *via* nmr, the loss of the methyl doublet for **3**.

From the data in Table I it is evident that directive effects do exist, both for **1** and 3-methylcyclohexene. For 3-methylcyclohexene the directive effects must be due to the methyl group, and there is the possibility of competing inductive and steric effects.[9] The conformationally more rigid **1** can exhibit similar effects due to its methyl group as well as effects associated with the fused tetrahydrofuran system.

(8) We realize that some important stereochemical data was lost in the conversion of the alcohols to the ketones. However, our initial studies were not concerned with any chemistry of the alcohols and we did not try to analyze them. Also, conversion to the ketone greatly reduces the analytical problems associated with the evaluation of gross directive effects.

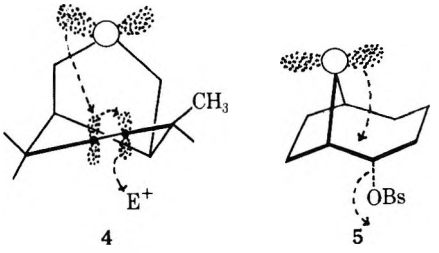
(9) D. J. Pasto and F. M. Kline, *J. Org. Chem.*, **33**, 1468 (1968).

Because of the conformational inhomogeneity of 3-methylcyclohexene, it is difficult to establish the source of directive effects. Diborane, a relatively small and highly reactive molecule, shows little regiospecificity, although there is a stereospecificity of addition trans to the methyl group.[9] Steric effects associated with oxymercuration should be expected to be minimal because of the low *A* values of mercury. However, the sevenfold preference of C-2 as the site of reaction with mercury demonstrates that this is the more nucleophilic carbon. An explanation for this increased nucleophilicity might be to attribute a fairly substantial inductive role to the methyl group. Alternately, the preferential addition may be a reflection of torsional angle effects.[2]

Hydroboration of 3-methylcyclohexene with disiamylborane again demonstrates that C-2 is the more reactive carbon, and the lesser reactivity of the hindered borane allows for the selectivity in reaction sites. The lack of steric interaction with the methyl group might be attributed to the 3-methylcyclohexene molecule adopting a reaction conformation in which the methyl group becomes axial, a condition quite common when considering conformations exhibited by molecules to relieve allylic strain.[10] Thus, the methyl group contributes little steric effect, but can maintain its inductive ability.

Examining the results of the phthalan reactions, it can be noted that *only those results obtained by hydration with disiamylborane are not consistent with the 3-methylcyclohexene data.* Since **1** is conformationally more rigid than 3-methylcyclohexene, it is not unreasonable that an interaction of the methyl group with the bulky hydroborating agent would occur. Why, however, is there not a dramatic steric effect noted?

An examination of several types of molecular models leads to the suggestion that the phthalan oxygen is playing a role in directing the course of reactions for the system. Because of the interaction of the methylene protons of C-3 with the methyl protons, the molecule is twisted in such a way that the ether oxygen orbitals lie directly over C-6. Thus, addition of any electrophilic agent to C-5 of **4** will result in a transition-state stabilization of the incipient positive charge at C-6. Although there would be a methyl steric effect, the increased reactivity of C-5 (due to oxygen participation and methyl induction) would force the boron to preferentially add to C-5.[11] Long range oxygen-



(10) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

(11) At this time we have no evidence related to the steric course of addition of the various hydrating agents. However, considering that both the hydroboration and oxymercuration reactions are run in excess tetrahydrofuran, we would suggest that there is no particular requirement for the hydrating agents to preferentially coordinate with the phthalan oxygen. We have also established with *cis*-3a,4,7,7a-tetrahydrophthalan that electrophilic addition occurs primarily anti to the phthalan ring. Details regarding the electronic and stereochemical course of addition to *cis*-3a,4,7,7a-tetrahydrophthalan will be presented in another paper.

orbital stabilization has been suggested by Paquette[12] for the solvolysis of **5**.

Experimental Section

The infrared spectra were recorded on a Beckman IR-5 instrument. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer, using TMS as an internal standard and deuteriochloroform as solvent. Melting and boiling points are not corrected. Gas chromatographic analysis were performed on an F & M Model 400 unit, using a hydrogen flame detector and Disc integrator.

Preparation of 4-Methyl-*cis*-3a,4,7,7a-tetrahydrophthalan (1).—The known *cis*-3-methyl-4-cyclohexene-*cis*-*cis*-1,2-dicarboxylic acid anhydride[13] (60 g) was dissolved in 600 ml of anhydrous ether and this was added to a refluxing solution prepared from 15.2 g of lithium aluminum hydride in 600 ml of anhydrous ether. After hydrolyzing the reaction mixture, the ethereal layer was separated, dried, and distilled [116–124° (0.5 mm)] to yield 33.0 g (59%) of a crude diol. The diol (21 g) was immediately dissolved in 40 ml of dry pyridine and heated to reflux while 38 g of *p*-toluenesulfonyl chloride in 40 ml of pyridine were added. The reaction mixture was refluxed for 12 hr, cooled, and poured over an ice–sulfuric acid mixture. The product was extracted with pentane and distilled to yield 14 g (73%) of a water-clear liquid, bp 44–48° (0.2 mm). The infrared spectrum exhibited the characteristic ether linkage of tetrahydrofuran derivatives at 9.2 μ (1087 cm^{-1}).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.00; H, 10.14.

Hydration of 1 by Hydroboration.—Sodium borohydride (1.43 g) was added to a solution containing 3.5 g of 1 and 15 ml of anhydrous THF. The reaction mixture was placed under a nitrogen atmosphere at 0° and BF_3 etherate (9.3 g, 0.056 mol) was slowly added. After hydrolysis of the boron complex, the reaction mixture was warmed to room temperature. After about 12 hr, the mixture was extracted with ether to yield a crude alcohol mixture. This was immediately subjected to Jones oxidation, giving the liquid ketones **2** and **3**, bp 76–82° (10 mm). These could be separated on a 6 ft × 6 mm glass column packed with 20M Carbowax on 30/60 firebrick or by column chromatography utilizing a 30 × 60 mm water-cooled column packed with silica gel (14 g silica gel G, 30 ml of H_2O, activated for 45 min) and eluted with solvent [chloroform–ether–pentane (55:28:17)]. The identity of **3** was established by deuterium exchange. No distinguishing features could be noted in the infrared spectrum. The nmr spectra of the ketones were consistent with the assigned structures. The 2,4-dinitrophenylhydrazones of 2 (mp 164–165°) and **3** (mp 176–177°) were prepared.

Anal. Calcd for $C_{15}H_{18}N_4O_5$ (the 2,4-dinitrophenylhydrazone of **2**): C, 53.89; H, 5.43. Found: C, 53.81; H, 5.31. Calcd for $C_{15}H_{18}N_4O_5$ (the 2,4-dinitrophenylhydrazone of **3**): C, 53.89; H, 5.43. Found: C, 53.92; H, 5.55.

Hydration of 1 by Disiamylborane.—The disiamylborane was prepared and used according to the procedure of Brown.[14] Products were worked up and after Jones oxidation the ketones were subjected to analytical glc.

Hydration of 1 by Oxymercuration–Demercuration.—Utilizing the procedure of Brown,[15] the alkene 1 was converted to the alcohol mixture and after Jones oxidation the ketones were analyzed.

Hydrations of 3-Methylcyclohexene.—These reactions were performed as discussed for 1.

Registry No.—**1**, 31684-77-2; **2**, 31684-78-3; **2** 2,4-DNPH, 31684-79-4; **3**, 31684-80-7; **3** 2,4-DNPH, 31731-95-0; 1-methylcyclohexene, 591-49-1; 3-methylcyclohexene, 591-48-0.

Acknowledgments.—We express our appreciation to the Endowment and Research Foundation of Montana State University for their generous support of this work. Special thanks also to Professor A. Paul Krapcho (University of Vermont, Burlington, Vermont) for analytical data on some of the compounds.

(12) L. A. Paquette and P. C. Storm, *J. Amer. Chem. Soc.*, **91**, 7657 (1969).

(13) R. L. Frank, R. D. Emmick, and R. S. Johnson, *ibid.*, **69**, 2363 (1947).

(14) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962, Chapter 13.

(15) H. C. Brown and P. J. Gaoghengan, Jr., *J. Org. Chem.*, **35**, 1844 (1970).

Epoxidation. III. The Relative Reactivities of Some Representative Olefins with Peroxybenzimidic Acid[1]

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We recently reported[3] that the stereochemistry of epoxidation of conformationally biased methylenecyclohexanes with peroxybenzimidic acid (formed *in situ* from benzonitrile and alkaline hydrogen peroxide[4]) differed significantly from the results obtained with a variety of peracids, and these results have been confirmed in an independent study by Sykes.[5] We earlier suggested that the observed difference in stereochemistry resulted from the greater reactivity of the peroxybenzimidic acid. In order to test this hypothesis we have examined the relative reactivities of some representative olefins with peroxybenzimidic acid utilizing the competition technique. The results of these studies are summarized in Table I along with some comparative data for peracid epoxidation[6] and methylenation.[7]

In addition, 4-vinylcyclohexene and *d*-limonene were epoxidized with 0.1 equiv of *m*-chlorperbenzoic acid and 0.1 equiv of peroxybenzimidic acid and the results of these experiments are summarized in Figures 1 and 2.

It is clear from these results that peroxybenzimidic acid is a far less selective reagent for the epoxidation of double bonds than are peracids. Although the reaction of peracids with alkenes is very markedly accelerated by the presence of electron-donating alkyl groups and a trisubstituted double bond is epoxidized approximately 275–300 times as fast as a monosubstituted double bond, the relative rates are greatly attenuated with peroxybenzimidic acid and the trisubstituted double bond is only five times as reactive as a monosubstituted olefin. As in peracid oxidations,[6] however, the cis isomer of a cis–trans pair is oxidized more rapidly. In contrast to a number of other addition reactions,[7] cyclopentene is oxidized less readily than both cyclohexene and cycloheptene.

This study indicates that peroxybenzimidic acid is a relatively indiscriminate reagent and is not the reagent of choice for selective epoxidation of polyunsaturated substrates. The data are consistent with a transition

(1) For part II, see R. G. Carlson and R. Ardon, *J. Org. Chem.*, **36**, 216 (1971).

(2) Alfred P. Sloan Foundation Research Fellow, 1970–1972.

(3) R. G. Carlson and N. S. Behn, *J. Org. Chem.*, **32**, 1363 (1967).

(4) G. B. Payne, *Tetrahedron*, **18**, 763 (1962), and references cited therein.

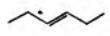
(5) J. D. Ballantine and P. J. Sykes, *J. Chem. Soc. C*, 731 (1970).

(6) D. Swern, *J. Amer. Chem. Soc.*, **69**, 1692 (1947).

(7) B. Rickborn and J. H. Chan, *J. Org. Chem.*, **32**, 3576 (1967).

TABLE I

RELATIVE RATES OF EPOXIDATION AND METHYLENATION OF SOME REPRESENTATIVE OLEFINS (CYCLOHEXENE = 1.00)

Olefin	Registry no.	PhC(=NH)-O$_2$H	CH$_3$-CO$_3$H	ICH$_2$ZnI
	563-79-1	3.5		1.29[a]
	513-35-9	2.1	7.95[b]	2.18[a]
	13269-52-8	0.9	1.00[c,d]	0.42[a]
	7642-09-3	1.3	1.00[c,d]	0.83[a]
	592-41-6	0.4	0.039[b]	0.36[a]
	498-66-8	3.8	1.2[e]	1.70[f]
	628-92-2	2.03	1.36[c]	1.18[f]
	142-29-0	0.92	1.43[b]	1.60[f]
	1192-37-6	1.46		3.84[f]

[a] E. P. Blanchard and H. E. Simmons, *J. Amer. Chem. Soc.*, **86**, 1337 (1964). [b] J. Boeseken and J. Stuurman, *Recl. Trav. Chim. Pays-Bas*, **56**, 1034 (1937). [c] J. Boeseken and C. J. Hanegraaff, *ibid.*, 61, 69 (1942). [d] The cis and trans isomers were not determined separately. [e] Value for perlauric acid in chloroform: K. D. Bingham, G. D. Meakins and G. H. Whitham, *Chem. Commun.*, 445 (1966). [f] Reference 7.

state that is reached somewhat earlier along the reaction coordinate than the corresponding transition state for peracid epoxidation.[3]

Experimental Section

Competition Experiments.—A solution of equimolar amounts of the appropriate olefin and cyclohexene in methanol was treated with 0.05 equiv of toluene (internal standard), benzonitrile, hydrogen peroxide, and potassium bicarbonate. The resulting solution was stirred overnight and analyzed by vapor phase chromatography on an F & M 700 gas chromatograph. The detector had been previously calibrated by preparing working curves from solutions containing varying amounts of toluene, cyclohexene oxide, and an authentic sample of the appropriate epoxide. All values reported in Table I are averages of two or more runs. Authentic samples of each epoxide were prepared by epoxidation of the appropriate olefin with *m*-chloroperbenzoic acid in methylene chloride.

Epoxidation of *d*-Limonene. A. With *m*-Chloroperbenzoic Acid.—To a solution of 2.00 g (14.6 mmol) of *d*-limonene in 75 ml of dry methylene chloride at 0° was added 3.15 g (14.6 mmol) of 80% *m*-chloroperbenzoic acid in 60 ml of methylene chloride over a period of 30 min. After the solution was stirred for 1 hr, the excess peracid was destroyed with 5 ml of 10% sodium sulfite solution and the methylene chloride solution was washed carefully with 100 ml of saturated sodium bicarbonate solution, the organic layer separated, and the aqueous layer was washed twice with methylene chloride. The organic layers were combined, washed with brine, dried, evaporated, and distilled to afford 1.28 g (58%) of product, bp 87–90° (15 mm) [lit.[8] bp 92–94° (20 mm)]. Vpc analysis[9] indicated the presence of 12% unreacted *d*-limonene, 87% 1,2-oxide,[10] and 0.5% 8,9-oxide. The 1,2-oxide was collected by preparative vpc and exhibited ir absorption at 3090 (vinyl H), 2985, 2945, 2870, 1645 (double bond), 1440, 1340, 1115, 887 (>C=CH$_2$), 838, and 668 cm^{-1} and nmr absorption at δ 4.67 (2 H, broad, >C=CH$_2$), 2.75–2.92 (1 H, epoxy CH), 1.68 (3 H, J = 1.0 Hz, >C=CCH$_3$), 1.3–2.3 (7 H, m), and 1.25 (3 H, s, epoxy CCH$_3$).

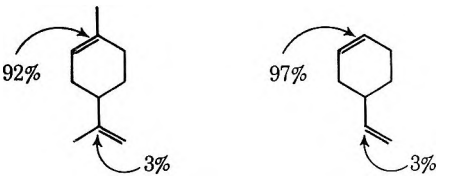


Figure 1.—Site of attack by *m*-chloroperbenzoic acid in methylene chloride in epoxidation of limonene and 4-vinylcyclohexene.

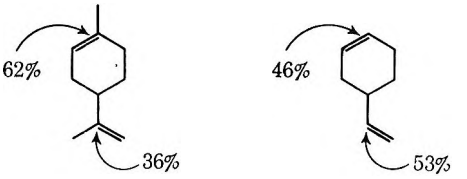


Figure 2.—Site of attack by peroxybenzimidic acid in epoxidation of limonene and 4-vinylcyclohexene.

B. With Hydrogen Peroxide–Benzonitrile.—A solution of 0.1 g (0.74 mmol) of *d*-limonene, 8 mg (0.074 mmol) of 30% hydrogen peroxide, 9 mg (0.074 mmol) of benzonitrile, 0.5 ml of methanol, and 25 mg of potassium bicarbonate was stirred at room temperature for 4 days. The mixture was diluted with water and extracted three times with pentane, and the combined pentane layers were washed with water and brine. The crude product obtained after distillation of the pentane was analyzed by vpc[9] and found to consist of 61% 1,2-oxide, 37% 8,9-oxide, and 2% diepoxide of undetermined stereochemistry. A sample of the 8,9-oxide[11] collected by preparative vpc exhibited ir absorption at 3050, 3020, 2980, 2920, 1440, 1345, 1150, 1109, 1070, 1045, 915, and 903 cm^{-1} and nmr absorption at δ 5.37 (1 H, broad s, >C=CH), 2.35–2.60 (2 H, dd, epoxy CH$_2$), 1.3–2.2 (10 H, m), 1.63 (3 H, s, >C=CCH$_3$), and 1.20 (3 H, s, epoxy CCH$_3$).

Epoxidation of 4-Vinylcyclohexene. A. With *m*-Chloroperbenzoic Acid.—Epoxidation of a 1.00-g (9.7 mmol) sample of 4-vinylcyclohexene with 1.95 g (9 mmol) of 80% *m*-chloroperbenzoic acid by the above procedure afforded 1.03 g (93%) of crude product. Vpc analysis[9] indicated the presence of 10% unreacted starting material, 88% 1,2-oxide,[12] and 2% 7,8-oxide. A sample of the 1,2-oxide collected by preparative vpc exhibited ir absorption at 3050, 3010, 2860, 1650, 1440, 1340, 1260, 992, 915, 871, 852, and 660 cm^{-1} and nmr absorption at δ 4.75–6.00 (3 H, m, CH=CH$_2$), 3.01 (2 H, m, epoxy CH), and 1.2–2.4 (7 H, m).

The previously uncharacterized 7,8-oxide exhibited ir absorption at 3050, 3010, 2990, 2945, 2855, 1655, 1480, 1455, 1440, 1360, 1250, 1192, 1141, 1044, 940, 932, 920, 878, 854, and 654 cm^{-1} and nmr absorption at δ 5.65 (2 H, br s, CH=CH), 2.3–2.5 (1 H, dd, J = 5.2, 2.7 Hz, epoxy CH), 2.5–2.85 (2 H, m, epoxy CH$_2$), and unresolved absorption in the region 1.2–2.3 (7 H).

B. With Hydrogen Peroxide–Benzonitrile.—Epoxidation of 0.1 g of 4-vinylcyclohexene using the same procedure as was used for *d*-limonene gave a crude product which was shown by vpc[9] to consist of 46% 1,2-oxide, 53% 7,8-oxide, and 1% diepoxide.

Registry No.—Peroxybenzimidic acid, 20996-66-1; *m*-chloroperbenzoic acid, 937-14-4; *d*-limonene, 5989-27-5; 4-vinylcyclohexene, 100-40-3; *d*-limonene 1,2-oxide, 10008-60-3; *d*-limonene 8,9-oxide, 31684-93-2; 4-vinylcyclohexene 1,2-oxide, 106-86-5; 4-vinylcyclohexene 7,8-oxide, 5116-65-4.

(8) E. E. Royals and J. C. Leffingwell, *J. Org. Chem.*, **31**, 1937 (1966).

(9) A 10 ft × 0.25 in. column packed with 10% Carbowax 20M and 10% sodium hydroxide on 60–80 mesh Chromosorb W was employed for this analysis.

(10) J. Richer and G. Perrault, *Can. J. Chem.*, **43**, 18 (1965).

(11) J. P. Bain, W. Y. Gary, and E. A. Klein, U. S. Patent 3,014,047 (1962); *Chem. Abstr.*, **57**, 12557a (1962).

(12) F. C. Frostick, Jr., B. Phillips, and P. S. Starcher, *J. Amer. Chem. Soc.*, **81**, 3350 (1959).

Dipole Moment and Structure Assignments of *cis*- and *trans*-Chloroiodoethene

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Van de Walle and Henne[1] prepared the geometric isomers of chloroiodoethene by absorption of acetylene gas by a solution of ICl in aqueous HCl. The isomers were resolved as azeotropic components by fractionally distilling the product mixture with an equal weight of 1-propanol. Their structural assignments were based on the relative rates of dehydrohalogenation with alcoholic KOH. Since trans elimination is faster than cis,[2] the faster isomer was assigned *cis*-chloroiodoethene (*i.e.*, hydrogen and iodine trans). The physical properties of the isomers (Table I) are consistent with this structural assignment. However, dielectric constants (ϵ) and dipole moments ($\bar{\mu}$) reported by Errera[3] are anomalous with respect to the Van Arkel dipole rule[4] (Table II) (*i.e.*, the isomer with the higher dipole moment has the higher value for each physical property).

TABLE I
PHYSICAL PROPERTIES OF CHLOROIODOETHENE[1]

	Trans	Cis
Bp of propanol azeotrope, °C	87.5–88.5	93.6–94.0
Bp, °C	113–114	116–117
Fp, °C	−41.0	−36.4
d^0_4	2.1355	2.2399
d^{15}_4	2.1048	2.2080
nD	1.57146	1.58288
Rel reaction rate with KOH	0.55	1.00

TABLE II
DIELECTRIC PROPERTIES OF CHLOROIODOETHENE OF ERRERA[3]

	Trans	Cis
ϵ	2.95	2.72
$\bar{\mu}$, D	1.27	0.57

In view of the electronegativity of chlorine and iodine, one would expect the dipole moment of the cis isomer to be greater than that of the corresponding trans isomer. This anomaly could be explained on the grounds that iodine may be electron donating rather than withdrawing. However, as pointed out by Eliel,[5] this seems unlikely in view of the fact that the dipole moment of *p*-chloroiodobenzene closely corresponds to the difference of the dipole moments of chlorobenzene and iodobenzene rather than the sum of these moments. It would seem that either the structures or the dipole moments of the chloroiodoethene isomers have been misassigned.

Both isomers were prepared in our laboratory by iodination of *cis*- and *trans*-chlorovinylmercuric chloride[6] and by the direct addition of iodine monochloride to acetylene.[1] Structure assignments were made from a study of the ir C–H out-of-plane bending frequencies and in particular, the nmr AB coupling constants. A second-order analysis of the AB spectra of the high- and low-boiling isomers of chloroiodoethene shows J_{AB} = 5.8 and 13.5 Hz, respectively. The molecular spectra clearly confirm the original dehydrohalogenation kinetic assignments of Van de Walle and Henne[1] (Table I). The spectral data also enable us to conclude that the iodination of chlorovinylmercuric chloride proceeds with retention of configuration. The dipole moments of the *trans*-chloroiodoethene in benzene and cyclohexane are 0.549 ± 0.006 and 0.519 ± 0.006 D, respectively. Since these values agree in magnitude with the moment Errera[3] reported for the cis isomer (Table II), we conclude that the measurements were assigned to the wrong isomer.

Experimental Section

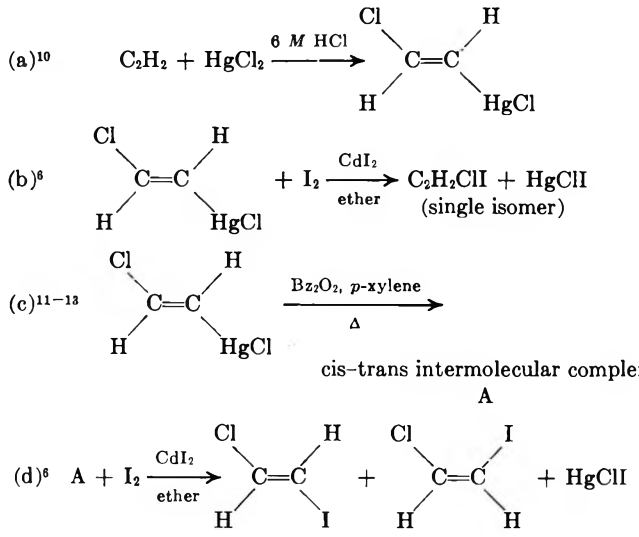
Measurements.—Thin layer chromatograms were obtained on silica gel G with methanol solvent using iodine vapor for detection. Vapor phase chromatograms were recorded with a Perkin-Elmer 154L vapor fractometer equipped with a 3 mm × 1.53 m column of 8% di-*n*-nonyl phthalate on 90–100 mesh Ankron ABS with a helium flow rate of 20 ml/min and column temperature of 115°. Ultraviolet spectra were obtained with a Beckman Model DBG spectrophotometer. Infrared spectra were measured with a Perkin-Elmer 337 spectrometer. The nmr spectra were recorded with Varian Models A-56/60 and A-60 spectrometers. Mass spectra were obtained with a Consolidated Electrodynamic Corp. CEC 21-104 spectrometer. Gc–mass spectra were recorded on a Finnigan Corp. Series 3000 system at 70 eV. The dipole moments were obtained from dielectric measurements made with a dielectrometer constructed in our laboratory. This instrument utilizes a circuit similar to that developed by Chien.[7] A Model 2TN20LV dielectric cell (purchased from Balsbaugh Laboratories, Duxbury, Mass.) was modified so that samples could be transferred into or out of the cell without disassembling or moving it. All dielectric constant measurements were made in cyclohexane or benzene at 25.00 ± 0.05°. Density measurements were made with a Sartorius Model 2743 balance and a 25-ml volumetric flask. The dipole moments were calculated from a least-squares analysis of dielectric and density data by the Hedestrand procedure,[8] ignoring atomic polarizations.

Materials.—Reagent grade benzene, cyclohexane, and *p*-xylene were purified by conventional methods.[9] Dielectric solvents were stored over type 4A molecular sieve under nitrogen in brown bottles and were distilled weekly. Analytical grade diethyl ether was purchased from Eastman Organic Chemicals. Iodine monochloride was purchased from Alfa Inorganics. The propanol, benzoyl peroxide, cadmium iodide, iodine, iodine monochloride, and mercuric chloride were Baker Analyzed reagent grade. Acetylene was purchased from local suppliers and scrubbed with a 30% solution of $HgCl_2$ in aqueous HCl.

The isomers of chloroiodoethene were prepared by two independent methods, I and II.

(1) H. Van de Walle and A. Henne, *Bull. Sci. Acad. Roy. Belg.*, [5] **11**, 360 (1925).
(2) M. Lepingle, *Bull. Soc. Chim. Fr.*, [4] **39**, 741 (1926).
(3) J. Errera, *Z. Physik.*, **29**, 689 (1928).
(4) A. E. Van Arkel, *Recl. Trav. Chim. Pays-Bas*, **52**, 719 (1933); **53**, 91 (1934).
(5) E. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 326.
(6) I. P. Beletskaya, O. A. Reutov, and V. I. Karpov, *Izv. Akad. Nauk SSR, Otd. Khim. Nauk*, 1961 (1961); *Chem. Abstr.*, **58** 6670 (1963).
(7) J.-Y. Chien, *J. Chem. Educ.*, **24**, 494 (1947).
(8) G. Hedestrand, *Z. Physik. Chem.*, **B2**, 428 (1929).
(9) A. Weissberger, "Technique of Organic Chemistry," 2nd ed, Vol. VII, Interscience, New York, N. Y., 1955.

Method I



trans-**2-Chlorovinylmercuric Chloride (Ia).**[10]—The product was recrystallized from chloroform: mp 122° (lit.[12] 123°); tlc R_f 0.52; uv max (EtOH) 212 nm (lit.[14] 212 nm); ir (KBr pellet) 3050–3100 (CH), 1570 (C=C), 940 cm^{-1} (CH, trans).

trans-**Chloroiodoethene (Ib).**[6]—The product was vacuum distilled from HgClI and CdI_2: bp 113° (755 mm) (lit.[1] 113–114° (760 mm) (trans), 116–117° (cis)]; vpc retention time 1.12 min; ir (KBr) 3080 (CH), 1545 (C=C), 1600 and 1630 (Fermi resonance of the C=C fundamental at 1545 and the first overtone of the strong band at 797), 902 cm^{-1} (CH, trans); nmr (acetone-d_6, TMS) δ 6.57 ppm (AB, $\delta\nu$ 10.7 Hz, J_{AB} = 13.5 Hz); mass spectrum *m/e* 188 ($C_2H_2ClI^+$) with prominent P + 2 at 190, characteristic of Cl, 61 (base), and 63 ($C_2H_2Cl^+$).

Cis–Trans Intermolecular Complex of Chlorovinylmercuric Chloride (Ic).[11-13]—*trans*-Chlorovinylmercuric chloride was isomerized in dry *p*-xylene with benzoyl peroxide catalyst at 95° for 10 hr. The hot mixture was filtered. The filtrate was cooled to give (75%) the complex (A) which was recrystallized from CCl_4: mp 74.5° (lit.[11,13] 76°); tlc R_f 0.73; uv max (EtOH) 211 nm; ir (KBr pellet) 3000–3075 (CH), 1585 (C=C), 930 (CH trans), and 692 cm^{-1} (CH, *cis*); nmr spectrum is identical with that reported by Wells and Kitching.[12]

cis- and *trans*-**Chloroiodoethene (Id).**[6]—The iodination of the intermolecular mercury complex (A) was carried out by a modification of the method of Beletskaya, Reutov, and Karpov.[6] Ten grams of the complex (A) and 8.40 g (0.0331 mol) of I_2 with 0.5 g of CdI_2 catalyst were stirred for 36 hr in 100 ml of diethyl ether. After removing the ether by distillation, the reaction mixture was treated with an equal volume of 1-propanol, and the azeotropic mixture of the *cis*- and *trans*-chloroiodoethene was resolved by distillation on a spinning-band column. The 87.5–88.5° fraction was found to contain the trans isomer, with properties identical with those of the product of Ib. The 93.6–94.0° fraction contained the cis isomer: vpc retention time 1.36 min; nmr (acetone-d_6, TMS) δ 6.81 ppm (AB, $\delta\nu$ 4.4 Hz, J_{AB} = 5.8 Hz); gc–mass spectrum is identical with the spectrum of the trans isomer. The preparation was not sufficiently pure for ir or dielectric measurements.

Method II[1]

$$C_2H_2 + ICl \xrightarrow{6\ M\ HCl} C_2H_2ClI + \text{other products}$$

A mixture of *cis*- and *trans*-chloroiodoethene was prepared by the direct addition of iodine monochloride to acetylene as described by Van de Walle and Henne.[1] The vpc retention times, nmr AB spectra, and gc–mass spectra of the cis and trans isomers were found to be identical with those of the products of reactions Ib and Id.

The dielectric constant and density data used for the calculation of the dipole moment of *trans*-chloroiodoethene in benzene and cyclohexane are summarized in Table III.

TABLE III
DIELECTRIC CONSTANT AND DENSITY OF *trans*-CHLOROIODOETHENE

Benzene			Cyclohexane		
N_2	d	ϵ	N_2	d	ϵ
0.00980	0.8781	2.280	0.01088	0.7826	2.036
0.01429	0.8831	2.282	0.01443	0.7851	2.039
0.02037	0.8906	2.286	0.02011	0.7922	2.042
0.03080	0.9027	2.290	0.03066	0.8034	2.048
0.03630	0.9095	2.293	0.04107	0.8148	2.054
α = 0.469, β = 1.19			α = 0.580, β = 1.08		
$P_{2\infty}$ = 35.0 CC			$P_{2\infty}$ = 35.0 CC		
ϵ_1 = 2.276, d_1 = 0.8663			ϵ_1 = 2.030, d_1 = 0.7703		

Registry No.—*trans*-2-Chlorovinylmercuric chloride, 1190-78-9; *trans*-chloroiodoethene, 28540-81-0; *cis*-chloroiodoethene, 31952-74-6.

Acknowledgment.—This research was supported by the Council for Faculty Research, Eastern Illinois University.

(10) A. N. Nesmeyanov and R. Kh. Freidlina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 150 (1945); *Chem. Abstr.*, **40**, 3451 (1946).

(11) A. N. Nesmeyanov and A. E. Borisov, *Akad. Nauk SSSR, Inst. Org. Khim., Sin. Org. Soedin., Sb.*, **2**, 146 (1952); *Chem. Abstr.*, **48**, 567d (1954).

(12) P. R. Wells and W. Kitching, *Aust. J. Chem.*, **17**, 1204 (1964).

(13) A. N. Nesmeyanov, A. E. Borisov, E. I. Fedin, V. S. Petrosyan, and O. A. Reutov, *Dokl. Akad. Nauk SSSR*, **178**, 1094 (1968).

(14) R. Freidlina and A. Nesmeyanov, *C. R. Acad. Sci. URSS*, **26**, 60 (1940).

O-Triphenylmethylhydroxylamine (Trityloxyamine), a Useful O-Protected Form of Hydroxylamine

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In connection with other work, a protected form of hydroxylamine was required in which substitution would be rigorously restricted to the nitrogen atom and which would be soluble in aprotic solvents.[1] It was also necessary that the protecting group be readily cleaved under mild acidic conditions. This report describes the preparation and some properties of *O*-triphenylmethylhydroxylamine (trityloxyamine), $(C_6H_5)_3CONH_2$, an O-protected hydroxylamine which fulfills these requirements.

Acylation of the amine function of hydroxylamine does not usually require protection of the hydroxyl group. The conditions under which such reactions are usually carried out give the *N*-acyl derivative as the only isolable product. Jencks[2] has described a number of cases, however, wherein certain acylating agents under controlled conditions can give high yields of the *O*-acyl derivative. Evidently, *O*-acylhydroxylamines are often the initial product. Unless the conditions of the reaction and work-up are carefully controlled, rearrangement to the more stable *N*-acyl form occurs.

(1) The preparation of solutions of free hydroxyamine of appreciable concentration usually requires the use of aqueous or alcoholic solvents due to the polar characteristics of hydroxylamine and the salts from which it is usually prepared.

(2) W. P. Jencks, *J. Amer. Chem. Soc.*, **80**, 4581 (1958).

Similarly, alkylation of hydroxylamine usually occurs at the nitrogen atom due to the greater nucleophilicity of the amino group in this type of reaction. However, when dialkylation with highly reactive halides is carried out, O,N disubstitution can occur in addition to the usual N,N-dialkylation.[3,4]

Trityloxyamine was readily prepared by the hydrazinolysis of *N*-trityloxyphthalimide[5] which was in turn prepared by the tritylation of *N*-hydroxyphthalimide according to the method of McKay, *et al.*[6] It is a stable solid which gives *O*-trityl oximes with reactive aldehydes and ketones. The reactions of trityloxyamine with benzaldehyde and with acetone were essentially complete in a few minutes. With the less reactive fluorenone, no reaction could be detected even after a long reflux period. The usual acid catalyst was necessarily avoided in these reactions. Examples of the facile acylation reactions which trityloxyamine undergoes will be published in connection with other work.

As expected, trityloxyamine and related compounds were readily detritylated by hydrogen chloride in benzene at room temperature.[7] The cleavage products were obtained in excellent yield (see Experimental Section).

Compounds described in the literature which have received some use as O-protected forms of hydroxylamine include *O*-benzylhydroxylamine (benzyloxyamine) and *O*-(2-tetrahydropyranyl)hydroxylamine. In the respective cases, reductive methods[8,9] and ethanolic hydrogen chloride[10] were used to remove the protecting groups.

The literature describes two unsuccessful attempts to prepare trityloxyamine. Schumann and coworkers[5] failed to obtain a pure product by essentially the method described here. Leffler and Bothner-By[11] were similarly unable to obtain it by the alkaline hydrolysis of trityl benzohydroxamate.

Experimental Section

Melting points were taken in capillaries and are uncorrected. Infrared spectra were determined on a Beckman IR-8 infrared spectrophotometer. Ultraviolet spectra were determined on a Beckman DK-2A recording spectrophotometer. Microanalyses were performed by the Analytical and Physical Chemistry Section, Warner-Lambert Research Institute, under the direction of Mr. Arnold Lewis.

N-Hydroxyphthalimide.—To a vigorously stirred solution of hydroxylamine prepared by adding a solution of 74.4 g (1.86 mol) of sodium hydroxide in 200 ml of water *to* a solution of 153.5 g (0.935 mol, 1.87 equiv) of hydroxylamine sulfate[12] in 200 ml of water was added 220 g (1.5 mol) of finely powdered phthalic anhydride.[13] As soon as crystals began to appear, an additional 500 ml of water was added and the mixture was allowed to stand overnight at *ca.* 4°. The solid was filtered, washed with ice water containing a little acetic acid, and air-dried. The product, mp 235–237°;[14] ir (mineral oil) 3130, 1790, 1740, 1710 cm^{-1}, weighed 196 g (80%).

N-Trityloxyphthalimide.—Powdered trityl chloride (16.7 g, 60 mmol) was added to a vigorously stirred solution of 9.8 g (60 mmol) of *N*-hydroxyphthalimide and 8.8 ml of triethylamine in 18 ml of *N*,*N*-dimethylformamide. The mixture was stirred for 20 min and allowed to stand for 36 hr. The solid mass was broken up, made pourable by the addition of 2-propanol, and added to 500 ml of water. The solid was filtered, redispersed with a Waring Blendor in water containing a little sodium carbonate solution, and filtered; the filter cake was washed with water and dried to give 23.6 g (97%) of white powder, mp 180–183.5°, softening above 175°. Analytically pure material, obtained by several recrystallizations from benzene–ligroin, had mp 182–184°;[15] ir (mineral oil) 1770, 1720 cm^{-1}.

Anal. Calcd for $C_{27}H_{19}NO_3$: C, 79.98; H, 4.72; N, 3.46. Found: C, 79.97; H, 4.74; N, 3.70.

Trityloxyamine.—To a stirred solution of 23.6 g (58 mmol) of *N*-trityloxyphthalimide in 75 ml of methylene chloride was added 6.0 ml (120 mmol) of hydrazine hydrate in 10 ml of methanol. After 30 min the solid phthalazine-1,4-dione was dissolved by the addition of 100 ml of 5 *M* ammonium hydroxide. The aqueous layer was removed and extracted with 20- and 10-ml portions of methylene chloride, and the combined extract was washed with brine, dried (K_2CO_3), stirred with decolorizing charcoal (Darco), and filtered, and the filtrate was evaporated on a rotating evaporator. The residue was recrystallized from 25 ml of methanol to give 12.0 g (75%) of white crystals, mp 83–88.5°. Additional recrystallizations from 2-propanol afforded an analytical sample: mp 82.5–85.5°; ir (CCl_4) 1580, 1490, 1450, 1035, 970, 705 cm^{-1}.

Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 83.08; H, 6.22; N, 5.08.

***O*-Tritylacetoxime.**—Trityloxyamine (137 mg) was dissolved in 0.2 ml of acetone. Separation of the crystalline product began within 10 min. After 3 days at −5°, the product was filtered and washed with 2-propanol at −5° to give 140 mg (89%) of product with mp 115.5–118°. Recrystallization of similar material twice from 2-propanol afforded pure material: mp 114–116.5°; ir (CCl_4) 1599, 1492, 1450, 970, 920, 700 cm^{-1}.

Anal. Calcd for $C_{22}H_{21}NO$: C, 83.77; H, 6.71. Found: C, 83.64; H, 6.93.

***O*-Tritylbenzaldoxime.**—Trityloxyamine (275 mg) and benzaldehyde (134 mg) in 2 ml of methanol, allowed to stand for 2 hr, afforded 333 mg (92%) of crude product, mp 100–110°. Three recrystallizations from 2-propanol gave material with constant mp 111–114°, uv (cyclohexane) λ_{max} 262 nm (log ϵ 4.27), λ_{min} 236 (3.95). Cope and Haven[3] prepared this compound by rearrangement of the nitrone obtained by condensing *N*-tritylhydroxylamine with benzaldehyde. They report mp 119.5–120.5°, uv λ_{max} 261.5 nm (log ϵ 4.28), λ_{min} 237 (4.0). Stieglitz and Leach[16] found mp 114° for material prepared by the nitrone method.

Cleavage of *N*-Trityloxyphthalimide with Hydrogen Chloride.—*N*-Trityloxyphthalimide (127 mg) in 3 ml of dry benzene was treated with hydrogen chloride gas until precipitation was complete. The mixture was centrifuged and the precipitate was washed several times with benzene by centrifugation. Evaporation of the combined supernatants afforded 87 mg (99%) of trityl chloride, mp 110–112°. The identity was confirmed by mixture mp and ir spectrum.

The residue consisted of 48 mg (104%) of *N*-hydroxyphthalimide, mp 224–229°. The identity was confirmed by the ir and by treatment with aqueous alkali to give an orange-yellow color.

Cleavage of Trityloxyamine with Hydrogen Chloride.—Trityloxyamine (350 mg) in 2 ml of dry benzene was treated with dry hydrogen chloride for 5 min. The precipitate was centrifuged, washed with benzene, and filtered to give 80 mg (90%) of hydroxylamine hydrochloride, mp 154–155.5°. The identity was confirmed by mixture melting point and ir spectrum.

(3) A. C. Cope and A. C. Haven, Jr., *J. Amer. Chem. Soc.*, **72**, 4896 (1950).
(4) W. Kliegel, G. Zinner, and R. Vollrath, *Justus Liebigs Ann. Chem.*, **736**, 173 (1970).
(5) E. L. Schumann, R. V. Heinzelman, M. E. Greig, and W. Veldkamp, *J. Med. Chem.*, **7**, 329 (1964).
(6) A. F. McKay, D. L. Garmaise, G. Y. Paris, and S. Gelblum, *Can. J. Chem.*, **38**, 343 (1960).
(7) E. Schröder and K. Lübke, "The Peptides," Academic Press, New York, N. Y., 1965, pp 46, 229.
(8) D. Ames and T. Grey, *J. Chem. Soc.*, 631 (1955).
(9) E. C. Taylor and J. W. Barton, *J. Org. Chem.*, **24**, 127 (1959).
(10) R. N. Warrener and E. N. Cain, *Angew. Chem.*, **78**, 491 (1966).
(11) J. E. Leffler and A. A. Bothner-By, *J. Amer. Chem. Soc.*, **73**, 5473 (1951).
(12) The hydrochloride is equally satisfactory.
(13) Commercial phthalic anhydride was ground in a ball mill and passed through a fine mesh sieve.
(14) (a) W. R. Orndorff and D. S. Pratt, *Amer. Chem. J.*, **47**, 89 (1912), report mp 220–226° for crude product prepared by a slightly different procedure. (b) L. Bauer and S. Miarka, *J. Amer. Chem. Soc.*, **79**, 1983 (1957), report mp 227–230° for crude and 233° for recrystallized product.
(15) Schumann, *et al.*,[3] give mp 186–187°.
(16) J. Stieglitz and P. Leech, *ibid.*, **36**, 272 (1914).

Evaporation of the benzene solution afforded 257 mg (72%) of trityl chloride, mp 108–111°. The identity was confirmed by mixture melting point and ir spectrum.

Registry No.—*N*-Hydroxyphthalimide, 524-38-9; *N*-trityloxyphthalimide, 31938-10-0; trityloxyamine, 31938-11-1; *O*-tritylacetoxime, 31938-12-2; *O*-tritylbenzaldoxime, 31938-13-3.

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Electron Spin Resonance Investigation of the 2-Furanylmethyl Radical. Calculation of Its Geometry and Rotational Barrier by INDO

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Because of its great importance in the theory of odd alternant radicals, the benzyl radical has been repeatedly investigated both experimentally and theoretically.[1-4] Heterocyclic analogs of benzylic and similar radical systems have been largely unstudied. One exception is Hudson's[5] report of the esr spectra of both the 2-thenyl and 3-thenyl radicals generated in solution during the steady-state photolysis of di-*tert*-butyl peroxide in the presence of 2-methyl- and 3-methylthiophene, respectively. In both the 2-thenyl and 3-thenyl radicals, the methylene protons were nonequivalent, but π-electron calculations of the McLachlan approximate SCF method did not provide any insight into this nonequivalence.[5] As long as the methylene group's rotational barrier is large, one would expect nonequivalence from a consideration of symmetry. Similar examples of magnetic inequivalence include the allyl[6] and substituted allyl[7] radicals. In these radicals more sophisticated, all-valence electron calculations, such as the INDO technique, correctly predict this inequivalence.[8]

We now report the esr spectrum of the 2-furanylmethyl radical, I, which was obtained during the steady-state photolysis of solutions of di-*tert*-butyl peroxide and 2-methylfuran at temperatures between −30 and −80° in the esr cavity.[9] The spectrum exhibited 32 lines due to the inequivalence of the methylene protons and showed a signal to noise ratio at −80° similar to that observed[5] for the 2-thenyl radical. The inequivalence persisted even at −30° and the only change in the spectrum observed on warming was a drastic decrease in intensity.

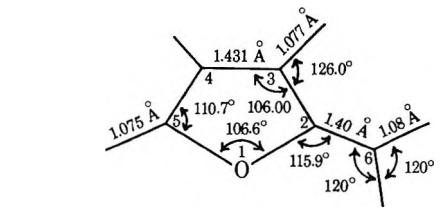


Figure 1.—Geometry of radical I used in INDO calculations.

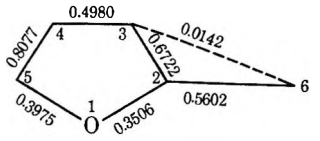
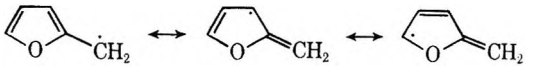


Figure 2.—Calculated π-bond orders of the 2-furanylmethyl radical.



a b c

I

The experimental hyperfine splittings, as determined by a computerized best fit to the experimental spectrum, are listed in Table I. Table II summarizes the g values determined for the benzyl, 2-thenyl, and 2-furanylmethyl radicals.[10] The g-value variation is both a function of the size of the spin–orbit coupling for carbon, oxygen, and sulfur and the energy of the molecular orbital occupied by the odd electron.[11] The 0.0004-g value increase for the 2-thenyl over the 2-furanylmethyl radical is a measure of the increase in the size of the spin–orbit coupling constant for sulfur and the amount of sulfur d- and p-orbital contribution to the radical. However, the difficulty of measuring the radical's excitation energy and the number of its excited states contributing to the Δg shift prevents a determination of the sulfur d-orbital contribution. Nevertheless, the larger isotropic g value of 2.0061 observed for the thiophene-2-carboxylic acid radical[12] suggests only a small sulfur d- and p-orbital contribution in the thenyl radical.

A series of INDO[8] calculations[13] were performed on I using the bond angles and lengths for the furan portion obtained by Bak[14] in his microwave study of furan. The methylene group was then attached and the parameters used are summarized in Figure 1.[15] The calcu-

(1) A. Carrington and I. C. P. Smith, *Mol. Phys.*, **9**, 137 (1965).
(2) A. Carrington, *Quart. Rev., Chem. Soc.*, **17**, 67 (1963).
(3) A. Carrington, J. R. Bolton, A. Forman, and L. E. Orgel, *Mol. Phys.*, **5**, 43 (1962).
(4) P. J. Krusic and J. K. Kochi, *J. Amer. Chem. Soc.*, **90**, 7155 (1968).
(5) A. Hudson, H. A. Hussain, and J. W. E. Lewis, *Mol. Phys.*, **16**, 519 (1969).
(6) R. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963).
(7) R. Livingston and H. Zeldes, *ibid.*, **44**, 1245 (1966).
(8) J. A. Pople, D. L. Beveridge, and P. A. Dobosh, *J. Chem. Phys.*, **47**, 2026 (1967); *J. Amer. Chem. Soc.*, **90**, 4201 (1968).
(9) The uv light from a 500-W PEK 500-2 lamp was filtered by a water filter and was focused on a sample held in a quartz variable-temperature esr dewar by a quartz condenser lens added to the quartz optics of a standard PEK M910 housing. Similar techniques to those previously reported by Kochi and Krusic were used. See J. K. Kochi and P. J. Krusic, *J. Amer. Chem. Soc.*, **91**, 1877, 1879, 3938, 3940, 3942, 3944, 6161 (1969); **93**, 846 (1971).
(10) The benzyl and 2-thenyl radicals were prepared in this study by the same photolysis technique used to generate the 2-furanylmethyl radical.
(11) A. J. Stone, *Mol. Phys.*, **6**, 509 (1963); **7**, 311 (1964). B. G. Segal, M. Kaplan, and G. K. Fraenkel, *J. Chem. Phys.*, **43**, 4191 (1965).
(12) B. Eda, R. J. Cook, and D. H. Whiffen, *Trans. Faraday Soc.*, **60**, 1497 (1964).
(13) The INDO program (CNINDO, QCPE No. 141) was obtained from the Quantum Chemistry Program Exchange, Indiana University, and it was modified for use on a Univac 1108 computer.
(14) B. Bak, D. Christensen, W. B. Dixon, L. Hansen-Hygaard, J. R. Anderson, and M. Schottlander, *J. Mol. Spectrosc.*, **9**, 124 (1962).
(15) The only bond which was optimized in the calculations was the 2–6 bond. While the bond distances in the ring will certainly change upon interaction with a CH_2· side chain, these changes would be relatively small.

TABLE I

THEORETICAL AND EXPERIMENTAL HYPERFINE SPLITTING CONSTANTS (IN GAUSS), CALCULATED CHARGE DENSITIES, AND S-ORBITAL SPIN DENSITIES FOR 2-FURANYLMETHYL RADICAL

	Position of hydrogen				
	3	4	5	6	6
Experimental hfs	8.79 ± 0.03	1.28 ± 0.02	7.87 ± 0.03	13.32 ± 0.03	13.01 ± 0.03
Calculated (INDO) *a*	9.40	3.29	6.44	14.79	14.67
b	8.23	2.93	5.59	16.59	16.49

	Atom					
	1	2	3	4	5	6
s-Orbital spin density	0.0011	−0.0180	0.0217	−0.0120	0.0153	0.0340
Charge density[c]	−217.0	+217.9	−43.9	−29.4	+164.9	−97.6

[a] Calculated using the 2–6 bond distance of 1.40 Å; this was the minimum energy calculation. [b] Calculated using the 2–6 bond distance of 1.46 Å. [c] Charge densities × 10^3.

TABLE II

THE *g* VALUES FOR BENZYL, 2-THENYL, AND 2-FURANYLMETHYL RADICALS IN SOLUTION

Radical	Average value of *g*, G[a]
Benzyl	2.00252
2-Furanylmethyl	2.00269
2-Thenyl	2.00312

[a] These values are the average of six individual determinations, with an approximate error of ±0.0001 G.

lated values of the hyperfine splittings summarized in Table I compare very closely with the observed spectrum and emphasize the inequivalence of the methylene protons. Table I also lists the s-orbital spin densities and atomic charge densities in I. The charge densities illustrate oxygen's high electronegativity, and adjacent carbons, 2 and 5, bear significant positive charge. As predicted by valence-bond theory, the largest amount of spin density is concentrated on carbons 6, 3, and 5. This is in agreement with the short 2–6 bond length of 1.40 Å, which indicates the existence of significant 2–6 double bond character and suggests that a large rotational barrier should exist. The calculated π-bond orders (shown in Figure 2) further substantiate this view. The 2–3 and 4–5 bonds have the highest π-bond order (see Ia), but the large π-bond order of the 2–6 bond indicates that resonance hybrids Ib and Ic may be correctly invoked in portraying a valence bond structure. Furthermore, the moderately high π-bond order of the 3–4 bond supports the use of Ic.

The barrier to rotation about the 2–6 bond was calculated. The planar conformation was found to be 25.16 kcal/mol more stable than the conformation in which the plane of the methylene group is perpendicular to the plane of the ring.[16] This large rotational barrier explains the observed spectral inequivalence of the methylene protons at −30° and further demonstrates the strong electronic interaction of the methylene group with the ring.

In conclusion, the inequivalence of the methylene protons in the 2-furanylmethyl radical has been explained, and good agreement with the esr hyperfine splittings has been obtained using an INDO molecular orbital calculation based on the experimental microwave structural data of furan providing that the 2–6 bond (methylene) distance has been optimized.

(16) As expected, the methylene protons become equivalent in this perpendicular conformation.

Registry No.—2-Furanylmethyl, 31902-01-9; benzyl, 2154-56-5; 2-thenyl, 25879-26-9.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research through Grant PRF-1495-G2, to the University of Alabama Computing Center for a generous amount of computer time, to Dr. Richard Fessenden of Carnegie-Mellon Radiation Labs for several discussions and circuit diagrams on the nmr tracking system used in this study, to Dr. Paul Krusic for valuable discussions, and to the National Science Foundation for a matching equipment grant for purchase of the Varian E-12 esr spectrometer and Varian Data machine's 620/i computer.

Polar Tautomer Dimerization of Ionic Arylazonaphthols in Water

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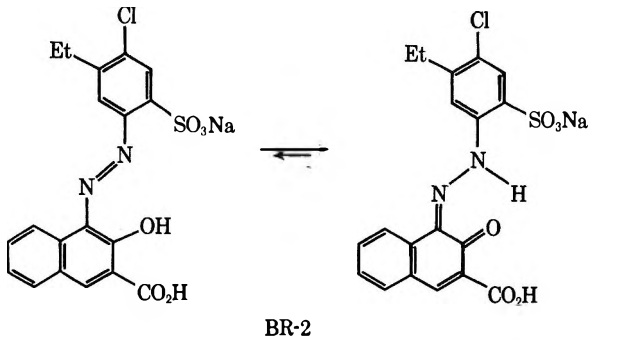
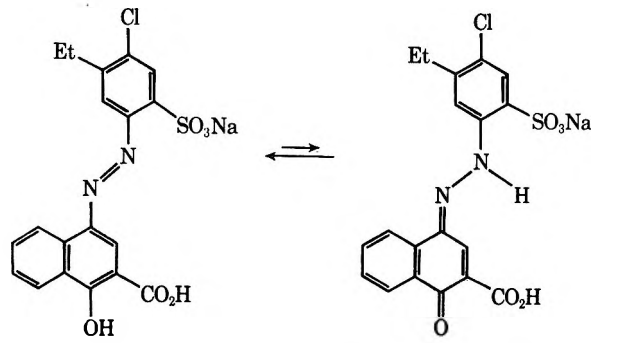
Recent spectroscopic investigations[1] on the aggregation of ionic 1-phenylazo-2-naphthols in aqueous and methanolic solutions have shown the existence of monomer–dimer equilibria in the 10^{-6}–10^{-4} *M* concentration range. The absorption spectra of the ionic hydroxy azo dyes with increasing dye concentration clearly indicate a decrease in the absorptive strength of the main absorption band accompanied by a hypsochromic shift in the peak maxima. The dimer spectra for several ionic 1-arylazo-2-naphthols show a strong H band on the high energy side of the monomer band and a weaker J band on the low energy side of the monomer transition. A study of the aggregation of this class of compounds is complicated by the fact that the molecules can exist in a quinone–hydrazone ⇌ azo–enol tautomeric equilibrium.

In this note we report on the dimerization processes involving the tautomeric species involved in eq 1. The BR-2 compound is a common ionic arylazonaphthol compound known as Bonadur Red. It has recently been spectroscopically shown to exist as a quinone–

(1) (a) A. R. Monahan and D. F. Blossey, *J. Phys. Chem.*, **74**, 4014 (1970); (b) A. R. Monahan, N. J. Germano, and D. F. Blossey, *ibid.*, **75**, 1227 (1971).



BR-2 (1)



BR-4

hydrazone species.[1] The BR-4 compound favors azo–enol tautomer formation, as do most 1-phenylazo-4-naphthols. The reasons for the shift in position of the tautomeric equilibrium are very complex and it is not the purpose of this note to explain them in detail. However, factors such as solvent stabilization of the 4-OH azo species and lower quinone stability (relative to the 2-OH quinone) of the respective hydrazone species[2,3] tend to favor azo-tautomer formation for the 4-OH dye.

The visible absorption spectra in aqueous acidic solution were measured in the concentration range 10^{-6}–10^{-4} M for the BR-2 and BR-4 molecules. The spectra were analyzed using previously reported computer techniques[1] which separate the monomer and dimer contributions to the spectra at each concentration along with a best fit equilibrium constant, where $K_{eq} = c_d/c_m^2$. Raman spectroscopy was used to determine the relative concentrations of tautomers in each dye system. Hence, the dramatic difference noted in the relative affinities of the two tautomers toward dimerization could be definitively proven for the first time. Possible reasons for the differences are discussed.

Experimental Section

BR-2 and BR-4 were prepared by standard preparative procedures[1b] from 2-amino-4-ethyl-5-chlorobenzenesulfonic acid (American Cyanamid) and 2-hydroxy-3-naphthoic acid (Eastman Organic Chemicals) or 1-hydroxy-2-naphthoic acid (Eastman Organic Chemicals). Purification of the starting materials was as reported previously.[1a] The isolated dyes were recrystallized twice from isopropyl alcohol–water solution, and subsequently vacuum dried prior to use.

Anal. Calcd for BR-2 ($C_{19}H_{13}N_2Na_2O_6SCl \cdot H_2O$): C, 45.8; H, 3.0; S, 6.4; Cl, 7.1; N, 5.6. Found: C, 46.0; H, 2.7; S, 6.2; Cl, 7.0; N, 5.9.

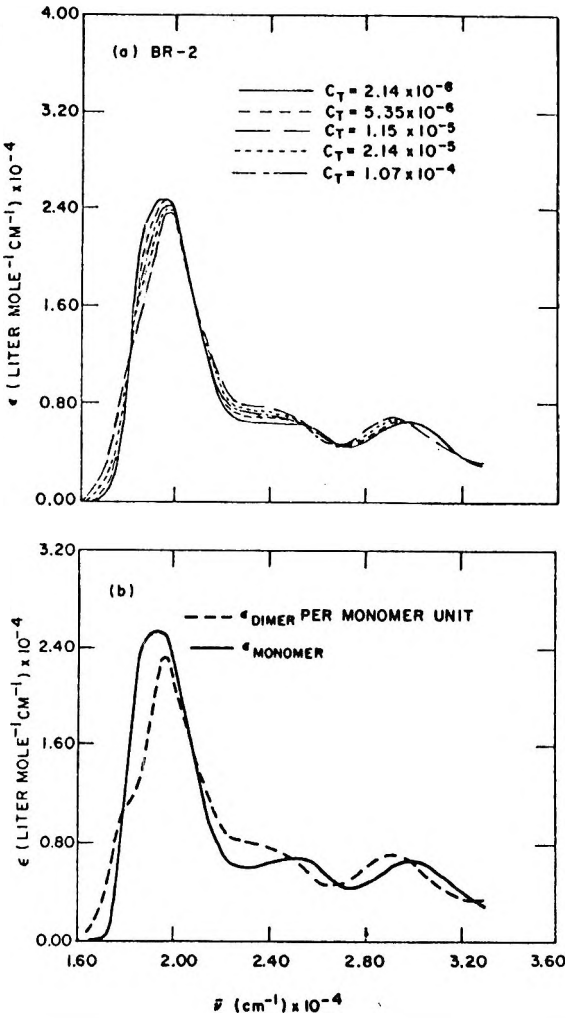


Figure 1.—(a) Concentration-dependent spectra of BR-2 in water at 22°; (b) calculated absorption spectra of pure monomer and dimer species of BR-2 in water.

Anal. Calcd for BR-4 ($C_{19}H_{13}N_2Na_2O_6SCl \cdot H_2O$): C, 45.8; H, 3.0; S, 6.4; Cl, 7.1; N, 5.6. Found: C, 45.7; H, 3.4; S, 6.3; Cl, 6.9; N, 5.5.

All spectroscopic measurements were performed using dye–water solutions having a pH of 3.15 ± 0.05 (10^{-3} M HCl). This pH was chosen in order to maintain a constant ionic strength in addition to ensuring precisely defined monomeric species of BR-2 and BR-4. At a pH of ~3 only the sulfonic acid group remains ionized in both compounds. Further details pertaining to pH effects on the nature of the dye monomer were presented in a previous publication.[1b] Solutions of both dyes in the 10^{-6}–10^{-4} M concentration range were run on a Cary Model 14R automatic spectrophotometer using 0.1-, 1-, 2-, 5-, and 10-cm matched quartz cells.

The molecular configurations existing in the hydrated crystalline phases of the sodium salts of Bonadur Red and its 4-hydroxy analog were determined by Raman spectroscopy. It was not possible to obtain the relative concentrations of the two tautomers in liquid media. Spectra were excited by 6328-Å radiation from a Spectra Physics Model 125 He–Ne laser operating cw at 90 mW. The sample, ~0.1 g of polycrystalline powder enclosed in a small Pyrex bottle, was mounted in a configuration allowing 45° incidence of the exciting light and normal collection of the scattered light. Spectra were analyzed by a Spex 1400 double grating monochromator and detected by a S-20 response photomultiplier. Signal was amplified by conventional phase-sensitive techniques and recorded on a strip chart.

Results and Discussion

The concentration dependence of the absorption spectra of BR-2 and BR-4 are shown in Figures 1a and

(2) G. Gabor, Y. F. Frei, D. Gegiou, M. Kaganowitch and E. Fischer, *Israel J. Chem.*, **5**, 193 (1967).

(3) A. Burowoy and A. R. Thompson, *J. Chem. Soc.*, 1443 (1953).

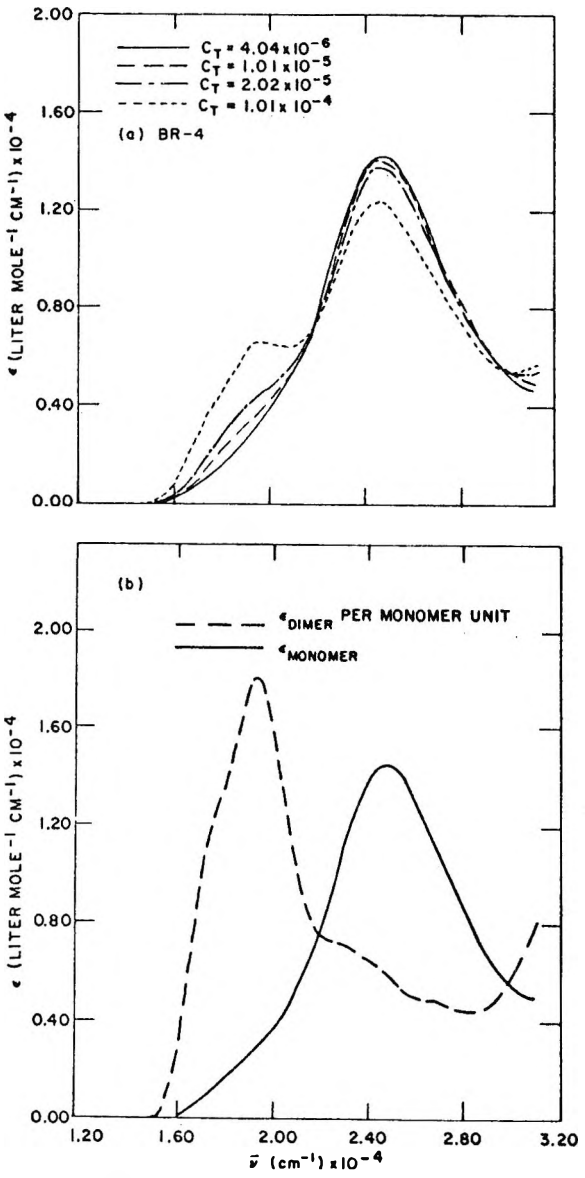


Figure 2.—(a) Concentration-dependent spectra of BR-4 in 22°; (b) calculated absorption spectra of pure monomer and dimer species of BR-4 in water.

2a, respectively. At very dilute concentrations (*ca.* 10^{-6} *M*), BR-2 is characterized by an intense hydrazone transition at 19,400 cm^{-1}. In agreement with previous work[4] on 1-arylazo-4-naphthols, the BR-4 compound in dilute aqueous media shows a band at 24,600 cm^{-1} which is assignable to that of the azo–enol tautomer. The measured concentration dependences of the two compounds under comparable conditions are quite different. With increasing dye concentration, BR-4 shows a decrease in observed extinction coefficient (ϵ) in the region of the azo-monomer transition. This is accompanied by an increase in ϵ near 20,000 cm^{-1}. Isosbestic points appear at 21,900 and 29,800 cm^{-1}. The concentration dependence of BR-2 has been reported previously.[1b] For BR-2, a slight blue shift of the hydrazone monomer transition occurs with increasing concentration. This is accompanied by a measurable decrease in the apparent extinction coefficient of the peak maximum. Isosbestic points appear at 17,900 and 20,600 cm^{-1}.

From each set of data, the pure monomer spectrum, pure dimer spectrum, and the equilibrium constant can be calculated using a least-squares fit computer procedure.[1] In the analysis, it is initially assumed that the monomer concentration c_m and dimer concentration c_d follow the law of mass action

$$K_{eq} = c_d/c_m^2 \quad (2)$$

where K_{eq} is the association (equilibrium) constant for dimer formation. This assumption is valid in the concentration range studied.[1a] The monomer concentration in the calculation is initially assumed to be pure hydrazone for BR-2 and pure azo for BR-4. The best fit was obtained at equilibrium constants of $K_{eq} = (5.55 \pm 0.39) \times 10^4$ l. mol^{-1} for BR-2 and $K_{eq} = (2.05 \pm 0.22) \times 10^3$ l. mol^{-1} for BR-4. The above equilibrium constants are calculated for the overall "pool" of azo plus hydrazone forms. The best fit monomer and dimer spectra are shown in Figures 1b and 2b for the hydrazone tautomeric system and the azo-rich system, respectively. The calculated dimer spectrum for BR-2 has been previously interpreted[1b] in terms of molecular excitation theory which predicts that the energy levels of the monomer species are split in the dimer species. Thus, BR-2 shows a strong H band at 19,700 cm^{-1} and a weaker J band at 18,000 cm^{-1} on the low energy side of the monomer band (19,500 cm^{-1}). The resolved dimer of BR-4 also shows bands at 19,600 cm^{-1} and a shoulder at *ca.* 18,000 cm^{-1}. The striking similarities in the two dimer spectra suggested that only the hydrazone component of the BR-4 molecule was active in the aggregation process. Raman spectroscopy was used to determine how much, if any, hydrazone tautomer existed in BR-4.

The solid state Raman spectra of Bonadur Red and its 4-hydroxy analog are shown in Figure 3 on traces A and B, respectively. The spectrum of azobenzene, trace C, is included for comparison. Inspection of traces B and C reveals a near correspondence in the two dominant Raman frequencies of both materials in the neighborhood of 1140 and 1440 cm^{-1}, respectively. Additional work indicates that this spectral signature is invariant for a wide variety of substituted azobenzenes, azophenols, and azonaphthalenes. Bassignana and Cogrossi[5] have assigned these lines on the basis of infrared spectroscopy of arylazo compounds to a stretching vibration associated with arylazo conjugation and to a stretching vibration of the –N=N– bond, respectively. Accordingly, the spectral signature comprising the intense lines near 1140 and 1440 cm^{-1} is assigned to the azo linkage. This spectral signature does not appear in trace A, the spectrum of BR-2, *i.e.*, there is a weak line near 1440 cm^{-1}, but the complementary line at 1140 cm^{-1} is missing. Furthermore, there are strong lines in the region below 500 cm^{-1} in trace A which do not appear in the spectra of typical arylazo compounds. This lack of an azo linkage spectral signature for Bonadur Red implies that this compound exists as the hydrazone modification in the crystalline state. Conversely, the dominance of the characteristic azo group frequencies in the spectrum of BR-4 is taken to indicate that this compound exists primarily as the azo modification. However, a small (10 ± 5%) hydrazone contribution to the spectrum of

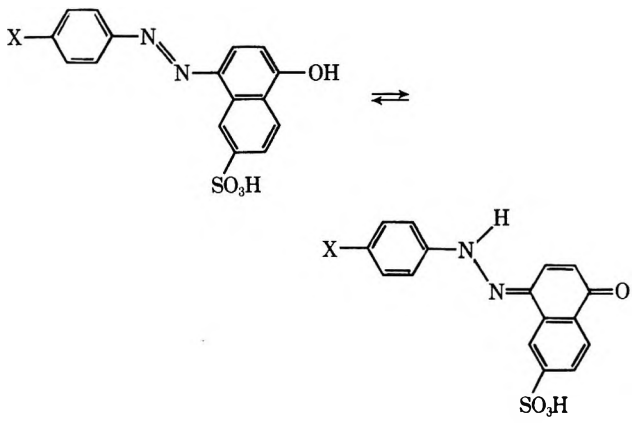
(4) E. Fischer and Y. F. Frei, *J. Chem. Soc.*, 3159 (1959).

(5) P. Bassignana and C. Cogrossi, *Tetrahedron*, **20**, 2361 (1964).

the 4-hydroxy dye is indicated since the lines near 1220, 1360, 1400, 1490, and 1550 cm^{-1} correspond closely with the more intense lines found in the spectrum of the 2-hydroxy compound.

The results using Raman spectroscopy seem to be an accurate indication of the molecular configuration of these compounds in aqueous media (*i.e.*, 10 ± 5% of BR-4 is hydrazone and 100% of BR-2 is hydrazone). If the assumption is made that only 10% of BR-4 (*i.e.*, only the hydrazone) aggregates, then a value of *ca.* 10^4 l. mol^{-1} is obtained for the hydrazone equilibrium constant (K_{eq}^{H}) for dimerization of the BR-4 compound. Differences in K_{eq}^{H} for the hydrazones of BR-2 and BR-4 were not within the scope of this investigation. This is due to the fact that the tautomeric concentrations from the Raman work are highly approximate. However, the approximate nature of the Raman spectra and equilibrium constant calculation are significant in light of the similar dimer spectra for BR-2 and BR-4.

It is somewhat surprising that such a dramatic difference in the capability toward aggregation exists for the two tautomers, and even more surprising perhaps that it has never been previously noted. Zollinger[6] in 1928 qualitatively observed dimer formation in H_2O in molecules of the type



In the concentration range 10^{-6}–10^{-4} *M*, increasing proportions of the above dye, at any concentration, were in the associated form as the electron-withdrawing nature of group X was increased. When X was $-NO_2$, the hydrazone absorption at 20,900 cm^{-1} was preceded by another band at 22,200 cm^{-1} as the concentration was increased from 5.0×10^{-6} to 4.0×10^{-4} *M*. The interpretation of this result, based on our study, is that withdrawing groups favor hydrazone[2] and therefore the molecule containing the NO_2 group (strong withdrawer) allows dimerization to be readily observed.

Reasons as to why this difference in aggregation tendency for the two tautomers exists are highly speculative at present. However, one possible reason for the difference in aggregation tendency for the two species is that there is a dramatic increase in negative charge density or ground-state charge transfer on the naphthyl moiety in going from the azo to the hydrazone tautomer. Therefore, the electrostatic interaction is probably stronger for hydrazone dimer formation relative to azo dimer formation. The extensively reported fact that

(6) H. Zollinger, "Azo and Diazo Chemistry," Interscience, New York, N. Y., 1961, pp 311–360.

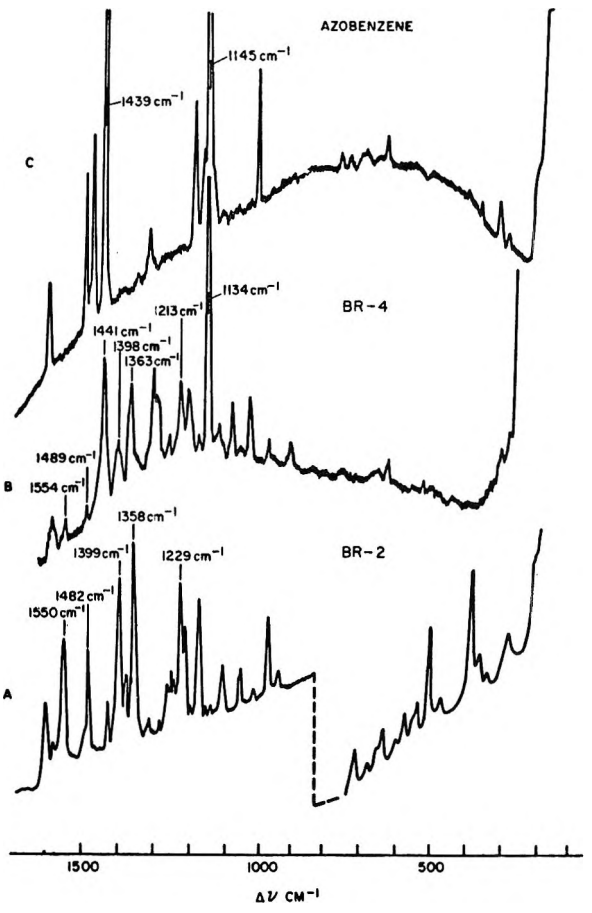


Figure 3.—Solid-state Raman spectra of azobenzene, BR-2, and BR-4.

the hydrazone tautomer is highly favored over the azo tautomer in polar solvents supports the large difference in dipole moment between the two molecules.[2] Past studies have indicated that hydrogen bonding may be important in dimer formation.[1a] This type of bonding would favor hydrazone aggregation, since a C=O ··· HN or =N ··· HN bond is probably stronger than a =N ··· HO bond in the case of the azo tautomer.[7]

Strong support for our result that the polar tautomer is preferential in the self-association of azo dyes can be found in the literature. For example, most of the work to date on the aggregation of azo dyes involves molecules having arylazonaphthol structures containing OH or NH_2 moieties either ortho or para to the azo linkage. Dyes such as Congo Red,[8] Solochrome Violet R,[9] Benzopurprine 4B,[10] and Sky Blue FF[11] fit into this category. On the other hand, Chrysophenine G,[8] which is a large planar ionic "pure" azo dye, does not aggregate to as great an extent. This is apparently because a polar hydrazone tautomer is nonexistent for the Chrysophenine molecule.

Registry No.—BR-2 hydrazone, 30425-34-4; BR-4, azo-enol, 32044-59-0; BR-4 hydrazone, 32044-57-8; water, 7732-18-5.

(7) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960, p 499.

(8) E. Coates, *J. Soc. Dyers Colour.*, **85**, 355 (1969).

(9) E. Coates and B. Rigg, *Trans. Faraday Soc.*, **57**, 1637 (1961).

(10) S. E. Sheppard and A. L. Geddes, *J. Amer. Chem. Soc.*, **66**, 1995 (1944).

(11) M. N. Inscoe, J. H. Gould, M. E. Corning, and W. R. Brode, *J. Res. Nat. Bur. Stand., Sect. A*, **60**, 65 (1958).

Acknowledgment.—The authors sincerely thank Dr. D. F. Blossey for proofreading the manuscript and for numerous helpful suggestions. Drs. J. B. Flannery, Jr., J. E. Kuder, and F. D. Saeva are also thanked for stimulating discussions.

Tautomeric Behavior Comparison of 4-Phenylazo-1-naphthol and 1-Phenylazo-2-naphthol Systems by Nuclear Magnetic Resonance

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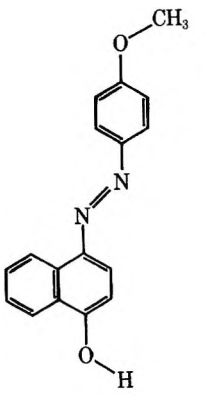
Azo–hydrazone tautomerism of arylazonaphthols has been the topic of many investigations[1-13] subsequent to Zincke's original observations in 1884.[14] However, to date the large difference between the tautomeric behavior of the 4-phenylazo-1-naphthol and 1-phenylazo-2-naphthol systems, which exist in solution predominantly as azo and hydrazone, respectively,[6,7,9,10,13] we believe has not been adequately explained. In this note we give the results of a thermodynamic study designed to provide an incisive explanation for this unusual difference in tautomeric behavior.

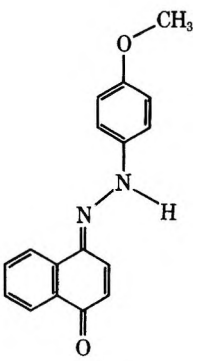
Since inter- and intramolecular proton exchange processes for 4-(*p*-methoxyphenylazo)-1-naphthol (**1**) and 1-(*p*-methoxyphenylazo)-2-naphthol (**2**) (in acetone-d_6) are sufficiently slow so that lifetimes of protons on oxygen and nitrogen are long compared to $1/(\nu_{OH} - \nu_{NH})$,[15] equilibrium constants, as a function of temperature, can be determined for the azo $\rightleftarrows$ hydrazone equilibrium process for these two compounds by nuclear magnetic resonance (nmr).

The proton nmr spectrum of 4-(*p*-methoxyphenylazo)-1-naphthol (**1**) at 10° (acetone-d_6) shows mobile proton resonances at δ 10.19 and 3.59 ppm downfield from tetramethylsilane. On the other hand, the nmr spectrum of 1-(*p*-methoxyphenylazo)-2-naphthol (**2**) at 38°, in the same solvent, shows a single acidic proton resonance at δ 16.2 ppm.

Assignment of the azo OH in **1a** and hydrazone NH in **1b** resonances were made on the basis of the temperature dependence[16] of the azo (~400 mμ) and hydrazone (~480 mμ) electronic transitions, which have been clearly established.[1,4] We found that the transition at ~480 mμ increased in intensity relative to the band at ~400 mμ (in acetone) with decreasing temperature. From this we conclude that the signals at δ 10.19 and 3.59 ppm are due to the hydrazone NH and azo OH protons, respectively.



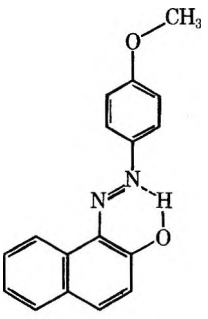
1a



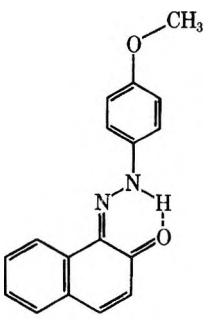
1b

The δ 16.2 ppm resonance in **2** possessed an integrated intensity considerably less than one proton using the time-averaged peri naphthalene proton as an internal standard. Assignment of this signal to the azo OH in **2a** was made on the basis of the visible spectrum temperature dependence using electronic transitions at ~420 and ~500 mμ for monitoring the relative concentrations of azo and hydrazone species,[3,4,11] respectively, as described for **1**.

The intensity of the band at ~500 mμ increased relative to that at ~400 mμ as the temperature was decreased, confirming earlier observations.[10] This temperature-induced equilibrium change indicates the resonance at δ 16.2 ppm to be from the azo OH proton.



2a



2b

Integration of the NH and OH proton resonances in **1** allowed direct evaluation of equilibrium constants for the tautomerization process. In the case of the 1-phenylazo-2-naphthol derivative (**2**), the hydroxyl proton resonance was integrated with respect to the time-averaged peri naphthalene proton (δ 8.65 ppm) for equilibrium constant evaluation. Table I presents

(1) R. Kuhn and F. Bar, *Justus Liebigs Ann. Chem.*, **516**, 143 (1935).
(2) H. Shingu, *Sci. Pap. Inst. Phys. Chem. Res., Tokyo*, **35**, 78 (1938).
(3) A. Burawoy, A. G. Salem, and A. R. Thompson, *J. Chem. Soc.*, 4793 (1952).
(4) A. Burawoy and A. R. Thompson, *ibid.*, 1443 (1953).
(5) D. Hadzi, *ibid.*, 2143 (1956).
(6) G. Gabor, Y. Frei, D. Gegiou, M. Kaganowiteh, and E. Fischer, *Israel J. Chem.*, **5**, 193 (1967).
(7) K. J. Morgan, *J. Chem. Soc.*, 2151 (1961).
(8) B. L. Kaul, P. Nair, A. V. Rama Rao, and K. Venkataraman, *Tetrahedron Lett.*, 3897 (1966).
(9) A. H. Berrie, P. Hampson, S. W. Longworth, and A. Mathias, *J. Chem. Soc. B*, 1308 (1968).
(10) V. Bekarek, K. Rothschein, P. Vetesnik, and M. Vecera, *Tetrahedron Lett.*, 3711 (1968).
(11) I. Saito, Y. Bansho, and M. Iwasaki, *Tokyo Kogyo Kagaku Zasshi*, **70**, 1725 (1967).
(12) V. Bekarek, J. Dobas, J. Socha, P. Vetesnik, and M. Vecera, *Collect. Czech. Chem. Commun.*, **35**, 1406 (1970).
(13) R. L. Reeves and R. S. Kaiser, *J. Org. Chem.*, **35**, 3670 (1970).
(14) T. Zincke and H. Bindewald, *Ber.*, **17**, 3026 (1884).
(15) J. Pople, H. Bernstein, and W. Schneider, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p 100.
(16) E. Fisher and Y. F. Frei, *J. Chem. Soc.*, 3159 (1959).

TABLE I
TAUTOMERIC EQUILIBRIUM CONSTANT TEMPERATURE DEPENDENCE

Compd	Temp, °K	K_{eq}[a]	Compd	Temp, °K	K_{eq}[a]
1	293	0.25	2	322	0.95
	283	0.34		311	1.13
	264	0.54		303	1.33
	252	0.84		293	1.54

[a] K_{eq} = [hydrazone]/[azo] or [b]/[a], determined from an average of four integrations, estimated error of ±5% in K_{eq}.

the calculated equilibrium constant temperature dependences for compounds 1 and 2 in acetone-d_6. The assignment of the δ 16.2 ppm signal in compound 2 is further substantiated by the fact that the experimental data in Table I are in general agreement with the work of Bekarek, *et al.*,[10] who used ^{15}N–H coupling constants to evaluate tautomer ratios for the parent phenylazo-2-naphthol. Thermodynamic parameters derived from the equilibrium constant (K_{eq} = [b]/[a]) temperature dependence data allow, for the first time, a quantitative comparison of the phenylazo-1- and -2-naphthol systems (see Table II).

TABLE II
TAUTOMERIC THERMODYNAMIC PARAMETERS

Compd	$\Delta G°_{293°}$, cal/mol	$\Delta H°$, kcal/mol[a]	$\Delta S°_{293°}$, cal/(mol deg)[a]
1	807	−4.5	−18.1
2	−250	−3.1	−9.7

[a] Estimated errors are *ca.* ±0.5 kcal/mol in $\Delta H°$ and *ca.* ±2.0 cal/mol deg in $\Delta S°$.

The thermodynamic data show the 2-naphthol derivative (at 293°K) to be mainly hydrazone **2b**, while the 1-naphthol analog, on the other hand, is predominantly azo **1a**. The enthalpy and entropy contributions to the thermodynamic free-energy difference between tautomers, for both systems, are of the same sign but differ in magnitude.

The enthalpy for the equilibrium process favors the hydrazone tautomer in both systems. The smaller $\Delta H°$ for system 2 is attributed to stabilization of the azo tautomer **2a** relative to the hydrazone species **2b** by intramolecular hydrogen bonding present only in system 2.

The entropy term, however, favors the less polar azo species for both systems. The larger negative entropy term in system 1 is ascribed to the existence of a more polar hydrazone species **1b** relative to the azo tautomer **1a**, than is present in system 2.

From the results which we have presented, it can be concluded that the difference in the tautomeric behavior between systems 1 and 2 is due to the fact that in system 1 the entropy term dominates and governs the free-energy difference between tautomers, while in system 2 the enthalpy contribution is the dominating factor (at 293°K in acetone solvent).

Experimental Section

Materials Characterization.—1-(*p*-Methoxyphenylazo)-2-naphthol (2) (mp 141–142°; lit.[17] mp 141°) and 4-(*p*-methoxyphenylazo)-1-naphthol (1) (mp 172–173°; lit.[18] mp 168°) were prepared from the corresponding substituted aniline by diazotization and coupling with 2- and 1-naphthol, respectively.

Spectroscopic Characterization.—A JEOL C-60-H nuclear magnetic resonance spectrometer equipped with a JES-VT-3 variable-temperature controller was employed for equilibrium constant determinations in acetone-d_6; the solutions were *ca.* 10% (w/v). The nmr probe temperature control was calibrated, with an estimated accuracy of ±1°, using anhydrous methanol and ethylene glycol solutions. The probe temperature accuracy was periodically checked by using a 5-mm probe thermometer supplied by JEOL.

Registry No.—**1a**, 3009-53-8; **1b**, 32159-06-1; **2a**, 13411-91-1; **2b**, 15096-03-4.

Acknowledgment.—Stimulating discussions with Lewis B. Leder, as well as the synthesis of 4-(*p*-methoxyphenylazo)-1-naphthol by Richard L. Schank, are gratefully acknowledged.

(17) J. M. Tedder, *J. Amer. Chem. Soc.*, **79**, 6090 (1957).
(18) L. N. Ogoleva and B. I. Stepanov, *Zh. Org. Khim.*, **1** (12), 2083 (1965).

A General Method of Preparation of Tetramethyl Alkyl-1-hydroxy-1,1-diphosphonates

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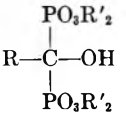
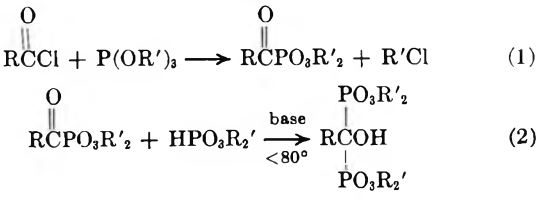
We recently developed a need in our laboratories for a series of esterified alkyl-1-hydroxy-1,1-diphosphonic acids (I). Where the specific acid was available, esterification was accomplished by the published[1] orthoformate route. For most of the esters envisioned the corresponding acids were either difficult to synthesize or not previously reported in the chemical literature. Hence, a search was begun for a direct method of preparation of tetraalkyl alkyl-1-hydroxy-1,1-diphosphonates.



I

The chemical literature describing this class of compounds is very ambiguous. Fitch and Moedritzer[2] and Pudovik, *et al.*,[3,4] have described the synthesis of I, where R = CH_3 and R′ = C_2H_5, by the route shown in Scheme I. The reaction is complicated by rearrange-

SCHEME I



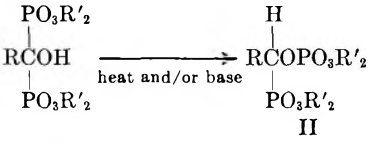
(1) D. A. Nicholson, W. A. Cilley, and O. T. Quimby, *J. Org. Chem.*, **35**, 3149 (1970).
(2) S. J. Fitch and K. Moedritzer, *J. Amer. Chem. Soc.*, **84**, 1876 (1962).
(3) A. N. Pudovik and I. V. Konovalova, *Dokl. Akad. Nauk SSSR*, **143**, 875 (1962); *Chem. Abstr.*, **57**, 3480a (1962).
(4) A. N. Pudovik, I. V. Konovalova, and L. V. Dedova, *Dokl. Akad. Nauk SSSR*, **153**, 616 (1963); *Chem. Abstr.*, **60**, 8060a (1964).

TABLE I
TETRAMETHYL ALKYL-1-HYDROXY-1,1-DIPHOSPHONATES

Compd	Registry no.	Mp, °C	^{31}P nmr, ppm	Yield, %	Calcd (found), % C	H	P	Mol wt (found)
$C_6H_5C(OH)[PO_3(CH_3)_2]_2$	32249-59-5	130–133[a]	−18.0	96	40.8 (40.9)	5.6 (5.6)	19.3 (19.6)	324 (340)
$CH_3C(OH)[PO_3(CH_3)_2]_2$	15207-88-2	68–71[b]	−22.0	70	27.4 (27.3)	6.1 (6.1)	23.7 (23.9)	262 (265)
m-$BrC_6H_4C(OH)[PO_3(CH_3)_2]_2$	32249-61-9	120–122[a]	−18.0	95	32.8 (32.5)	4.2 (4.3)	15.4 (16.1)	403 (435)
$CH_2{=}CH(CH_2)_8C(OH)[PO_3(CH_3)_2]_2$	32249-62-0	[c]	−22.0	86	46.6 (45.8)	8.3 (8.2)	15.9 (15.8)	388 (410)
$(CH_3)_3CC(OH)[PO_3(CH_3)_2]_2$	32249-63-1	108–110[b]	−22.0	75[d]	35.9 (36.0)	7.2 (7.3)	20.4 (20.8)	304 (330)
$CH_3(CH_2)_7CH{=}CH(CH_2)_7C(OH)[PO_3(CH_3)_2]_2$	32304-07-7	[c]	−22.0	91	54.6 (54.7)	9.5 (9.4)	12.8 (12.8)	484 (525)
p-$CH_3OC_6H_4C(OH)[PO_3(CH_3)_2]_2$	32304-08-8	103–104[a]	−18.0	81	40.7 (40.8)	5.7 (6.0)	17.5 (18.0)	354 (380)

[a] Crystallized from ethyl ether. [b] Crystallized from a 50:50 mixture of benzene and hexane. [c] Compound failed to crystallize; yield based on crude oil isolated from reaction mixture. [d] Yield based on crude solid isolated from reaction mixture.

ment of the tetraalkyl alkyl-1-hydroxy-1,1-diphosphonate (I) to the phosphate phosphonate (II) (eq 3).[2-4]



(3)

No materials of structure I with R other than CH_3 have apparently been prepared. Fitch and Moedritzer attempted the synthesis of I where R = C_6H_5 and R′ = C_2H_5.[2] They could find no reaction conditions which prevented rearrangement to II.

Compounds purported to have structure I have been described.[5-7] However, the methods of preparation employed by these workers involved both a strong base (Na or NaOR) and elevated temperatures (>120°). When Fitch and Moedritzer[2] repeated portions of these studies only rearranged products (II) were obtained. Our own early efforts in this area, using the methods of McConnell and Coover[5] and Cade,[7] also yielded only phosphate phosphonates.

In an attempt to remove some of the confusion in the literature concerning esters of hydroxydiphosphonic acids, we have reexamined the reactions leading to compounds I and II. By making some relatively minor but very significant changes in procedure, we have devised a general method for preparing pure materials of structure I.

When the acylphosphonates prepared *via* eq 1 (Scheme I) were sufficiently pure, addition of the hydrogen dialkyl phosphite to the carbonyl group (Scheme I, eq 2) occurred at low temperatures (0°) in ether solution in the presence of a relatively weak base, di-*n*-butylamine. Apparently this secondary amine is not a strong enough base to promote isomerization under the conditions employed.

We chose to work exclusively with methyl esters, since they are much more prone to crystallize than are longer chain esters. Purification of compounds of structure I can be a problem since the alternative of vacuum distillation results in isomerization.[2,4] Even when the hydroxydiphosphonates do not crystallize there is an advantage to working with methyl esters. While the starting materials in eq 2 are soluble in cold ether, the products (I) are not and can be rapidly removed from the reaction system. The resulting short contact time with the basic reaction medium probably helps to prevent rearrangement to II.

Table I lists the tetramethyl alkyl-1-hydroxy-1,1-diphosphonates prepared by the above procedure. That we are dealing with materials of structure I and not II is demonstrated conclusively by ^{31}P nmr spectroscopy. Fitch and Moedritzer[2] have shown that the diphosphonate structure (I) results in a single ^{31}P resonance at about −20 ppm (relative to 85% H_3PO_4) while the phosphate phosphonate isomer (II) gives two resonances of equal intensity, one in the range of −16 to −21 ppm and one at 0 to +1 ppm. Phosphorus nmr spectra of our compounds were devoid of signals other than the one in the −18 to −22 ppm range.

As indicated earlier, acyl phosphonates were prepared *via* eq 1.[8] They were generally purified by vacuum distillation. Purity was determined by ^{31}P nmr spectroscopy; all acyl phosphonates gave a single resonance in the 0 to +2 ppm range.

As opposed to treatment with base, exposure of esters of structure I to acid does not result in rearrangement. Hydrolysis of the phenyl derivative (compound I, R = C_6H_5, R′ = CH_3) proceeded normally to the expected acid.

Experimental Section

All melting points reported herein are uncorrected. Elemental analyses were carried out in these laboratories. Phosphorus nmr spectra were recorded on a Varian HR-60 spectrometer operating at 24.3 MHz. Chemical shifts are accurate to ±0.5 ppm and were measured from an external 85% H_3PO_4 reference. Molecular weights were determined on a Model 302 Mechrolab osmometer.

Tetramethyl alkyl-1-hydroxy-1,1-diphosphonates were all prepared by the same general procedure. The preparation of $C_6H_5C(OH)[PO_3(CH_3)_2]_2$ is considered typical and is given in detail below. Table I reports yields, analyses, and physical characteristics of the materials prepared in this study.

Tetramethyl Phenylmethanehydroxydiphosphonate.—Benzoyl chloride (14.05 g, 0.1 mol) was placed in a mechanically stirred reaction flask and cooled to 0°. Trimethyl phosphite (12.4 g,

(5) R. L. McConnell and H. W. Coover, *J. Amer. Chem. Soc.*, **78**, 4450 (1956).
(6) P. Schmidt, Swiss Patent 321,397 (1957).
(7) J. A. Cade, *J. Chem. Soc.*, 2272 (1959).
(8) G. M. Kosolapoff, "Organophosphorus Compounds," Wiley, New York, N. Y., 1950, p 122.

0.1 mol) was added dropwise with rapid stirring. Vigorous evolution of a gas (CH_3Cl) was noted. After addition was complete the reaction mixture was allowed to warm to room temperature and then vacuum distilled. Dimethyl benzoylphosphonate (18.2 g, 85%) was collected as a yellow oil, bp 130–134° (3 Torr). A ^{31}P nmr spectrum of the product showed a single resonance at +1 ppm.

Hydrogen dimethyl phosphite (5.16 g, 0.047 mol) was placed in a reaction flask to which 100 ml of diethyl ether had been added. Following the addition of di-*n*-butylamine (0.5 g, 0.0026 mol), the solution was cooled to 0°. Dimethyl benzoylphosphonate (10.0 g, 0.047 mol) was introduced slowly with rapid stirring. The reaction was moderately exothermic; external cooling was required to maintain the temperature at 0°. A white solid began to form almost immediately. After all the dimethyl benzoylphosphonate had been introduced the reaction mixture was allowed to warm to room temperature. Filtration yielded 14.6 g (96%) of the title compound.

The tetramethyl ester of phenylmethanehydroxydiphosphonic acid was hydrolyzed by refluxing for 3 hr with an excess of concentrated HCl. The monosodium salt was crystallized by the method of Pflaumer and Filcik.[9] A ^{31}P nmr spectrum consisted of a single resonance at −15.5 ppm.

Anal. Calcd for $C_7H_9O_7P_2Na$: C, 29.0; H, 3.1; P, 21.2; Na, 7.9. Found: C, 28.6; H, 3.0; P, 21.0; Na, 8.3.

Registry No.—Phenylmethane hydroxydiphosphonic acid (monosodium salt), 32247-16-8.

(9) P. F. Pflaumer and J. P. Filcik, Belgian Patent 712,159 (1968).

On the Mechanism of the Desulfonylation of Phenyl Sulfone in Molten Sulfur

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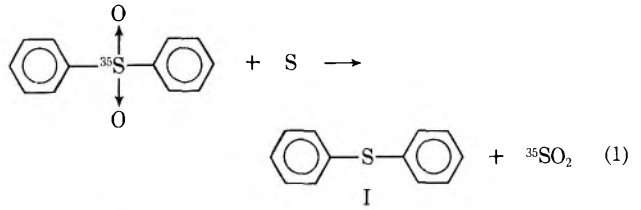
The reaction between sulfur-35 labeled phenyl sulfone and ordinary sulfur has been studied[1] at temperature above 300°. It has been found that, in addition to reaction 1, the reduction process 2 also takes



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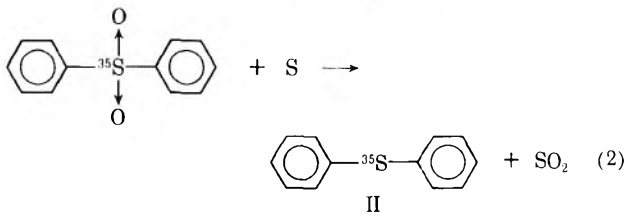

(2)

place in about 25% yield. This work has some serious limitations since it is based upon 80% recovery of products.

Suggestions have been made that thermal decomposition of sulfones normally occurs by homolytic cleavage of RSO_2R into R· and RSO_2· radicals, followed by loss of sulfur dioxide and subsequent recombination of the two R· radicals.[2]

Since the reaction studied in these laboratories proceeds in molten sulfur, the attack by sulfur radical should also be considered. If the rate-determining step were to be a concerted displacement by sulfur radical, then a very small sulfur-34 isotope effect should be found. On the other hand, in a homolytic cleavage into RSO_2· and R· radicals a substantial isotope effect should be observed.

The kinetics of the overall process in nitrogen atmosphere at 243, 262, 288, and 297° were studied, and the corresponding first-order rate constants, $k \times 10^6$ sec^{-1}, found to be 5.21 ± 0.12, 19.2 ± 0.3, 120 ± 1, and 209 ± 9, respectively (uncertainties are standard deviations of the mean). Using the technique of least squares the energy of activation for the overall reaction was found to be 41 ± 1 kcal mol^{-1}, and the frequency factor 1.0×10^{12} sec^{-1}. The entropy of activation was found to be −7 eu. Oae, *et al.*,[1] determined that the ratio of product yields from reactions 1 and 2 (I/II) remain unchanged even at the boiling point of sulfone (379°). This observation indicates that the energies of activation of both reactions must be similar and approximately equal to the energy of activation determined by us for the overall process (41 kcal mol^{-1}).

The maximum isotope effect in breaking a C–S bond can be calculated from Bigeleisen theory.[3] Assuming the C–S stretching frequency[4] of 700 cm^{-1} the maximum isotope effect for decomposition of the hypothetical C–S molecule was calculated to be 1.07% ($^{32}k/^{34}k$ = 1.0107) at 243°.

The sulfur-34 isotope effect for the overall reaction at 243° was determined with $^{32}k/^{34}k$ = 1.0043 ± 0.0012. On the assumption that about 75% of SO_2 is formed by reaction 1 with an isotope effect (IE), and 25% of SO_2 by reaction 2 with an isotope effect (IE′), it follows that 0.43 = 0.75 IE + 0.25 IE′. The isotope effect (IE) of reaction 1 can only be estimated, since the isotope effect of reaction 2 (IE′) is not known. Reaction 2 may occur by a bimolecular attack of sulfur radicals from the melt. In this case a positive isotope effect related to the formation of sulfur radicals by sulfur–sulfur bond breaking will be reduced by the negative isotope effect caused by the bimolecular attack of sulfur radicals on the substrate. The resulting isotope effect of reaction 2, IE′, is therefore most probably not far from zero. If zero, IE is about 0.6%. It can be concluded that the measured isotope effect is primarily that due to reaction 1, and that its value is roughly one-half of the maximum isotope effect for breaking a C–S bond. This substantial isotope effect for reaction 1 indicates appreciable C–S bond weakening in the transition state, suggesting dissociation as a rate-determining step, followed by loss of sulfur dioxide and subsequent recombination of Ph· and S· radicals. The negative entropy of activation of −7 eu can be explained by assuming almost free rotation about the two C–S bonds in starting material, while this rotation may be quite

(1) S. Oae and S. Kawamura, *Bull. Chem. Soc. Jap.*, **36**, 163 (1963).

(2) W. K. Busfield and K. J. Ivin, *Trans. Faraday Soc.*, **57**, 1044 (1961); W. K. Busfield, K. J. Ivin, H. Mackle, and P. A. G. O'Hare, *ibid.*, **57**, 1054 (1961); E. M. Lacombe and B. Stewart, *J. Amer. Chem. Soc.*, **83**, 3457 (1961).

(3) J. Bigeleisen and M. G. Mayer, *J. Chem. Phys.*, **15**, 261 (1947); J. Bigeleisen, *ibid.*, **17**, 675 (1949).

(4) W. O. George, R. C. W. Goodman, and J. H. S. Green, *Spectrochim. Acta*, **22**, 1749 (1966).

restricted in $PhSO_2\cdot$ radical. Our entropy of activation ($\Delta S^{\pm}$) of -7 eu is in good accord with Bartlett's[5] observation of lowering of $\Delta S^{\pm}$ in *tert*-butyl perester decomposition.

Experimental Section

Kinetics.—The sulfur dioxide was expelled from the melted reaction mixture (243–297°) by a stream of nitrogen which was purified by passing through alkaline alcoholic solution of pyrogallol. The SO_2 was then absorbed in aqueous sodium hydroxide and titrated in the presence of 1% H_2O_2. The reaction mixture consisted of 0.0025 mol of phenyl sulfone and 0.05 g-atom of sulfur.

Mass Spectrometry.—A Nier-type double collector mass spectrometer, MS-6, produced at the Institute Jožef Stefan, Ljubljana, Yugoslavia, was used. For the isotope effect determination natural abundance of sulfur-34 was utilized. Samples of SO_2 gas from the reaction carried out to about 2% completion, and to complete decomposition of phenyl sulfone, respectively, were collected in a liquid air trap and purified in a vacuum line, and the $^{32}S/^{34}S$ mass ratios were determined as previously described.[6]

Registry No.—Phenyl sulfone, 127-63-9; sulfur, 7704-34-9.

Acknowledgment.—The authors thank Professor Maurice Kreevoy for helpful discussion.

(5) P. D. Bartlett and R. R. Hiatt, *J. Amer. Chem. Soc.*, **80**, 1398 (1958).
(6) W. H. Saunders, Jr., and S. Ašperger, *ibid.*, **79**, 1612 (1957).

A Mannich-Type Condensation of Ethylenedinitramine with Carbethoxyhydrazine and Formaldehyde

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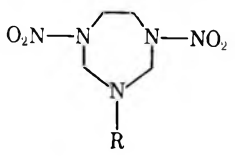
Primary nitramines have an active hydrogen atom on nitrogen and readily undergo the Mannich reaction with amines and formaldehyde.[1,2] Reaction conditions generally are milder than in the condensation of compounds which have the active hydrogen on carbon. The reaction of amines and formaldehyde with ketones which have active hydrogen atoms requires heating,[3] whereas the reaction with nitramines generally occurs at 0–25°.

Ethylenedinitramine ($O_2NNHCH_2CH_2NHNO_2$, EDNA) forms a linear condensation product, *N*,*N*′-bis(*N*-piperidinomethyl)ethylenedinitramine, $[C_5H_{10}NCH_2N(NO_2)CH_2]_2$, with piperidine and formaldehyde.[1] With primary amines the condensation reaction yields cyclic products, 3-alkyl-1,5-dinitrohexahydro-1*H*-1,3,5-triazepines[4] (**1a**).



a, R = alkyl
b, R = $NHCO_2C_2H_5$

1

In a recent investigation we required a sample of 3-carbethoxyamino-1,5-dinitrohexahydro-1*H*-1,3,5-triazepine (**1b**) as an intermediate. The condensation reaction of ethyl carbazate[5] ($NH_2NHCO_2C_2H_5$) with EDNA and formaldehyde was examined as a route to this compound.

The use of hydrazines in place of amines in a Mannich-type condensation reaction has received very little attention. We found only four references to reactions of this type.[6] No examples of a Mannich-type condensation of nitramines with hydrazines have been reported.

The reaction of ethyl carbazate with EDNA[7] and formaldehyde proceeded readily to afford a good yield of **1b**. Undoubtedly, the method could be employed for the condensation of other hydrazine derivatives with various nitramines, but our current research interests do not lie in this area. We plan no further experiments of this type.

Experimental Section

A mixture of 7.0 g (46.6 mmol) of EDNA, 9.8 g (121 mmol) of 37% formaldehyde, and 24.5 ml (49.0 mmol) of 2.0 *N* sodium hydroxide in 42 ml of water was magnetically stirred at ambient temperature for 45 min to obtain a somewhat cloudy solution (A). Potassium acid phthalate (10.5 g, 51.5 mmol) was dissolved with warming in 47 ml of water, and ethyl carbazate (4.9 g, 47.1 mmol) was added after allowing the solution to cool to 55°. This solution was immediately added to A in one portion with magnetic stirring, and 5 ml of water was used to rinse the flask and complete the addition. Product began to precipitate after 6 min. The mixture was stirred overnight to complete the reaction. The white solid was filtered off, washed with water, and dried *in vacuo* over phosphorus pentoxide. The yield was 10.4 g (80%). Recrystallization from an acetone–carbon tetrachloride mixture yielded 8.8 g (68%) of **1b**: mp 181° (frothing) at 1°/min; ir (Nujol) 2.98 (m, NH), 5.72 (vs, C=O), 6.52 and 6.58 (vs, NNO_2), 7.66 (vs), 7.84 (vs), 9.11 (ms), and 10.65 μ (s); λ_{EtOH}^{max} 243 mμ (ϵ 11,000); nmr (acetone-d_6) τ 1.53 (NH, broad s), 4.71 (NCH_2N, s), 5.69 (NCH_2CH_2N, s), 5.98 (q, J = 7 cps), 8.84 (t, J = 7 cps).

Anal. Calcd for $C_7H_{14}N_6O_6$: C, 30.21; H, 5.07; N, 30.21; mol wt, 278. Found: C, 30.44; H, 5.23; N, 30.20; mol wt, 280.

Substantially lower yields were obtained when potassium acid phthalate was not employed. This was due to an increase in pH which resulted from the liberation of sodium hydroxide as EDNA was used up. An attempt to use hydrochloric acid in place of potassium acid phthalate resulted in the formation of a sticky, viscous material. Another experiment in which 33% more potassium acid phthalate was used gave an impure product. The infrared spectrum of this crude product was very similar to that of the pure material except that an additional N–H band occurred at 3.09 μ. A similar type of impure product resulted when exactly 2 mol of formaldehyde were employed for each mole of EDNA instead of the 30% excess described above.

Registry No.—**1b**, 32121-18-9; EDNA, 505-71-5; carbethoxyhydrazine, 4114-31-2; formaldehyde, 50-00-0.

Acknowledgment.—This work was supported by the U. S. Atomic Energy Commission under Contract AT(04-3)-115, Project Agreement 74, monitored by Lawrence Radiation Laboratory, Livermore, Calif.

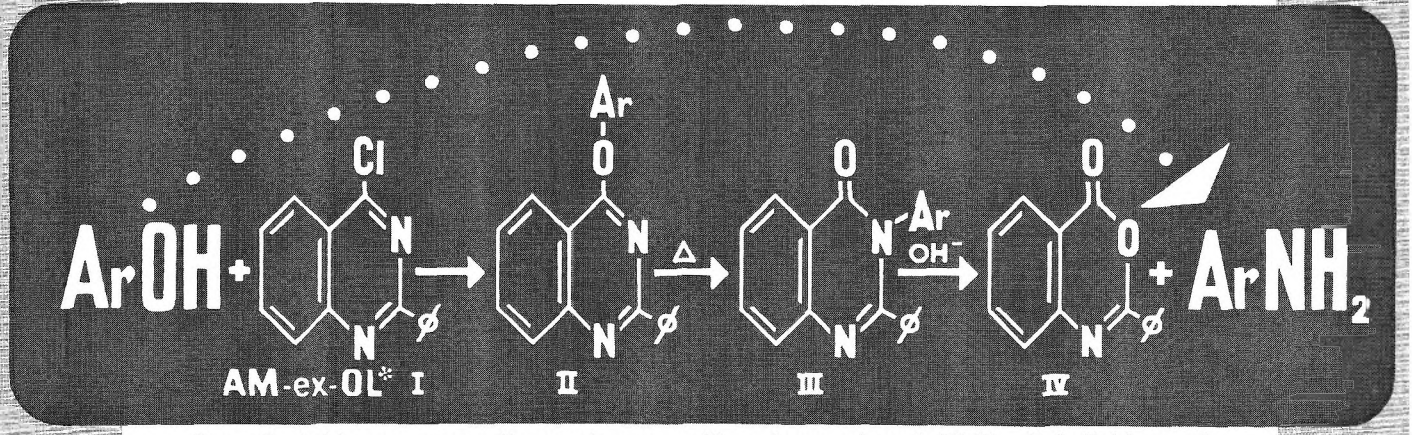
(1) A. P. N. Franchimont, *Recl. Trav. Chim. Pays-Bas*, **29**, 296 (1910).
(2) C. C. Bombardieri and A. Taurins, *Can. J. Chem.*, **33**, 923 (1955).
(3) F. F. Blicke, *Org. React.*, **1**, 303 (1942).
(4) (a) G. S. Myers and G. F. Wright, *Can. J. Res.*, **27B**, 489 (1949); (b) F. Chapman, P. G. Owston, and D. Woodcock, *J. Chem. Soc.*, 1638 (1949); (c) M. B. Frankel, *J. Org. Chem.*, **26**, 4709 (1961); (d) J. A. Bel and I. Dunstan, *J. Chem. Soc. C*, 862 (1966); 562 (1967); (e) S. S. Novikov, A. A. Dudinskaya, N. V. Makarov, and L. I. Khmel'nitskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1833 (1967); *Chem. Abstr.*, **68**, 29687*u* (1968); (f) N. V. Makarov, A. A. Dudinskaya, S. S. Novikov, and L. I. Khmel'nitskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1837 (1967); *Chem. Abstr.*, **68**, 29688*v* (1968).
(5) O. Diels, *Ber.*, **47**, 2183 (1914).
(6) (a) M. B. Frankel and K. Klager, *J. Amer. Chem. Soc.*, **79**, 2953 (1957); (b) W. Ried and K. Wesselborg, *Justus Liebigs Ann. Chem.*, **611**, 71 (1958); (c) R. L. Hinman, E. D. Ellefson, and R. D. Campbell, *J. Amer. Chem. Soc.*, **82**, 3988 (1960); (d) E. E. Hamel, *Tetrahedron*, **19**, Suppl. 1, 93 (1963).
(7) (a) A. P. N. Franchimont and E. A. Klobbie, *Recl. Trav. Chim. Pays-Bas*, **7**, 12 (1888); (b) W. E. Bachmann, *et al.*, *J. Amer. Chem. Soc.*, **72**, 3132 (1950).

What Every Chemist Has Often Wanted To Do -- But Couldn't:

CONVERT PHENOLS TO ANILINES

While anilines are usually easily converted to phenols via diazonium salts, the reverse has been very difficult.

Now, however, there is a quite general procedure[1] which involves reacting AM-ex-OL* (4-chloro-2-phenylquinazoline) I with the phenol to yield the 4-aryloxy-2-phenylquinazoline II, which rearranges neat or in mineral oil at 275-325° to the 3-aryl-2-phenyl-4(3H)-quinazolinone III which is easily hydrolyzed by alkali to the aniline and 2-phenyl-4H-3,1-benzoxazin-4-one IV.



Overall yields are generally good; e.g. aniline from phenol 71%, 2,4-dichloroaniline and 2,3,6-trimethylaniline from the corresponding phenols 64 and 70% respectively. Even two steroidal phenols have been converted[2] to the amines in 67 and 58% yields.

In a typical procedure, 10 g. of phenol was added to a suspension of 5 g. of sodium hydride dispersed in mineral oil in 35 ml. of diglyme. (Sodium hydride is of course not needed if the sodium phenoxide is available. Alternatively, II can be obtained in almost quantitative yield by reacting AM-ex-OL* with the phenol and anhydrous potassium carbonate in acetone.[3]) When hydrogen evolution ceased, 24 g. of Am-ex-OL* was added. The mixture was heated to 110° for 10 minutes, cooled and poured onto ice, to yield 29.8 g. of 4-phenoxy-2-phenylquinazoline II, m.p. 112-116°.

Heating this quinazoline under nitrogen at 325° for 130 minutes yielded 2, 3-diphenyl-4(3H)-quinazolinone III almost quantitatively. III need not be isolated. Thus, heating 16.3 g. of II in 30 ml. mineral oil under nitrogen for 4 hours at 325°, and then heating this mixture with a solution of 32 g. of KOH in 160 ml. ethylene glycol under nitrogen at 130° overnight, yielded on treatment with water, extraction with ether and treatment with HCl gas, 5.2 g. (76%) of aniline hydrochloride. The completion of the thermal rearrangement is best determined by IR or UV (II absorbs strongly at 259 mμ; III does not).

(1) a. R. A. Scherrer, Abstracts of Papers, 145th national meeting of the American Chemical Society, New York, N.Y., Sept. 1963, p. 33Q.
b. R. A. Scherrer and H. R. Beatty, J. Org. Chem., in preparation.

(2) a. D. F. Morrow and M. E. Butler, J. Org. Chem. **29**, 1893 (1964).
b. D. F. Morrow and R. M. Hofer, J. Med. Chem., **9**, 249 (1966).

(3) R. B. Conrow and S. Bernstein, Steroids, **11**, 151 (1968).

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