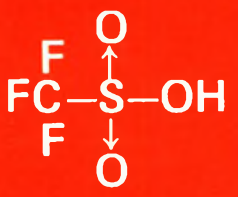
VOLUME 36 JANUARY 15, 1971 NUMBER 1 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED MONTHLY BY THE AMERICAN CHEMICAL SOCIETY



Trifluoromethane Sulphonic Acid Strongest Monobasic Acid Known

CF_3SO_3H "TFMS Acid" F.W. 150.02

Form: Colorless liquid (fumes in moist air).
Odor: Strong, pungent.
Boiling point: 162°C/760mm; 84°C/43mm; 54°C/8mm.
Density (grams/cc): 1.696 (24.5°C). n_D^{25} 1.3250.
Dissociation constant (in acetic acid), $K = 1.26 \times 10^{-5}$.

Trifluoromethane sulfonic acid is a stable, colorless liquid with a strong and pungent odor. It fumes copiously in moist air. It is non-oxidizing and conductivity measurements in acetic acid have shown it to be the strongest proton acid known.[1] Acid strength, relative to nitric acid is shown as follows: CF_3SO_3H, 427; $HClO_4$, 397; HBr, 164; H_2SO_4, 30; CH_3SO_3H, 17; HCl, 9; CF_3CO_2H, 1; HNO_3, 1.

Distillations of the acid with an equimolar amount of water produces a stable crystalline monohydrate with a melting point of 34°C and a boiling point of 96°C at 1mm.[2,4]

The acid is very soluble in acetonitrile[4] and liquids containing oxygen such as water, alcohols, ethers, ketones and DMF. *(Use extreme caution! Highly exothermic reaction, may be violent; heat of solution is high!)* Oxonium compounds are the first products and further reaction often occurs, particularly upon heating. With ethyl ether the acid gives a colorless liquid complex; upon heating, the complex gives the ethyl ester and ethylene:

$$CF_3SO_3H + (C_2H_5)O \rightarrow [(C_2H_5)_2OH^+CF_3SO_3^-] \xrightarrow{heat} CF_3SO_3C_2H_5 \textit{ (b.p. 115°C)} + (C_2H_5)O + C_2H_4 + CF_3SO_3H + CF_3SO_3H \cdot H_2O.$$

Reaction with ethanol produces the expected ethyl ester, but dehydration and ether formation also occur:

$$CF_3SO_3H + C_2H_5OH \rightarrow CF_3SO_3C_2H_5 + H_2O.$$

Reaction with ethylene at room temperature produces the ethyl ester and a low polymer of ethylene:[2]

$$CF_3SO_3H + C_2H_4 \rightarrow CF_3SO_3C_2H_5 + (C_2H_4)_n.$$

Metallic salts are readily prepared from the acid and corresponding hydroxide or carbonate. The acid is readily characterized by its organic salts; e.g., anilinium, triethylammonium and s-benzylthiuronium.

Esters have been prepared from the silver salt and an alkyl iodide, from the acid anhydride and an alcohol and by other methods. A number of esters are stable in the absence of moisture and impurities. The esters are excellent alkylating agents since the powerful electron-attracting CF_3SO_3 group facilitates alkyl-oxygen scission. O-alkylation of alcohols and ethers, aromatic alkylation and N-alkylation of amines takes place readily.[2,5]

A number of the simple alkyl esters have been shown to be very reactive alkylation agents. $CF_3SO_3CH_3$, for instance, is more than 10^4 times as reactive as methyl toluenesulfonate in acetolysis.[6,7] Thus, these esters are useful in alkylation of weak or hindered nucleophiles.

The use of the CF_3SO_3 group as a good leaving group enhances the reactivity of many unreactive systems. For example, the 1,1-dihydroperfluoro alcohols form trifluoromethanesulfonate esters which are quite reactive toward nucleophiles and are useful for introduction of the R_fCH_2 group.

Other interesting and useful properties of CF_3SO_3H have been described in our technical bulletin "TFMS Acid"; it will be sent on request.

Trifluoromethane sulfonic acid is available as follows:

TRIFLUOROMETHANE SULFONIC ACID
"TFMS Acid" $10/10 gm ampule
$60/10 x 10 gm ampules

References cited:
1. Gramstad, *Tidsskr. Kjemi, Bergvesen Met.*, **19**, 62 (1959); C.A., **54**, 12739 (1960).
2. Gramstad and Haszeldine, *J. Chem. Soc.*, **1957**, 4069.
3. Burdon, Farazmand, Stacey, and Tatlow, *J. Chem. Soc.*, **1957**, 2574.
4. Tiers, *U. S. Patent* 3,427,336.
5. Brown, 128th Meeting American Chemical Society, Minneapolis, Minnesota, 29M, September, 1955.
6. Hansen *J Org. Chem.*, **30**, 4322 (1965).
7. Streitweiser, *et al., J. Am. Chem. Soc.*, **90**, 1598 (1968).

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THE JOURNAL OF Organic Chemistry

Published biweekly by the American Chemical Society at 20th and Northampton Streets, Easton, Pennsylvania

Published biweekly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second-class postage paid at Easton, Pa.

Production Staff: Manager, Editorial Production, CHARLES R. BERTSCH; Production Editor, EILEEN SEGAL; Assistant Editor, FERN S. JACKSON; Editorial Assistant, DEBORAH K. MILLER

Advertising Office: Century Communication Corporation, 142 East Ave., Norwalk, Conn. 06851.

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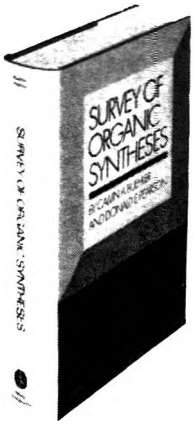

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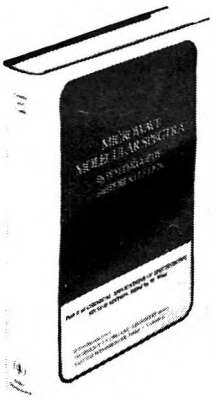

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VOLUME 36, NUMBER 1 JANUARY 15, 1971

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(In nmr descriptions, s = singlet, d = doublet, t = triplet, m = multiplet.)

"The ethereal extract was dried ($MgSO_4$), concentrated, and distilled giving 10.23 g (65%) of the acetoxy ketone 12: bp 82-83° (2.9 mm); n_D^{25} 1.4266 [lit.[6] bp 80-82° (3 mm); n_D^{25} 1.4261]; d_4^{25} 0.823; $[\alpha]_D^{25}$ 0.0° (c 6, CH_3OH); uv max (95% EtOH) 275 mμ (ε 21); ir (CCl_4) 1725 (C=O), 1740 cm^{-1} (ester C=O); nmr (CCl_4) δ 3.98 (t, 2, J = 6 Hz, CH_2OAc), 2.43 (t, 2, J = 6 Hz, CH_2CO), 2.07 (s, 3), 1.97 (s, 3), and 1.6 (m, 4); mass spectrum (70 eV) m/e (rel intensity) 158 (5), 143 (5), 115 (6), 100 (50), 99 (11), 98 (100), 85 (10)."

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THE JOURNAL OF Organic Chemistry®

VOLUME 36, NUMBER 1

JANUARY 15, 1971

Phenylglyoxime. Separation, Characterization, and Structure of Three Isomers

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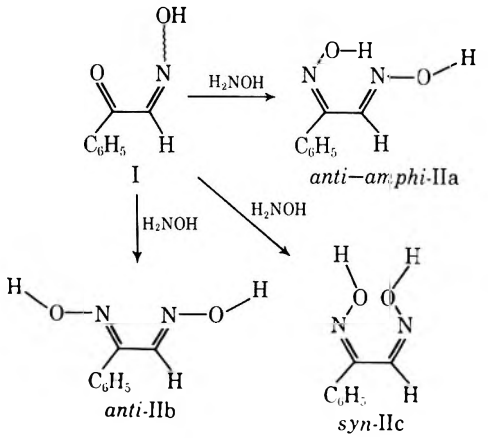
Received July 6, 1970

Three isomers of phenylglyoxime have been isolated by fractional recrystallization of the reaction product of ω-isonitrosoacetophenone and hydroxylamine hydrochloride in alkaline medium. The physical and spectral properties of each isomer are described. Structure is assigned to each of the isomers on the basis of the relative rates of complexing with nickelous acetate, the relative stabilities of the isomers, and spectroscopic information. The fourth possible isomer of phenylglyoxime was not detected.

Although isolations of three isomers of many disubstituted glyoximes have been reported in the literature, this is not the case with monosubstituted glyoximes. For example, phenylglyoxime (II) has been the subject of numerous investigations in the past, but characterization and structure studies have been attempted on only two of the four possible isomers.[1] Since most of the structural work on the isomers of phenylglyoxime occurred before the advent of modern, sophisticated spectral and analytical techniques, there is much confusion in the literature and a reexamination of the problem appeared justified.



Tlc analysis of crude phenylglyoxime obtained by reaction of ω-isonitrosoacetophenone (I) with hydroxylamine hydrochloride in alkaline medium clearly showed the presence of three isomers. These were separated by fractional recrystallization and each isomer was subjected to ir, nmr, uv, and mass spectral analyses. Significant differences were observed in the various spectra and these were useful for characterization.

Structures were assigned to the isomers through arguments based on relative rates and the nature of complexing of the isomers with nickelous acetate and also on the relative stabilities of the isomers. Corroborative evidence for the assignments was then found in the various spectra. The isomers were shown to be *anti*-phenyl-*amphi*-glyoxime (IIa), phenyl-*anti*-glyoxime (IIb), and phenyl-*syn*-glyoxime (IIc).

Results and Discussion

The reaction between ω-isonitrosoacetophenone (I) and hydroxylamine hydrochloride in aqueous ethanol containing sodium acetate proceeded in greater than 90% yield to give phenylglyoxime (II). The broad melting point range, satisfactory microanalysis, and tlc of the product indicated a three-isomer mixture.

Several reports describe the isolation of two of the isomers present in similar syntheses[1] (see Table I), *anti*-phenyl-*amphi*-glyoxime (IIa) and phenyl-*anti*-glyoxime (IIb). These reports generally indicated that isomer IIa melted at 168° and IIb at 180°, although conflicting melting points have been reported (Table I). In the present work, sharp melting points matching those reported for the pure isomers were obtained on mixtures.

Fractional recrystallization proved to be an expedient means of separation (see Experimental Section). *anti*-Phenyl-*amphi*-glyoxime (IIa), mp 178–180°, was fastest moving on tlc, appearing at 0.45 R_f. Phenyl-*anti*-glyoxime (IIb) melted at 166–168° and appeared at 0.40 R_f on tlc. There is a modification of this material which melts at 177–180° as shown below. Phenyl-*syn*-glyoxime (IIc) was slowest moving on tlc, 0.35 R_f, and melted at 168–170°.

* To whom correspondence should be addressed.

(1) For reviews on phenylglyoxime, see "Beilsteins Handbuch der Organischen Chemie," 4th ed, Vol. VII, B. Prager, P. Jacobson, P. Schmidt, and D. Stern, Ed., Springer Verlag, Berlin, 1925, pp 672–673; 2nd suppl, F. Richter, Ed., 1948, pp 601–602.

TABLE I

REPORTED MELTING POINTS OF PHENYLGLYOXIME ISOMERS

Mp, °C	Isomer designation	Recrystn solvent	Mp, °C	Isomer designation	Recrystn solvent
168	anti-amphi	Ether[a]	180	anti	anti-amphi + HCl[a]
168	"α"	Acetone[b]	180	"β"	Chloroform, toluene[b]
168	"α"	Chloroform[c]	180	"β"	Chloroform[c]
176	"α"	Acetone[c]			
169	"α-syn"[d]		177	"β-anti"	"α" + HCl[d]
176	amphi	Alcohol-water[e]	180	anti	Alcohol-water[e]

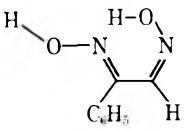
[a] A. Russanow, *Chem. Ber.*, **24**, 3497 (1891). [b] G. Ponzio and L. Avogadro, *Gazz. Chim. Ital.*, **53**, 25 (1923). [c] J. Meisenheimer and W. Theilacker, *Ann. Chem.*, **469**, 128 (1929). [d] L. Kahovec and K. W. F. Kohlrausch, *Monatsh. Chem.*, **83**, 615 (1952). [e] K. L. Hill, U. S. Patent 3,410,676 (1968).

The pure isomers are stable and can be stored at room temperature for months with no isomerization. However, IIa and IIc can be transformed into a mixture of isomers by heating them in a solvent or upon prolonged sublimination. The significant differences in the various spectra (Experimental Section)[2] combined with the differing R_f values on tlc serve to unambiguously characterize the isomers.

The phenyl-*anti*-glyoxime structure was assigned to isomer IIb (0.40 R_f) on the basis of the following experiments involving complexing with nickelous acetate. Isomer IIa (0.45 R_f) formed a green complex (1 phenylglyoxime:1 Ni^{2+}) upon admixture with nickelous acetate, whereas isomer IIb formed a red complex (2 phenylglyoxime:1 Ni^{2+}) which is indicative of an *anti*-glyoxime.[3,4] Both reactions appeared immediate to the eye. Isomer IIc (0.35 R_f) formed a dirty white precipitate only after long standing. Competition experiments were performed to determine the relative order of rate of complexing among the isomers. Two component mixtures (1:1) of IIa and IIb, IIb and IIc, and IIa and IIc were treated with 0.5 molar equiv of nickelous acetate. The nickel complexes were removed by filtration and the mother liquors were subjected to tlc analyses. In each experiment only one isomer was detected in the mother liquor, thus showing selective removal of the more rapidly reacting isomer. The relative order of rate of complexing was determined to be IIb > IIa > IIc. Isomer IIb was assigned the *anti*-glyoxime configuration because it gave the red precipitate characteristic of *anti*-glyoximes and because it was the most rapid to complex with the nickel salt.

Isomerization studies in water at 100° allowed the assignment of structures to the other two isomers. Phenyl-*anti*-glyoxime (IIb) did not undergo isomerization nor was it the product of isomerization of the other two isomers during 2 hr. Phenyl-*syn*-glyoxime (IIc) was more rapidly isomerized into *anti*-phenyl-*amphi*-glyoxime (IIa) than conversely.

Aldoximes are more rapidly equilibrated than aromatic ketoximes.[5] Isomer IIa or IIc cannot be *syn*-phenyl-*amphi*-glyoxime (IId), the fourth possible isomer of phenylglyoxime. The aldoxime in IId would be first equilibrated leading to phenyl-*anti*-glyoxime (IIb). Isomer IIb was not observed in the equilibration of IIa and IIc. Thus only two structures are possible for isomers IIa and IIc, *anti*-phenyl-*amphi*-glyoxime and phenyl-*syn*-glyoxime.



syn–amphi-IId

Phenyl-*syn*-glyoxime (IIc) is the most sterically strained of the isomers and can achieve planarity of its glyoxime group only under unfavorable interaction between the electronegative oxygen atoms. Its aldoxime should be rapidly equilibrated to form *anti*-phenyl-*amphi*-glyoxime (IIa). For the same reason, *anti*-phenyl-*amphi*-glyoxime (IIa) has little incentive to equilibrate to phenyl-*syn*-glyoxime (IIc). Thus the more rapidly equilibrating isomer, IIc, must be phenyl-*syn*-glyoxime and isomer IIa must be *anti*-phenyl-*amphi*-glyoxime.

Once the structures had been established, corroborative evidence can be found in the various spectra of the isomers (Experimental Section).[3] The mass spectrum of phenyl-*anti*-glyoxime (IIb) shows practically exclusive loss of hydroxyl ($M^+ - 17$); thus cis elimination of water in the aldoxime function did not occur. The mass spectrum of *anti*-phenyl-*amphi*-glyoxime (IIa) shows loss of hydroxyl as in IIb but also significant loss of water ($M^+ - 18$) by interaction of the two hydroxyl groups which can be reasonably near to each other in the cisoid conformation. Mainly water is lost in the mass spectrum of phenyl-*syn*-glyoxime (IIc) either through collision of the hydroxyl groups or through trans elimination on the aldoxime. The remaining ions in the mass spectra of the phenylglyoxime isomers appear to result from complex fragmentation. One possible route is given below (Scheme I), but other routes can be written.

The uv spectra of the isomers show a difference in absorption maxima between phenyl-*syn*-glyoxime (IIc, 252 nm) and the other two isomers (230 and 228 nm).

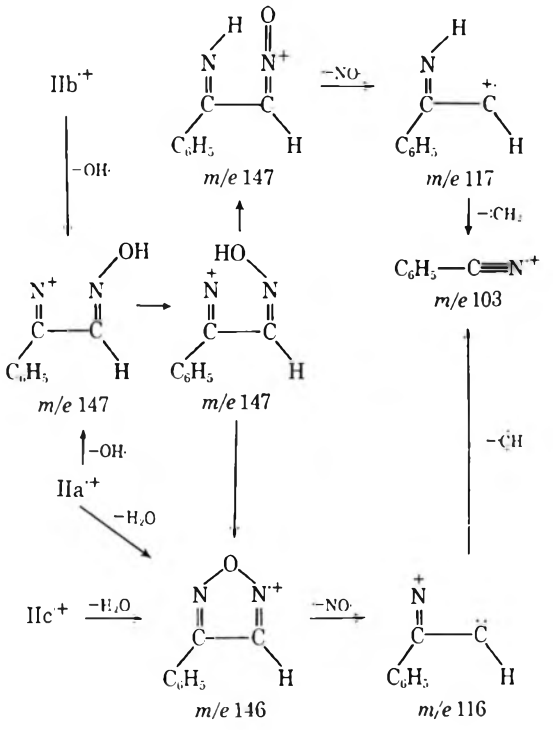
(2) Ir, nmr, and mass spectra of the isomers will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, American Chemical Society Publications, 1155 Sixteenth Street, N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit $3.00 for photocopy or $2.00 for microfiche.

(3) L. L. Merritt, Jr., *Anal. Chem.*, **25**, 718 (1953).

(4) L. E. Godycki and R. E. Rundle, *Acta Crystallogr.*, **6**, 487 (1953); R. C. Voter, C. V. Banks, V. A. Fassel, and P. W. Kehres, *Anal. Chem.*, **23**, 1730 (1951).

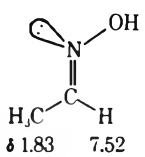
(5) P. A. S. Smith in "Molecular Rearrangements, Part One," P. de Mayo, Ed., Interscience, New York, N. Y., 1963. pp 483–488. Compare the relative stabilities of aldoxime isomers *vs.* aromatic ketoxime isomers in the following publications: I. Pejković-Tadić, M. Hranisavljević-Jakovljević, and S. Nešić, *J. Chromatogr.*, **21**, 239 (1966); R. F. Rekker and J. U. Veenland, *Recl. Trav. Chim. Pays-Bas*, **78**, 739 (1959).

SCHEME I



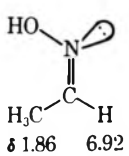
Planarity of the glyoxime group in IIc is disallowed because this requires an unfavorable interaction between the two electronegative oxygen atoms. Thus, it is not surprising that the uv spectrum of isomer IIc reflects only the uv absorption of an *anti*-phenylketoxime chromophore or of α-benzaldoxime (phenyl and hydroxyl groups are anti) each of which absorbs at 251 nm as shown by Rekker and Veenland.[5] The shorter wavelength absorption of IIa and IIb suggests a lack of coplanarity between the phenyl group and the glyoxime; aliphatic glyoximes absorb at 230 nm (ϵ 1800).[6] If the whole molecule were planar, *anti*-phenyl-*amphi*-glyoxime (IIa) would be expected to show a uv maximum either more intense or shifted to a longer wavelength than that of the *anti*-phenylketoxime chromophore (251 nm, ϵ 14,500). Similar arguments apply to phenyl-*anti*-glyoxime (IIb) using β-benzaldoxime as a model (246 nm, ϵ 14,500).[5] The lack of coplanarity may arise from an interaction between the nitrogen electron pair of the aldoxime and the phenyl group, if the molecules adopt a transoid conformation to maximize the distance between the oxime nitrogens.[6,7]

Supporting evidence for the structural assignments can also be found in the nmr spectra of the isomers. Karabatsos and Taller have shown that the group anti to the hydroxyl of an oxime is shielded with respect to the group syn.[8] Presumably the electron pair of the nitrogen is responsible for the phenomenon as shown in the case of acetaldoxime (III).



δ 1.83 ppm 7.52 ppm

IIIa



δ 1.86 ppm 6.92 ppm

IIIb

(6) H. E. Ungnade, G. Fritz, and L. W. Kissinger, *Tetrahedron Suppl.*, **19**, 235 (1963).

Examination of the phenylglyoxime isomers reveals that only isomer IIc, phenyl-*syn*-glyoxime, has the aldehydic proton anti to the hydroxyl and thus continually under the influence of an electron pair on nitrogen. It should be the most shielded of those in the three isomers and does appear farthest upfield (7.4 ppm). The aldehydic proton of *anti*-phenyl-*amphi*-glyoxime (IIa) does not come under the influence of any nitrogen electron pair and consequently appears farthest downfield (8.4 ppm). The aldehydic proton of phenyl-*anti*-glyoxime (IIb) should resonate between those of the other isomers since it is under the influence of the more distant electron pair on the nitrogen of the α-oxime. This is the case (7.8 ppm).

The absence of the fourth possible isomer, *syn*-phenyl-*amphi*-glyoxime (IId), might be explained by considering the unfavorable steric interaction between the phenyl group and the two hydroxyls when the molecule assumes the preferred transoid conformation. It should be present in the equilibration of phenyl-*anti*-glyoxime (IIb). Although it is possible that it has the same R_f value as IIb and that it could be present in the equilibration study, it should be noted that all indications are that phenyl-*anti*-glyoxime (IIb) as described above is one isomer. The nmr of that isomer clearly shows both hydroxyl protons, the aldehydic proton, and the aromatic protons. Correct integrals were obtained for these signals. Extra peaks and incorrect integrals would be observed if a mixture were present.

The argument can be made that formation of the red nickel salt by the isomer appearing at 0.40 R_f is not conclusive proof of an *anti*-glyoxime structure in studies of monosubstituted glyoximes. It can be argued that *syn*-phenyl-*amphi*-glyoxime (IId) could also give the same red complex by rapid isomerization of its aldoxime group. The possibility that the isomer at 0.40 R_f is not phenyl-*anti*-glyoxime appears remote in light of the nmr spectrum of isomer IIb. Isomer IId would be expected to have the aldehydic proton resonate at at least as high field as the aldehydic proton on phenyl-*syn*-glyoxime (IIc) since it would be under the influence of the electron pairs of both oxime nitrogens. In fact, this proton would be expected to appear farthest upfield of those in all the possible isomers. Further the mass spectrum of isomer IIb does not show the significant loss of water ($M^+ - 18$) as observed for an *amphi*-glyoxime in the mass spectrum of *anti*-phenyl-*amphi*-glyoxime (IIa).

When the aqueous solution of phenyl-*anti*-glyoxime (IIb) from the stability study was allowed to evaporate freely in an open container, crystals were obtained which melted at 177–180°. Again the mass spectrum did not show the significant loss of water ($M^+ - 18$) expected for an *amphi*-glyoxime but there is the possibility that sublimation in the mass spectrometer inlet may transform a mixture of the two isomers into one. Attempts to prepare a large sample of this material by exactly similar treatment of isomer IIb (mp 166°) failed to give the higher melting substance. No change was observed in the nmr spectrum of the residue in this experiment. Correct integrals were obtained for all sig-

(7) We thank a referee for this interpretation of the uv data.

(8) G. J. Karabatsos and R. A. Taller, *Tetrahedron*, **24**, 3347 (1968). For additional information on the nmr spectra of oximes, see G. C. Kleinspehn, J. A. Jung, and S. A. Studniarz, *J. Org. Chem.*, **32**, 460 (1967), and additional references contained therein.

nals, thus indicating the presence of only one isomer. The difference in melting points might reflect polymorphism rather than the presence of the fourth possible isomer.

Experimental Section[9]

Phenylglyoxime (II).—Phenylglyoxime can be readily synthesized by several methods reported in the literature[1] (Table I). The highest yields were obtained by reacting ω-isonitrosoacetophenone and hydroxylamine hydrochloride in aqueous ethanol containing sodium acetate (Table I). In a typical experiment, a solution of 48 g of sodium acetate and 24 g of hydroxylamine hydrochloride in 75 ml of water was added to a solution of 50 g of ω-isonitrosoacetophenone (Aldrich Chemical Co., Inc.) in 150 ml of ethanol. The mixture was refluxed for 4 hr and was then allowed to cool. Most of the solvent was then removed under reduced pressure and the precipitate which formed was collected by filtration and was washed with water. The product was air-dried on the funnel. The phenylglyoxime was obtained in 92% yield (51 g) and melted at 150–158°. Tlc using silica gel G as adsorbent,[10] benzene–ethyl acetate (7:3) as solvent, and iodine vapor for detection showed the presence of three components at 0.45, 0.40, and 0.35 R_f.

The microanalyses of the three-component mixture and of various mixtures of the components were in agreement with those expected for phenylglyoxime. The material can be readily sublimed [50° (1.4 mm)] but with no observable change in component ratio.

Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.44; H, 4.91; N, 17.01.

***anti*-Phenyl-*amphi*-glyoxime (IIa).**[11]—One gram of crude three-component phenylglyoxime was recrystallized from acetone–chloroform five times to give 150 mg of pure *anti*-phenyl-*amphi*-glyoxime (IIa): mp 178–180°; uv max (95% C_2H_5OH) 230 nm (ε 14,800); nmr (DMSO) δ 7.4 (m, 5, phenyl), 8.4 [s, 1, –C(=N)H], and 11.7 ppm (s, 2, hydroxyls); mass spectrum (70 eV) *m/e* (rel intensity), 164 (95), 147 (38), 146 (24), 117 (100). The material was homogeneous on tlc[10] appearing at 0.45 R_f. An alcohol–water solvent system may be substituted for acetone–chloroform in this isolation.

Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.33; H, 4.68; N, 17.21.

Phenyl-*anti*-glyoxime (IIb).[11]—The solvent was removed from the mother liquor of the first recrystallization performed during the above separation. The residue was recrystallized by adding chloroform to an acetone solution of the substance at room temperature. This process was repeated until the precipitate appeared homogeneous on tlc[10] at 0.40 R_f. The sample at this point melted at 170–172° but failed to give a satisfactory microanalysis. The solid was then sublimed [90° (0.2 mm)] to give analytically pure phenyl-*anti*-glyoxime: mp 166–168°; 0.40 R_f on tlc;[10] uv max (95% C_2H_5OH) 228 nm (ε 14,380); nmr (DMSO) δ 7.4 (s, 5, phenyl), 7.8 [s, 1, –C(=N—)**H**], 11.4 (s, 1, –**OH**), and 11.6 ppm (s, 1, **OH**); mass spectrum (70 ev) *m/e* (rel intensity) 164 (43), 147 (25), 117 (100), 103 (45). This isolation procedure yielded only about 1% of the pure isomer based on the starting three-component phenylglyoxime. Here also an alcohol–water solvent system may be substituted for acetone–chloroform in the separation.

Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.81; H, 4.74; N, 17.29.

Phenyl-*syn*-glyoxime (IIc).[11]—The crude three-component phenylglyoxime (2 g) was recrystallized from a dilute solution of ethyl acetate. The precipitate (180 mg, mp 170–171°) was pure by tlc analysis[10] appearing at 0.35 R_f. Further recrystallization changed the melting point to 168–170° without a change in R_f: uv max (95% C_2H_5OH) 252 nm (ε, 12,200); nmr (DMSO) δ 7.4 [m, 6, phenyl, –C(=N—)**H**], and 11.4 ppm (s, 2, hydroxyls); mass spectrum (70 eV) *m/e* (rel intensity) 164 (100), 146 (45), 116 (89), 103 (36).

Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.45; H, 4.85; N, 16.82.

In hindsight, it would seem that the yields in these separations could be increased through initial enrichment of the isomers by selective formation of nickel complexes. Either isomer IIb or both IIa and IIb can be selectively removed from a solution of the three-component phenylglyoxime by adding portions of nickelous acetate with monitoring by tlc.

Preparation of Nickel Complexes.—The competition experiments were performed by treating 0.06 mol of a mixture (1:1) of two isomers with 0.03 mol of nickelous acetate in alcohol–water. The mother liquors were then examined on chromatoplates.

anti-Phenyl-*amphi*-glyoxime (IIa) gave a green nickel complex, whereas phenyl-*anti*-glyoxime (IIb) gave a red one.

Anal. Calcd for $C_8H_6N_2NiO_2$ (green complex): C, 43.51; H, 2.74; N, 12.68. Found: C, 43.33; H, 3.15; N, 12.93.

Anal. Calcd for $C_{16}H_{14}N_4NiO_4$ (red complex): C, 49.92; H, 3.67; N, 14.55. Found: C, 49.68; H, 3.62; N, 14.49.

Thermal Isomerization Study.—The experiments were performed by dissolving the pure phenylglyoxime isomers in water surrounded by an oil bath kept at 100°. The transformations were monitored by tlc and the concentrations were visually estimated. There was no evidence by tlc for the isomerization of phenyl-*anti*-glyoxime (IIb) even after 5 hr of heating. After 20 min, isomer IIc was approximately 20% converted into IIa; after 60 min, it was 50% converted. After 20 min, isomer IIa was only 5% converted into IIc, and, after 60 min, it was approximately 25% converted into IIc. Isomer IIb was not observed in the transformations of IIa and IIc during 2 hr.

Registry No.—IIa, 26527-40-2; IIb, 17016-15-8; IIc, 26527-42-4.

(9) All melting points were determined with a Mettler FP1 melting point apparatus equipped with a Bausch and Lomb VOM 5 recorder. Infrared spectra were recorded on a Perkin-Elmer 421 grating spectrophotometer. A Varian A-60 spectrometer was used to obtain the nmr spectra and tetramethylsilane was used as the internal standard. The mass spectra were determined on a Consolidated Electrodynamics Corporation Model 21-103C spectrometer. The uv spectra were recorded on a Cary M14 spectrophotometer.

(10) Several samples of commercially available precoated chromatoplates proved unsatisfactory for this separation. Chromatoplates freshly prepared from Merck (Darmstadt) silica gel G were used exclusively. All R_f values quoted in this article were determined with this adsorbent and benzene–ethyl acetate (7:3) as solvent.

(11) A note of caution must be interjected regarding the isolation of the isomers. Often the results depended on several factors including relative concentrations of the isomers in the mixture, concentration of phenylglyoxime in the recrystallization solvent, duration of heating, etc. Thus it has occurred that recrystallization of the crude three-component mixture from ethyl acetate has led to an enrichment of IIa rather than IIc. Continuous monitoring by tlc[10] must be employed throughout the separations.

Phenylfurazan Oxide. Structure

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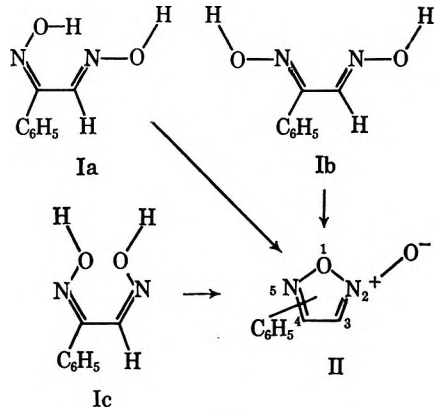
Received July 6, 1970

Three isomers of phenylglyoxime have been oxidized to the same phenylfurazan oxide in separate reactions. The 4-phenylfurazan 2-oxide structure has been assigned to the product on the basis of nmr spectroscopic arguments. Isomerization of 4-phenylfurazan 2-oxide into 3-phenylfurazan 2-oxide was not observed although an equilibrium between the two is possible.

Phenylfurazan oxide is readily synthesized by oxidation of phenylglyoxime by dinitrogen tetroxide.[1] Two structures can be written for the product, 3-phenylfurazan 2-oxide (IIa) or 4-phenylfurazan 2-oxide (IIb).



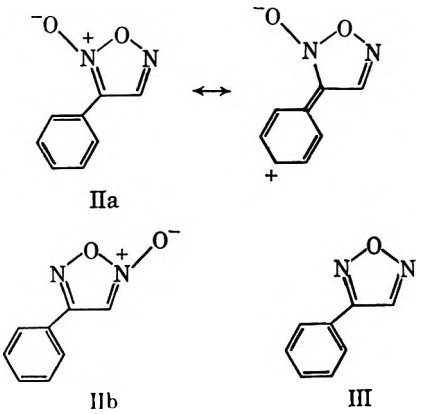
Ia Ib Ic II

An equilibrium between isomeric furazan oxides has been demonstrated in disubstituted furazan oxides and benzofurazan oxides.[2] The equilibration presumably involves the corresponding dinitroso intermediates. Thus, there was the possibility that phenylfurazan oxide existed as a mixture of IIa and IIb.

Reports claim the isolation of two phenylfurazan oxides by separate oxidation of two isomers of phenylglyoxime,[1] but characterization centered on small differences in melting point, 108° *vs.* 111°, and structures were not firmly assigned. Three isomers of phenylglyoxime have now been isolated. The physical constants of each of the pure isomers were not in agreement with those reported for the phenylglyoxime isomers used in previous syntheses of phenylfurazan oxide.[3] It would appear that the previous studies of phenylfurazan oxide involved oxidation of mixtures of phenylglyoxime isomers. In this work, the presence of two isomers of phenylfurazan *N*-oxide was not observed even though three isomers of phenylglyoxime were oxidized in separate reactions.

Nmr measurements at varied temperature have been used to demonstrate equilibration in furazan oxides.[2] Nmr spectroscopy was used in the present work to show the lack of detectable equilibrium in phenylfurazan oxide and to determine that the compound exists as 4-phenylfurazan 2-oxide (IIb).

A firm prediction as to the correct structure of phenylfurazan oxide could not be made *a priori*. 3-Phenylfurazan 2-oxide (IIa) may be stabilized by facile charge delocalization into the phenyl ring. Such is not the case with 4-phenylfurazan 2-oxide (IIb). However, IIa has an unfavorable stereochemical interaction between the phenyl group and the oxide; this interaction is missing in IIb. It was not clear which factor would predominate.



IIa IIb III

Results and Discussion

The same phenylfurazan oxide (II) was synthesized from each of three phenylglyoxime isomers (Ia–Ic) by oxidation with dinitrogen tetroxide in ether.[1] The reaction proceeded smoothly with *anti*-phenyl-*amphi*-glyoxime (Ia) and phenyl-*syn*-glyoxime (Ic), whereas impurities were observed when phenyl-*anti*-glyoxime (Ib) was oxidized. The isomers can yield the same product by isomerization before reaction in the acidic reaction medium. The impurities observed in the reaction with phenyl-*anti*-glyoxime (Ib) appeared to be nitro derivatives as detected in infrared spectral measurement. Nitro compounds are known products of reaction between oximes and dinitrogen tetroxide.[4]

The products of these oxidations were crystalline solids, melting over two degrees in the 105–110° range. Recrystallization from *m*-xylene raised the melting points to 108–110° (usually reported[1]) without change in ir or nmr spectra. Phenylfurazan oxide was found to be stable at its melting point since the resolidified melt showed no change in its ir spectrum.[5] Table I and Figure I contain nmr and mass spectral data on II and III.

The mass spectrum of phenylfurazan oxide is readily interpretable (Table I). It is questionable whether or

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(1) For reviews on phenylfurazan oxide, see "Beilstein's Handbuch der Organischen Chemie," 4th ed, Vol. XXVII, B. Prager, P. Jacobsen, and F. Richter, Ed., Springer Verlag, Berlin, 1937, p 575; 2nd suppl, F. Richter, Ed., 1955, pp 632–633. J. S. Michelman, Ph.D. Thesis, Harvard University, Cambridge, Mass., 1965. K. L. Hill, U. S. Patent 3,410,676 (1968).

(2) P. Diehl, H. A. Christ, and F. B. Mallory, *Helv. Chim. Acta*, **45**, 504 (1962); F. B. Mallory and A. Cammarata, *J. Amer. Chem. Soc.*, **88**, 61 (1960).

(3) J. V. Burakevich, A. M. Lore, and G. P. Volpp, *J. Org. Chem.*, **35**, 1 (1970).

(4) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. II, W. A. Benjamin, New York, N. Y., 1966, pp 57–58.

(5) For data on the ir absorption of furazan oxides, see J. H. Boyer, D. I. McCane, W. J. McCarville, and A. T. Tweedie, *J. Amer. Chem. Soc.*, **75**, 5298 (1953); N. E. Boyer, G. M. Czerniak, H. S. Gutowsky, and H. R. Snyder, *ibid.*, **77**, 4238 (1955).

TABLE I
SPECTRAL DATA COLLECTED ON PHENYLFURAZAN OXIDE, PHENYLFURAZAN, AND FURAZAN

Compd	Nmr (CCl_4), δ, ppm	Nmr ($CDCl_3$), δ, ppm	Mass spectrum *m/e* (rel intensity), assignment
4-Phenylfurazan 2-oxide (IIb)	7.13 [s, 1, -C(=N-)H] 7.62 (m, 5, phenyl)	7.26 [s, 1, -C(=N-)H] 7.60 (m, 5, phenyl)	162 (15), M^+ 146 (6.0), $M^+ - O$ 145 (2.0), $M^+ - OH$ 132 (14), $M^+ - NO$ 103 (44), $C_6H_5CN^+$ 102 (100), $C_6H_5C{\equiv}CH^+$
Phenylfurazan[a] (III)	8.42 [s, 1, -C(=N-)H] 7.83 (m, 2, phenyl) 7.48 (m, 3, phenyl)	8.60 [s, 1, -C(=N-)H] 7.83 (m, 2, phenyl) 7.54 (m, 3, phenyl)	146 (56), M^+ 119 (100), $C_6H_5CNO^+$ 116 (38), $M^+ - NO$ 103 (46), $C_6H_5CN^+$
Furazan[a] (VI)	8.19		

[a] See ref 9.

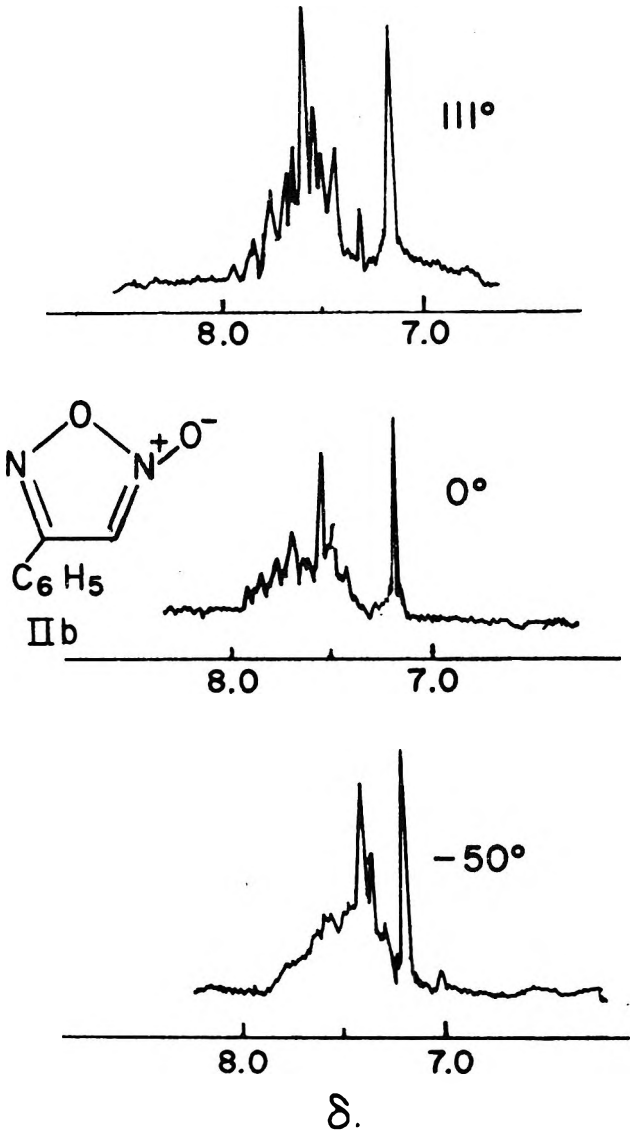
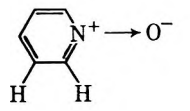


Figure 1.—Nmr spectra of phenylfurazan oxide in chloroform-*d* solution at various temperatures.

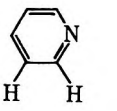
not the small $(M - 17)^+$ ion indicating loss of -OH in the fragmentation can be associated with the structure of the parent phenylfurazan oxide although it did suggest the 4-phenylfurazan 2-oxide structure in agreement with the conclusion reached from nmr considerations.

The nmr spectrum of phenylfurazan *N*-oxide (Figure 1) showed the phenyl protons as a multiplet and the lone heterocyclic ring proton as a singlet. Thus, the nmr integration indicates that only one isomer was present. The positions of the nmr signals of phenylfurazan oxide (II) and phenylfurazan (III) listed in Table I were found to be concentration independent in both carbon tetrachloride and chloroform-*d* solutions 0.2 *M* or less. The difference in chemical shift between the protons on the heterocyclic rings in phenylfurazan oxide and phenylfurazan was used to determine structure.

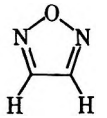
The proton on the heterocyclic ring in phenylfurazan oxide appears at much higher field than that in phenylfurazan in at least two solvents (Table I). *N*-Oxide groups shield protons located on the α-carbon atoms relative to those in the corresponding base, as seen by comparison of the nmr values reported for pyridine *N*-oxide (IV) and pyridine (V)[6] given on the structural drawings. In the present study, it was shown that these values are concentration independent in chloroform in solutions 0.2 *M* or less. The nmr data, therefore, indicate that phenylfurazan *N*-oxide exists as 4-phenylfurazan 2-oxide.



IV



V



VI

The large differences in chemical shift between the heterocyclic protons of II and III (1.29 ppm in carbon tetrachloride and 1.34 ppm in chloroform) eliminate the possibility that phenylfurazan *N*-oxide exists as 3-phenylfurazan 2-oxide. These large upfield shifts cannot result from diamagnetic shielding by the phenyl group rotated out of planarity with the heterocyclic ring through steric interaction with the *N*-oxide. Such shifts would arise from the elimination of deshielding caused by coplanarity of the heterocyclic ring proton and the phenyl group (0.23 ppm, compare III and VI in Table I) and shielding of this proton by the phenyl group when the rings are orthogonal (0.2 ppm, estimated from Dreiding Molecular Models and the dia-

(6) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates (National Press), U. S. A., 1962, spectrum 96; P. D. Kaplan and M. Orchin, *Inorg. Chem.*, 4, 1393 (1965).

gram of Johnson and Bovey[7]). Thus, under such conditions, the maximum upfield shift would be predicted to be only about 0.5 ppm in contrast to the observed shifts of 1.29 and 1.34 ppm. Another argument against this situation is that orthogonality of the rings would prevent charge delocalization, the favorable factor present in 3-phenylfurazan 2-oxide when compared to 4-phenylfurazan 2-oxide.

Only minor variations were observed in the nmr spectra of 4-phenylfurazan 2-oxide at high and low temperature (Figure 1). The small peak at δ 7.0 ppm in the spectrum at $-50°$ presumably arises from rotamer fixation and not from isomerization which should produce a downfield shift, not an upfield one. The peak at δ 7.3 ppm in the spectrum at 111° is suspiciously close to chloroform solvent resonance. At temperatures higher than 111°, the nmr solution turned into a gel.[8]

The phenylfurazan used in the nmr study was synthesized by dehydration of phenylglyoxime.[9] The spectral data collected on it appear in Table I. The mass spectrum of phenylfurazan can be interpreted according to the fragmentation pattern previously recorded for furazans.[10]

Experimental Section[8,11]

4-Phenylfurazan 2-Oxide from *anti*-Phenyl-*amphi*-glyoxime.[1,3]—An ice-cooled solution of 2 g of *anti*-phenyl-*amphi*-glyoxime (Ia)[3] in 20 ml of anhydrous ether was treated with gaseous dinitrogen tetroxide until a green-colored solution resulted. The ice bath was removed and the solution was concentrated by passing a stream of nitrogen over it. The precipitated II was removed by filtration as a white powder (1.4 g, 71% yield): mp 108–110°; ir spectrum ($CHCl_3$) 3165 (w), 1610 (s), 1603 (m), 1471 (w), 1451 (m), 1399 (m), 1182 (w), 1000 (w), 985 (w), and 935 cm^{-1} (w). The nmr spectrum is reproduced in Figure 1.[5]

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.41; H, 4.01; N, 17.02.

A stream of nitrogen was then used to completely remove the solvent from the filtrate obtained during the isolation of the above product. The infrared and nmr spectra of the residue were virtually the same as the pure product.

4-Phenylfurazan 2-Oxide from Phenyl-*anti*-glyoxime.[1,3]—Dinitrogen tetroxide gas was passed into an ice-cooled solution of 2 g of phenyl-*anti*-glyoxime (Ib)[3] in 75 ml of anhydrous ether for 15 min. A stream of nitrogen was then used to evaporate solvent from the reaction mixture to near dryness. The precipitate that formed was collected by filtration, yield 800 mg (40% yield), mp 98–102°. The infrared and nmr spectra of samples isolated at this point were essentially superimposable upon those of the product of oxidation of *anti*-phenyl-*amphi*-glyoxime (see above). Only minor extraneous peaks resulting from impurities were observed. Recrystallization of the crude product first from *m*-xylene and then from *m*-xylene–petroleum ether (bp 30–60°) afforded 200 mg of 4-phenylfurazan 2-oxide, mp 106–108°.

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.02; H, 3.76; N, 16.84.

Further evaporation of the solvent from the reaction mother liquor gave a residue whose ir spectrum was complex in the region 1689–1346 cm^{-1}. The spectrum suggested the presence of nitro derivatives which are known to be products of reaction between oximes and dinitrogen tetroxide.[4]

4-Phenylfurazan 2-Oxide from Phenyl-*syn*-glyoxime.[1,3]—The synthesis was accomplished by following the procedure outlined above in the oxidation of *anti*-phenyl-*amphi*-glyoxime but with use of a solution of 200 mg of phenyl-*syn*-glyoxime (Ic)[3] in 10 ml of anhydrous ether. A white powder was obtained, 50 mg (25% yield), mp 105–107°. The infrared and nmr spectra were the same as obtained from the product of oxidation of *anti*-phenyl-*amphi*-glyoxime (see above).

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.50; H, 3.99; N, 17.06.

Here, also, a stream of nitrogen was used to completely remove the solvent from the filtrate obtained during the isolation of the pure product. Again, the infrared and nmr spectra of the residue were virtually the same as the pure product.

Registry No.—IIb, 7707-64-4.

(7) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958); L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 95.

(8) The nmr spectra of phenylfurazan oxide at low temperatures were determined by Dr. G. Dudek, Department of Chemistry, at Harvard University on a Varian A60 instrument equipped with a variable temperature probe. The high temperature nmr spectra were determined by Dr. S. Young at FMC Corp., Niagara Division, on a similar instrument. The authors wish to thank them for their kind cooperation.

(9) R. A. Olofson and J. S. Michelman, *J. Org. Chem.*, **30**, 1854 (1965).

(10) H. E. Ungnade and E. D. Loughran, *J. Heterocycl. Chem.*, **1**, 61 (1964).

(11) All melting points were determined with a Mettler FP1 melting point apparatus equipped with a Bausch and Lomb VOM 5 recorder. Infrared spectra were recorded on a Perkin-Elmer 421 grating spectrophotometer. A Varian A-60 spectrometer was used to obtain the nmr spectra at room temperature and tetramethylsilane was used as the internal standard. The mass spectra were determined on a Consolidated Electrodynamics Corporation Model 21-103C spectrometer.

Mesoionic Compounds. XIII. 1,4-Dipolar-Type Cycloaddition Reactions of *anhydro*-2-Hydroxy-1-methyl-4-oxopyrido[1,2-*a*]pyrimidinium Hydroxide[1]

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The title six-membered mesoionic compound (**1**) undergoes cycloaddition reactions with acetylenic dipolarophiles to yield 1,2-disubstituted 4*H*-quinolizin-4-ones (**3**), with extrusion of methyl isocyanate. With tetracyanoethylene and diethyl azodicarboxylate, no cycloadducts were obtained; rather, substitution occurred at the 3 position of the nucleus. Reaction of 2-*N*-methylaminopyridine with carbon suboxide provided an extremely facile synthesis of the mesoionic compound **1**.

In recent years numerous examples of the use of mesoionic compounds in cycloaddition reactions have been described.[2] These involved predominantly five-membered ring systems[3] and the ambident nature of the 1,3 dipole has been clearly shown.[4] Several six-membered mesoionic type ring systems have also been found[5] to undergo cycloadditions involving a 1,3-dipolar type intermediate and, in all cases, these cycloadditions have provided new and facile routes to new products. Our interest in mesoionic ring systems has led us to study a mesoionic type compound which would be capable of undergoing a 1,4-dipolar type cycloaddition reaction, and these results are described in this communication.

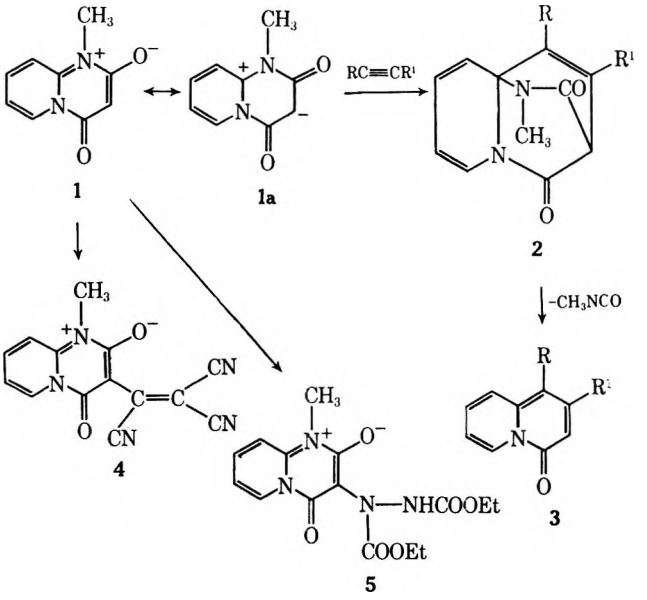
Cycloadditions[6] of the type [4 + 2 → 6] include the Diels–Alder reaction which has been the most extensively studied[7] of all cycloadditions. It has recently been shown that the reaction of isoquinoline and phenyl isocyanate is a cycloaddition of this general type. A two-step process involving a 1,4-dipolar intermediate is involved and this then undergoes reaction with additional phenyl isocyanate acting as a dipolarophile.[8] The considerable scope of the principle of 1,4-dipolar cycloadditions has recently been pointed out and our present results, with an endocyclic 1,4 dipole, are thus of particular interest.

Condensation of 2-aminopyridine with malonic ester has been shown to yield "malonyl α-aminopyridine" (pyrido[1,2-*a*]pyrimidine-2,4-dione) which has been shown to have considerable polar character.[9] Methylation occurred predominantly at N-1 and the resultant product **1** appeared to be a very good candidate for participation in 1,4-dipolar type cycloaddition reactions. *anhydro*-2-Hydroxy-1-methyl-4-oxopyrido[1,2-*a*]pyrimidinium hydroxide (**1**) may be regarded as a six-membered mesoionic type compound and the 1,4-dipolar form represented by **1a** is consistent with the octet–sextet representation of a 1,4 dipole employed earlier.[10]

Methylation of pyrido[1,2-*a*]pyrimidine-2,4-dione yields **1** in a moderate degree of purity only, and vacuum sublimation has to be used to obtain a pure product. We have now found that **1** can be prepared in excellent yield in a pure state from the reaction of 2-*N*-methylaminopyridine and carbon suboxide.

Dimethyl acetylenedicarboxylate was found to undergo reaction with **1** over 24 hr in boiling xylene with the formation of dimethyl 4*H*-quinolizin-4-one-1,2-dicarboxylate (**3**, R = R[1] = COOMe) in 64% yield. Nmr spectral data clearly showed (Table I) that cycloaddition had occurred and that methyl isocyanate had been extruded during the course of the reaction. The spectral characteristics (Experimental Section) of this product were consistent with those reported for an earlier preparation of **3** from methyl 2-pyridylacetate and dimethyl acetylenedicarboxylate.[11]

Reaction of **1** with ethyl propiolate gave an analogous product, ethyl 4*H*-quinolizin-4-one-1-carboxylate (**3**, R = COOEt; R[1] = H) whose structure was immediately apparent from its nmr spectral characteristics (Table I). Two AX doublets at τ 3.45 and 1.65 (the 3 H and 2 H, respectively), were particularly important in



establishing structure **3** (R = COOEt; R[1] = H) and in eliminating alternate modes of addition. This product was found to be identical with one reported to have

* To whom correspondence should be addressed.

(1) Support of this work by U. S. Public Health Service Research Grant CA 08495-04, National Cancer Institute, is gratefully acknowledged.

(2) Recent reviews which discuss this aspect follow: M. Ohta and H. Kato in "Nonbenzenoid Aromatics," J. P. Snyder, Ed., Academic Press, New York, N. Y., 1969, Chapter 4; R. Huisgen in "Aromaticity," Chemical Society Special Publication No. 21, London, 1967, p 51.

(3) *E.g.*, see R. Huisgen and H. Gotthardt, *Chem. Ber.*, **101**, 839 (1968), and references listed therein; K. T. Potts, E. Houghton, and U. P. Singh, *Chem. Commun.*, 1129 (1969), and references listed therein.

(4) H. Kato, S. Sato, and M. Ohta, *Tetrahedron Lett.*, 4261 (1967).

(5) J. Honzl and M. Sorm, *ibid.*, 3339 (1969); K. T. Potts and M. Sorm, unpublished observations.

(6) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **7**, 321 (1968).

(7) A recent review of this topic follows: J. Sauer, *ibid.*, **5**, 211 (1966); **6**, 16 (1967). See also J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961).

(8) R. Huisgen, M. Morikawa, K. Herbig, and E. Brunn, *Chem. Ber.*, **100**, 1094 (1967); R. Huisgen, K. Herbig, and M. Morikawa, *ibid.*, **100**, 1107 (1967).

(9) A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 1544 (1962).

(10) R. Huisgen, *Z. Chem.*, **8**, 290 (1968).

(11) E. Wintersfeld, *Chem. Ber.*, **98**, 3537 (1965).

Table I
Nmr Data of Products Derived from 1 and Dipolarophiles

Compd	Chemical shifts (ppm)							Coupling constants (Hz)				
	τ_1	τ_2	τ_3	τ_6[a]	τ_7[b]	τ_8[c]	τ_9[a]	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$	$J_{7,9}$	$J_{8,9}$
1[d]	*6.47*, s		5.12, s	0.87	2.55	1.7	2.22	7.0	1.5	7.0	1.5	9.0
3, R = R¹ = $COOCH_3$[e,f]	*6.10*, s	*6.17*, s	3.32, s	0.80	2.87	2.42	2.20	7.0	1.5	7.0	1.5	9.0
3, R = $COOC_2H_5$; R = H[f,g]	*8.6*, t 5.5, qt	1.65, d	3.54, d	0.75	2.87	2.39	0.75	6.5	1.5	6.5	1.5	9.0
3, R = R¹ = CN[d]			2.94, s	0.75	1.90	2.37	2.00	6.0	2.0	6.0	2.0	8.0
4[d]	*6.40*, s			0.80	2.42	1.52	2.2	7.0	1.5	7.0	1.5	9.0
5[f]	*6.33*, s		*8.76*,[h] t 5.90,[h] qt 2.50,[i] s	0.69	2.64	1.77	2.42	7.0	1.5	7.0	1.5	9.0

[a] Quartets. [b] Singlets. [c] Octets. [d] Spectra determined in DMSO-d_6. [e] Methyl resonances italicized. [f] Spectra determined in $CDCl_3$. [g] $J_{2,3}$ = 9.5 Hz. [h] J_{CH_2,CH_3} = 7.0 Hz. [i] NH, exchanged with D_2O.

this structure formed from ethyl 2-pyridylacetate and diethyl ethoxymethylenemalonate, followed by hydrolysis and decarboxylation of the resulting diester.[12]

Dicyanoacetylene also underwent reaction with **1** forming in good yield 1,2-dicyano-4*H*-quinolizin-4-one (**3**, R = R¹ = CN). Analytical data and nmr spectral characteristics (Table I) showed that addition of the dipolarophile had occurred and that methyl isocyanate had been lost during the course of the reaction. As with all other acetylenic dipolarophiles in cycloadditions of this type, the driving force in the reaction may be attributed in part to the aromatization of the primary cycloadduct by the elimination of a stable species. In cases where aromatization cannot occur, as in the cycloadduct from dimethyl acetylenedicarboxylate and *anhydro*-4-hydroxy-2-methylcinnolinium hydroxide, a stable 1:1 adduct was formed.[13]

In contrast to the above acetylenic dipolarophiles, tetracyanoethylene and ethyl azodicarboxylate did not undergo cycloaddition but gave instead "ene-type" reaction products. Thus, tetracyanoethylene and **1** in refluxing chlorobenzene gave a 42% yield of a yellow product of molecular formula $C_{14}H_7N_5O_2$, indicating that HCN had been lost from a simple 1:1 condensation product. The infrared spectrum of **4**, besides a strong CN absorption at 2255 cm^{-1}, showed the presence of two amide groups (ν_{CO} 1715, 1665 cm^{-1}) which were very similar to those of **1**. The nmr spectrum (Table I) indicated that all the components of **1**, other than the 3 H, were present. These data can be readily accommodated in terms of structure **4**, *anhydro*-2-hydroxy-1-methyl-4-oxo-3-(tricyanoethenyl)pyrido[1,2-*a*]pyrimidinium hydroxide. This may be regarded as an "ene-type" reaction[14] in which the initial product lost HCN under the reaction conditions. Examples of this type of reaction have been observed with other mesoionic systems.[15]

Ethyl azodicarboxylate also underwent an analogous type reaction[16] with **1**. Analytical data and spectral characteristics (Table I and Experimental Section) indicated that the product formed was a 1:1 adduct which is best represented as *anhydro*-3-(1,2-dicarbethoxyhydrazino)-2-hydroxy-1-methyl-4-oxopyrido[1,2-*a*]-pyrimidinium hydroxide (**5**). Infrared absorptions at 3315 and 3225 cm^{-1}, a low melting point, and good solubility in nonpolar solvents indicate the presence of H bonding[16] in **5**, most likely between the NH group and the carbonyl group at the 2 position. The absorption of this carbonyl group has shifted from 1665 cm^{-1} in the original mesoionic system to 1640 cm^{-1}, indicating some degree of interaction with a neighboring group.

The formation of these substitution products is most likely the result of steric influences. In attempts to prepare cycloadducts from dipolarophiles such as diphenylacetylene, phenyl isocyanate and phenyl isothiocyanate, maleic anhydride, and dimethyl maleate, no well-defined products were obtained.

Experimental Section[17]

***anhydro*-2-Hydroxy-1-methyl-4-oxopyrido[1,2-*a*]pyrimidinium Hydroxide (1).**—2-*N*-Methylaminopyridine (0.108 g, 1.0 mmol) dissolved in anhydrous ether (5 ml) with a catalytic amount of anhydrous $AlCl_3$ was added slowly to a stirred ethereal solution of a slight excess of carbon suboxide.[18] Crystals started to form toward the end of this addition and the reaction mixture was then refluxed for 12 hr. The crude product (100%) crystallized from methanol as yellow prisms: mp 243–245° (lit.[10] mp 245–252°); ir (KBr) 3100, 2950 (CH), 1720, 1665 (CO) cm^{-1}; $\lambda_{max}^{CH_3OH}$, nm (log ϵ), 322 (3.67), 257 (4.07), 230 (4.50); mass spectrum (70 eV) *m/e* (rel intensity) 176 (20), 148 (5), 107 (3), 80 (12), 79 (38), 78 (20), 69 (20), 32 (70), 31 (100). This product was identical with that obtained by methylation of "malonyl-α-aminopyridine."

Dimethyl 4*H*-Quinolizin-4-one-1,2-dicarboxylate (3, R = R¹ = COOMe).—*anhydro*-2-Hydroxy-1-methyl-4-oxopyrido[1,2-*a*]-pyrimidinium hydroxide (0.528 g, 3.0 mmol), dimethyl acetylenedicarboxylate (0.852 g, 6.0 mmol), and dry xylene (500 ml) were heated under reflux for 24 hr. The dark, insoluble matter was filtered, the hot filtrate concentrated *in vacuo*, and the crude residue chromatographed on silica gel (Florosil F-100) using ether as eluent. The product crystallized from cyclohexane and then from methanol as yellow prisms: 0.5 g (64%); mp 113–115° (lit.[11] mp 115°); ir (KBr) 3145, 2980 (CH), 1740, 1720 (COOMe), 1670 (amide CO) cm^{-1}; $\lambda_{max}^{CH_3OH}$, nm (log ϵ), 385 (3.98), 275 (3.67), 258 (3.86), 250 (3.88), 220 (4.06); mass spectrum, M^+, *m/e* 261 (15).

Anal. Calcd for $C_{13}H_{11}NO_5$: C, 59.81; H, 4.24; N, 5.36. Found: C, 59.79; H, 4.22; N, 5.22.

Similarly, **ethyl 4*H*-quinolizin-4-one-1-carboxylate (3, R = COOEt; R¹ = H)** was obtained in 47% yield from **1** and ethyl propiolate on refluxing in chlorobenzene for 5 days. It crystallized from cyclohexane as yellow prisms: mp 113–114° (lit.[12] mp 117–118°); ir (KBr) 3120, 3080, 3000 (CH), 1730 (COOEt), 1690 (amide CO) cm^{-1}; $\lambda_{max}^{CH_3OH}$, nm (log ϵ), 370 (4.09), 274 (3.96),

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255 (3.89), 248 sh (3.85), 207 (4.20); mass spectrum, M^+, m/e 217 (100).

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.45; H, 5.11; N, 6.46. Found: C, 66.18; H, 5.02; N, 6.14.

In a similar fashion, **1,2-dicyano-4*H*-quinolizin-4-one** (**3**, **R** = **R**^{1} = **CN**) was obtained from 1 and dicyanoacetylene on refluxing in chlorobenzene overnight. It crystallized from benzene as yellow prisms: mp 263–265° (33%); ir (KBr) 3150, 3140 (CH), 2225 (CN), 1710 (amide CO) cm^{-1}; $\lambda_{max}^{CH_3OH}$, nm (log ϵ), 415 (4.20), 394 (4.12), 278 (3.69), 261 (4.02), 235 (4.31), 212 (4.23); mass spectrum, M^+, m/e 195 (45).

Anal. Calcd for $C_{11}H_5N_3O$: C, 67.65; H, 2.58; N, 21.53. Found: C, 67.69; H, 2.55; N, 21.49.

***anhydro*-2-Hydroxy-1-methyl-4-oxo-3-(tricyanoethenyl)pyrido[1,2-*a*]pyrimidinium Hydroxide** (**4**).—*anhydro*-2-Hydroxy-1-methyl-4-oxopyrido[1,2-*a*]pyrimidinium hydroxide (0.528 g, 3.0 mmol), tetracyanoethylene (0.561 g, 4.5 mmol), and chlorobenzene (750 ml) were heated under reflux for 15 hr. After removal of the dark, insoluble matter the hot filtrate was evaporated to dryness under reduced pressure. Trituration of the residue with a small amount of cold acetone caused it to crystallize, and it was recrystallized from acetone and then from acetonitrile–ether (1:1) from which it separated as yellow prisms: mp 301–302° (42%); ir (KBr) 3140, 2920 (CH), 2255 (CN), 1715, 1665 (CO) cm^{-1}; $\lambda_{max}^{CH_3OH}$, nm (log ϵ), 416 (3.20), 250 (3.98), 218 (4.36); mass spectrum, M^+, m/e 277 (60).

Anal. Calcd for $C_{14}H_7N_5O_2$: C, 60.65; H, 2.54; N, 25.21. Found: C, 60.56; H, 2.39; N, 25.32.

Similarly, ***anhydro*-3-(1,2-dicarbethoxyhydrazino)-2-hydroxy-1-methyl-4-oxopyrido[1,2-*a*]pyrimidinium hydroxide** (**5**) was obtained from the mesoionic compound 1 and ethyl azodicarboxylate in refluxing chlorobenzene over 24 hr. In this case the crude residue was dissolved in acetone and purified[19] by chromatography on silica gel. It crystallized from benzene–*n*-heptane (2:1) as yellow, irregular prisms: mp 106–109° (24%); ir (KBr) 3315, 3225 (NH), 3100, 2998 (CH), 1770, 1750 (COOEt), 1720, 1640 (amide CO) cm^{-1}; $\lambda_{max}^{CH_3OH}$, nm (log ϵ), 340 sh (3.02), 330 (3.14), 265 (3.54), 230 (4.23); mass spectrum (70 eV) m/e (rel intensity), M^+, 350 (1), 277 (5), 276 (10), 217 (15), 203 (10), 189 (15), 135 (20), 133 (15), 108 (15), 79 (32), 78 (100), 77 (15).

Anal. Calcd for $C_{15}H_{18}N_4O_6$: C, 51.43; H, 5.18; N, 15.99. Found: C, 52.72; H, 5.15; N, 15.72.

Registry No.—**1**, 26460-93-5; **3** (R = R^1 = $COOCH_3$), 4627-24-1; **3** (R = $COOC_2H_5$; R^1 = H), 24403-35-8; **3**(R = R^1 = CN), 26460-96-8; **4**, 26460-97-9; **5**, 26460-98-0.

Acknowledgments.—The award of a grant from the National Science Foundation (NSF GP 6905) for the purchase of the mass spectrometer used in this study is gratefully acknowledged.

(19) This product always separated with fractional amounts of solvent of crystallization and several determinations of carbon contents gave results of this order.

1,2,4-Triazoles. XXVII. Synthesis of the Thiazolo[2,3-*c*]-*s*-triazole and the Thiazolo[3,2-*b*]-*s*-triazole Systems[1]

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Received July 9, 1970

2-Triazolylhydrazines underwent ring closure with aliphatic acids or ortho esters to thiazolo[2,3-c]-s-triazoles, cyanogen bromide, and carbon disulfide readily giving the corresponding 3-amino and 3-mercapto derivatives. The isomeric thiazolo[3,2-*b*]-*s*-triazole system was readily obtained from *s*-triazole-3-thiols and α-halo ketones. Spectral characteristics of these ring systems are described.

Fusion of the thiazole and the *s*-triazole nuclei can be effected in two ways, represented by thiazolo[2,3-*c*]-*s*-triazole (**2**) and thiazolo[3,2-*b*]-*s*-triazole (**4**). The only hitherto reported[2] examples of these ring systems are relatively complex. We now describe the synthesis and properties of alkyl- and aryl-substituted derivatives of both systems, as well as some amino and mercapto derivatives. Though the isomerization of *s*-triazolo[4,3-*a*]pyridines to *s*-triazolo[1,5-*a*]pyridines has been reported[3] as well as isomerizations in related [5,6] ring-fused systems,[4] no such isomerizations have been found in [5,5] ring-fused systems. Thiazolo-[2,3-*c*]-*s*-triazole (**2**) is particularly suitable for studying such isomerizations.

Cyclization of 2-thiazolylhydrazines[5] (**1**), a synthetic approach well documented for the preparation of ring-fused *s*-triazoles,[6] has provided a simple synthesis of the fused-ring system **2** (Table I). Cyclization of 4-methyl-2-thiazolylhydrazine (**1**, R = CH_3) with formic, acetic, or propionic acids under reflux for 6–8 hr led directly to **2**. However, 4-phenyl-2-thiazolylhydrazine (**1**, R = Ph) gave the intermediate hydrazides (**3**, R = Ph; R^1 = CH_3, Et) with acetic and propionic acids and these hydrazides underwent a smooth cyclization to the fused system **2** with phosphoryl chloride. Ortho esters were equally effective as cyclization agents but slightly longer reaction periods were required. Attempts to prepare the fused system **2** with 3-phenyl substituents by the cyclization of the 2-thiazolylhydrazines (**1**) with benzoic acid were unsuccessful. However, phosphoryl chloride cyclization of 2-[4-methyl(phenyl)thiazol-2-yl]benzhydrazide [**3**, R = CH_3(Ph); R^1 = Ph], prepared from 1-benzoylthiosemicarbazide and chloroacetone, or phenacyl bromide, respectively, gave **2**. The ease of these cyclizations are particularly interesting in view of the formation of 2-azidothiazole on attempted ring closure of 2-amino or 2-hydrazinothiazole to thiazolo[3,2-*d*]-tetrazole.[7]

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(1) Support of this work by U. S. Public Health Service Research Grant CA 08495, National Cancer Institute, is gratefully acknowledged.

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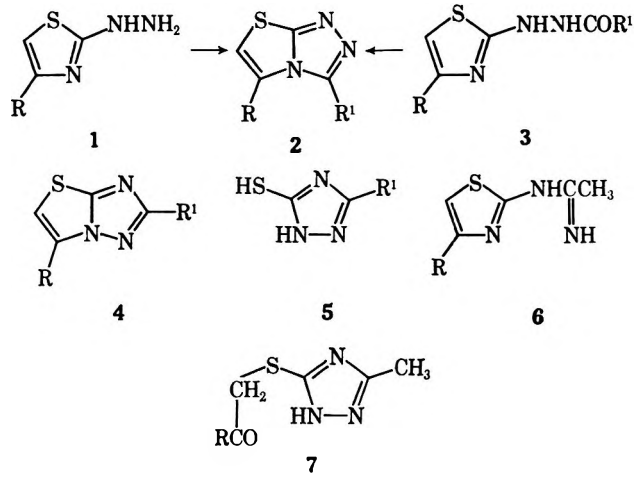
Table I

R	R¹	Mp, °C	Yield, %	Spectral characteristics,[c] Uv data,[d] λ_{max}, nm (log ϵ)	Ir data,[e] cm^{-1}	Nmr data[f] τ_3	τ_5	τ_6	Mass spectral data,[g] m/e (rel intensity)
Some Derivatives of Thiazolo[2,3-*c*]-*s*-triazole (2)[a,b]									
CH_3	H	111–112	60	248 (3.89), 204 (3.75)	3125, 3070, 1600, 1480	1.40 (s)	*7.48* (d, J = 1.20 Hz)	3.33 (q, J = 1.20 Hz)	140 (6), 139 (80), 112 (4), 71 (17), 67 (100)
CH_3	CH_3	181–182	20	246 (3.88), 201 (3.82)	3040, 2925, 1625, 1600	8.27 (s)	*7.50* (d, J = 1.20 Hz)	3.50 (q, J = 1.20 Hz)	154 (6), 153 (40), 112 (35), 71 (15), 67 (100)
CH_3	C_2H_5	96–97	16	247 (3.94), 207 (3.73)	3040, 2975, 1600, 1500	6.90 (q), *8.65* (t) (J = 7.50 Hz)	*7.50* (d, J = 1.20 Hz)	3.54 (q, J = 1.20 Hz)	168 (6), 167 (62), 112 (54), 71 (19), 67 (100)
CH_3	Ph	149	61	262 (4.07), 200 (4.23)	3050, 1595, 1450	2.42 (s)	*7.88* (d, J = 1.20 Hz)	3.39 (q, J = 1.20 Hz)	216 (11), 215 (75), 112 (80), 71 (20), 67 (100)
CH_3	SH	246–247	25	297 (4.25), 214 (3.90)	3100, 3000, 2720, 1600, 1530	*ca.* 6.7 (broad) (D_2O exchange)	*7.27* (d, J = 1.20 Hz)	3.35 (q, J = 1.20 Hz)	172 (7), 171 (78), 112 (30), 71 (4), 67 (100)
CH_3	SCH_3	108–110	92	267 (4.0), 202 (3.84)	3120, 1600, 1475	*7.23* (s)	*7.42* (d, J = 1.20 Hz)	3.48 (q, J = 1.20 Hz)	186 (9), 185 (100), 152 (40), 112 (44), 71 (24), 67 (100)
Ph	H	128	20	275 (4.06), 210 (4.03)	3080, 1615, 1600, 1470	1.20 (s)	2.44 (s)	3.00 (s)	202 (13), 201 (100), 174 (87), 129 (86), 103 (16), 77 (79), 51 (46)
Ph	CH_3	245	48	264 (3.92), 200 (4.34)	3025, 1610, 1580, 1500	*7.77* (s)	2.5 (s)	3.27 (s)	216 (12, 215 (78), 174 (100), 129 (77), 77 (72), 51 (35)
Ph	C_2H_5	145	43	263 (3.91), 202 (4.20)	3075, 2940, 1605, 1560	7.40 (q), 8.92 (t), (J = 7.50 Hz)	2.45 (s)	3.24 (s)	230 (13), 229 (79), 174 (100), 129 (50), 77 (40)
Ph	Ph	165	48	271 (4.17), 218 (4.27), 202 (4.50)	3050, 1550, 1490, 1450	2.83 (s)	2.83 (s)	3.12 (s)	278 (12), 277 (58), 174 (100), 129 (50), 77 (40)
Ph	SH	213–214	50	308 (3.92), 185 (4.15)	3075, 2900, 2700, 1590, 1560	*ca.* 6.4 (broad) (D_2O exchange)	2.46 (m)	2.77 (s)	234 (13), 233 (100), 174 (58), 129 (61), 103 (26), 77 (76), 51 (30)
Ph	SCH_3	166	46	275 (4.00), 197 (4.47)	3075, 2925, 1475, 1400	*8.25* (s)	2.48 (s)	3.25 (s)	248 (16), 247 (100), 214 (33), 174 (64), 147 (17), 129 (58), 103 (12), 77 (44), 51 (19)
Ph	NH_2	229–230	28	283 (3.76), 226 (4.01), 205 (4.20)	3350, 3280, 1625, 1550	4.78 (s) (D_2O exchange)	2.44 (s)	2.87 (s)	217 (12), 216 (100), 174 (63), 129 (63), 103 (15), 102 (30), 77 (80), 51 (50)
Some Derivatives of Thiazolo[3,2-*b*]-*s*-triazole (4)[h]									
CH_3	CH_3	68–69	63	246 (3.91), 201 (3.80)	3075, 3000, 1575, 1495	*7.43* (s)	*7.48* (d, J = 1.50 Hz)	3.45 (q, J = 1.50 Hz)	154 (10), 153 (100), 112 (36), 67 (80), 42 (36), 40 (66)
CH_3	Ph	124–125	84	258 (4.36), 223 (4.10), 203 (4.43)	3100, 1475, 1400	2.57–1.87 (m)	*7.47* (d, J = 1.50 Hz)	3.50 (q, J = 1.50 Hz)	216 (16), 215 (10), 103 (14), 77 (9), 72 (32), 71 (12)
Ph	Ph	137–138	72	262 (4.40), 198 (4.55)	3050, 1500 1470	3.08–2.32 (m)	3.08–2.32 (m)	3.48 (s)	278 (20), 277 (100), 174 (13), 134 (64), 129 (16), 103 (23), 77 (80), 76 (38), 51 (13)
Ph	CH_3	100–101	52	270 (4.14), 227 (4.18), 202 (4.24)	3050, 1550 1495	*7.40* (s)	2.52–2.94 (m)	3.01 (s)	216 (12), 215 (100), 174 (40), 129 (22), 103 (8), 77 (19), 51 (9)

[a] Satisfactory analyses (±0.35% for C, H, N) were reported for all compounds in table: Ed. [b] Registry numbers are, respectively, 26542-55-2, 26599-13-3, 26542-56-3, 26542-57-4, 26542-58-5, 26542-59-6, 26542-60-9, 26542-63-9, 26599-18-8, 26542-64-3, 26542-65-4, 26542-66-5, 26542-67-6. [c] Spectra were determined under the conditions given in footnotes *d–f*. Methyl resonances are in italics. [d] Methanol. [e] KBr. [f] $CDCl_3$. [g] At 70 eV. [h] Registry numbers are, respectively, 26542-68-7, 26542-69-8, 26542-70-1, 26542-71-2.



Reaction of the hydrazines **1** (R = CH_3, Ph) with carbon disulfide provided a convenient synthesis of the thiazolo[2,3-*c*]-*s*-triazole-3-thiols (**2**, R = CH_3, Ph; R^1 = SH). These were readily converted into the corresponding methylthio compounds with methyl iodide. Cyanogen bromide was found to react readily with 4-phenyl-2-thiazolylhydrazine (**1**, R = Ph), giving the 3-amino derivative of **2** (R^1 = NH_2). The structures of these products were evident from analytical and spectral data (Table I). They were found to be stable to acid, alkali, or heat, and no evidence for isomerization to the thiazolo[3,2-*b*]-*s*-triazole system was obtained.

Attempts to prepare authentic examples of **4** by lead tetraacetate cyclization of the amidines **6** failed. Also, amination of 2-aminothiazoles with hydroxylamine-*O*-sulfonic acid to the corresponding 1,2-diamino products was unsuccessful in this system, results similar to those obtained with 2-amino-1,3,4-thiadiazoles.[8] However, reaction of *s*-triazole-3-thiols **5** with α-halogeno ketones was found to be a very effective route to the thiazolo[3,2-*b*]-*s*-triazoles. The 5 substituent of the *s*-triazole nucleus had a pronounced effect on the ease of ring closure. Thus 5-phenyl-*s*-triazole-3-thiol (**5**, R^1 = Ph) with phenacyl bromide or chloroacetone gave the appropriately substituted thiazolo[3,2-*b*]-*s*-triazole system in greater than 70% yield using a 4-hr reaction period. Under the same conditions, 5-methyl-*s*-triazole-3-thiol gave the intermediate products **7** (R = CH_3, Ph); however, increasing the reaction period to 24 hr gave the thiazolo[3,2-*b*]-*s*-triazole system directly. Cyclization of **7** to a bicyclic system was effected with phosphoryl chloride in xylene but, instead of **4**, the thiazolo[2,3-*c*]-*s*-triazole system (**2**) was formed. This difference in behavior is understandable in terms of the influence of the reaction conditions on the basicity of the nitrogen atoms. Under thermal conditions, the more basic center is associated with N_1 (or N_2) but with phosphoryl chloride, N_4 would be more basic owing to the formation of an intermediate phosphorous compound[9] at N_1 (or N_2).

The nmr characteristics of these isomeric ring systems are particularly useful for structural determinations. The chemical shift of the 6 proton is in the range τ 2.77–3.54, the actual value depending upon the inductive character of the other substituents in the nucleus (Table I). The 6 proton is coupled in a characteristic way to the 5-methyl substituent (J = 1.20–1.50 Hz) and occurs as a sharp singlet in the 5-phenyl compounds. The observed chemical shift is consistent with that reported[10] for the 2 proton in 4-methylthiazole (τ 3.13), though in the latter the corresponding coupling constant (J = 1.00 Hz) is smaller. The magnitude of this benzylic coupling in the fused ring system agrees well with those found in other heteroaromatic systems[11] and, in this present case, may indicate some degree of bond fixation.

In 3,5-dimethylthiazolo[2,3-*c*]-*s*-triazole the chemical shift of the 3-methyl group is τ 8.27, whereas in 2,5-dimethylthiazolo[3,2-*b*]-*s*-triazole the chemical shift of the corresponding 2-methyl group has undergone a downfield shift of 0.84 ppm to τ 7.43. However, this juxtapositioning of the nitrogen atoms had very little effect on the chemical shifts of the 5 and 6 substituents (Table I).

The influence of phenyl groups on the chemical shifts of other ring substituents is interesting. Thus, in 5-phenylthiazolo[3,2-*c*]-*s*-triazole the chemical shift of the 3 proton is τ 1.20, a downfield shift of 0.20 ppm from that observed in the corresponding 5-methyl compound. Similarly, the chemical shift of the 3-methyl group has also undergone a small downfield shift (0.50 ppm) in the analogous 3-methyl compounds. This is most likely due to the inductive effect of the 5-phenyl group, as in 3-ethyl- and 3-methylthiothiazolo[3,2-*c*]-*s*-triazole the chemical shifts of the 3 substituents are now at a higher field than those observed in the corresponding 5-methyl compounds. This is not unexpected as steric requirements would tend to place these bulky 3 substituents in the shielding zone of the 5-phenyl group. This steric effect is also reflected in the ultraviolet absorption spectra of these compounds (Table I).

In the thiazolo[3,2-*b*]-*s*-triazole system, very little cross-ring interaction is evident. Thus, in 2,5-dimethylthiazolo[3,2-*b*]-*s*-triazole and 5-methyl-2-phenylthiazolo[3,2-*b*]-*s*-triazole, the chemical shifts of the 5-methyl groups are identical. Similarly, reversing the methyl–phenyl substitution pattern does not have an appreciable effect on the chemical shift of the 2-methyl group. These compounds also show clearly the influence of a nuclear nitrogen atom on the ortho proton in a phenyl substituent (Table I).

In the mass spectra of these fused ring systems (Table I), molecular ions were obtained for all compounds studied. As has been found in other fused *s*-triazole systems, fragmentation of the *s*-triazole moiety was observed as the initial decomposition. Thus, in 3,5-dimethylthiazolo[2,3-*c*]-*s*-triazole, acetonitrile was lost from the molecular ion, giving an ion, m/e 112. This then lost HCS to give an ion, m/e 67 (100%), which is common to all the 5-methyl compounds. The corresponding ion in the 5-phenyl compounds was observed at m/e 129 and was a relatively intense ion. The mass spectra of 3-methyl-5-phenylthiazolo[2,3-*c*]-*s*-triazole and 2-methyl-5-phenylthiazolo[3,2-*b*]-*s*-triazole are practically identical. They illustrate the danger in

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(10) P. Haake and W. B. Miller, *J. Amer. Chem. Soc.*, **85**, 4044 (1963).

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making structural assignments in isomeric systems based on mass spectral data.

Experimental Section[12]

General Procedures for the Cyclization of 2-Thiazolylhydrazines. A. With Carboxylic Acids.—4-Methyl-2-thiazolylhydrazine[13] (0.5 g) and formic acid (1.0 ml) were refluxed for 6 hr, the excess of formic acid removed under reduced pressure, and the residue recrystallized from benzene (charcoal) affording colorless needles of **2** (R = CH_3; R^1 = H), 0.6 g, mp 111–112° (Table I). A minimum reflux period of 6 hr was essential to prevent contamination of the cyclized product with the hydrazide **3**.

B. With Ortho Esters.—4-Methyl-2-thiazolylhydrazine (1.0 g) and ethyl orthoacetate (5 ml) were heated under reflux for 6 hr. Reaction work-up as above and final recrystallization from methanol–benzene afforded **2** (R = R^1 = CH_3) as colorless needles, mp 181–182°.

C. With Carbon Disulfide.—4-Phenylthiazol-2-ylhydrazine[6b] (1.0 g), methanol (50 ml), potassium hydroxide (0.3 g), and carbon disulfide (3 ml) were refluxed for 4 hr. After removal of the methanol, dilute potassium hydroxide was added and the alkaline solution was filtered. After precipitation with dilute hydrochloric acid, **2** (R = Ph; R^1 = SH) crystallized from methanol–benzene (charcoal) as colorless needles, mp 213–214°.

D. With Cyanogen Bromide.—4-Phenylthiazol-2-ylhydrazine (1.0 g) in methanol (50 ml of 75%) and cyanogen bromide (0.5 g) were heated under reflux for 4 hr. The cooled reaction mixture was poured into ether (1000 ml) and the red solid that separated was dissolved in water and sodium acetate was added. Crystallization of the free base from methanol–benzene (charcoal) afforded colorless needles of **2** (R = Ph; R^1 = NH_2), mp 229–230°.

E. Phosphoryl Chloride Cyclization of the Acylhydrazines.—2-(4-Phenylthiazol-2-yl)acethydrazide (1.0 g), dry xylene (20 ml), and phosphoryl chloride (2 g) were refluxed for 8 hr. The cooled reaction mixture was diluted with petroleum ether (bp 60–80°) and the supernatant liquor decanted. The residue was dissolved in water, ammonium hydroxide added, and the product extracted with chloroform. The chloroform extract was dried (anhydrous Na_2SO_4) and the solvent removed; the residue crystallized from methanol–benzene (charcoal) forming colorless needles of **2** (R = Ph; R^1 = CH_3), mp 245°.

Reaction of 5-Methyl(phenyl)thiazolo[2,3-c]-s-triazole-3-thiols with Methyl Iodide.—The thiol (0.7 g), dissolved in water and *ca.* 0.5 ml of potassium hydroxide (50%), was shaken with methyl iodide (5 ml) for 5 min. Excess of methyl iodide was evaporated and the residue recrystallized from benzene (charcoal), forming colorless needles of the products described in Table I.

Reaction of 5-Phenyl-s-triazole-3-thiol (5, R^1 = Ph) with Phenacyl Bromide (or Chloroacetone).—The thiol (0.01 mol) in absolute ethanol (100 ml) was treated with phenacyl bromide (0.01 mol) and the reaction mixture refluxed for 4 hr. Ethanol was evaporated and the residue was treated with a concentrated, aqueous solution of sodium acetate. The product which separated was recrystallized from benzene–petroleum ether (bp 60–80°) forming colorless needles of **4** (R = R^1 = Ph), mp 137–138° (Table I).

Reaction of 5-Methyl-s-triazole-3-thiol (5, R^1 = CH_3) with Chloroacetone.—The thiol (0.01 mol), chloroacetone (0.01 mol), and absolute ethanol (100 ml) were refluxed for 4 hr. The residue, after evaporation of the ethanol, was dissolved in water and aqueous sodium acetate added. Water was evaporated and the residue extracted several times with hot chloroform (20 ml). Evaporation of the chloroform and recrystallization of the residue from benzene gave small, colorless irregular prisms of 3-(acetonylthio)-5-methyl-s-triazole: mp 125–126° (47%); ir (KBr) 3150, 3050 (CH), 1720 (CO), 1580 cm^{-1} (C=N); $\lambda_{max}^{CH_3OH}$ 207 nm (log ϵ 3.62); mass spectrum (70 eV) *m/e* (rel intensity) 171 (26), 129 (100), 128 (52), 96 (12), 84 (24).

Anal. Calcd for $C_6H_9N_3OS$: C, 42.10; H, 5.30; N, 24.55. Found: C, 41.89; H, 5.26; N, 24.39.

Similarly, **3-(phenacylthio)-5-methyl-s-triazole** crystallized from benzene as colorless needles: mp 120–121° (70%); ir (KBr) 2900, 2850 (CH), 1680 (CO), 1595 cm^{-1} (C=N); $\lambda_{max}^{CH_3OH}$, nm (log ϵ), 280 (3.16), 247 (4.08), 202 (4.33); mass spectrum (70 eV) *m/e* (rel intensity) 233 (7), 205 (5), 191 (5), 106 (100), 91 (4), 78 (15), 77 (40), 51 (13).

Anal. Calcd for $C_{11}H_{11}N_3OS$: C, 56.65; H, 4.72; N, 18.02. Found: C, 56.50; H, 4.72; N, 17.90.

Reflux of the above 3-thio compounds with phosphoryl chloride in xylene for 8 hr gave the corresponding thiazolo[2,3-c]-s-triazoles. However, extension of the reaction time to 24 hr in the initial condensation with the α-halo ketone resulted in formation of the thiazolo[3,2-b]-s-triazoles.

***N*-(4-Phenylthiazol-2-yl)acetamidine.**—2-Amino-4-phenylthiazole (8.8 g, 0.05 mol) and acetonitrile (3.0 g, 0.07 mol) were mixed and anhydrous aluminum chloride (6.6 g, 0.05 mol) was added. After the vigorous reaction had subsided, the reaction mixture was heated at 170–175° for 3 hr and then, on cooling, decomposed by the cautious addition of water. After basification of the resultant solution with sodium hydroxide, it was extracted with ether, the ether extract treated with charcoal, and the ether then evaporated. After recrystallization of the residue from ether–petroleum ether (bp 60–80°), the amidine was obtained as colorless needles: mp 108–110°; 5.6 g (52%); ir (KBr) 3280 (NH), 3020 (CH), 1630 cm^{-1} (C=N); $\lambda_{max}^{CH_3OH}$, nm (log ϵ), 295 sh (4.16), 283 (4.22), 277 sh (4.18), 242 (4.10), 212 (4.15).

Anal. Calcd for $C_{11}H_{11}N_3S$: C, 60.82; H, 5.07; N, 19.35. Found: C, 60.92; H, 5.07; N, 19.25.

Registry No.—3-(Acetonylthio)-5-methyl-s-triazole, 26542-72-3; 3-(phenacylthio)-5-methyl-s-triazole, 26542-73-4; *N*-(4-phenylthiazol-2-yl)acetamidine, 26542-74-5.

Acknowledgments.—The award of a grant from the National Science Foundation (NSF GP 6905) for the purchase of the mass spectrometer used in this study is gratefully acknowledged.

(12) All evaporations were done under reduced pressure using a rotatory evaporator. Ultraviolet spectra were determined on a Cary Model 14 spectrophotometer and infrared spectra were measured on a Perkin-Elmer Model 337 infrared spectrophotometer. Nmr spectra were determined on a Varian A-60 spectrometer using TMS as internal standard and mass spectra were measured on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Melting points were taken in capillaries and microanalyses were by Galbraith Laboratories, Inc., Knoxville, Tenn., and Instranal Laboratories, Rensselaer, N. Y.

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The Synthesis and Some Reactions of 1,2,4-Thiadiazolylsulfenyl Chlorides

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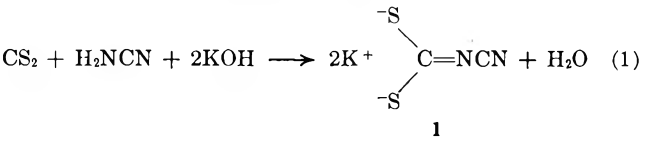
Received May 27, 1970

Cyanodithioimidocarbonate anion undergoes a novel reaction with halogens to produce 3-halo-1,2,4-thiodiazol-5-yl sulfenyl halides or the corresponding disulfides. Although chlorination produced 3-chloro-1,2,4-thiadiazol-5-yl sulfenyl chloride (2) directly, bromination gave the bis(3-bromo-1,2,4-thiadiazol-5-yl) disulfide (6) which was converted to the 3-bromo-1,2,4-thiadiazol-5-yl sulfenyl chloride (7) by subsequent chlorination. Treatment of cyanodithioimidocarbonate ion with sulfur and subsequent chlorination provided a convenient route to the 1,2,4-thiadiazol-3,5-yl bis(sulfenyl chloride) (11). The preparations and some reactions of 1,2,4-thiadiazolylsulfenyl chlorides are described

Hantzsch and Wolvekamp[1] established the structure of dipotassium cyanodithiomidocarbonate (1) in 1934 by means of a convenient synthesis from cyanamide and carbon disulfide (eq 1). The chemistry of



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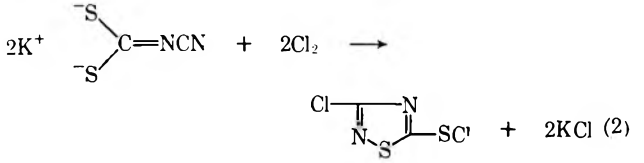
this salt has received comparatively little attention until quite recently when several publications appeared concerning alkyl,[2,3] acyl,[3] and organotin[4] derivatives. The dithiolate anion has also proved useful for the preparation of metal complexes.[5,6] The halogenation reactions of the cyanodithioimidocarbonate anion had not been investigated, and it was felt that they might provide an interesting route to either geminal bis(sulfenyl halides) or to heterocyclic sulfenyl halides.

Halogenation of Cyanodithioimidocarbonate Anion.—Chlorination of a slurry of **1** in methylene chloride conveniently provided an 85–100% yield of 3-chloro-1,2,4-thiadiazol-5-yl sulfenyl chloride, after filtering off the KCl precipitate and evaporating the solvent (eq 2).



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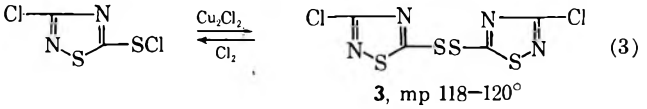
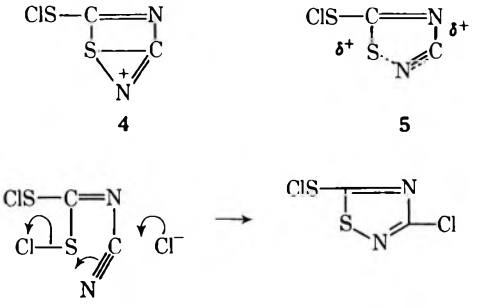


3, mp 118–120°

The product is a stable yellow solid which can be kept at room temperature for a prolonged period without any noticeable decomposition. On heating above 40°, it melted with decomposition but was recovered unchanged after refluxing with sulfuryl chloride in CCl_4 solution for 3 days. The ultraviolet spectra (run in cyclohexane) showed an absorption maximum at 225 mμ (log ε 3.73). The parent compound, 1,2,4-thiadiazole,[7,8] has a maximum at 229 mμ (log ε 3.7). The sulfenyl chloride was readily reduced to the corresponding disulfide **3** by treatment with cuprous chloride while chlorination of the disulfide regenerated compound **2** (eq 3). The disulfide exhibited five absorption bands in the infrared which were almost identical with that of its sulfenyl halide precursor. During chlorination, the formation of a cyclized thiadiazole ring could occur either by an attack of a sulfenyl chloride upon the nitrile group *via* an episulfonium type ion[9,10] (**4**), by an acyl type ion[11] (**5**), or by an attack of a chloride ion upon the nitrile carbon with concommittant nucleophilic attack of nitrogen on sulfur (eq 4). The



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latter mechanism has been postulated by Hatchard[12] and by Timmons and Wittenbrook[3] for cyclizations also presumably involving transient sulfenyl chloride intermediates.

Although sulfenyl halides do not commonly react with nitriles, the addition of sulfur chlorides to aminonitriles and cyanogen[13] and of trifluoromethanesulfenyl chloride to a nitrile group of tetracyanoethylene[14] has been reported. Here again, the mechanism is not certain, although in the case of the tetracyanoethylene–F_3CSCl reaction, chloride ion serves as a catalyst. With four powerful electron-withdrawing groups on ethylene, it appears likely that initial attack by chloride is on the carbon–carbon double bond rather than upon the nitrile group. Possibly cyclization to aromatic ring systems provides the driving force for the sulfenyl chloride addition to the nitrile group of cyanogen and cyanoimidiocarbonate molecules. No analogous addi-

* To whom correspondence should be addressed.

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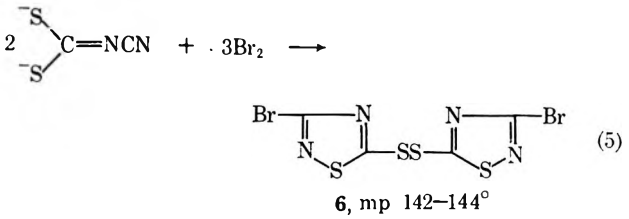
(14) H. D. Hartzler, *ibid.*, **29**, 1194 (1964).

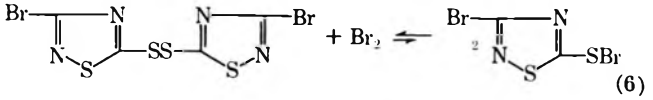
tions to nitriles resulting in acyclic structures have to our knowledge been observed.

The bromination of cyanodithioimidocarbonate ion, in contrast to the chlorination, does not produce a sulfenyl chloride but gives instead bis(3-bromo-1,2,4-thiadiazol-5-yl) disulfide (**6**) in excellent yield (eq 5).



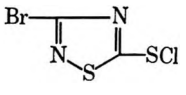
6, mp 142–144° (5)

The disulfide appeared inert to excess bromine and, despite the fact that aromatic disulfides such as phenyl disulfide are readily cleaved by bromine, the thiadiazole disulfide displayed no such tendency. Possibly thermodynamic considerations are important here, and what is observed is an equilibrium very strongly favoring the disulfide, rather than any intrinsic inertness of this disulfide bond (eq 6). The disulfide is however



(6)

readily cleaved by chlorine, thereby providing the 3-bromo-1,2,4-thiadiazol-5-yl sulfenyl chloride (**7**). Here again the sulfenyl chloride **7** exhibited an infrared spec-



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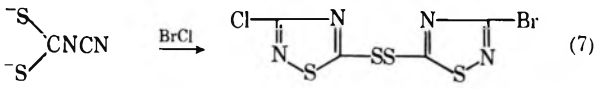
trum with absorptions nearly identical with those of the disulfide precursor **6**. The 3-bromo compounds, however, showed significant shifting of absorptions compared to the 3-chloro compounds (see Experimental Section) permitting convenient distinction between the two systems.

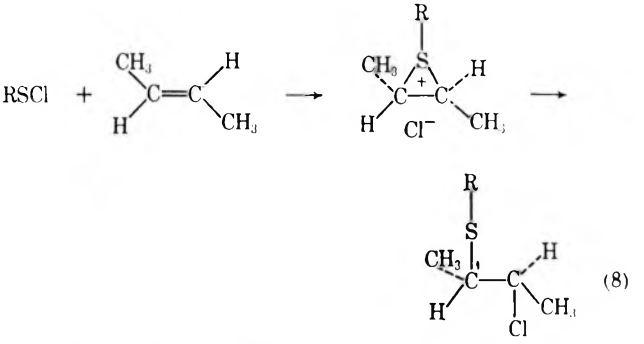
The reaction of bromine chloride with **1** gives a 92% yield of a disulfide which after one recrystallization (69%) melts at 118–120° (eq 7). Elemental



8, mp 118–120° (7)

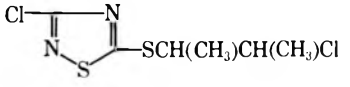
analysis indicated that the product was either a disulfide with a chlorine and a bromine in the 3 and 3′ positions (**8**) or else an exactly equal mixture of the dichloro and dibromo disulfides (**3** and **6**). The infrared spectrum was the same as the combined spectrum of **3** and **6**, a fact which is inconclusive since either the unsymmetrical disulfide or a mixture of the two disulfides could be expected to show similar infrared characteristics. The sharp melting point suggested that the product was a single compound **8**. In support of this, a 1:1 mixture of **3** and **6** had a broad melting point range (120–135°) which did not change even after recrystallization of the mixture. Furthermore, mixture melting points of **8** and **3** and of **8** and **6** also exhibited a broad range. Since it would have been quite fortuitous to have obtained an equal mixture of **3** and **6** directly from the reaction, and such a mixture exhibited different melting point characteristics, it was concluded that the reaction product was indeed the unsymmetrical disulfide **8**.

Reactions of 3-Halo-1,2,4-thiadiazol-5-yl Sulfenyl Chloride with Olefins.—The reaction of **2** or **7** with olefins at −40° in methylene chloride solution is a very rapid exothermic process wherein the olefin is consumed almost as rapidly as it is introduced. The addition to *trans*-butene produces a single diasteriomer which according to nmr analysis is different from the single diasteriomer obtained from reaction with *cis*-butene. Such stereospecific additions of sulfenyl chlorides have been attributed to an episulfonium ion reaction mechanism resulting in exclusively trans addition[15,16] (eq 8).



(8)

It would appear, therefore, that *trans*-butene gives rise to the erythro adduct and *cis*-butene to the threo adduct. Infrared and uv analyses demonstrate that the heterocyclic ring system is not itself involved in the reaction with olefins. Mass spectroscopic analysis of the *cis*-butene adduct shows parent and cracking peaks consistent with an adduct of structure **9**.



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The products from the reaction of **2** or **7** with several olefins were examined by nmr (Table I). Yield, and analyses for these adducts are presented in Table II. The direction of the addition (Markovnikoff or anti-Markovnikoff) of sulfenyl halides to terminal olefins, is usually easily determined by nmr analysis[16] because of the marked downfield shift of methylene or methine protons on carbons bonded to chlorine, relative to those on carbons bonded to sulfur. (Sulfenyl chlorides are polarized with the positive charge on sulfur, $RS^{\delta+}$–$Cl^{\delta-}$. Therefore, adducts with the chlorine bonded to the more highly substituted position of the hydrocarbon skeleton are designated Markovnikoff addition products.) However, the difference in chemical shift due to a chlorine substituent is very close to that of the strongly electron-withdrawing 3-chloro-1,2,4-thiodiazol-5-yl sulfenyl substituent, and it is difficult to make unequivocal structural assignments based on chemical shifts. Chemical shifts of adducts from symmetrical olefins were assigned by attributing the larger downfield shift to protons on the chlorine-bearing carbon. These values were utilized to assign

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TABLE I

NMR PARAMETERS OF 3-CHLORO-1,2,4-THIADIAZOLE-5-SULFENYL CHLORIDE–OLEFIN ADDUCTS

Olefin	Registry no.	Group assignments 1	2	3	4	5	6	Chemical shifts,[a] ppm 1	2	3	4	5	6	Coupling constants, cps
Ethylene	26542-82-5	$RSCH_2$		CH_2Cl				3.67[b] m						
				$ClCH_2$	RSCH		CH_3			3.89[b] m				
										3.95[b] dd	4.17[c] q dd		1.59 d	$J_{3,3'} = 10.8$, $J_{3,4} = 4.1$, $J_{3',4} = 7.4$, $J_{4,6} = 6.8$
										3.76[c] dd				
Propylene[f]	26542-83-6	$RSCH_2$				CHCl	CH_3	3.66 d				4.34 qt	1.66 d	$J_{1,5} = 6.5$, $J_{5,6} = 6.8$
	26542-84-7													
Isobutylene	26542-35-8	$RSCH_2$					$C(Cl)(CH_3)_2$	3.79 s					1.69 s	
3,3-Dimethyl-1-butene	26542-36-9			$ClCH_2$	RSCH		$C(CH_3)_3$			4.09[c] dd	3.70[c] dd		1.13 s	$J_{3,3'} = 4.0$, $J_{3,4} = 8.5$, $J_{3',4} = 12.5$
										4.04[c] dd				
trans-2-Butene	26542-87-0		CH_3		RSCH	CHCl	CH_3		1.55 d		4.20[d] dq	4.48[d] dq	1.61 d	$J_{2,4} = 6.8$, $J_{4,5} = 3.8$, $J_{5,6} = 6.8$
cis-2-Butene			CH_3		RSCH	CHCl	CH_2		1.59 d		4.36[d] dq	4.45[d] dq	1.61 d	$J_{2,4} = 6.8$, $J_{4,5} = 3.0$, $J_{5,6} = 6.8$
2-Methyl-2-butene	26542-88-1		CH_3		RSCH		$C(Cl)(CH_3)_2$		1.66 d		4.28 q		1.73 s	$J_{2,4} = 7.0$
1,4-Butadiene	26542-89-2	$RSCH_2$				CHCl	H H′ C=C H″	3.73 d			4.73[e] dtt		5.96[e] ddd	$J_{1,6} = 6.5$, $J_{5,6} = 8.0$, $J_{5,6} = 1.0$, $J_{5,6} = 1.0$
													5.29[e] dt	
													5.41[e] dt	$J_{6,6'} = 10.0$, $J_{6,6''} = 17.0$, $J_{6,6''} = 1.0$

[a] Abbreviations used: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; dq, double quartet; qt, quartet of triplets; ddd, double double doublet; dt, double triplet; dtt double triplet of triplets; m, multiplet. [b] Protons form an AA′BB′ type system; chemical shifts evaluated by comparison to calculated spectrum 5-4 "Interpretation of NMR Spectra," Wiberg and Nist, W. A. Benjamin, New York, N. Y., 1962. [c] Protons 3, 3′, and 4 form ABC type systems; chemical shifts are approximated from a first-order analysis. [d] Protons 4 and 5 form AB part of ABX_3Y_3 system; chemical shifts for A and B are calculated from decoupled AB quartet. [e] Protons 5, 6, 6′, and 6″ form an ABCX system; chemical shifts are approximated from a first-order analysis. Chemical shift values are listed in the order, 6, 6′, 6″. Protons 6 and 6″ are trans. [f] Addition to propylene produced an anti-Markovnikoff product (60%) and a Markovnikoff product (40%); the mixture was not separated.

TABLE II

REACTION OF 1,2,4-THIADIAZOLYLSULFENYL CHLORIDES WITH SOME UNSATURATED HYDROCARBONS[a]

A. 3-Halo-1,2,4-thiadiazol-5-yl Sulfenyl Chlorides

Reagent	Olefin	Yield, % Crude	Yield, % Purified
2	Ethylene	97	80
2	Propylene	100	79
2	Isobutylene	91	71
7	Isobutylene	100	95
2	*cis*-Butene-2	91	85
2	*trans*-Butene-2	94	81
2	3,3-Dimethylbutene-1	88	74
2	Butadiene	96	
2	2-Methylbutene-2	98	76

B. 1,2,4-Thiadiazol-2,5-yl Bis(sulfenyl chloride)

Reagent	Olefin	Yield, %[b]
11	Ethylene	100
11	Propylene	97
11	*cis*-Butene-2	104
11	Isobutylene	94
11	Allyl chloride	102
11	Butadiene	92

[a] Satisfactory analytical values (±0.35%) for C, H, N were obtained on all adducts. [b] All diadducts with the exception of the ethylene adduct were nondistillable oils and were analyzed without further purification.

analogous methylene and methine signals from adducts of unsymmetrical olefins. The chemical shifts assigned in this fashion appear to be internally consistent (Table I).

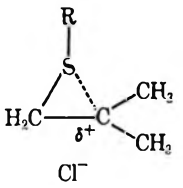
The reactions of 3-halo-1,2,4-thiadiazol-5-yl sulfenyl chlorides with terminal olefins were remarkably specific. With the exception of unbranched olefins such as propylene where similar quantities of the two positional isomers were obtained, reactions with substituted olefins such as isobutylene and 3,3-dimethyl-1-butene gave single products. The Markovnikoff or anti-Markovnikoff structure of these products assigned tentatively by analogy with other sulfenyl halide–terminal olefin adductions was completely consistent with assignments based on nmr analysis.

In general, increased electron-withdrawing character of R decreases the anti-Markovnikoff and increases the Markovnikoff adducts from the reaction of RSCl with terminal olefins.[10,17] Thus the adducts derived from isobutylene were reported to contain 80, 32, and 19% anti-Markovnikoff product when R was the CH_3, $CH_3C(O)S$, or $(CH_3O)_3P(O)$ substituent, respectively. Furthermore, with an electron-withdrawing substitute such as the $CH_3C(O)S$ group, the tendency toward Markovnikoff product increased in going from propylene to isobutylene (40% Markovnikoff product from propylene, 68% Markovnikoff product from isobutylene). This behavior has been attributed to increased positive charge on carbon when R tends to destabilize the positive charge on the sulfur atom in the episulfonium ion. Thus the direction of episulfonium ring opening *via* chloride ion attack is controlled by steric factors which favor attack at the terminal carbon, and opposing electronic factors which favor attack at the more highly substituted carbon. Electron-withdrawing R groups destabilize the positive charge on sulfur and therefore increase the importance

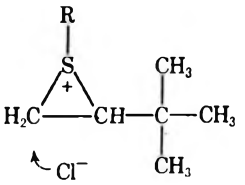
(17) W. H. Mueller and P. E. Butler, *J. Org. Chem.*, **32**, 2925 (1967).

of electronic factors, thus bringing about enhanced chloride attack at a more highly substituted internal carbon atom.

The powerful electron-withdrawing character of the 3-halo-1,2,4-thiadiazol-5-yl (R) group is attested by the large downfield shift of adjacent protons and the proximity of chemical shifts to those of analogous protons on chlorine-bearing carbons. Thus, a strong tendency toward Markovnikoff product formation would be expected and would explain the formation of single products from olefins such as isobutylene which are well suited for charge stabilization on carbon.

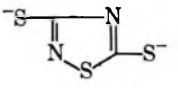


In contrast, the product from 3,3-dimethyl-1-butene has been assigned the anti-Markovnikoff orientation. Since unhindered terminal olefins which have a single alkyl group bonded to ethylene (*e.g.*, propylene) give similar quantities of isomeric adducts, it would be anticipated that more hindered analogs would enhance chloride attack at the terminal carbon. Indeed, the strong tendency to form anti-Markovnikoff products from 3,3-dimethyl-1-butene[10,17,18] is well documented even with sulfenyl chlorides containing strongly electron-withdrawing R groups.

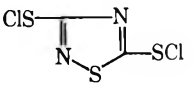


The reaction of **2** with butadiene is noteworthy. To avoid multiple additions, the sulfenyl chloride was added to an excess of diene (18.5 mol diene/mol RSCl). Under these conditions, the product contained 29% isobutylene adduct in conjunction with the simple 1,2-addition product from butadiene ($RSCH_2CHClCH{=}CH_2$). Analysis of the butadiene reagent revealed 1.84% isobutylene impurity. The product composition corresponds to complete removal of the isobutylene from the butadiene. On this basis, the isobutylene is at the very least 21.8 times more reactive than butadiene. This number only represents a minimum value since isobutylene may have been consumed during the initial stages of reaction. It is significant, however, that even this minimal value for the relative reactivity indicates that **2** is a more selective reagent than methanesulfenyl chloride which shows a relative reactivity of 4.85[19] [k(isobutylene)/k(butadiene)]. The increased selectivity toward more nucleophilic double bonds is consistent with the greater electron-withdrawing power of the thiadiazole ring. The thiadiazolylsulfenyl chloride in comparison to methanesulfenyl chloride, should exhibit even more preference for *cis* olefins since it is even more important for the bulky substituents on sulfur to be oriented away from the ethylenic substituents in transition state for this first reaction step.[19] A similar tetravalent sulfur structure has been proposed as an actual intermediate rather than a contributing transition state structure in reactions involving cyclooctene.[20]

1,2,4-Thiadiazol-3,5-yl Bis(sulfenyl chloride) (11).—The dipotassium salt of 3,5-dimercapto-1,2,4-thiadiazole (perthiocyanic acid) and its salts have been obtained by a number of routes,[21] but the dianion **10** is most conveniently prepared by refluxing a methanol solution of **1** with sulfur. The salt is readily chlorinated to give the bis(sulfenyl chloride) **11** which is a stable yellow solid.



10



11

The bis(sulfenyl chloride) rapidly consumed 2 mols of an olefin giving fairly pure 1:2 adducts in high yield (Table II). With the exception of the ethylene adduct which was a solid, the products were all nondistillable liquids. Theoretically, the products from unsymmetrical olefins can be comprised of four different adducts (excluding geometrical isomers). Four different types of olefin incorporation could be verified with products giving relatively simple nmr spectra. The reaction of **11** with isobutylene showed four different methyl and methylene signals: two from Markovnikoff addition (in equal quantities) comprising 78% of the mixture (δ_{CH_3} 1.652, 1.672; δ_{CH_2} 3.730, 3.760), and two from anti-Markovnikoff addition (in equal quantities) comprising 22% of the mixture (δ_{CH_3} 1.715, 1.578; δ_{CH_2} 4.115, 3.870). The observed increase in anti-Markovnikoff product from the bis(sulfenyl chloride) **11** in contrast to the reaction of isobutylene with the monosulfenyl chloride (**2** or **7**) is consistent with the decrease in electron-withdrawing ability of R when the chlorine substituent is no longer bonded directly to the 1,2,4-thiadiazole ring.

Experimental Section

Infrared analyses were determined on Beckman IR-5 and IR-20 spectrophotometers. Gas chromatographic analyses were determined on an F & M Model 810 gas chromatograph using a 5 ft × 1/8 in. Dowfax column at 165°. Nuclear magnetic resonance spectra were obtained on Varian A-60 and HA-100 spectrometers. Extinction coefficients were determined on a Beckman DK-2 spectrophotometer. All melting points were taken upon a Fisher–Johns block and are uncorrected.

Dipotassium Cyanodithioimidocarbonate (1).—To a stirred solution of 100 g (2.38 mol) of cyanamide (Eastman) in 250 ml of absolute alcohol 199 g (2.62 mol) carbon disulfide was added. The mixture was maintained below 20° while a solution of 314 g of 85% potassium hydroxide in 600 ml of absolute alcohol was added over the period of 30 min. The mixture was stirred for an additional 45 min and then suction filtered, washed with tetrahydrofuran, and dried in a vacuum oven at 50° yielding 416 g (90%) of product, mp 225°.

3-Chloro-1,2,4-thiadiazol-5-yl Sulfenyl Chloride (2).—A slurry of 103 g (0.53 mol) of potassium cyanodithioimidocarbonate (**1**) in 750 ml of methylene chloride was cooled to −40° and 75.3 g (1.06 mol) of chlorine was slowly added to the stirred mixture. The reaction mixture was then stirred at 0° for 1 hr and suction

(18) G. M. Beverly and D. R. Hogg, *Chem. Commun.*, 138 (1966).
(19) W. A. Thaler, *J. Org. Chem.*, **34**, 871 (1969).
(20) D. C. Owsley, G. K. Helmkamp, and M. F. Rettig, *J. Amer. Chem. Soc.*, **91**, 5239 (1969).
(21) L. L. Bambas, "The Chemistry of Heterocyclic Compounds," Interscience, New York, N. Y., 1952, pp 35–51.

filtered under dry nitrogen, and the methylene chloride evaporated under reduced pressure yielding 85 g (86%) of the yellow solid.

Anal. Calcd for $C_2S_2N_2Cl_2$: C, 12.84; N, 14.98; Cl, 37.90. Found: C, 12.86; N, 15.63; Cl, 37.69.

The uv spectrum in cyclohexane showed maximum at 261 mμ (log ε 3.78) and 225 (3.73). [The parent compound 1,2,4-thiadiazole has an absorption maximum at 229 mμ (log ε 3.7).] Infrared analysis (CCl_4) shows a five-peak pattern with maxima at 6.97, 8.20, 9.38, 10.91, and 14.3 μ.

Bis(3-chloro-1,2,4-thiadiazol-5-yl) Disulfide (3).—A solution of 9.35 g (0.05 mol) of **2** in 100 ml of dry tetrahydrofuran was stirred with 4.9 g (0.025 mol) Cu_2Cl_2 for 1 hr at room temperature, during which time the green cuprous chloride changed to the brown cupric chloride. The solid was filtered off, and the solution evaporated, redissolved in methylene chloride, and filtered again. Evaporation of the methylene chloride yielded 7.6 g (100%) of the disulfide product which was recrystallized from CH_2Cl_2–methanol giving 5.0 g of a pale yellow solid, mp 118–120°.

Anal. Calcd for $C_4N_4S_4Cl_2$: C, 15.84; N, 18.48; S, 42.30. Found: C, 15.47; N, 18.46; S, 41.90.

The infrared spectrum (CCl_4) was very similar to that of the corresponding sulfenyl chloride **2** showing five maxima at 6.97, 8.23, 9.46, 10.97, and 14.2 μ.

Bis(3-bromo-1,2,4-thiadiazol-5-yl) Disulfide (6).—A slurry of 9.7 g (0.05 mol) of **1** in 75 ml of CH_2Cl_2 was stirred at −40° while 16 g (0.1 mol) of Br_2 was added dropwise. The mixture was then stirred at 10° for an additional 2 hr, after which excess bromine and some solvent were removed at reduced pressure. The solid was filtered and the solvent was removed *in vacuo* yielding 8.5 g (87%) of a yellow solid product. The product (8.0 g) was recrystallized from CH_2Cl_2–*tert*-butylethylene to give 7.5 g of a white solid, mp 142–144.

Anal. Calcd for $C_4N_4S_4Br_2$: C, 12.25; N, 14.29; S, 32.71; Br, 40.76. Found: C, 12.62; N, 14.13; S, 32.67; Br, 40.90.

The infrared spectrum (CCl_4) was very similar to the analogous disulfide **3** with small shifts in the corresponding peaks. Absorptions were observed at 7.01, 8.39, 9.46, 11.21, and 15.0 μ.

3-Bromo-1,2,4-thiadiazol-5-yl Sulfenyl Chloride (7).—A solution of 8.0 g (0.020 mol) of **4** in 150 ml of CH_2Cl_2 was stirred at −40° while 1.5 g (0.020 mol) of Cl_2 was added slowly. The reaction mixture remained at ambient for 3 hr before the solvent was evaporated *in vacuo* yielding 9.5 g (100%) of product. Satisfactory elemental analysis could not be obtained on the crude product which analyzed correctly for nitrogen and chlorine but was approximately 1% high in carbon and bromine. Infrared analysis showed similar absorptions to that of the disulfide with peaks at 7.01, 8.29, and 8.37 (doublet), 9.37, 11.18, and 15.0 μ.

3-Bromo-3′-chloro-1,2,4-thiadiazol-5-yl Disulfide (8).—To a slurry of 9.7 g (0.05 mol) of **1** in 150 ml of CH_2Cl_2 stirred at −40°, a cold solution of bromine chloride was added slowly. The bromine chloride solution, prepared by combining 8.0 g (0.05 mol) of Br_2 and 3.6 g (0.05 mol) of Cl_2 at −45° and adding cold CH_2Cl_2 after 0.5 hr, was maintained below −45° during the course of the reaction. The mixture was then allowed to come to room temperature and filtered, and the solvent was removed *in vacuo* yielding 8.0 g (92%) of crude yellow solid which melted at 118–120° after one recrystallization (69%) from methylene chloride–methanol.

Anal. Calcd for $C_4N_4S_4BrCl$: C, 13.81; N, 16.14; S, 36.88; Cl, 10.19; Br, 22.98. Found: C, 13.99; N, 16.18; S, 37.22; Cl, 10.04; Br, 23.00.

Infrared analysis provided a spectrum which resembled the superimposed spectra of combined **3** and **4**. Absorption maxima were observed at 6.97, 7.01, 8.23, 8.39, 9.48, 10.97, 11.21, 14.7, and 15.0 μ.

General Procedure for Sulfenyl Chloride–Olefin Adducts.—In a typical experiment 18.7 g (0.1 mol) of sulfenyl chloride was dissolved in 200 ml of CH_2Cl_2, 0.1 g of $CaCO_3$ was added, and the mixture cooled to −50°. *trans*-Butene-2, 5.6 g (0.1 mol), was slowly condensed into the solution at a rate such that the solution temperature remained below −20°. Almost immediately after the addition was completed, the solution temperature began to drop and cooling was discontinued. The solvent was then removed at reduced pressure leaving 23 g (94%) of an oil. Distillation, 98–99° (0.1 mm), provided an 81% overall yield of pure product. Both the undistilled and distilled products were analyzed by vpc and nmr. The distilled products were subject to elemental analyses.

1,2,4-Thiadiazol-3,5-yl Bis(sulfenyl chloride) (11).—A solution of 19.4 g (0.1 mol) of dipotassium cyanodithioimidocarbonate in 500 ml of methanol was refluxed with 3.2 g (0.1 g-atom) of sulfur for 15 min. The dipotassium salt of 3,5-dimercapto-1,2,4-thiadiazole (**10**) (perthiocyanic acid) was isolated by evaporation of solvent at reduced pressure and the product (22.6 g) was dried under vacuum at 80°.

A slurry of 113 g (0.5 mol) of **10** in 900 ml of CH_2Cl_2 was cooled to −50° and stirred while 71 g (0.1 mol) of chlorine was added slowly. The mixture was then allowed to come to ambient temperature, the KCl filtered off (under N_2), and the solvent removed by means of a rotary evaporator, yielding 82 g (74% yield) of the yellow solid bis(sulfenyl chloride) **11**.

Anal. Calcd for $C_2N_2S_3Cl_2$: C, 10.96; N, 12.78. Found: C, 11.29; N, 12.87.

General Procedure for 1,2,4-Thiadiazol-3,5-yl Bis(sulfenyl chloride)–Olefin Adducts.—In a typical experiment, 8.2 g (0.0375 mol) of the bis(sulfenyl chloride) **11** was dissolved in 75 ml of CH_2Cl_2, cooled to −50°, and stirred while propylene in slight excess was added. The solution was then stripped of solvent on a rotary evaporator. Traces of residual volatiles were removed by means of a high vacuum pump, yielding 11.0 g (97% yield) of product.

Registry No. —**1**, 13145-41-0; **2**, 26542-76-7; **3**, 26542-77-8; **6**, 26542-78-9; **7**, 26542-79-0; **8**, 26542-80-3; **11**, 2254-82-2.

Acknowledgment.—The able technical assistance of Mr. W. Longchamp is gratefully acknowledged.

Cycloaddition Reactions of 3,4-Diazacyclopentadienone Oxides with Olefins and Acetylenedicarboxylic Ester[1]

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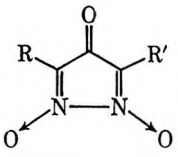
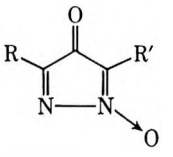
Received June 15, 1970

3,4-Diazacyclopentadienone *N,N'*-dioxides, **1**, and *N*-monoxides, **2**, undergo cycloaddition with olefins to produce isoxazolo[1,2-*b*]pyrazole derivatives **4** and **5**, respectively. These heterocycles undergo ring opening upon hydrolysis and hydrogenolysis to 4-ketopyrazoline derivatives. With acetylenedicarboxylic ester, **1** and **2** both yield 8-oxabicyclo[3.2.1]octane derivatives. Proof of the structure of these derivatives is based upon spectroscopic studies and a variety of oxidation and reduction products.

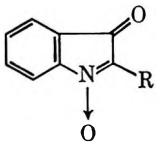
Recently, some representatives (**1**, **2**) of the 3,4-diazacyclopentadienone *N*-oxide family of heterocycles were reported.[3] The presence of the cross-conjugated keto–nitrone system and their bright colors suggested that these compounds might bear some chemical similarity to the isatogens, **3**. The latter compounds have been reported to undergo a number of unusual cycloaddition reactions.[4]



1a, R = C_6H_5; R′ = CH_3
b, R = C_6H_5; R′ = C_6H_5
c, R = CH_3; R′ = CH_3
d, R = C_6H_5; R′ = C_2H_5

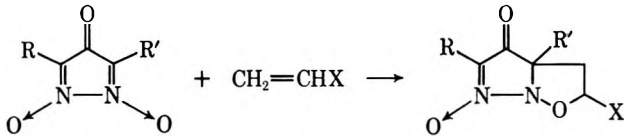


2a, R = C_6H_5; R′ = CH_3
b, R = C_6H_5; R′ = C_6H_5



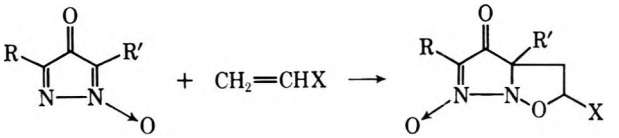
3

Olefin Additions.—Condensation of **1** with acrylonitrile, methyl acrylate, and butyl vinyl ether yielded 1:1 cycloadducts (Table I). All of these compounds resulted from the same regiospecific cycloaddition in which the nitrone oxygen is attached to the carbon atom of the olefin which bears the functional group. This orientation is that expected on the basis of previous results with simple nitrones[5] and supports the suggestion that steric factors are mainly responsible for this regiospecificity.[6] Proof for this orientation will be outlined below.



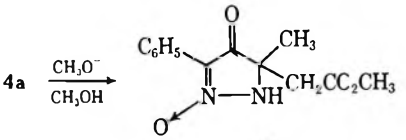
With unsymmetrical derivatives of **1**, such as **1a**, there is a second source of structural uncertainty in the cycloadducts and that is to which nitrone function addition occurs. In all cases examined, addition took place exclusively at the aliphatic nitrone group. This point was immediately apparent from a comparison of the nmr spectra of the adducts with those of the starting materials. The alkyl group hydrogens underwent an upfield shift of about δ 0.5, wholly compatible with the change of hybridization at the nitrone carbon from sp^2 to sp^3.

In the report[3] of compounds of structure **2**, it was noted that there was an unsettled ambiguity about the unsymmetrical derivatives. There was presumptive evidence that an alkyl rather than an aryl group was preferentially associated with the nitrone function, but spectral data alone could not unequivocally establish this point. The results of cycloaddition reactions of **2** (Table I) show conclusively that the original suggestion was correct as again the nmr spectra showed that the alkyl groups suffered an upfield shift upon cycloaddition.



2, R = Ar, R′ = Alkyl
5, R = Ar, R′ = Alkyl

The heterocyclic adducts **4a** and **5a**, X = CN, underwent a base-catalyzed ring opening and solvolysis that served both to substantiate their structures and to produce new heterocyclic derivatives. This ring opening is similar to that observed with isatogen cycloadducts.[7]



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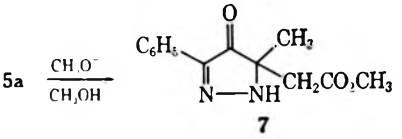


7

One previous example of the heterocyclic nucleus of **6** has been reported and it was established in that investigation that the keto–nitrone tautomer correctly represented the structure.[8] The spectral properties of **6** were very similar to those previously reported.[8]

* To whom correspondence should be addressed.

(1) This research was supported by a research grant (CA 10752) from the National Cancer Institute of the National Institutes of Health.

(2) National Defense Education Act Fellow, 1966–1969. Abstracted in part from the Ph.D. Thesis of M. J. Hoare.

(3) J. P. Freeman, J. J. Gannon, and D. L. Surbey, *J. Org. Chem.*, **34**, 187 (1969).

(4) W. E. Noland and R. F. Modler, *J. Amer. Chem. Soc.*, **86**, 2086 (1964).

(5) R. Huisgen, H. Hauck, R. Grashey, and H. Seidl, *Chem. Ber.*, **101**, 2568 (1968).

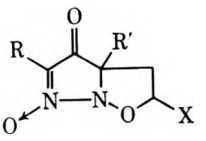
(6) N. A. LeBel, *Trans. N. Y. Acad. Sci.*, **27**, 858 (1965).

(7) W. E. Noland and D. A. Jones, *Chem. Ind. (London)* 363 (1962).

(8) J. P. Freeman, *J. Org. Chem.*, **27**, 2881 (1962).

TABLE I

CYCLOADDUCTS



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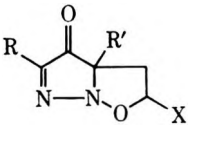
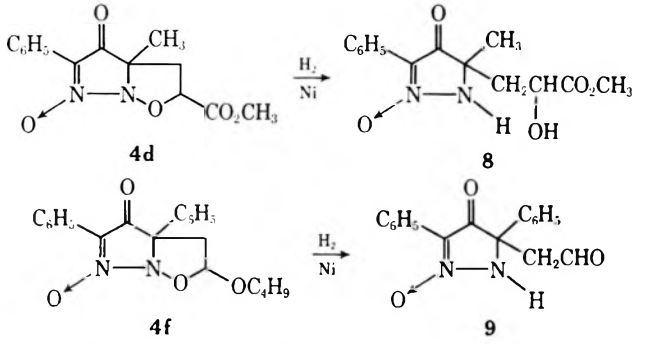


5

Compd no.	R	R′	X	Yield, %	Mp, °C	Ir (Nujol), cm⁻¹	Nmr (CDCl₃), δ	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
4a	C_6H_5	CH_3	CN	60	158–160	1735 (C=O), 1570 (–C=N→O), 1120 (N→O)	1.67 (s, 3, CH_3), 2.99 (m, 2, $-CH_2CH-$), 5.30 (q, 1, $>CHCH_2-$), 7.60 (m, 3), 8.30 (m, 2)	60.70	4.31	16.33	60.90	4.59	16.17
4b	CH_3	CH_3	CN	34	110–111	1725 (C=O), 1590, 1570 (–C=N→O), 970 (N→O)	1.67 (s, 3, CH_3), 2.05 (s, 3, CH_3), 2.75 (m, 2), 4.80 (m, 1)	49.20	4.65	21.50	48.92	4.66	21.69
4c	C_6H_5	C_2H_5	CN	72	117–118	1715 (C=O), 1565, 1100	1.06 (t, 3, J = 7.5 Hz), 2.05 (q, 2, J = 7.5 Hz), 2.80 (m, 2), 4.06 (m, 1), 7.50 (m, 3), 8.35 (m, 2)	61.99	4.83	15.49	62.20	4.90	15.52
4d	C_6H_5	CH_3	CO_2CH_3	62	145–147	1750 (ester C=O), 1720, 1565, 1120	1.40 (s, 3), 2.65 (m, 2), 3.80 (s, 3), 4.59 (m, 1), 7.50 (m, 3), 8.40 (m, 2)	57.93	4.86	9.65	57.65	5.06	9.79
4e	C_6H_5	C_6H_5	CO_2CH_3	68	150–151	1750, 1710, 1550, 1130	3.62 (s, 3), 3.33 (m, 2), 5.05 (m, 1), 7.45 (m, 10), 8.35 (m, 2)	64.77	4.58	7.95	64.84	4.59	8.23
4f	C_6H_5	C_6H_4	n-OC_4H_9	75	106–107	1725, 1550, 1380, 1050	1.00 (m, 7), 2.90 (q, 2), 3.65 (m, 2), 5.55 (t, 1), 7.50 (m, 10), 8.40 (m, 2)	68.84	6.05	7.65	68.70	6.22	7.69
5a	C_6H_5	CH_3	CN	46	150–152	1750, 1450	1.66 (s, CH_3), 2.62 (m, 2), 4.62 (m, 1), 7.50 (m, 3), 8.20 (m, 2)	64.72	4.60	17.42	64.87	4.85	17.35

[a] See Experimental Section.

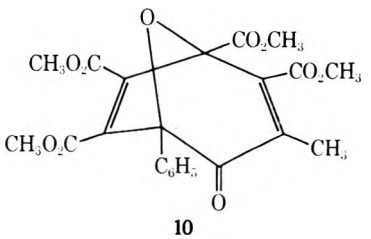
Hydrogenolysis of the cycloadducts also affords derivatives of the 4-ketopyrazoline 2-oxide system. Catalytic hydrogenation of **4d** yielded the α-hydroxy ester **8**, while similar treatment of **4f** yielded aldehyde **9** isolated as its 2,4-DNP derivative.



4d 8

4f 9

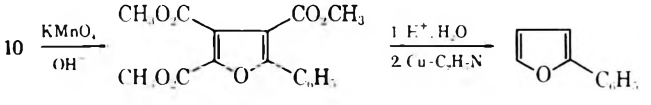
Acetylenes.—The dioxide **1a** condensed with acetylenedicarboxylic ester in boiling benzene to yield a nitrogen-free product derived from 2 equiv of the ester and 1 equiv of the dioxide. Nitrous oxide was evolved during the reaction. Structure **10** is proposed for the adduct: R = C_6H_5; R′ = CH_3.



10

Spectral Evidence.—The infrared spectrum of **10** contains carbonyl bands at 1760, 1740, 1720, and 1710 cm^{-1}, and a medium intensity band at 1660 cm^{-1}. Its nmr spectrum shows the ester methyl groups at δ 3.66 (3 H), 3.82 (6 H), and 3.88 (3 H), and a lone methyl singlet at δ 2.02. The phenyl group appears as a multiplet at δ 7.55. The mass spectrum of **10** showed a small molecular ion peak at m/e 444 and the 100% ion peak at 105 ($C_6H_5CO^+$). Its fragmentation pattern is consistent with the structure proposed. The ultraviolet spectrum of **10** showed absorption at λ_{max} 218, 245, and 370 nm, consistent with the α,β-unsaturated ketone and maleate ester chromophores.

Compound **10** was thermally stable at its melting point and it did not form carbonyl derivatives (under the usual conditions). Oxidation of **10** with alkaline permanganate yielded trimethyl 2-phenylfurantricarboxylate. The structure of this ester was established by its elemental analysis, its spectral properties, and its

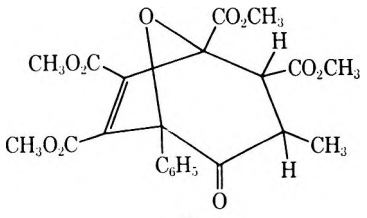


degradation to 2-phenylfuran by hydrolysis and decarboxylation.

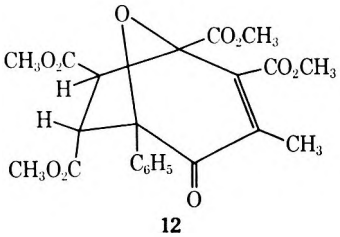
A series of reductions was also carried out to substantiate structure **10**. Catalytic hydrogenation yielded a mixture of two monohydrogenation products, **11** and **12**. The nmr spectrum of **11** had, in addition to signals due to the ester methyl groups, a doublet at δ 1.20 (3 H, J = 7 Hz) and multiplets at 7.50 (5 H), 3.45 (1 H), and 4.20 (1 H), fully consistent with structure **11** and confirming the structural feature in **10** of a methyl group attached to a double bond substituted with carbonyl functions.[9] The nmr spectrum of **12** showed that the *C*-

(9) Structures **11** and **12** represent the stable isomers (based upon study of models) obtained after base-catalyzed epimerization of the original hydrogenation products, which appeared to consist of mixtures of stereoisomers.

methyl group was still in the same magnetic environment as in **10** and was otherwise consistent with the structure proposed. All attempts to fully saturate **11** or **12** were unsuccessful. It may be of some interest that the ultraviolet spectra of compounds **10**, **11**, and **12** were virtually identical, but the significance of this fact is not known.

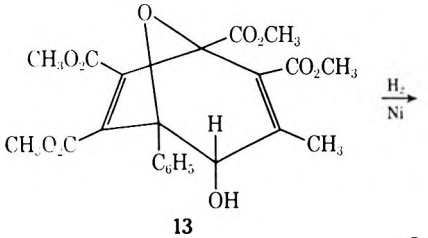


11

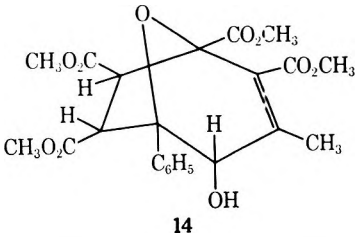


12

Sodium borohydride reduction of **10** yielded an alcohol **13** which could be reoxidized with chromic acid to **10**. The orientation of the hydroxyl group is not known although it is probably endo based upon the lactonization described below. Catalytic hydrogenation of **13** produced **14**. The structure of **14** is based

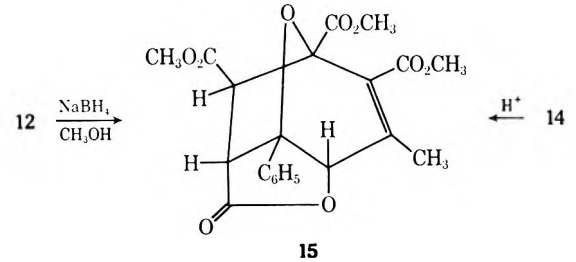


13



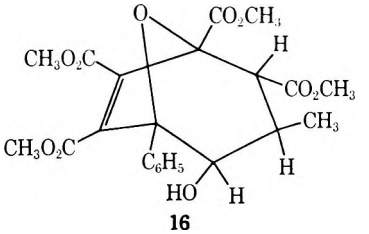
14

upon its nmr spectrum which showed that the *C*-methyl group was still a singlet and in the same magnetic environment as in **10** and **13**. In addition, oxidation of **14** yielded ketone **12**. Sodium borohydride reduction of **12** in methanol produced a lactone **15** which was identical with that produced by acid treatment of **14**. The lactone **15** is the only one that could be constructed using models and this requires that **14** have the structure shown. Thus borohydride reduction of **10** probably occurs from the exo side to give the endo alcohol **13**. The catalytic hydrogenation of **13** may yield the thermodynamically stable trans diester **14**, directly, but in any case the lactonization conditions are such as to produce the requisite epimer.



15

Borohydride reduction of ketone **11** produced an alcohol **16** isomeric with **14** but one which could not be lactonized. Oxidation of **16** regenerated **11**. Model studies indicated that no lactone could be formed between the ester at C-2 and the hydroxyl group at C-4.[10] The "α" relationship of the ketone carbonyl group and the *C*-methyl group is shown in the increased complexity of the nmr signal of the hydrogen coupled to the methyl group in **11** upon reduction to **16**. On the other hand,



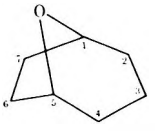
16

the signal for the CH group of the alcohol in **14** was a simple doublet (coupling to OH) which collapsed to a singlet when the spectrum was measured in the presence of trifluoroacetic acid.

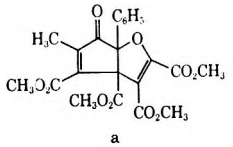
All the data assembled support the structure of the condensation product as **10**.[11] An attempt to convert **12** to a tropone by acid-catalyzed ring opening and dehydration in polyphosphoric acid was unsuccessful, possibly due to complicating side reactions with the several ester functions.

A possible route from dioxide **1a** to compound **10** may be envisioned as shown in Scheme I. The formation of adducts which are analogous to **17** has been postulated in other nitrone–acetylene cycloadditions. The rearrangement of **17** to **18** might be anticipated on the basis of the reported instability of the 4-isoxazoline nucleus.[12] Compounds similar to **19** have been postulated as the compounds responsible for the color produced upon heating epoxycyclopentadienones.[13] In one instance, such a compound was trapped by acety-

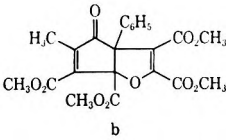
(10) Numbering according to Ring Index of the 8-oxabicyclo[3.2.1]octane skeleton.



(11) Other structures considered that were compatible with the spectral data were the following.



a



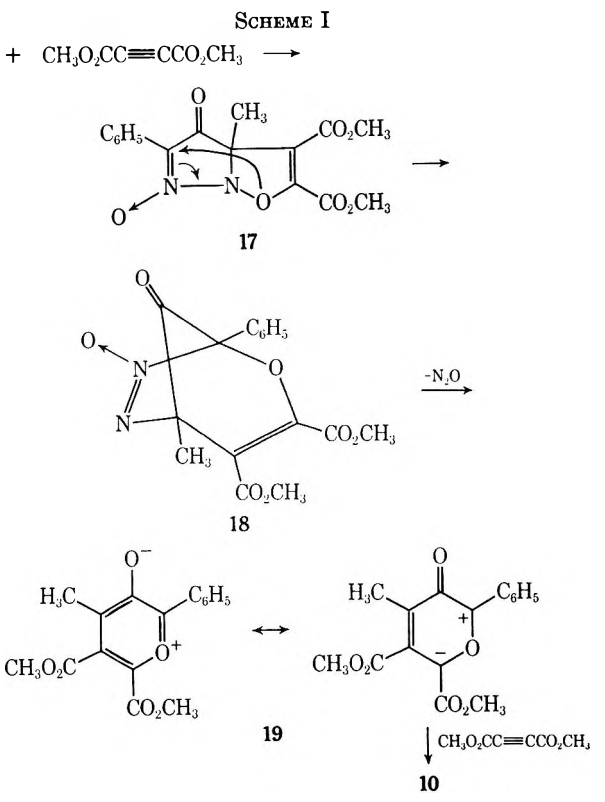
b

Both suffer from the fact that **10** is stable to acid-catalyzed hydrolysis, a reaction expected to cleave the vinyl ether function. Additionally b would yield trimethyl 3-phenylfurantricarboxylate instead of the 2-phenyl isomer.

(12) J. E. Baldwin, R. G. Pudussery, A. K. Qureschi, and B. Sklarz, *J. Amer. Chem. Soc.*, **90**, 5325 (1968).

(13) (a) E. F. Ullman and J. E. Milks, *ibid.*, **86**, 3814 (1964); (b) J. M. Dunston and P. Yates, *Tetrahedron Lett.*, 505 (1964).

SCHEME I



lenedicarboxylic ester to give a derivative analogous to **10**.[13a,14] As this mechanism would suggest, compound **10** was also obtained from the reaction of the mono-*N*-oxide **2a** with acetylenedicarboxylic ester.

Experimental Section

Cycloaddition Reactions with Alkenes. 1. The Cycloadducts (Table I).—2-Phenyl-4-methyl-6-cyano-3-ketoisoxazolo[1,2-*b*]pyrazole *N*-Oxide (4a).—A 2.0-g (9.8 mmol) sample of 2-phenyl-5-methyl-3,4-diazacyclopentadienone *N,N'*-dioxide[3] (**1a**) and 20 ml (0.30 mol) of acrylonitrile were refluxed for 4 hr. There was a color change from bright orange to pale yellow as the reaction proceeded. The acrylonitrile was removed under vacuum and the residual oil slowly crystallized. A single recrystallization from methylene chloride–hexane gave colorless needles, mp 158–160°, 60% yield.

2-Phenyl-4-methyl-6-cyano-3-ketoisoxazolo[1,2-*b*]pyrazole (5a).—A 0.5-g (2.66 mmol) sample of **2-methyl-5-phenyl-3,4-diazacyclopentadienone 3-oxide (2a)**[3] and 10 ml (0.15 mole) of acrylonitrile were dissolved in 10 ml of benzene and the solution was refluxed for 4 hr. The solution turned from dark red to pale yellow during the reaction period. The benzene and excess acrylonitrile were removed under vacuum and the solid residue was crystallized from methanol. Recrystallization from methylene chloride–hexane gave pale yellow crystals, 0.30 g (46%), mp 150–152°.

2. The Cycloadduct Derivatives. 5-Carbomethoxymethyl-5-methyl-3-phenyl-2-pyrazolin-4-one 2-Oxide (6).—A solution containing 0.5 g (2 mmol) of **4a** in 50 ml of methanol and 2 ml of 10% NaOH solution was refluxed for 3 hr, and then cooled and acidified to congo red with HCl. After a long period of cooling, 0.3 g (60%) of white needles were isolated: mp 113–115°; ir (Nujol) 3300 (NH), 1720 (ester C=O), 1550 and 1250 cm^{-1}; nmr ($CDCl_3$) δ 1.34 (s, 3, CH_3), 2.94 (d, 2), 3.55 (s, 3, OCH_3), 7.50 (m, 3), and 8.20 (m, 2). *Anal.* Calcd for $C_{13}H_{14}N_2O_4$: C, 59.5; H, 5.38; N, 10.68. Found: C, 59.60; H, 5.56; N, 10.60.

5-Carbomethoxymethyl-5-methyl-3-phenyl-2-pyrazolin-4-one (7).—To a solution of 0.5 g (2.0 mmole) of **5a** in 50 ml of methanol was added 2 ml of 10% NaOH. The solution was refluxed for 4 hr and worked up as described for **6**. Pale yellow crystals were isolated: 0.3 g (60%); mp 99–100°; ir (Nujol) 3320 (NH), 1720 and 1705 (CO); nmr ($CDCl_3$) δ 1.42 (s, 3, CH_3), 2.66 (d, 2), 3.73 (s, 3, OCH_3), 7.40 (m, 3), and 3.15 (m, 2). *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 61.68; H, 5.73; N, 11.55.

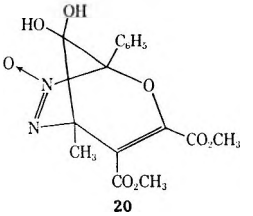
5-(2-Hydroxy-2-carbomethoxy)ethyl-5-methyl-3-phenyl-2-pyrazolin-4-one 2-Oxide (8).—A 0.8-g (2.7 mmol) sample of **4d** was hydrogenated in 50 ml of ethyl acetate with Raney Ni (0.5 g) over a 4-hr period. The solution was filtered and the solvent removed under reduced pressure. The residual oil was swirled in 25 ml of CCl_4. Pale green crystals were isolated by this method. Recrystallization from $CHCl_3$–*n*-C_6H_{12} gave 0.6 g (76%) of pale yellow crystals: mp 95–96°; ir (Nujol) 3400 (NH), 3120 (OH), 1735 and 1683 (C=O), and 1545 cm^{-1} (O=CC=N→O) vs; nmr ($CDCl_3$) δ 1.48 (s, 3, CH_3), 2.35 (m, 2), 3.34 (m, 1), 3.76 (s, 3, OCH_3), 4.23 (m, 1), 7.35 (m, 3), and 8.30 (m, 2 H). *Anal.* Calcd for $C_{14}H_{16}N_2O_5$: C, 57.5; H, 5.52; N, 9.58. Found: C, 57.15; H, 5.79; N, 9.80.

5-Formylmethyl-3,5-diphenyl-2-pyrazolin-4-one 2-Oxide.—A 0.8-g (2.2 mmol) sample of **4f** was hydrogenated in 50 ml of ethyl acetate with Raney Ni (0.5 g) for 4 hr. The residual oil after removal of solvent and catalyst was dissolved in ethanol and added to 15 ml of 0.17 *M* 2,4-dinitrophenylhydrazine reagent in ethanol. The resulting yellow 2,4-dinitrophenylhydrazone was recrystallized from $CHCl_3$–*n*-hexane: mp 196–198°; yield 0.45 g (42%); nmr ($CDCl_3$) δ 3.50 (m, 2), 7.70 (m, 12), 8.32 (m, 2), and 8.89 (d, 1). *Anal.* Calcd for $C_{23}H_{18}N_6O_6$: C, 58.3; H, 3.80; N, 17.70. Found: C, 58.0; H, 4.04; N, 1781.

2-Phenyl-5-methyl-3,4-diazacyclopentadienone *N,N'*-Dioxide and Dimethyl Acetylenedicarboxylate. Preparation of 4-Keto-3-methyl-5-phenyl-1,2,6,7-tetracarbomethoxy-8-oxabicyclo[3.2.1]octa-2,6-diene (10).—A solution of 5 g (25 mmol) of dioxide **1a** in 10 ml of benzene and 10 ml of dimethyl acetylenedicarboxylate [Aldrich, bp 65% (0.1 mm)] was heated under reflux for 4 hr while its color changed from bright red to pale yellow. The mixture was cooled and the benzene and excess ester were removed under vacuum. The residual oil crystallized from methanol as fine needles. Recrystallization from $CHCl_3$–*n*-C_6H_{12} gave 6 g (55%) of yellow needles of **10**: mp 110–112°; ir (Nujol) 1760, 1740, 1720, and 1710 (C=O), and 1660 cm^{-1}; uv max (95% EtOH) 370 nm (ϵ 300), 218 (9800), and 245 (5000); nmr ($CDCl_3$) δ 3.66 (s, 3), 3.82 (bs, 6), 3.88 (s, 3), 2.02 (s, 3), and 7.55 (m, 5); mass spectrum (70 eV) *m/e* (rel intensity) 444 (10), 105 (100).[15] *Anal.* Calcd for $C_{22}H_{20}O_{10}$: C, 59.90; H, 4.97. Found: C, 59.94; H, 4.92.

Sodium Borohydride Reduction of 10. 4-Hydroxy-3-methyl-5-phenyl-1,2,6,7-tetracarbomethoxy-8-oxabicyclo[3.2.1]octa-2,6-diene (13).—A solution of 4.44 g (10 mmol) of **10** and 0.2 g (5.5 mmol) of $NaBH_4$ in 200 ml of methanol was stirred for 4 hr at 10–15°. The solution was acidified to congo red with HCl, concentrated, and then poured into 50 ml of distilled water. The white precipitate was collected, washed a few times with water, and crystallized from methanol. Recrystallization from methanol gave 3.5 g (80%) of white crystals of **13**: mp 146–148°; ir (Nujol) 3405 (OH), 1760, 1735, and 1705 (C=O), and 1645 cm^{-1}; nmr ($CDCl_3$) δ 2.20 (s, 3), 3.87 (s, 6), 3.78 (s, 3), 3.66 (s, 3), 4.75 (d, 1, J = 8.5 Hz), 4.05 (d, 1, J = 8.5 Hz), and 7.60 (m, 5); uv max (95% EtOH) 217 nm (ϵ 12,000). The mass spectrum (70 eV) showed a molecular ion peak at *m/e* 446. *Anal.* Calcd for $C_{22}H_{22}O_{10}$: C, 59.19; H, 4.97. Found: C, 59.04; H, 5.12. Compound **13** was oxidized back to **10** by the Jones Method.[16]

(14) Some evidence for the intermediacy of compound **18** was obtained when the cycloaddition was carried out at room temperature. The hydrate of a 1:1 adduct was obtained whose spectral properties could be interpreted in terms of structure **20**. See Experimental Section for details.



20

(15) The mass spectral analysis was prepared by the High Resolution Mass Spectrometry Center, Battelle Memorial Institute, Columbus, Ohio.

(16) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

Catalytic Hydrogenation of 10. 4-Keto-3-methyl-5-phenyl-1,2,6,7-tetracarbomethoxy-8-oxabicyclo[3.2.1]octene-6 (11) and 4-Keto-3-methyl-5-phenyl-1,2,6,7-tetracarbomethoxy-8-oxabicyclo[3.2.1]octene-2 (12).—A solution of 5 g (11 mmol) of 10 in 200 ml of methanol containing 0.2 g of Pd–C was stirred under 1 atm of hydrogen for 5 days. The catalyst was removed, the colorless solution concentrated to 100 ml, and the precipitate was recrystallized from methanol giving 1.85 (36%) of white crystals of 11: mp 150–153°; ir (Nujol) 1760, 1740, and 1735 (C=O), and 1650 cm^{-1}; nmr ($CDCl_3$) δ 3.83 (s, 3), 3.76 (s, 6), 3.67 (s, 3), 1.20 (d, 3, J = 7.5 Hz, $CH_3CH<$), 3.45 (q, 1, J = 7.5 Hz, $CH-CH_3$), 4.20 (m, 1), and 7.50 (m, 5); uv max (95% EtOH) 320 nm (ϵ 500), 240 (4000), 217 (9200). The mass spectrum showed a M^+ at m/e 446. *Anal.* Calcd for $C_{22}H_{22}O_{10}$: C, 59.19; H, 4.97. Found: C, 58.95; H, 5.06.

Further concentration of the mother liquor gave a second crop of crystals. Recrystallization from methanol gave 2.0 g (50%) of pale yellow crystals of 12: mp 100–102°; ir (Nujol 1750 and 1725 cm^{-1}; nmr ($CDCl_3$) δ 2.26 (s, 3), 3.87 (s, 3), 3.82 (s, 3), 3.67 (s, 6), 3.90 (d, 1, J = 12 Hz), 4.40 (d, 1, J = 12 Hz), and 7.38 (s, 5); uv max (95% EtOH) 370 nm (ϵ 280) 248 (7300), 211 (7300). The mass spectrum showed M^+ at m/e 446. *Anal.* Calcd for $C_{22}H_{22}O_{10}$: C, 59.19; H, 4.97. Found: C, 58.99; H, 5.10.

Catalytic Hydrogenation of 13. 4-Hydroxy-3-methyl-5-phenyl-1,2,6,7-tetracarbomethoxy-8-oxabicyclo[3.2.1]octene-2 (14).—A solution of 1 g (2.2 mmol) of 13 in 100 ml of methanol, containing 0.2 g of Pd–C was stirred under H_2 gas at 1 atm for 2 hr. The catalyst and solvent were removed and the residue was crystallized from methanol. Recrystallization from ethanol gave 0.8 g (80%) of white crystals of 14: mp 170–173°; ir (Nujol) 3480 (OH), 1775, 1750, and 1695 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.17 (s, 3), 3.61 (s, 3), 3.70 (s, 3), 3.73 (s, 3), 3.84 (s, 3), 4.20 (m, 4), and 7.50 (m, 5). *Anal.* Calcd for $C_{22}H_{24}O_{10}$: C, 58.53; H, 5.39. Found: C, 58.87; H, 5.47. Compound 14 was oxidized to compound 12 with the Jones reagent.[16]

Sodium Borohydride Reduction of 11. 4-Hydroxy-3-methyl-5-phenyl-1,2,6,7-tetracarbomethoxy-8-oxabicyclo[3.2.1]octene-6 (16).—To a cold solution of 2 g (4.5 mmol) of 11 in 200 ml of methanol was added 0.1 g (2.5 mmol) of $NaBH_4$. The solution was stirred constantly in an ice bath for 4 hr and worked up as described for compound 13. Recrystallization from methanol gave 1.6 g (80%) of white crystals of 16: mp 140–142°; ir (Nujol) 3440, 1750, 1730, and 1710 (C=O), and 1650 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.06 (d, 3, J = 8.0 Hz), 2.90 (q, 1, J = 8.0 Hz), 3.55 (d, 1, J = 7.0 Hz), 3.67 (s, 3), 3.72 (s, 3), 3.82 (s, 6), 4.00 (d, 1, J = 12 Hz), 4.45 (q, 1), and 7.50 (m, 5). *Anal.* Calcd for $C_{22}H_{24}O_{10}$: C, 58.53; H, 5.39. Found: C, 59.09; H, 5.57. Jones oxidation[16] of 16 regenerated ketone 11.

Sodium Borohydride Reduction of 12. Formation of Lactone 15.—To a cold solution of 1 g (2.2 mmol) of compound 12 in 50 ml of methanol was added 0.1 g (2.5 mmol) of $NaBH_4$. The mixture was stirred constantly and allowed to warm to room temperature during a 4-hr period. The reaction was worked up as described for compound 13. Recrystallization of the white powder from methanol gave 0.2 g (24%) of white crystals of 15: mp 131–133°; ir (Nujol) 1790 (lactone C=O), 1760 (ester C=O), and 1700 cm^{-1} (unsaturated ester C=O); nmr ($CDCl_3$) δ 2.26 (s, 3), 3.70 (s, 3), 3.73 (s, 3), 3.84 (s, 3), 3.28 (d, 1, J = 12 Hz), 4.28 (d, 1, J = 12 Hz), 5.06 (d, 1), and 7.45 (s, 5). *Anal.* Calcd for $C_{21}H_{20}O_9$: C, 60.58; H, 4.84. Found: C, 60.67; H, 5.03.

Potassium Permanganate Oxidation of 10. Trimethyl 2-Phenylfuran-3,4,5-tricarboxylate.—A mixture of 5 g (11 mmol) of compound 10 and 10 g (64 mmol) of $KMnO_4$ in 300 ml of acetone was stirred at 25° for 2 hr, and then heated on the steam bath for 1 hr. The solution was filtered and concentrated, and the solid residue was crystallized from ethanol and recrystallized from CH_2Cl_2–C_6H_{12} to give 2 g (58%) of white needles: mp 67–69°; ir (Nujol) 1745, 1725, and 1615 cm^{-1}; nmr ($CDCl_3$) 3.83 (s, 3), 3.92 (s, 3), 3.99 (s, 3), and 7.70 (m, 5); uv max (95% EtOH) 290 nm (ϵ 15,000), 217 (9200). The mass spectrum showed a M^+ peak at m/e 318. *Anal.* Calcd for $C_{16}H_{14}O_7$: C, 60.38; H, 4.43. Found: C, 60.55; H, 4.52.

2-Phenylfuran-3,4,5-tricarboxylic Acid.—Trimethyl 2-phenylfuran-3,4,5-tricarboxylate (1 g, 3 mmol) was refluxed for 1 hr with 20 ml of 35% aqueous KOH. The solution was filtered and acidified to congo red with HCl. On cooling, the potassium salt precipitated. Recrystallization from water gave 0.7 g of white needles, mp 300° dec. The potassium salt (0.7 g) was dissolved in 50 ml of 20% aqueous HCl. On cooling, white needles were deposited. Recrystallization from water gave 0.5 g (74%) of long needles: mp 212–215°; ir (KBr) 3540 and 3440 (OH), 1730 and 1685 (C=O), and 1210 cm^{-1}; nmr (acetone-d_6) δ 7.70 (m, 5), and 8.20 (s, 3). *Anal.* Calcd for $C_{13}H_8O_7$: C, 56.53; H, 2.92. Found: C, 55.84; H, 3.11.

Decarboxylation of 2-Phenylfuran-3,4,5-tricarboxylic Acid to 2-Phenylfuran.—A 1.0-g sample of **2-phenylfuran-3,4,5-tricarboxylic acid** was placed in a small flask with 5 ml of freshly distilled quinoline and 0.2 g of Cu powder. The mixture was heated in an oil bath at 240° for 4 hr while N_2 gas was passed over it. The mixture was cooled and filtered, and the filtrate was distilled under reduced pressure. Quinoline and 2-phenylfuran were isolated as one fraction [115° (20 mm)]. The quinoline was removed from this fraction by treatment with ethereal HCl. 2-Phenylfuran was isolated as a high boiling liquid: bp 110° (20 mm) [lit.[17] 107–108° (18 mm)]; ir (CCl_4) 1600 (C=C), 1475 and 1155 cm^{-1}; nmr (CCl_4) δ 6.35 (q, 1, J_{AB} = 1.5 Hz, J_{BC} = 3.5 Hz), 6.53 (d, 1, J_{BC} = 3.5 Hz), and 7.40 (m, 6). This spectrum corresponds to that reported.[18]

Reaction of 2-Methyl-5-phenyl-3,4-diazacyclopentadienone 3-Oxide (2a) with Dimethyl Acetylenedicarboxylate.—To a solution of 0.3 g (1.6 mmol) of 3a in 5 ml of anhydrous benzene was added 5 ml of dimethyl acetylenedicarboxylate. The solution was refluxed at 90° for 4 hr. The benzene and the acetylenic ester were removed under reduced pressure and the residual oil was dissolved in CH_2Cl_2 and chromatographed on a silica gel column. The first fraction obtained was a pale yellow oil which crystallized from methanol to give 0.2 g (30%) of pale yellow crystals, 10, mp 106–108°.

Reaction of 2-Methyl-5-phenyl-3,4-diazacyclopentadienone *N,N'*-Dioxide (1a) with Dimethyl Acetylenedicarboxylate at 25°.—A 2.0-g (9.6 mmol) sample of 1a was suspended in 25 ml of dimethyl acetylenedicarboxylate. The suspension was stirred at room temperature for 72 hr. An additional 2 g of 1a was added and stirring was continued for 72 hr. The mixture was filtered to give 1 g of white powder, 20, mp 162–165°. This process was repeated and subsequent 2.0-g samples of 1a added to the above dimethyl acetylenedicarboxylate solution gave 2.3 g and 2.6 g of compound 20 (total yield 5.9 g, 42%): ir (Nujol) 3400 and 3220 (OH), 1750 and 1705 (C=O), and 1520 cm^{-1} (N=NO); nmr (acetone-d_6) δ 1.50 (s, 3), 3.78 (s, 3), 3.82 (s, 3), 6.06 (s, 1), 6.67 (s, 1), and 7.50 (m, 5). *Anal.* Calcd for $C_{16}H_{16}N_2O_8$: C, 52.75; H, 4.43; N, 7.69. Found: C, 52.39; H, 4.48; N, 7.76.

Registry No.—**4a**, 26732-93-4; **4b**, 26732-94-5; **4c**, 26732-95-6; **4d**, 26732-96-7; **4e**, 26732-97-8; **4f**, 26732-98-9; **5a**, 26732-99-0; **6**, 26733-00-6; **7**, 26733-01-7; **8**, 26785-68-2; **9** (2,4-DNP), 12441-10-0; **10**, 26733-02-8; **11**, 26733-03-9; **12**, 26733-04-0; **13**, 26866-79-5; **14**, 26733-05-1; **15**, 26733-06-2; **16**, 26733-07-3; **20**, 26733-08-4; trimethyl 2-phenylfuran-3,4,5-tricarboxylate, 26733-09-5; 2-phenylfuran-3,4,5-tricarboxylic acid, 26733-10-8; 2-phenylfuran, 17113-33-6.

Acknowledgment.—The A-60A nmr instrument used in this investigation was acquired under NSF Equipment Grant GP-6875. We are indebted to Drs. E. M. Burgess and J. F. Hansen for helpful discussions.

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Organic Photochemistry. I. The Synthesis of 2-Oxo-2,3,4,5-tetrahydro-1*H*-naphth[1,8-*de*]azocine by the Photolysis of *N*-Chloroacetyl-2-(α-naphthyl)ethylamine

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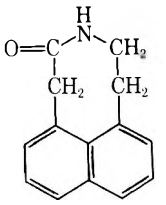
Received April 27, 1970

N-Chloroacetyl-2-(α-naphthyl)ethylamine (**2**) on irradiation in methanol–water solution (1:1) with a high-pressure mercury vapor lamp fitted with a Vycor filter was converted to the tricyclic lactam **3**, 2-oxo-2,3,4,5-tetrahydro-1*H*-naphth[1,8-*de*]azocine, in yields up to 47%. The lactam was converted to the amine **4**, 2,3,4,5-tetrahydro-1*H*-naphth[1,8-*de*]azocine, which was acetylated to produce the amide **5**, *N*-acetyl-2,3,4,5-tetrahydro-1*H*-naphth[1,8-*de*]azocine. The results of some phototitrations of **2** are also reported and discussed.

In 1966 the facile photocyclization of *N*-chloroacetyl-L-tryptophan to a tricyclic eight-membered lactam was reported.[1] Interesting applications of the reaction to certain benzene derivatives such as tyrosines, tyramines, catecholamines, and normescaline[2] and 3,4-dimethoxyphenethylamine[3] have since been reported. As a part of our continuing study of this reaction, it was of interest to apply the reaction to *N*-chloroacetyl-2-(α-naphthyl)ethylamine (**2**) as a prototype of aromatic polycyclic systems.

2-(α-Naphthyl)ethylamine (**1**) was prepared in 78% yield by reduction of 1-naphthylacetonitrile with lithium aluminum hydride and converted to **2**. Irradiation of **2** in methanol–water solution (1:1, v/v) with a high-pressure mercury vapor lamp fitted with a Vycor filter resulted in photolysis of **2** and the formation of a tricyclic eight-membered lactam **3**, 2-oxo-2,3,4,5-tetrahydro-1*H*-naphth[1,8-*de*]azocine, which was isolated in 47% yield.



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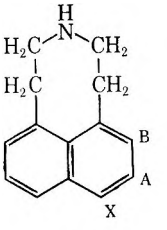
The mass spectrum and combustion analysis indicated that **3** had been formed with the loss of the elements of hydrogen chloride. The ir [(Nujol) 1666 cm^{-1}, C=O of a lactam with six or more members], uv (typical naphthalene spectrum with a shift of λ_{max} from 282 to 288 mμ on going from **2** to **3**),[4] and nmr (six aromatic protons) spectra established that **3** was a disubstituted naphthalene. The second position of substitution of the naphthalene moiety could be assigned on the basis of the nmr spectra. In order to obtain symmetrical compounds (in the case of the 1,8 derivative) with improved solubilities, **3** was reduced with diborane to the amine **4**, 2,3,4,5-tetrahydro-1*H*-naphth[1,8-*de*]-azocine, which was acetylated to obtain **5**, *N*-acetyl-2,-3,4,5-tetrahydro-1*H*-naphth[1,8-*de*]azocine. The nmr spectra of **3**, **4**, and **5** exhibit ABX-type spectra for the six aromatic protons with a multiplet of intensity four protons (naphthalene β protons) occurring upfield from a multiplet of intensity two protons (naphthalene α protons) (Figure 1). In the spectrum of **4**, these multiplets consist of two overlapping quartets and an isolated quartet, respectively. This spectrum could be analyzed algebraically as an ABX system[5] (δ_A 7.36, δ_B 7.24, δ_X 7.75 ppm; J_{AB} = 6.9, J_{AX} = 8.4, J_{BX} = 1.4 Hz). These values are in good agreement with those reported



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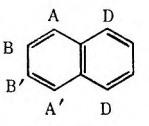

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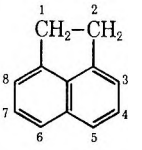

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for 1,4-dideuterionaphthalene (**6**) (100 MHz, CCl_4, TMS internal reference; δ_A 7.67, δ_B 7.32 ppm; $J_{BB'}$ = 6.86, J_{AB} = 8.29, $J_{AB'}$ = 1.22 Hz)[6] and acenaphthene (**7**) (40 MHz, CCl_4, TMS internal reference; δ_4 7.32, δ_3 7.11, δ_5 7.46 ppm; J_{34} = 6.7, J_{45} = 8.1, J_{35} = 1.2 Hz).[7] The nmr spectrum of **4** thus establishes the fact that the aromatic protons of **4** exist as two similar groups of three protons, the members of each group of which have different chemical shifts and are mutually spin coupled. The protons of the 1,2-disubstituted naphthalene do not meet these criteria and the spectrum of the aromatic protons of 1,2-dimethylnaphthalene ($CDCl_3$, δ 7.10–8.08 ppm, complex multiplet), determined as a reference spectrum, is more complex and of a different character from those of **3**, **4**, and **5**. Of the disubstituted naphthalenes only the 1,5 and 1,8 derivatives possess the required groupings of protons. The results of an nmr study of dimethylnaphthalenes[8] support this conclusion. In the case of the compounds under consideration, the length of the chloroacetamidoethyl group of **2**, as indicated by molecular models and by the intramolecular acylation studies with ω-(1-naphthyl)alkanoyl halides,[9] is clearly insufficient to allow the formation of a 1,5-

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(2) O. Yonemitsu, T. Tokuyama, M. Chaykovsky, and B. Witkop, *ibid.*, **90**, 776 (1968).

(3) O. Yonemitsu, Y. Okuno, Y. Kanaoka, I. Karle, and B. Witkop, *ibid.*, **90**, 6522 (1968).

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(5) E. D. Becker, "High Resolution NMR, Theory and Chemical Applications," Academic Press, New York, N. Y., 1969, p 157.

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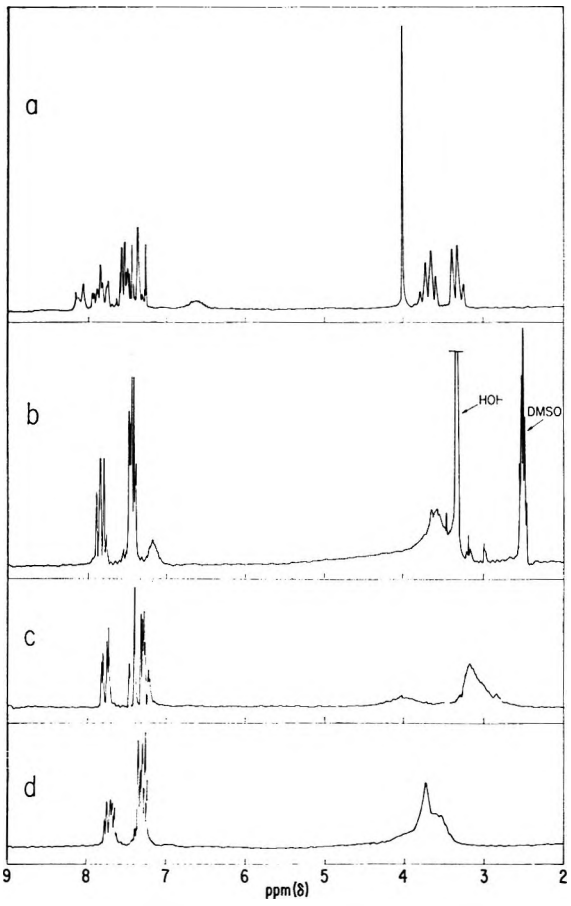

Figure 1.—100-MHz nmr spectra: (a) compound **2** in $CDCl_3$, (b) compound **3** in DMSO-d_6, (c) compound **4** in $CDCl_3$, and (d) compound **5** in $CDCl_3$.

disubstituted naphthalene. Compounds **3**, **4**, and **5** are thus shown to be 1,8-disubstituted naphthalenes.

The nmr signals of the aliphatic protons of **3**, **4**, and **5** occur as broad structureless overlapping bands (Figure 1). The nature of the temperature dependence of the spectrum of **5** indicates that the character of these signals is primarily a result of incomplete averaging produced by a slow rate of inversion of the eight-membered ring on the nmr time scale;[10] at 117° the signals, which are broad and structureless at 40°, appear as two triplets, each of intensity four protons. These results undoubtedly are a manifestation of restraints placed on the eight-membered ring by the 1,8 substitution of the rigid naphthalene system and are in accord with the assignment of cyclization to the 8 position of the naphthalene moiety. Such broadening was not observed with the tricyclic eight-membered lactam derived from *N*-chloroacetyl-L-tryptophan[1] or with the tricyclic 2,3-disubstituted naphthalene, 3-methoxycarbonyl-2,3,4,5-tetrahydro-1*H*-naphth[2,3-*d*]azepine.[11]

Automatic titration of the protons generated during photolysis has been found to be a useful technique for following the course of this photodehydrohalogenation and for studying its scope. This technique affords a measure of the rate of photolysis from the initiation of irradiation of the substrate. Some titration results already have been reported[2] and similar results had been found with *N*-chloroacetyl derivatives of tryptamine and analogs of tryptamine.[12] Results of phototitrations of **2** are given in Figure 2. The rate of photolysis of **2** under nitrogen with a Vycor filter ($t_{1/2}$ = 2.8 min) is comparable to that of *N*-chloroacetyltryptamine ($t_{1/2}$ = 2.6 min), which was used as a reference substrate. Careful tlc and uv spectroscopy of the titration mixtures indicated that the products of the reactions conducted with a given filter under nitrogen or oxygen were nearly indistinguishable and that the products obtained using a Vycor or a Pyrex filter were qualitatively the same with small differences in the relative amounts of several of the components. These results suggest that similar reactions take place with both filters. The fact that the reaction proceeds well in the presence of oxygen and that the rates for the reactions under nitrogen or oxygen are similar may indicate that free-radical intermediates or triplet states are not important to the course of the reaction. The reaction rates indicate that the Pyrex filter (30% transmission at 300, 10% at 290, and 0% at 280 mμ)[13] greatly reduced the amount of effective radiation reaching the substrate and suggest that the effective radiation may be acting through excitation of the naphthalene band which is labeled ^1L_a in the system of Platt[4] [for this band **2** has $\lambda\lambda_{max}^{MeOH}$ 272 mμ (log ε 3.78), 282 (3.86), 289 (3.69), 293 (3.69)] and which is considered to be transversely polarized. Results obtained so far show that the nature of the aromatic moiety affects the rate as well as the course of the reaction[1-3] and suggest that a photoexcited state of the aromatic portion of the molecule may a play a key role. The fact that photolysis of chloroacetamide itself in aqueous methanol produces protons at a much slower rate than photolysis of **2** may point to such a mechanism.[12] However, cyclization actually may be a concerted reaction in which photoexcitation of the chloroacetamido function also is involved. It has been pointed out that the n–π* excited state of an α-halocarbonyl group has the potential to facilitate the homolysis

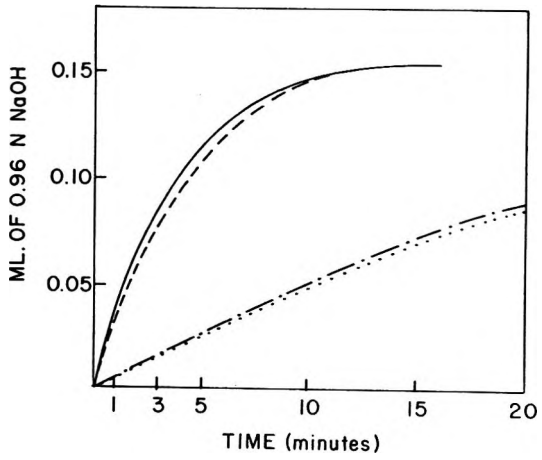

Figure 2.—Phototitrations of **2**, 0.15 × 10^{-3} mol in 20 ml of methanol and 80 ml of water in each case, with a high-pressure mercury vapor lamp. Titrations were carried out under the following conditions: under N_2 with a Vycor filter (—), $t_{1/2}$ = 2.6 min; under N_2 with a Pyrex filter (···), $t_{1/2}$ = 17.6 min; under O_2 with a Vycor filter (---), $t_{1/2}$ = 2.9 min; under O_2 with a Pyrex filter (-···-), $t_{1/2}$ = 16.6 min.

(10) For recent reviews, see J. E. Anderson, *Quart. Rev. (London)*, **19**, 426 (1966); G. Binsch in "Topics in Stereochemistry," Vol. 3, E. L. Eliel and N. L. Allinger, Ed., Interscience, New York, N. Y., 1968, p 97.

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(12) Unpublished results of C. M. Foltz.

(13) Specifications of the supplier of the filter.

or the heterolysis of the carbon–chlorine bond and that the polarity of the medium might be expected to favor one process or the other.[14] This has been found to be the case in the case of the photolysis of certain α-tosyloxy ketones.[15] On the basis of these results and observations, a reasonable mechanism for the reaction would seem to be one in which photoexcitation of the naphthalene moiety of the substrate results in the formation of a $\pi-\pi^*$ singlet state with increased electron density at the 8 position. Such an intermediate could displace chloride ion from the side chain, which also may have been predisposed to reaction by photoexcitation, to produce a tricyclic lactam which could lose a proton to complete the reaction. Studies of the acidities of a number of naphthalene derivatives[16] and phenols[17] indicate that in such compounds the contributions of polar structures are much greater in the lowest excited singlet state than in the lowest excited triplet state. Among recently reported photochemical reactions of aromatic compounds, which are believed to proceed in part or largely by ionic mechanisms, are the following: the photohydrolysis of *m*-nitrophenyl phosphates and sulfates,[18] the photosolvolyses of *m*-methoxybenzyl acetates,[19] and the photocyclization of certain ortho-substituted biphenyls.[20] Further studies on the scope and mechanism of this photocyclodehydrohalogenation reaction are in progress.

Experimental Section

All melting points were determined with a Kofler micro hot stage and are uncorrected. Spectra were measured with a Cary recording spectrophotometer, Model 15, using hexane (spectrograde, Matheson Coleman and Bell) and methanol (analytical reagent, Baker) as solvents; with a Perkin-Elmer 421 grating infrared spectrophotometer; with a Varian Associates Model HA-100 instrument using the frequency sweep mode of operation, probe temperatures were 32.4–36° depending on the season, chemical shifts were recorded as δ values (ppm) relative to tetramethylsilane as an internal reference; and with a Hitachi Perkin-Elmer RMU-7 mass spectrometer. The high-pressure mercury vapor lamp (200 W, No. 654A-36), water-cooled quartz immersion well, and glass filter sleeves (Vycor 7910 and Pyrex 7740) were obtained from Engelhard Hanovia, Inc., Newark, N. J. *N*-Chloroacetyltryptamine was synthesized by chloroacetylating tryptamine (Aldrich Chemical Co.).

2-(α-Naphthyl)ethylamine Hydrochloride (1).—An ethereal solution of 13.9 g (0.083 mol) of 1-naphthylacetonitrile (Aldrich Chemical Co.) was added dropwise under nitrogen to a stirred suspension of 5.7 g (0.15 mol) of lithium aluminum hydride (Alfa Inorganics, Inc.) in ether. The mixture was stirred an additional hour and then treated with 100 ml of ether saturated with water, 22 ml of water, and 4.5 ml of 20% sodium hydroxide solution. The ether was decanted and the solid was extracted by trituration with ether. A 1 *N* hydrochloric acid extract of the ethereal solution was alkalinized with sodium hydroxide and extracted with ether. The ethereal extract was washed, dried, and treated with hydrogen chloride to obtain 1, 13.5 g (78%), mp 240–245° (lit.[21] mp 243–248°).

***N*-Chloroacetyl-2-(α-naphthyl)ethylamine (2).**—A mixture of 4.15 g (0.02 mol) of 1, 250 ml of ether, and 20 ml of 1 *N* sodium hydroxide was stirred vigorously and treated dropwise with 2.83 g (0.025 mol) of chloroacetyl chloride with concurrent addition of portions of 30 ml of 1 *N* sodium hydroxide. The mixture was stirred 15 min more, acidified with 2 *N* sulfuric acid, and extracted with ether. The extract was washed with 5% sodium bicarbonate solution and water and dried; 4.0 g (80%) of **2** crystallized from the concentrated solution. Recrystallization from ether–petroleum ether (30–60°) afforded the analytical sample: mp 111–113°; ir (Nujol) 3258 (NH), 3078, 1642 (amide I), 1565 cm^{-1} (amide II); uv (hexane) 225 mμ (log ε 4.95), 283 (3.87), 315 (2.6); uv (methanol) 225 (4.92), 282 (3.86), 314 (2.58); nmr ($CDCl_3$) δ 3.22–3.44, 3.56–3.84 (4 H, two multiplets, $-CH_2CH_2-$), 4.01 (2 H, singlet, $-CH_2Cl$), 7.2–8.2 (7 H, multiplet, aromatic protons) (Figure 1); mass spectrum, molecular ion *m/e* 247.

Anal. Calcd for $C_{14}H_{14}NOCl$: C, 67.88; H, 5.70; N, 5.65. Found: C, 67.45; H, 5.76; N, 5.38.

Photolysis of *N*-Chloroacetyl-2-(α-naphthyl)ethylamine (2). Synthesis of 2-Oxo-2,3,4,5-tetrahydro-1*H*-naphth[1,8-*de*]azocine (3).—A solution of 0.91 g of **2** in 350 ml of methanol and 350 ml of water was irradiated for 2.5 hr with a high-pressure mercury vapor lamp fitted with a Vycor filter. Tlc (0.25 mm silica gel, ether–methanol 9:1) at that point indicated complete conversion of the starting material. The volume of the mixture was reduced to about 250 ml at reduced pressure. The mixture was adjusted to pH 6 with sodium bicarbonate and taken to dryness *in vacuo*. Two additional photolyses were carried out in the same way. Each residue was extracted several times with hot ethanol and the extracts were combined, diluted with 2 vol of ether, and allowed to stand overnight at room temperature. The mixture was then filtered and concentrated *in vacuo*. The crystals which separated from the concentrated solution were collected and washed with cold methanol, 1.09 g (47%) of tan crystals, mp 272–276°. Treatment with charcoal and recrystallization from methanol afforded the analytical sample: mp 276–279°; ir (Nujol) 3180 (NH), 3062 and 1666 cm^{-1} (C=O in a large lactam); uv (methanol) 230 mμ (log ε 4.66), 288 (3.85), 317 (2.73), 322 (2.55); nmr (DMSO-d_6) δ 3.6 (center of a very broad signal, aliphatic protons), 7.17 (broad singlet, $-C(=O)NH-$), 7.28–7.56 (4 H, multiplet, naphthalene β protons), 7.70–7.94 (2 H, multiplet, naphthalene α protons) (Figure 1); mass spectrum, molecular ion *m/e* 211.

Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.52; H, 6.03; N, 6.80.

Reduction of 2-Oxo-2,3,4,5-tetrahydro-1*H*-naphth[1,8-*de*]azocine (3) with Diborane. A. Preparation of 2,3,4,5-Tetrahydro-1*H*-napth[1,8-*de*]azocine (4).—A solution of diborane (50 ml) in tetrahydrofuran (1 *M* BH_3, Alfa Inorganics, Inc.) was added to a solution of 1.055 g (0.005 mol) of **3** in 800 ml of dry tetrahydrofuran. The mixture was boiled under reflux under nitrogen for 5 hr and then treated with 50 ml of 6 *N* hydrochloric acid and boiled under nitrogen for 1.25 hr. The resulting mixture was concentrated *in vacuo* to 50 ml, alkalinized with sodium hydroxide, and extracted with ether. Ether was removed from the dried extract and the oil which remained was boiled under reflux under nitrogen for 3 hr with a mixture of 50 ml of ethanol, 2 g of potassium hydroxide, and 10 ml of water. The mixture was then concentrated *in vacuo* and extracted with ether. The extract was washed, dried, and concentrated *in vacuo*. The residue was a brown oil which was dissolved in ether and decolorized with charcoal. Removal of the ether yielded an oil which was redissolved in ether and treated with hydrogen chloride. The amine hydrochloride was 0.75 g of a white solid which was recrystallized from ethanol and from methanol–ether, mp 245–247°.

Anal. Calcd for $C_{14}H_{15}N \cdot HCl$: C, 71.95; H, 6.90; N, 5.99. Found: C, 72.13; H, 6.68; N, 6.17.

The amine **4** was prepared from the hydrochloride as needed and sublimed at 1 mm at bath temperatures of 50–68°. The sublimate was a white solid, mp 111–114°, which was the analytically pure amine: ir (KBr) 3435 cm^{-1} (NH); uv (hexane) 229 mμ (log ε 4.84), 288 (3.86), 318 (2.8), 323 (2.8); nmr ($CDCl_3$) δ 1.49 (about 1 H, broad singlet, removed on D_2O treatment, NH), 2.3–4.4 (8 H, broad overlapping bands, two $-CH_2CH_2-$ groups), 7.18–7.48 (4 H, octet, naphthalene β protons, AB part of an ABX system), 7.66–7.84 (2 H, quartet, naphthalene α protons, X part of an ABX system with the following constants:[5] δ_A 7.36, δ_B 7.24, δ_X 7.75; J_{AB} = 6.9, J_{AX} = 8.4, J_{BX} = 1.4 Hz) (Figure 1); mass spectrum, molecular ion *m/e* 197.

Anal. Calcd for $C_{14}H_{15}N$: C, 85.24; H, 7.66; N, 7.10. Found: C, 85.39; H, 7.50; N, 6.81.

(14) H. E. Zimmerman in "Advances in Photochemistry," Vol. 1, W. A. Noyes, Jr., G. S. Hammond, and J. N. Pitts, Jr., Ed., Interscience, New York, N. Y., 1963, p 183.

(15) S. Iwasaki and K. Schaffner, *Helv. Chim. Acta*, **51**, 557 (1968).

(16) G. Jackson and G. Porter, *Proc. Roy. Soc., Ser. A*, **260**, 13 (1961).

(17) E. L. Wehry and L. B. Rogers, *J. Amer. Chem. Soc.*, **87**, 4234 (1965).

(18) E. Havinga, R. O. deJongh, and W. Dorst, *Recl. Trav. Chim. Pays-Bas*, **75**, 378 (1956).

(19) H. E. Zimmerman and V. R. Sandel, *J. Amer. Chem. Soc.*, **85**, 915 (1963).

(20) N. C. Yang, L. C. Lin, A. Shani, and S. S. Yang, *J. Org. Chem.*, **34**, 1845 (1969).

(21) F. Mayer and A. Sieglitz, *Ber.*, **55**, 1847 (1922).

B. Preparation of *N*-Acetyl-2,3,4,5-tetrahydro-1*H*-naphth-[1,8-*de*]azocine (5).—In another reduction 0.51 g (0.0024 mol) of **3** in tetrahydrofuran was boiled under reflux under nitrogen for 5 hr with 35 ml of a solution of diborane in tetrahydrofuran (1 *M* BH_3, Ventron Corp.). Boiling the mixture under reflux with hydrochloric acid and the usual work-up yielded a crystalline product, 80% of which was dissolved in ether and acetylated with 1.11 g (0.014 mol) of acetyl chloride added in portions to the stirred solution with concurrent additions of 1 *N* sodium hydroxide. The usual isolation and recrystallization of the product from ether yielded **5** as white crystals: 0.25 g; mp 133–135°; ir (Nujol) 1630 cm^{-1} (amide C=O); uv (hexane) 228 mμ (log ε 4.78), 287 (3.87), 317 (2.7), 322 (2.65); nmr ($CDCl_3$) δ 1.30 [3 H, singlet, $CH_3C(=O)$, the Dreiding molecular model shows that the methyl group is held over by naphthalene moiety with the result that the methyl group is shielded by the diamagnetic ring current], 3.72 (8 H, center of broad overlapping signals, two $-CH_2CH_2-$ groups), 7.14–7.48 (4 H, multiplet, naphthalene β protons), 7.52–7.84 (2 H, multiplet, naphthalene α protons) (Figure 1); nmr [toluene-d_8, 40°, $(Me_3Si)_2$ internal reference] δ 3.1 and 3.8 (broad overlapping signals, aliphatic protons); nmr (toluene-d_8, 117°) δ 3.18 (4 H, triplet, two $-CH_2-$ groups), 3.54 (4 H, triplet, two $-CH_2-$ groups); mass spectrum, molecular ion *m/e* 239.

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.34; H, 7.27; N, 5.85.

Continuous Titration of Protons Generated during Photolyses of Compound 2.—In all cases 0.15×10^{-3} mol of the substrate was dissolved in 20 ml of methanol and that solution was diluted with 80 ml of water. The solution was placed in a semicircular two-neck quartz cell with an inner radius of 3.8 cm and a distance between inner cell walls of 0.7–1 cm. The electrode was introduced through one opening and the other was available for withdrawal of aliquots, etc. The cell was placed in a stainless steel cylinder with a polished inner surface with inner diameter of 15 cm and was supported by hooks on the wall of the cylinder. The water-cooled well containing the lamp and filter was also placed within the cylinder. The substrate solution was agitated by a vigorous stream of a gas which was introduced through two polyethylene tubes. A steel shield supported in grooves on the inner surface of the metal cylinder was positioned between the substrate cell and the immersion well. This shield could be removed rapidly after the lamp had been allowed a warm-up period of 3 min. In doing a series of phototitrations, a given arrangement of equipment could be reproduced precisely. During irradiation the protons produced were titrated with a Radiometer Titrator, type TTTlC, fitted with an Ole Dich No. 38 recorder and a Radiometer GK 2302C glass electrode which was immersed in the substrate solution. The titration curves obtained with this equipment indicate that relative rates of production of protons under various conditions. Reaction half-lives were taken from the curves (Figure 2). Each reaction was allowed to continue nearly to completion and then was taken to dryness *in vacuo*. Examination of the residues in methanol solution by uv spectroscopy and tlc afforded information on the character of the product mixtures. Tlc plates (0.25 mm, silica gel GF, Analtech, Inc.) were developed with ether–methanol (9:1, v/v) or benzene–methanol (3:1, v/v). Developing solvents were allowed to evaporate before visualization with a uv lamp or iodine vapor.

Registry No.—**2**, 25055-69-0; **3**, 25055-70-3; **4**, 26630-82-0; **4** HCl, 26595-66-4; **5**, 26595-67-5.

Acknowledgment.—The author wishes to thank Dr. E. D. Becker of the National Institute of Arthritis and Metabolic Diseases for assistance in the interpretation of nmr spectra and Mr. E. A. Sokoloski of the Laboratory of Chemistry of the National Heart Institute, who determined all of the nmr spectra, for his generous and skillful assistance.

Some Unusual Oxidation Reactions of 1,3-Diaryl-3,4-dihydro-7-methoxy-2(1*H*)-quinoxalinones

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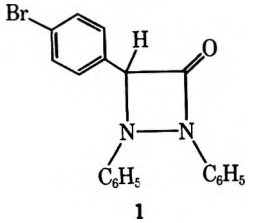
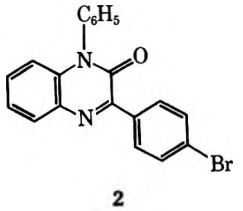
Received April 11, 1969

Acid-catalyzed air oxidation of 3-aryl-3,4-dihydro-7-methoxy-1-(*p*-methoxyphenyl)-2(1*H*)-quinoxalinones (**4**) proceeded rapidly to give the corresponding 3,4-dehydro compounds **5**. In contrast, a similar oxidation of the 4-methyl derivative **9** afforded anisic acid and 5-methoxy-3-(*p*-methoxyphenyl)-1-methyl-2(3*H*)-benzimidazolone (**10**). Photolytic oxidation of 3,4-dihydroquinoxalinones by 4,4′-dimethoxyazobenzene proceeded smoothly to give the quinoxalinones **5** and *p*-anisidine.

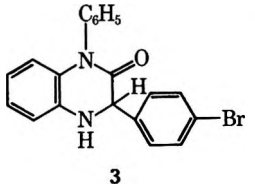
The acid-catalyzed ortho-semidine type of rearrangement of 4-aryl-1,2-diphenyldiazetidinones (*e.g.*, **1**) to 3-aryl-1-phenyl-2(1*H*)-quinoxalinones (**2**) was reported in 1967 by Fischer and Fahr.[2] Surprisingly, no notice appeared to be taken at that time of the unusual oxidation of the expected product, a 3,4-dihydro-2(1*H*)-quinoxalinone (**3**), to the compound which was actually isolated. We have investigated this reaction and found that, in the absence of air, none of the quinoxalinone **2** was formed, and that 3-aryl-3,4-dihydro-2(1*H*)-quinoxalinones readily undergo a novel acid-catalyzed air oxidation.



1



2



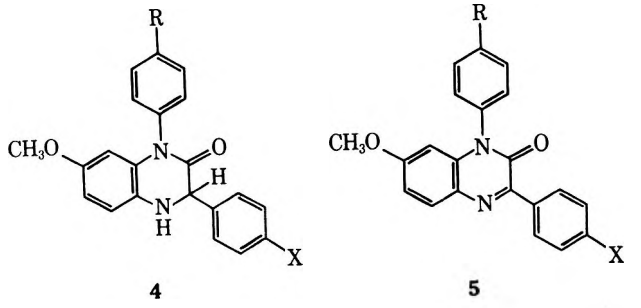
3

We have prepared a series of 7-methoxydihydroquinoxalinones (**4**) in good yield by catalytic reduction of the corresponding quinoxalinones **5**. These compounds were found to be stable to air in the presence of small amounts of base (*e.g.*, triethylamine or sodium bicarbonate), but in slightly acidic solutions were rapidly reoxidized to the quinoxalinones by air. The dihydro compounds were also stable to acid in the absence of air and were recovered unchanged under these conditions. The *N*-acetyl derivative of the dihydroquinoxalinone **6**

(1) To whom correspondence should be addressed: Mead Johnson Research Center, Evansville, Ind. 47721.

(2) W. Fischer and E. Fahr, *Angew. Chem., Int. Ed. Engl.*, **6**, 630 (1967).

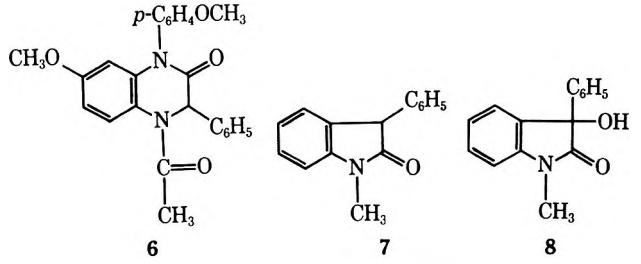
was stable to air in acidic solution, indicating the necessity for a protonated basic center at the 4 position for oxidation to occur.



4 5

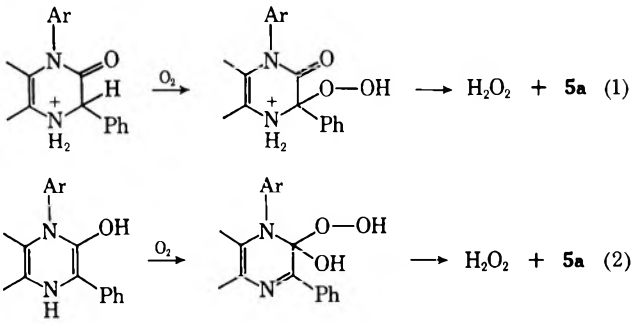
a, R = OCH_3; X = H
b, R = OCH_3; X = OCH_3
c, R = H; X = OCH_3

We have been unable to find any precedent in the literature for an acid-catalyzed air oxidation of this type. However, a structurally similar *base*-catalyzed air oxidation of oxindoles (**7** → **8**) has been reported,[3] in which a methine hydrogen flanked by two phenyls and a carboxamide group was readily converted to a hydroxyl group.

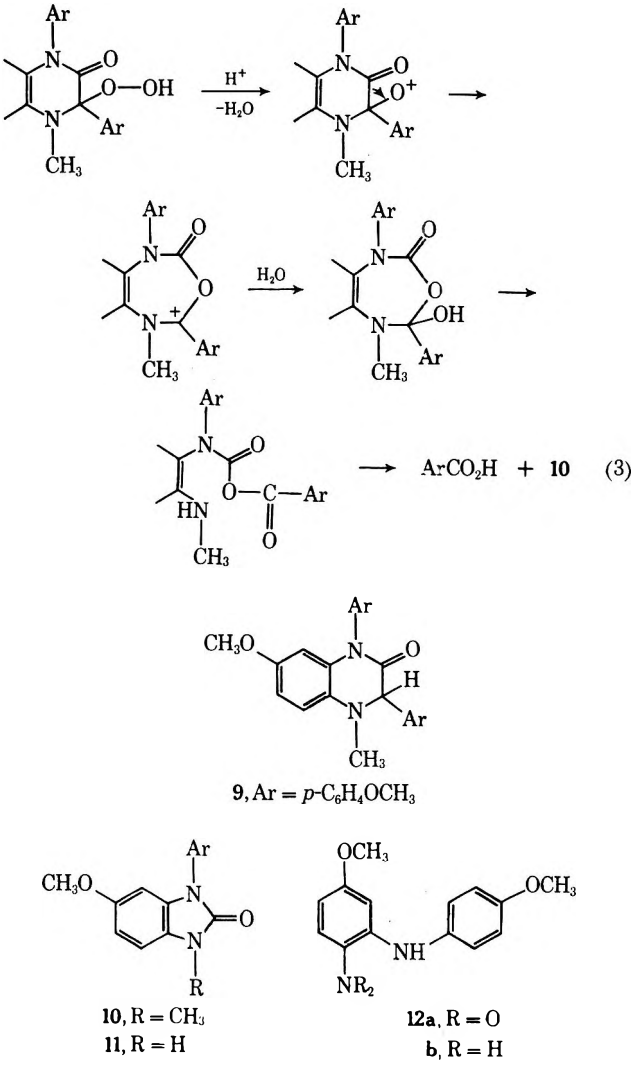


6 7 8

One possible process through which the oxidation of **4** to **5** could proceed involves a free-radical oxidation at the highly activated 3 position to give a hydroperoxide, followed by elimination of hydrogen peroxide (eq 1). Alternatively, an allylic enamine oxidation, similar to that in the formation of 3-hydroperoxyindolenines from indoles,[4] could be postulated (eq 2).



In order to distinguish between these possible mechanisms, the 4-methyl derivative **9** was prepared by alkylation of **4b** and subjected to treatment with air and acid. By blocking a possible elimination reaction, we hoped to be able to isolate the 3-hydroperoxy or 3-hydroxy derivative which would be formed if eq 1 were operative. However, the air oxidation of **9** gave instead anisic acid and 5-methoxy-3-(*p*-methoxyphenyl)-1-methyl-2(3*H*)-benzimidazolone (**10**) in good yield. The structure of **10** was proven by an independent unambiguous synthesis from *m*-fluorophenol. Nitration by known methods[5] gave the 4-nitrophenol, which was converted to the methyl ether. The fluorine atom was readily displaced by *p*-anisidine to give 3,4′-dimethoxy-6-nitrodiphenylamine (**12a**), which was easily reduced to the corresponding diamine **12b**. Ring closure with phosgene afforded 6-methoxy-1-(*p*-methoxyphenyl)-2(3*H*)-benzimidazolone (**11**), which was alkylated with methyl iodide to give the 1-methyl derivative, 5-methoxy-3-(*p*-methoxyphenyl)-1-methyl-2(3*H*)-benzimidazolone (**12**), identical in all respects with the air oxidation product of **9**.



9, Ar = *p*-$C_6H_4OCH_3$

10, R = CH_3
11, R = H

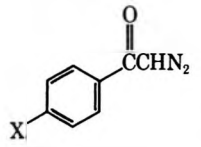
12a, R = O
b, R = H

The isolation of anisic acid from the oxidation of **9** indicates that oxygenation does indeed occur at C-3, eliminating the latter mechanism. The 3-hydroperoxy intermediate, now unable to undergo the simple elimination reaction with the 4 proton, instead undergoes a rearrangement (eq 3) similar to that of a Baeyer–Villiger reaction of an α-diketone to an anhydride.[6] Thus, a 3-hydroperoxy derivative of the 3,4-dihydro-2(1*H*)-quinoxalinones can serve as a common intermediate to explain the products formed from the oxidation reaction of both **4** and **9**.

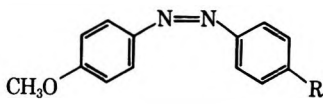
The starting quinoxalinones, **5a** and **5b**, were prepared by photolysis of the appropriate diazoacetophenone **13**

(3) P. Aeberli and W. J. Houlihan, *J. Org. Chem.*, **33**, 1640 (1968).
(4) B. Witkop, *J. Amer. Chem. Soc.*, **72**, 1428 (1950).
(5) H. H. Hodgson and J. Nixon, *J. Chem. Soc.*, 1879 (1928).
(6) C. H. Hasall, *Org. React.*, **9**, 73 (1957).

with 4,4′-dimethoxyazobenzene (**14a**). The structure of the photoproducts **5** was proven by an unambiguous synthesis from the diamine **12b**. This was condensed[7] with benzoylformic acid to give 7-methoxy-1-(*p*-methoxyphenyl)-3-phenyl-2(1*H*)-quinoxalinone (**5a**), which was identical in all respects with the photoproduct **5a**. The use of 4-methoxyazobenzene (**14b**)[8] in place of **14a** afforded the corresponding 7-methoxy-1-phenylquinoxalinone (**5c**), rather than the 7-unsubstituted 1-(*p*-methoxyphenyl) isomer, as shown by both the ultraviolet and nmr spectra of the product.

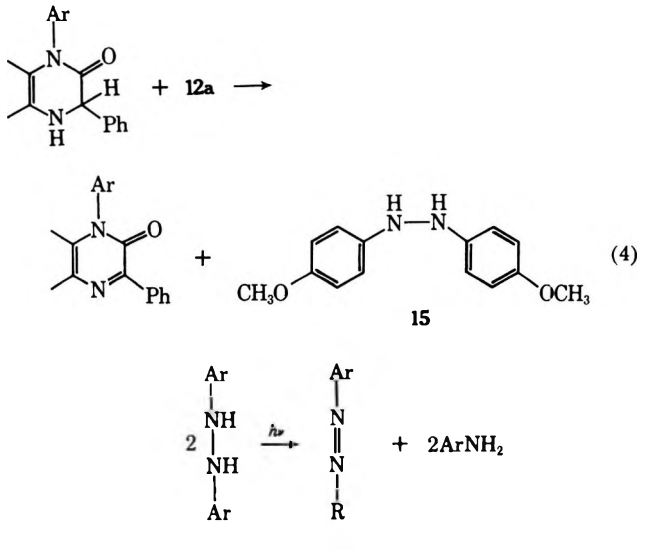


13a, X = H
b, X = OCH_3



14a, R = OCH_3
b, R = H

The photosynthesis of **5** from **13** and **14** probably proceeds through an initially formed diazetidinone,[9] which, presumably catalyzed by a trace of HCl present in the dichloromethane, undergoes an ortho-semidine rearrangement such as that reported by Fischer and Fahr,[2] to a 3,4-dihydro-2(1*H*)-quinoxalinone (**4**), which is then dehydrogenated to the quinoxalinone product **5**. This oxidation must, however, occur by a quite different process, for the reaction was run under an inert atmosphere of helium. That this dehydrogenation had indeed occurred during the photolysis and not by air oxidation during the work-up procedure was shown by the presence of **5** by tlc in the reaction mixture immediately after photolysis, and by direct crystallization, under an atmosphere of nitrogen, of **5a** in 8% yield from this mixture. The agent responsible for this dehydrogenation was shown to be 4,4′-dimethoxyazobenzene (**14a**). Irradiation of **4a** with 0.5 equiv of **14a** in the absence of air rapidly produced *p*-anisidine and the quinoxalinone **5a** in good yield. Although it is not possible to rule out a direct reduction of **14a** to *p*-anisidine by **4a**, a more likely process would involve a dehydrogenation of **4a** to give 4,4′-dimethoxyhydrazobenzene (**15**).[10] We have shown that **15** rapidly disproportionates to *p*-anisidine and dimethoxyazobenzene under photolytic conditions, so that the overall stoichiometry of the reaction involves 2 equiv of dihydroquinoxalinone and 1 equiv of dimethoxyazobenzene reacting to give quinoxalinone and 2 equiv of *p*-anisidine (eq 4).



(4)

Experimental Section[11]

7-Methoxy-1-(*p*-methoxyphenyl)-3-phenyl-2(1*H*)-quinoxalinone (5a).—A solution of 6.05 g (0.025 mol) of 4,4′-dimethoxyazobenzene (**14a**)[12] and 3.65 g (0.025 mol) of diazoacetophenone (**13a**)[13] in 900 ml of dichloromethane was irradiated for 6 hr with a Hanovia 450-W lamp (Model 679A), using a Vycor filter, while a slow stream of helium was bubbled through the solution. At the end of this time, the solution was concentrated to dryness under reduced pressure. The dark residue was combined with that from another similar run and chromatographed on Florisil. The first fraction eluted with benzene was shown by vpc to contain mostly *N*-benzylidine-*p*-methoxyaniline, contaminated with smaller amounts of benzaldehyde, phenacyl chloride, and unreacted 4,4′-dimethoxyazobenzene. Further elution with 10% ether in benzene afforded the product, which was recrystallized from acetonitrile to give 2.71 g (15%) of **5a**: mp 208.5–209.5°; ir (KBr) 1652 cm^{-1} (C=O); nmr 8.4 (m, 2, *o*-H's of 3-Ph), 7.84 (d, 1, J = 9 Hz, 5 H), 7.40 (m, 3, *m*- and *p*-H's of 3-Ph), 7.16 (d, 4, J = 3 Hz, 1-C_6H_4OMe), 6.87 (dd, 1, J = 3, 9 Hz, 6 H), 6.13 (d, 1, J = 3 Hz, 8 H), 3.83 (s, 3, 4′-OMe), and 3.68 (s, 3, 7-OMe); uv max 368 mμ (ε 20,800), 271 (11,000), and 221 (43,300).

Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.69; H, 5.16; N, 7.90.

7-Methoxy-1,3-bis(*p*-methoxyphenyl)-2(1*H*)-quinoxalinone (5b).—A similar photolysis of 4-methoxydiazoacetophenone (**14b**) with **13a** afforded **5b** in 13% yield: mp 204–205° (MeOH); uv max 375 mμ (ε 25,100), 273 (11,200), and 224 (43,400).

Anal. Calcd for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.09; H, 5.19; N, 7.13.

7-Methoxy-3-(*p*-methoxyphenyl)-1-phenyl-2(1*H*)-quinoxalinone (5c).—A similar photolysis of diazoacetophenone (**14a**) with 4-methoxyazobenzene (**13b**)[8] afforded **5c** in 14% yield: mp 215–217° (MeOH); uv max 373 mμ (ε 25,700), 273 (9700), and 223 (42,200).

Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.67; H, 4.95; N, 7.94.

3,4-Dihydro-7-methoxy-1-(*p*-methoxyphenyl)-3-phenyl-2(1*H*)-quinoxalinone (4a).—A solution of 1.00 g of 7-methoxy-1-(*p*-methoxyphenyl)-3-phenyl-2(1*H*)-quinoxalinone (**5a**) in 40 ml of tetrahydrofuran and 40 ml of ethanol was added to a prereduced suspension of 1.0 g of 10% platinum on carbon in 20 ml of tetrahydrofuran and 20 ml of ethanol and hydrogenated at atmospheric pressure and room temperature. Hydrogen uptake ceased when 1 equiv of hydrogen had been absorbed (*ca.* 5 min). The solution was filtered and concentrated to dryness under reduced pressure. The residue was crystallized from ether affording 0.82 g (82%) of product: mp 153–155°; ir ($CHCl_3$) 1687 (C=O), 3400 cm^{-1} (NH); uv max 322 mμ (ε 4200), 223 (40,300); nmr 3.55 (s, 3, OMe), 3.78 (s, 3, OMe), 4.00 (s, 1, NH), 5.03 (s, 1, 3 H), 5.97 (d, 1, J = 3 Hz, 8 H), 6.32–6.87 (m, 2, 5 H and 6 H), 7.04 (d, 4, J = 3 Hz, 1-$C_6H_4OCH_3$), 7.33 (m, 5, C_6H_5). A small amount of acid was added to the ultraviolet solution which was left exposed to the air. A peak at 368 mμ began to appear, ε 4570 (1 min), 8100 (5 min), 18,600 (16 hr).

(7) A. H. Cook and C. A. Perry, *J. Chem. Soc.*, 394 (1943).

(8) J. Burns, H. McCombie, and H. A. Scarborough, *ibid.*, 2982 (1928).

(9) It has previously been shown that photolysis of equimolar mixtures of substituted diazoacetophenones and azobenzene in dichloromethane solution afforded 4-aryl-1,2-diphenyl-1,2-diazetidinones, such as **1**: W. Fischer and E. Fahr, *Tetrahedron Lett.*, 5245 (1966). Similarly, photolysis of preformed diphenylketene and 4,4′-dimethoxyazobenzene in benzene or ether solution has been shown to give the corresponding 1,2-bis(*p*-methoxyphenyl)-4,4-diphenyl-1,2-diazetidin-3-one: J. H. Hall and R. Kellogg, *J. Org. Chem.*, **31**, 1079 (1966).

(10) Other photochemical dehydrogenations with an azo compound have been reported: G. O. Schwenck and H. Formaneck, *Angew. Chem.*, **70**, 505 (1958); R. C. Cookson, I. D. R. Stevens, and C. T. Watt, *Chem. Commun.*, 259 (1965).

(11) Melting points were determined on a Fisher–Johns block and are corrected. The ultraviolet spectra were run in methanol. The nmr spectra were obtained on a Varian A-60 instrument; the spectra were determined in deuteriochloroform solutions, and the shifts are expressed as parts per million downfield from Me_4Si used as an internal standard. The infrared spectra were determined on a Beckman IR-9 instrument. All compounds had infrared and nmr spectra which agreed with the assigned structures.

(12) Prepared by lithium aluminum hydride reduction of 4,4′-dimethoxyazoxybenzene (Aldrich Chemical Co.): T. Rotarski, *Ber.*, **36**, 3158 (1903); R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, **70**, 3738 (1948).

(13) A. Burger and S. Avakian, *J. Org. Chem.*, **5**, 606 (1940).

Anal. Calcd for $C_{22}H_{20}N_2O_3$: C, 73.31; H, 5.59; N, 7.77. Found: C, 73.15; H, 5.34; N, 7.60.

3,4-Dihydro-7-methoxy-1,3-bis(*p*-methoxyphenyl)-2(1*H*)-quinoxalinone (4b).—A similar hydrogenation of **5b** afforded **4b** in 80% yield: mp 145–147° (ether); uv max 322 mμ (ε 4220), 225 (45,600), shifting to 375 mμ (ε 22,000) 16 hr after acidification.

Anal. Calcd for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.18. Found: C, 70.98; H, 5.70; N, 7.14.

3,4-Dihydro-7-methoxy-3-(*p*-methoxyphenyl)-1-phenyl-2(1*H*)-quinoxalinone (4c).—A similar reduction of **5c** afforded **4c** in 80% yield: mp 133–135° (ether); uv max 322 mμ (ε 4180), 224 (38,900), changing to 374 mμ (ε 22,900) 18 hr after acidification.

Anal. Calcd for $C_{22}H_{20}N_2O_3$: C, 73.31; H, 5.59; N, 7.77. Found: C, 73.41; H, 5.79; N, 7.76.

4-Acetyl-3,4-dihydro-7-methoxy-1-(*p*-methoxyphenyl)-3-phenyl-2(1*H*)-quinoxalinone (6).—The crude oily **4a** prepared by reduction of 1.00 g of **5a** was dissolved in 100 ml of ether and treated with 3 ml of triethylamine and 1 ml of acetic anhydride. The solution was left at room temperature overnight and then washed with sodium carbonate solution and with water. The dried solution was concentrated to give an oil which was chromatographed on Florisil. Elution with 10% ether in benzene gave an early fraction containing 0.05 g of **5a**. Further elution with 50% ether in benzene afforded the product, which was recrystallized from ether to give 0.73 g (65%) of **6**: mp 120–122°; ir (KBr) 1693 (2 C=O) and 1672 (NAc) cm^{-1}; uv max 229 mμ (ε 37,800), no change with acid; nmr 2.37 (s, 3, NAc), 3.58 (s, 3, OMe), 3.82 (s, 3, OMe), 6.02 (d, 1, J = 2.5 Hz, 8 H), 6.48–6.93 (m, 2, 5 H and 6 H), 7.11 (d, 4, J = 3.5 Hz, $C_6H_4OCH_3$), and 7.29 (s, 6, C_6H_5 and 3 H).

Anal. Calcd for $C_{24}H_{22}N_2O_4$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.85; H, 5.67; N, 7.04.

Air Oxidation of 3,4-Dihydro-7-methoxy-1-(*p*-methoxyphenyl)-3-phenyl-2(1*H*)-quinoxalinone.—A solution of 4.20 g of **4a** in 750 ml of methanol was treated with 1 ml of 12 *N* hydrochloric acid, and air was bubbled through the solution for 2 hr. The precipitate which had formed was filtered, affording 2.34 g (56%) of 7-methoxy-1-(*p*-methoxyphenyl)-3-phenyl-2-(1*H*)-quinoxalinone (**5a**), mp 208–209°, uv max 368 mμ (ε 20,800). The mother liquors were concentrated to about 250 ml and air was bubbled through for another 2 hr. Filtration yielded 1.60 g (38%) of **5a**, mp 207–209°, uv max 368 mμ (ε 20,400). Similarly a third crop of **5a** was obtained, 0.15 g (3.6%), mp 205–208°, uv max 368 mμ (ε 19,800).

A similar oxidation of 50 mg of **4a** in 10 ml of benzene and 0.4 ml of acetic acid for 3 hr afforded 30 mg (60%) of **5a**, mp 206–207°, uv max 369 mμ (ε 19,900).

3,4-Dihydro-7-methoxy-1,3-bis(*p*-methoxyphenyl)-4-methyl-2(1*H*)-quinoxalinone (9).—A solution of 3.12 g of 3,4-dihydro-7-methoxy-1,3-bis(*p*-methoxyphenyl)-2(1*H*)-quinoxalinone (**4b**) in 75 ml of acetonitrile was treated with 1.5 g of potassium carbonate and 6 ml of methyl iodide. The mixture was stirred and refluxed under an atmosphere of nitrogen for 24 hr. The mixture was then filtered, and the filtrate was concentrated to dryness under reduced pressure. The residue was dissolved in dichloromethane and water, and the organic layer was separated, dried, and concentrated to dryness under reduced pressure. The residue was crystallized from methanol containing a little triethylamine, affording 2.61 g (81%) of product, mp 154–157°. Concentration of the mother liquors yielded a second crop, 0.22 g (7%), mp 153–156°. Recrystallization from methanol (plus Et_3N) afforded analytically pure material: mp 156–158°; ir (KBr) 1688 cm^{-1} (C=O); nmr 2.83 (s, 3, NMe), 3.63 (s, 3, OMe), 3.73 (s, 3, OMe), 3.80 (s, 3, OMe), 4.95 (s, 1, 3 H), 6.05 (dd, 1, J = 1, 2 Hz, 8 H), 6.56–7.24 [m, 10, 5 H, 6 H, $(C_6H_4OCH_3)_2$]; uv max 328 mμ (ε 4040), 226 (42,000). A peak at 426 mμ developed after acidification in the presence of air which rose to ε 22,100 after 18 hr. However, the original spectrum was obtained again immediately after the acidic solution was basified with potassium hydroxide. (Attempts to isolate the 426 mμ product gave a red oil which could not be crystallized or characterized.)

Anal. Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.37; H, 5.94; N, 7.01.

Air Oxidation of 3,4-Dihydro-7-methoxy-1,3-bis(*p*-methoxyphenyl)-4-methyl-2(1*H*)-quinoxalinone.—A solution of 0.69 g of 9 in 70 ml of benzene was treated with 3.5 ml of acetic acid, and air was bubbled through the solution for 4 hr. The solution was washed with a small amount of sodium bicarbonate solution and with water. The dried solution was concentrated to dryness, and the residue was recrystallized from methanol, affording 0.40 g (82%) of 5-methoxy-3-(*p*-methoxyphenyl)-1-methyl-2(3*H*)-benzimidazolone (**10**), mp 152–155°. A sample was recrystallized from methanol for analysis: mp 155.5–156°; ir (KBr) 1708 cm^{-1} (C=O); uv max 290 mμ (ε 8450); nmr 3.43 (s, 3, NMe), 3.74 (s, 3, OMe), 3.86 (s, 3, OMe), 6.5–7.5 (m, 7, aromatic H's).

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.31; H, 5.64; N, 9.77.

The sodium bicarbonate solution was washed with benzene, acidified with dilute hydrochloric acid, saturated with sodium chloride, and extracted with dichloromethane. The extract was dried and concentrated, and the residue was recrystallized from aqueous ethanol, affording 0.12 g (48%) of anisic acid, mp 182–183° (lit.[14] mp 185°). A mixture melting point with known anisic acid (mp 182–183°) showed no depression.

3-Fluoro-4-nitroanisole.—A solution of 42.1 g of 3-fluoro-4-nitrophenol, prepared by nitration of *m*-fluorophenol,[5,15] in 840 ml of acetonitrile was treated with 37.1 g of potassium carbonate and 126 ml of methyl iodide. The mixture was stirred and refluxed for 3 hr and then concentrated to dryness under reduced pressure. The residue was dissolved in ether and water, and the ether layer was washed with water, dried, and concentrated. The residue was crystallized from methanol to give 39.8 g (87%) of product, mp 55–57° (lit.[5] mp 56.5°).

3,4′-Dimethoxy-6-nitrodiphenylamine (12a).—A solution of 10.0 g of 3-fluoro-4-nitroanisole in 100 ml of dimethyl sulfoxide was treated with 15.0 g of *p*-anisidine and heated at 60–65° under an atmosphere of nitrogen for 24 hr. The solution was cooled and poured into 3 l. of dilute (2%) hydrochloric acid. The precipitate was collected, washed with water, dried, and recrystallized from 95% ethanol, affording 15.30 g (96%) of product, mp 103.5–104.5° (lit.[16] mp 106–106.5°).

6-Methoxy-1-(*p*-methoxyphenyl)-2(3*H*)-benzimidazolone (11).—A solution of 1.00 g of 3,4′-dimethoxy-6-nitrodiphenylamine (**12a**) in 40 ml of tetrahydrofuran and 40 ml of ethanol was added to a prereduced suspension of 10% platinum on carbon in 20 ml of tetrahydrofuran and 20 ml of ethanol and hydrogenated at atmospheric pressure and room temperature. Hydrogen uptake ceased after 3 equiv had been absorbed (*ca.* 15 min). The solution of 2-amino-4′,5-dimethoxydiphenylamine (**12b**)[16] was filtered and evaporated to dryness under reduced pressure. The residue was dissolved in 10 ml of methanol and 50 ml of 1.2 *N* hydrochloric acid, and phosgene was bubbled into the solution for 1 hr.

The mixture was cooled and the precipitate was collected by filtration, washed with water, and dried, affording 0.42 g (43%) of **11**: mp 249–251° (lit.[17] mp 245–246°); ir (KBr) 1700 cm^{-1} (C=O); uv max 297 mμ (ε 8200).

The mother liquors were cooled in ice and again treated with phosgene for 1 hr. The new precipitate was collected, washed, and dried, yielding an additional 0.43 g (44%) of **11**, mp 249–251°.

5-Methoxy-3-(*p*-methoxyphenyl)-1-methyl-2(3*H*)-benzimidazolone (10).—A suspension of 0.83 g of 6-methoxy-1-(*p*-methoxyphenyl)benzimidazolone (**11**) in 30 ml of dimethyl sulfoxide was treated with 0.25 g of a 55% dispersion of sodium hydride in mineral oil and then with 1 ml of methyl iodide. The mixture was stirred overnight at room temperature and then poured into water. The precipitate was collected by filtration, washed with a little petroleum ether to remove the mineral oil, and recrystallized from methanol, affording 0.59 g (68%) of **10**, mp 154–155°. A mixture melting point with the product of air oxidation of **9** melted at 154–155°, and the infrared spectra of the two compounds were identical.

Concentration of the mother liquors afforded a second crop of **10**, 0.08 g (9%), mp 152.5–154°. The overall yield of **10** from **12a** was 67%.

7-Methoxy-1-(*p*-methoxyphenyl)-3-phenyl-2(1*H*)-quinoxalinone (5a).—A solution of 2-amino-4′,5-dimethoxydiphenylamine (**12b**), prepared as before by catalytic reduction of 1.0 g of **12a**, was treated with 0.62 g of phenylglyoxylic acid and left at room tem-

(14) E. E. Harris and G. B. Frankforter, *J. Amer. Chem. Soc.*, **48**, 3144 (1926).

(15) T. L. Fletcher, M. J. Namkung, W. H. Wetzel, and H.-L. Pan, *J. Org. Chem.*, **25**, 1342 (1960).

(16) A. P. Kottenkahn, E. T. Seo, and H. W. Stone, *ibid.*, **28**, 3114 (1963).

(17) L. Rosnati, *Gazz. Chim. Ital.*, **86**, 275 (1950).

perature for 3 hr. The solution was concentrated to dryness under reduced pressure, and the residue was crystallized by trituration with ethanol to give 0.85 g of fairly pure product. This was recrystallized from acetonitrile, affording 0.75 g (58%) of **5a**, mp 206–207°. A mixture melting point with the photochemical product **5a** was 207–208°.

Photochemical Oxidation of 3,4-Dihydro-7-methoxy-1-(*p*-methoxyphenyl)-3-phenyl-2(1*H*)-quinoxalinone.—A solution of 0.79 g (2.20 mmol) of **4a** and 0.26 g (1.07 mmol) of 4,4′-dimethoxyazobenzene (**14a**) in 250 ml of deoxygenated dichloromethane was irradiated for 4 hr at 300 mμ in a quartz vessel in a Rayonet photochemical reactor Model RPR-100 while a stream of helium was passed through the solution. At the end of this time, tlc indicated the presence of **5a** and no **14a** or **4a**. The solution was treated with 2 ml of triethylamine and concentrated to dryness under reduced pressure. The residue was recrystallized from methanol (containing a little triethylamine), affording 0.58 g (74%) of **5a**, mp 203–206°, uv max 368 mμ (ε 19,800). The mother liquors contained *p*-anisidine as shown by vpc.

4,4′-Dimethoxyhydrazobenzene (18).—A solution of 2.42 g of 4,4′-dimethoxyazobenzene (**14a**) in 50 ml of tetrahydrofuran and 50 ml of ether was treated with 0.35 g of lithium aluminum hydride and then with an ether solution of 0.10 g of ferric chloride.[18] The mixture was stirred at room temperature for 2 hr, and then treated successively with 0.35 ml of water, 0.35 ml of 15% sodium hydroxide solution, and 1.05 ml of water. The mixture was filtered, and the filtrate was concentrated to dryness at room temperature under reduced pressure. The residue contained about 15% of the azo compound **14a** (by uv), but could not be purified further. Mild heating, such as attempted recrystallization from ether, effected disproportionation to **14a** and *p*-anisidine: ir (KBr) 3355, 3340 (NH); uv max 353 mμ (ε 4830) and 311 (5650).

(18) G. A. Olah, *J. Amer. Chem. Soc.*, **81**, 3165 (1959).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.94; H, 6.56; N, 11.66.

Photochemical Disproportionation of 4,4′-Dimethoxyhydrazobenzene.—A solution of 0.40 g of the above crude 4,4′-dimethoxyhydrazobenzene in 40 ml of dichloromethane was irradiated for 30 min at 300 mμ in a Rayonet photochemical reactor. The solution turned dark, and the ultraviolet spectrum showed an intense peak at 354 mμ due to the azobenzene. (A control solution of **15** in dichloromethane in the dark showed little change in its ultraviolet spectrum after 1 hr at 25°.) The solution was concentrated to dryness under reduced pressure. The residue was extracted with ether and water, leaving a large amount of black insoluble material. The ether layer, concentrated under reduced pressure, afforded 0.14 g of 4,4′-dimethoxyazobenzene, mp 163–164°. Concentration of the aqueous solution gave a residue which was recrystallized from acetonitrile, affording 0.04 g of *p*-anisidine hydrochloride, mp 208–212°, having an infrared spectrum identical with that of an authentic sample.

Registry No.—**4a**, 26596-02-1; **4b**, 26596-03-2; **4c**, 26596-04-3; **5a**, 26596-05-4; **5b**, 26596-06-5; **5c**, 26596-07-6; **7**, 26596-08-7; **9**, 26596-09-8; **10**, 26596-10-1; **11**, 19950-86-8; **18**, 1027-40-3.

Acknowledgment.—The authors wish to express their deep appreciation to Mr. Ernest Schoeb, Mrs. Gloria Cook, and Mrs. Carola Spurlock for their efforts in obtaining the many spectra needed in this work. We also wish to thank Mr. Charles Childs and the staff of our Microanalytical Laboratory and Mr. William Pearlman of our High-Pressure Laboratory for their valuable technical assistance.

The Singlet Oxygen Oxidation of *N*-Phenylpyrroles. Its Application to the Synthesis of a Model Mitomycin

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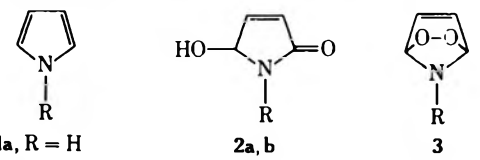
Received June 23, 1970

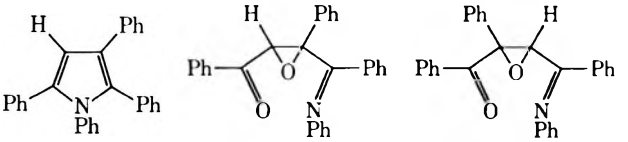
The photooxygenation of *N*-phenylpyrroles to produce pyrrolinones is described. The conversion of pyrrolinone **14** to a tetracyclic framework **22** related to the aziridine-containing mitomycin antibiotics is elucidated. A tabulation of nmr data for protons on the ring fusion of bicyclic fused aziridines is presented.

The photooxygenation of heterocycles is an area in which a steady level of interest has been maintained through the years.[2] The precedent for our research in pyrrole oxidations was based on the report of De Mayo and Reid,[3] on the photooxidation of pyrrole **1a** and *N*-methylpyrrole **1b** to form the hydroxylactams **2a** and **2b**. A possible mechanism for the reaction invokes the Diels–Alder reaction of singlet oxygen with pyrrole to form the *endo*-peroxide **3**. Prototropic rearrangement including O–O bond fission affords **2**. Other oxidations of pyrroles that appear to be reactions with singlet oxygen have been reported.[4,5] In the case of highly substituted pyrroles such as **4**, Wasserman and Miller have isolated photooxidation products **5** and **6** whose formation can be rationalized by postulating rearrangements of an initially formed *endo*-peroxide.



1a, R = H
b, R = CH_3

2a, b **3**



4 **5** **6**

Our research on the singlet oxygen oxidation of *N*-phenylpyrrole (**7**) began because we saw a similarity between the predicted oxidation product **8** and certain features of the mitomycin antibiotics **9**.[6] The double bond

(1) (a) Abstracted from the Ph.D. Thesis of J. A., Fordham University, 1970. (b) Supported in part by grants from the National Cancer Institute, CA 11421, and the National Institute of General Medical Sciences, GM 12758. (c) Preliminary reports of portions of this work have appeared: J. Auerbach and R. W. Franck, *Chem. Commun.*, 991 (1969); J. Auerbach and R. W. Franck, Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, ORGN 148. (d) To whom correspondence should be addressed.

(2) S. T. Reid, *Advan. Heterocycl. Chem.*, **11**, 116 (1970).

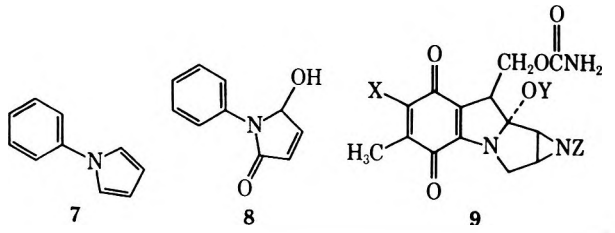
(3) P. De Mayo and S. T. Reid, *Chem. Ind. (London)*, 1576 (1962).

(4) A. R. Katritzky and E. Hoft, *Tetrahedron Lett.*, 2028 (1968).

(5) H. H. Wasserman and A. H. Miller, *Chem. Commun.*, 199 (1969).

(6) (a) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmore, C. Pidacks, and J. E. Lancaster, *J. Amer. Chem. Soc.*, **84**, 3187 (1962); (b) J. B. Patrick, R. P. Williams, W. E. Meyer, W. Fulmor, D. B. Cosulich, R. W. Broschard, and J. S. Webb, *ibid.*, **86**, 1889 (1964).

in **8** was visualized as the aziridine precursor, with the Scheiner aziridine synthesis as the eventual functionalization method.[7] This route requires the cycloaddition of an azide to a double bond to form a triazoline which is converted to an aziridine by subsequent extrusion of nitrogen.

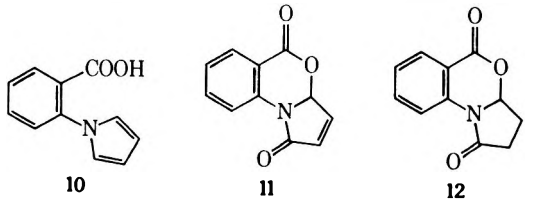


7 **8** **9**

	X	Y	Z
mitomycin A	CH_3O	CH_3	H
mitomycin B	CH_3O	H	CH_3
mitomycin C	NH_2	CH_3	H
porfiromycin	NH_2	CH_3	CH_3

Results and Discussion

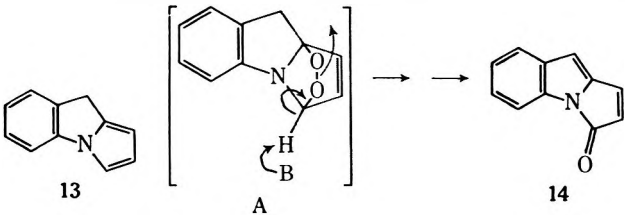
The oxygenation of **7** was performed using several methods of singlet oxygen generation.[8] In every case, low yields of lactam **8** were obtained. The structural assignment was derived from its ir [($CHCl_3$) 3551 (OH), 1705 cm^{-1} (C=O)], nmr [(DMSO) δ 6.05 (m, 1, C-5), 6.23 (d with fine structure, 1, J_{3-4} = 5.5 Hz, C-3), 7.00–7.78 (m, 7, C-4, aromatics, OH)], elemental analysis, and its oxidation with manganese dioxide to form *N*-phenylmaleimide. The yield in this singlet oxygen oxidation route does not compare favorably with a synthesis of 5-hydroxy-Δ^3-pyrrolin-2-ones involving Grignard addition to maleimides.[9] However, the Grignard method cannot be used to prepare the 5-unsubstituted derivatives as in our oxidation. Upon treatment with singlet oxygen, *N*-(2-carboxyphenyl)pyrrole **10** afforded the lactam–lactone **11**, regardless of whether the reaction was performed with the free acid or its sodium salt. The structural assignment was straightforward with the exception that its ir exhibited a single carbonyl peak in several solutions and in KBr pellets. Therefore, hydrogenation of **11** to **12** was undertaken. The ir spectrum



10 **11** **12**

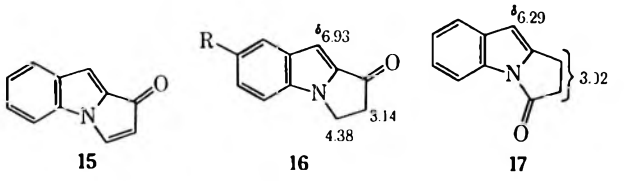
of the resulting dihydro derivative **12** contained two carbonyl bands (1730 and 1710 cm^{-1}).

When the heterocycle **13** was treated with singlet oxygen under a variety of conditions,[10] rapid oxygenation took place and the indole–lactam **14** was isolated. Although the various oxidations seemed "clean," work-up always led to tarry residues and the eventual yield of **14** was low. Our hypothesis was that adduct A was forming, but that an efficient base-catalyzed opening of the *endo*-peroxide was not occurring. Thus, triethylamine



13 **A** **14**

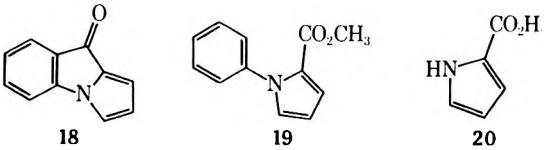
was added to the normal solvent for a photooxidation experiment and it was discovered that no photooxidation took place. Ouannès and Wilson have observed this effect with tertiary amines. They have developed their experiments in an elegant way and demonstrated that tertiary amines quench singlet oxygen.[11] However, added pyridine in aqueous solvents does not act as a quencher, but does serve to improve the yield of **14**, with 70% isolation being routine. The structural assignment for **14** was derived as follows: ir ($CHCl_3$) 1718 cm^{-1} (C=O); uv (ethanol) λ_{max} 208 nm (ϵ 30,000) end absorption, 266 (11,000), 273 (10,000), 355 (11,000); nmr ($CDCl_3$) δ 5.93 (d, 1, J_{1-2} = 5.5 Hz, C-2), 6.31 (s, 1, C-9), 6.90–7.45 (m, 4, H–C_1, H–$C_{6,7,8}$), 7.69 (m, 1, C-5). The formation of an isomeric compound **15** was considered since there is a record of unusual rearrangements in the pyrrolo[1,2-a]indole series.[12]



15 **16** **17**

Thus, hydrogenation of **14** was performed to afford **17**. The reported melting point, ir, and uv for **16** (R = H)[13] which would have been the dihydro product from **15**, differ from that of our hydrogenation product **17**. Also, comparison of nmr data obtained for lactam **17** with the published data for **16** (R = benzyloxy) revealed significant differences in the methylene and indolic hydrogen resonances.[12b] Thus, the prediction of structure **14**, based on mechanistic considerations, was shown to be on firm ground.

The use of pyridine as a cosolvent for photooxidation did not improve the yields of pyrrolinone products from pyrroles **7**. Our oxidation experiments were extended to the deactivated pyrroles **18**, **19**, and **20**, none of which



18 **19** **20**

consumed oxygen. The main conclusion we draw from our work to date is that nondeactivated *N*-phenylpyrroles react rapidly with singlet oxygen. The control of the subsequent decomposition of the presumed *endo*-peroxide intermediate is not yet fully understood and

(7) (a) P. Scheiner, *J. Org. Chem.*, **30**, 7 (1965); (b) P. Scheiner, *Tetrahedron*, **24**, 2757 (1968).

(8) (a) C. S. Foote, S. Wexler, W. Ando, and R. Higgins, *J. Amer. Chem. Soc.*, **90**, 975 (1968); (b) D. R. Kearns, P. Radlick, P. Hollins, and R. Chambers, *ibid.*, **89**, 5456 (1967); (c) H. H. Wasserman and S. R. Scheffer, *ibid.*, **89**, 3073 (1967).

(9) A. Queen and A. Reipas, *J. Chem. Soc. C*, 2459 (1967).

(10) V. J. Mazzola, K. Bernady, and R. W. Franck, *J. Org. Chem.*, **32**, 486 (1967).

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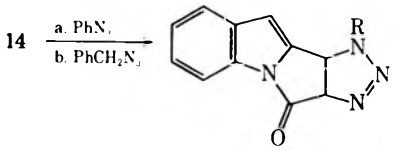
(12) (a) W. A. Remers, *ibid.*, **86**, 4608 (1964); (b) G. R. Allen and M. J. Weiss, *J. Org. Chem.*, **30**, 2904 (1965); (c) E. E. Schweizer and K. K. Light, *ibid.*, **31**, 870, 2912 (1966).

(13) W. A. Remers and M. J. Weiss, *J. Med. Chem.*, **8**, 700 (1965).

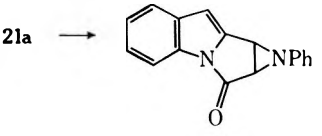
remains the crucial factor in obtaining useful yields of a single product.

The lactam **14**, now readily available, has a double bond in a location appropriate for the fusion of an aziridine ring. Thus, cycloadditions to **14** with benzyl and phenyl azides were attempted, as the first step in the Scheiner aziridine synthesis.[7] Triazolines **21a** and **21b** were formed in good yield. It is not certain that the direction of addition is as depicted, but the assign-



21a, R = Ph
b, R = CH_2Ph

ments are based on the precedents in Huisgen's work on dipolar additions of azides to dipolarophilic double bonds conjugated with carbonyls.[14] Also, the different nmr shifts for the indolic protons in **21a** and **21b** suggest differing shielding effects of the R groups in proximity to the indole proton, rather than the effects of identical N=N linkages. The photochemical elimination of nitrogen was the step remaining for the attainment of a model mitomycin. The phenyltriazoline **21a**, with significant uv absorption above 300 nm, could be photolyzed with a sun lamp and a plate glass filter which effectively excluded light with wavelengths shorter than 310 nm. Nitrogen elimination proceeded smoothly and rapidly to afford aziridine **22** in essentially quantitative yield. Continued irradiation of the photolysate beyond the time required for complete nitrogen evolution resulted in destruction of **22**. The triazoline **21b** had no significant absorption above 300 nm. Thus, the photoextrusion reaction did not take place under the conditions defined for **21a**. Instead, a high-pressure mercury lamp with Corex glass filtering and, in some cases, benzene solvent was used in the photolysis of **21b**. Starting material was consumed; however, no aziridine-like product could be isolated. It was assumed that the desired product had undergone further photochemistry, since the photolability of aziridines conjugated with carbonyl groups has been well established.[15] It could be predicted that the product aziridine would be a good chromophore at wavelengths below 300 nm, based on the extinctions *inter alia* of **17** of 2500 at 293 nm and 2400 at 300 nm. Thus, the failure to isolate an aziridine as the primary photoextrusion product when light of wavelength below 310 nm was used might be rationalized. The structural assignment for **22** was based



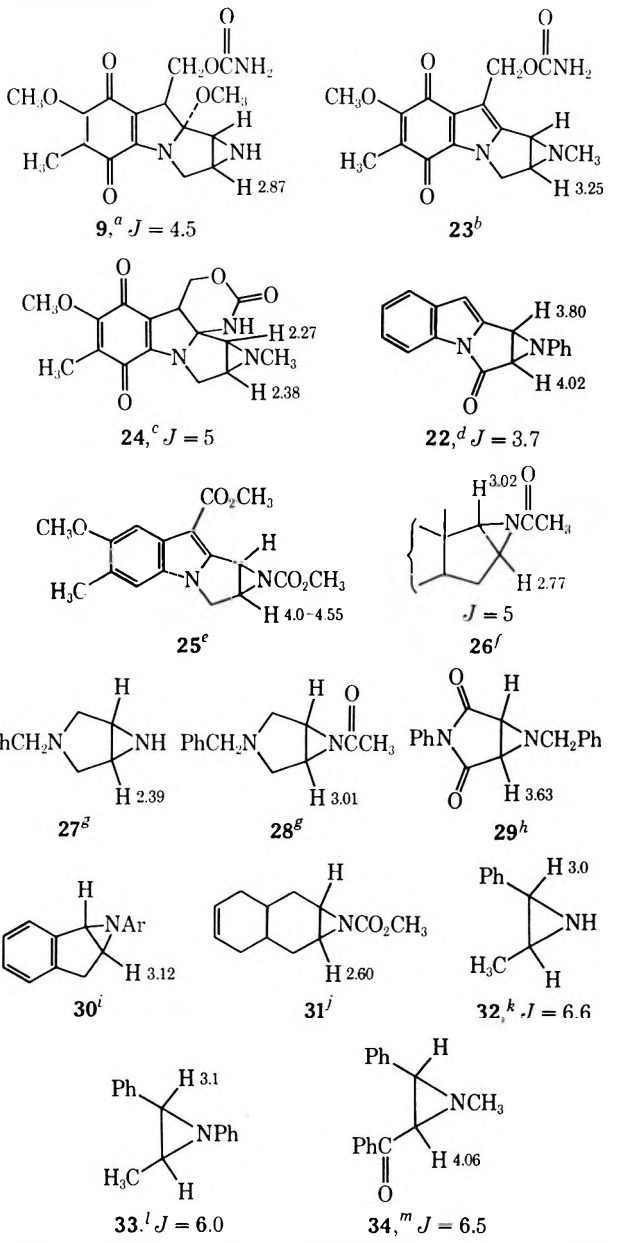
22

on the method of synthesis as well as a consistent ir, uv, nmr, and mass spectral data. Scheme I summarizes nmr data for several aziridine functions including examples of mitomycins and others fused to a five-membered ring. It can be seen that the chemical shifts of hydrogens on aziridine rings are upfield from the usual values of hydrogens adjacent to nitrogen. Also, it should be noted that, when an aziridine is fused to a ring, the J_{vic} of the ring fusion protons is decreased, in a manner anal-

(14) R. Huisgen, G. Szeimes, and L. Mobius, *Chem. Ber.*, **99**, 475 (1966).
(15) A. Padwa and L. Hamilton, *J. Amer. Chem. Soc.*, **89**, 102 (1967).

SCHEME I

A LISTING OF CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS (HERTZ) FOR PROTONS ON AZIRIDINES



9,[a] $J = 4.5$ **23**[b]

24,[c] $J = 5$ **22**,[d] $J = 3.7$

25[e] $J = 5$ **26**[f]

27[g] **28**[g] **29**[h]

30[i] **31**[j] **32**,[k] $J = 6.6$

33,[l] $J = 6.0$ **34**,[m] $J = 6.5$

[a] G. O. Morton, Lederle Laboratories Division, American Cyanamid Co., private communication; δ midpoint of multiplet. [b] Reference 6b. [c] G. O. Morton, G. E. Van Lear, and W. Fulmor, *J. Amer. Chem Soc.*, **92**, 2588 (1970). [d] This work. [e] Reference 17. [f] G. J. Mathews and A. Hassner, *Tetrahedron Lett.*, 1833 (1969). [g] E. Ohki, S. Oida, and H. Saeki, *Ann. Rep. Sankyo Res. Lab.*, **21**, 1 (1969). [h] R. Friary, Fordham University, private communication. [i] P. Walker and W. A. Waters, *J. Chem. Soc.*, 1632 (1962). *Cf.* A. Hassner, G. J. Matthews, and F. W. Fowler, *J. Amer. Chem. Soc.*, **91**, 5046 (1969), for an aziridine of indene which has apparently rearranged. [j] L. A. Paquette, D. E. Kuhla, J. H. Barrett, and R. J. Haluska, *J. Org. Chem.*, **34**, 2866 (1969). [k] S. Brois and L. Beardsley, *Tetrahedron Lett.*, 5116 (1966). [l] J. Deyrup and R. Greenwald, *J. Amer. Chem. Soc.*, **87**, 4538 (1965). [m] A. E. Pohland, R. C. Badger, and N. H. Cromwell, *Tetrahedron Lett.*, 4639 (1965); δ midpoint of AB quartet.

ogous to J_{vic} for epoxides.[16] It is our belief that the mitomycin analog **22** described in this report exhibits nmr shifts and a coupling constant, when substituent and ring fusion effects are taken into account, within the bounds of expectation. We take a note of a recent, revised claim of synthesis of a mitomycin analog **25** which has nmr shifts in a range slightly outside the limits expected. A knowledge of the coupling constant for J_{vic} in **25** would greatly clarify its structural assignment.[17] It is our conclusion that the unambiguous preparation of a tetracyclic molecule with a framework related to the mitomycins has been achieved in our laboratory.

Experimental Section[18]

Synthesis of 5-Hydroxy-1-phenyl-3-pyrrolin-2-one (8).—In a 500-ml gas washing cylinder was placed 500 mg of *N*-phenylpyrrole (**7**) (3.5 mmol) plus 10 mg of methylene blue, 250 ml of THF, 50 ml of pyridine, and 200 ml of distilled water. This vessel was placed in the center of a bank of four General Electric cool-white fluorescent lamps (15 W per tube). The reaction solution was magnetically stirred. The lights were switched on, and oxygen gas, passing through the dispersion disk at the bottom, was bubbled through the solution.

The disappearance of starting material **7** from the reaction solution was followed by tlc. After 45 min, the originally blue solution turned green and no more starting material **7** could be detected. However, photooxygenation was allowed to proceed for another 20 min. Work-up consisted of removal of the THF by vacuum evaporation with warming at 40°. The green pyridine solution was salted out with solid sodium chloride and then extracted into methylene chloride leaving a blue aqueous layer. The methylene chloride was cross-washed with 2 *N* HCl, water and sodium bicarbonate solution, and saturated sodium chloride and dried with anhydrous sodium sulfate. The methylene chloride extract was filtered and taken to dryness, yielding 482 mg of a crude black tar-like product. The crude product was dissolved in methylene chloride and spotted in a 1-cm wide band, the width of a single preparative silica gel coated tlc plate 20 × 20 cm × 0.5 mm thick. Elution with 10% ethyl acetate–ether gave two bands which were observed on the plate by visual inspection. The R_f of the pure compound **8** on a silica gel coated microscope slide was at least 0.5, eluting with either ether or 10% ethyl acetate–ether (v/v). The plate presented a 3-cm wide black band at the bottom and a 15-cm broad band above this which was light yellow. The entire light yellow band was removed and eluted with acetone from the substrate yielding 266 mg of material. This solid was crystallized from benzene yielding 48 mg of **8**, mp 138–140°, and a second crop of compound **8**: 32 mg; mp 136–140°; 14.2% overall yield; uv (ethanol) end absorption 204 nm (ϵ 14,600), 223 (6750), 280 (2760); ir (chloroform) 3551 (OH, w), 2970 (br, w), 1705 (C=O, s), 1580 cm^{-1} (m); ir (potassium bromide) 3170 (br, m), 1670 (C=O, s), 1610 (m), 1600 (m), 1500 (m), 1480 (w), 1440 (w), 1395 (m), 1320 (w), 1300 (m), 1270 cm^{-1} (w); nmr (DMSO) (DMSO reference) 6.02–6.12 (m, 1, C-5), 6.23 (d, 1, J_{3-4} = 5.5 Hz, C-3), 7.00–7.78 ppm (m, 7, aromatics, OH and C-4).

Anal. Calcd for $C_{10}H_9O_2N$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.6; H, 5.2; N, 8.0.

Conversion of 8 to *N*-Phenylmaleimide.—A sample of 28 mg of sublimed 5-hydroxy-1-phenyl-3-pyrrolin-2-one (**8**) (0.16 mmol), mp 144–147°, was mixed with 250 mg of activated manganese dioxide. Then 5 ml of benzene was added and the mixture was refluxed 1 hr with stirring. The mixture was filtered and the solvent was evaporated yielding yellow needles, mp 86–87°. A mixture melting point with *N*-phenylmaleimide was undepressed. Also, the ir spectra of *N*-phenylmaleimide and the isolated product were superimposable.

Hypochlorite–Peroxide Singlet Oxygen Oxygenation of *N*-Phenylpyrrole (7).—A sample of 1.430 g of *N*-phenylpyrrole (**7**) (10 mmol) was dissolved in 35 ml of methanol and 15 ml of *tert*-butyl alcohol. The stirred solution was kept at 15° and then 4 ml of 30% H_2O_2 (35.5 mmol) was added to the reaction mixture. The *N*-phenylpyrrole (**7**) is stable to 30% H_2O_2 solution under these conditions. A total of 50 ml of 0.645 M sodium hypochlorite (32.5 mmol) was added slowly (thus generating 32.2 mmol of O_2 gas) which is a 3.2-fold excess. Work-up yielded 1.373 g of crude product showing a carbonyl band in the ir (1700 cm^{-1}) in chloroform. A small scale column chromatography was performed on the crude product in a 9-in. Pasteur pipet filled with Florisil and eluting with benzene. The crude product was identified as mostly *N*-phenylpyrrole. Column chromatography of 1.287 g of crude product on 40 g of silica gel packed in hexane eluting first with hexane, benzene–hexane, benzene, chloroform, chloroform–ether, and ether yielded 115 mg (6.6%) of material, mp 135°, showing the correct ir of **8**. Also obtained was 288 mg of recovered *N*-phenylpyrrole (**7**). The remaining materials were dark oils and solids of a complex nature. Sublimation of a small amount of material **8** at 0.1 Torr and 115° for 1 hr yielded material, mp 138–140.5°, a slightly yellow product.

Synthesis of 5*H*-Pyrrolo[1,2-*a*][3,1]benzoxazine-1,5(3a*H*)-dione (11).—A solution 500 mg of (1-pyrrolyl)-2-benzoic acid (**10**) (2.67 mmol), mp 106–107°, 10 mg of methylene blue, and 500 ml of methylene chloride was photooxygenated at room temperature as previously described. The reaction was followed by ir. After 45 min, the spectrum displayed a new carbonyl band at 1740 cm^{-1} in chloroform. The split carbonyl band for starting material **10** [1740 (weak), 1695 cm^{-1} (strong)] in chloroform was completely absent. The photooxygenation was terminated after 1 hr and 5 min. The blue reaction solution was evaporated to dryness yielding a green gum. The gum was dissolved in acetone and filtered through a 9-in. Pasteur pipet filled with activity no. II neutral alumina. This procedure removes much of the blue dye and some polar material. The filtrate was chilled and a 97-mg (18%) yield of product **11** was collected, mp 189–193°. A second crop of material was recovered by repeating the process again on the mother liquors and crystallizing a second 59-mg sample of material which had mp 165–166°. Tlc showed the material to be less pure than the 97-mg first crop. A total combined yield of 28.5% was obtained: uv (ethanol) 218 nm (ϵ 25,400), 242 (7050), 318 (3800); ir (chloroform) 1730 (C=O, s), 1600 (w), 1480 (m), 1460 (w), 1395 (m), 1340 (w), 1165 (w), 1160 (w), 1115 (w), 1075 m), 1043 (w), 1023 (w), 990 (w), 965 (w), 845 cm^{-1} (w); ir (potassium bromide) 3080 (w), 2905 (w), 2840 (w), 1735 (C=O, s), 1600 (m), 1490 (m), 1460 (w), 1395 (m), 1225 (w), 1075 (w), 990 (w), 813 (w), 755 (w) 698 (w), 535 (w), 525 cm^{-1} (w); nmr (dimethyl sulfoxide) (DMSO reference) 6.62 [d, 1, J_{2-3} = 5 Hz showing apparent (methine) coupling J_{2-3a} < 1 Hz, C-2], 6.68 (s, 1, C-3a), 7.2–8.05 ppm (m, 5, H-$C_{3,6,7,8,9}$). The addition of D_2O did not reveal any exchangeable protons. Material **11** was recrystallized from acetone to afford material softening at 190°, mp 202–205°, to a red liquid.

Anal. Calcd for $C_{11}H_7NO_3$: C, 65.67; H, 3.51; N, 6.96. Found: C, 65.4; H, 3.4; N, 6.8.

Photooxygenation of the Sodium Salt of (1-Pyrrolyl)-2-benzoic Acid (10).—A solution of 500 mg of (1-pyrrolyl)-2-benzoic acid (**10**) (2.66 mmol), 10 mg of eosin dye, 100 ml of THF, 400 ml of distilled water, and 2.6 ml of 1 *N* sodium hydroxide solution was photooxygenated at room temperature in the usual manner. Small portions of solution were withdrawn and acidified with aqueous HCl. The presence of starting material **10** could be followed now by tlc on silica gel coated microscope slides developed in 5% acetic acid–methylene chloride (v/v). After 3 hr, starting material was consumed. The solution was then partially evaporated under vacuum to remove the THF. The aqueous solution remaining was extracted with ethyl acetate in a continuous liquid extractor for 50 hr. The extract was washed with sodium bicarbonate solution, water, and brine, and dried with $MgSO_4$. The solvent was vacuum evaporated, yielding a red tar-like product (107 mg) which was triturated with methanol, at which point 23 mg of product **11** (4.25%) separated. The aqueous

(16) K. Tori, T. Komeno, and T. Nakagawa, *J. Org. Chem.*, **29**, 1137 (1964).

(17) T. Hirata, Y. Yamada, and M. Matsui, *Tetrahedron Lett.*, 4107 (1969).

(18) Commercially available solvents were used as supplied without further purification except as noted. Thin layer chromatograms were performed on silica gel coated microscope slides using iodine to visualize the spots. New compounds were tested for purity by thin layer chromatography in at least two solvents. Melting points were performed on a Fisher–Johns melting point block and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer spectrophotometer Model 137 with sodium chloride optics. Also used was a Perkin-Elmer Model 337 grating spectrophotometer. Nmr spectra were recorded on a Varian Associates Model A-60 or A-60A spectrometer. Spectra were calibrated using tetramethylsilane as internal standard set at δ 0.00 ppm, except where noted, when dimethyl sulfoxide has been used as an internal standard.

layer in the extractor was now acidified to pH 5.5 with 26.6 ml of 0.1 *N* sulfuric acid. The solution was extracted again for 24 hr with ethyl acetate and worked up as above to afford 207 mg of a product which was dissolved in boiling acetone and treated with charcoal and filtered yielding 51 mg (9.5%) of a white product 11, identified by ir and melting point, softening at 190° and melting at 202–205° to a red liquid.

Synthesis of 3,3a-Dihydro-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazine-1,5(2*H*)-dione (12).—A mixture of 18 mg of 5*H*-pyrrolo[1,2-*a*]-[3,1]benzoxazine-1,5(3a*H*)-dione (11), mp 204–206° (0.0895 mmol), dissolved in 25 ml of acetone and 10 mg of 10% palladium on carbon was hydrogenated at atmospheric pressure for 20 min. The catalyst was filtered off yielding a 16-mg (88%) yield of a white solid 12, mp 206–208°, melting to a clear liquid. The material was crystallized from acetone: mp 206–208°; uv (ethanol) 223 nm (ε 23,000), 248 (8600), 307 (3110); ir (potassium bromide) 2910 (w), 2840 w), 1730 (C=O, s), 1710 C=O, s), 1590 (m), 1480 (s), 1460 (m), 1395 (s), 1240 (m), 1218 (m), 1088 (m), 773 cm^{-1} (m); ir (chloroform) 1730 (C=O, sh, s), 1720 (C=O, s), 1590 (m), 1470 (m), 1460 (m), 1395 (s), 1320 (m), 1290 (m), 1070 (m), 1020 cm^{-1} (w); nmr (dimethyl sulfoxide-d_6) 3.25 (s, 4, $W_{1/2}$ = 1 Hz, CH_2CH_2), 6.02–6.29 (m, 1, C-3a), 7.20–8.13 ppm (m, 4, H-$C_{6,7,8,9}$).

Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.9; H, 4.5; N, 6.8.

In a separate experiment, the starting material 11 was allowed to stir in acetone in the presence of the catalyst under an atmosphere of either oxygen or nitrogen. No reaction of the starting material 11 was apparent from observation of the ir of this material for times exceeding the time of the hydrogenation experiment.

Synthesis of 3*H*-Pyrrolo[1,2-*a*]indol-3-one (14).—In a 500-ml gas washing bottle, 500 mg of pure 9*H*-pyrrolo[1,2*a*]indole (13) (3.2 mmol) and 10 mg of methylene blue was dissolved in 250 ml of THF, 50 ml of pyridine, and 200 ml of distilled water. The contents of the cylinder were cooled to 0–5° in an ice–water bath. This was photooxygenated as previously described. It proceeded for 1.25 hr and was shown to be completed by the disappearance of the starting material 13 by silica gel tlc, eluting with benzene. This photooxygenation was repeated twice to give 1000 ml of reaction solution. The THF was evaporated under reduced pressure. The aqueous pyridine solution remaining was cooled and extracted with ether (200 ml per extraction) three times. The ether was washed twice with water, then with 2 *N* HCl (200 ml), and then with a solution of aqueous acidified 1 *N* ferrous sulfate. The ether was then washed with water, aqueous sodium bicarbonate, water, and brine. The ether was dried with anhydrous sodium sulfate and then filtered. Five drops of pyridine were added to the etherate which was then evaporated, leaving a crude material which was dark and crystalline. The solid was dissolved in methylene chloride and 5 g of activity no. II neutral alumina was added. The solvent was removed with the vacuum evaporator, leaving the crude product adsorbed on the alumina. Dry column chromatography (on 160 g of no. II neutral alumina eluting with methylene chloride, according to the method of Loev and Goodman)[19] was performed. An intense yellow band moved down the column near the solvent front which, after full development, was 3 in. wide. The rest of the column was quite clear except for green material remaining on the alumina at the top of the column. The R_f value on an alumina coated microscope slide was 0.95. The yellow band was cut out and the product eluted from it with benzene. The benzene solution evaporated to dryness and yielded 793 mg of material 14 (71.5%): mp 86–89°; ir (chloroform) 1718 (C=O, s), 1608 (m), 1575 (m), 1464 (w), 1443 (w), 1383 (m), 1374 (m), 1337 (s), 1328 (s), 1289 (m), 1152 (m), 1068 (m), 963 cm^{-1} (w); uv (ethanol) end absorption 208 nm (ε 30,300), 266 (11,400), 273 (10,300), 355 (10,800); nmr (deuteriochloroform) 5.93 upfield half of AB quartet (d, 1, J_{1-2} = 5.5 Hz, C-2), 6.31 (s, 1, C-9), 6.90–7.45 (m, 4, H-$C_{1,6,7,8}$), 7.6–7.75 ppm (m, 1, C-5). A spin decoupling experiment was performed; irradiation at −1.15 ppm downfield from the doublet centered at δ 5.95 caused it to collapse to a singlet. This demonstrates that C-2 is coupled to C-1. The corollary experiment of irradiating at 5.93 ppm with a spin decoupling field caused an alteration of the aromatic region of the spectrum but did not unequivocally identify C-2. However, the signal for C-2 should be centered at δ 7.08. An analytical sample of 14 was prepared by repeated sublimation at 35° (0.10 Torr) yielding material 14, mp 94–95°.

Anal. Calcd for $C_{11}H_7NO$: C, 78.09; H, 4.17; N, 8.28. Found: C, 78.1; H, 4.2; N, 8.2.

Synthesis of 14. Photooxygenation in Methylene Chloride.—A solution of 250 mg of 9*H*-pyrrolo[1,2-*a*]indole (13) (1.6 mmol), 5 mg of methylene blue, and 250 ml of methylene chloride was photooxygenated at room temperature as described previously. After 1 hr, no more starting material 13 could be detected by tlc. The solution was green. Work-up consisted of washing the methylene chloride solution with water, aqueous sodium carbonate solution, and saturated sodium chloride. The solution was dried with anhydrous magnesium sulfate and evaporated to dryness yielding a green tar-like product. The crude product was column chromatographed on 30 g of silica gel eluting with hexane–benzene, benzene, and chloroform yielding 43 mg (15.8%) of yellow amide 14, mp <70°. However, tlc showed the material 14 to be quite pure. Comparison of the ir with previously characterized 14 showed it to be of good quality.

A Quenching Experiment.—A mixture of 250 mg of 13 (1.6 mmol) with 10 mg of methylene blue, 0.25 ml of triethylamine, and 250 ml of methylene chloride was charged in the oxygenation apparatus. The mixture was photooxygenated at room temperature for 1 hr. The reaction solution turned green. However, the starting material 13 was not consumed as judged by tlc and its recovery by the usual work-up procedure.

Synthesis of 14. Demonstration of the Necessity of Pyridine.—A solution of 500 mg of 13 (3.2 mmol), 10 mg of methylene blue, 250 ml of water, and 250 ml of commercial THF was photooxygenated between 0–10° as described previously. After 1 hr, no more starting material 13 could be detected by tlc on silica gel. The greenish-blue photooxygenation solution was vacuum evaporated to remove all the THF. Work-up afforded an organic extract showing one spot on tlc plate. The solution was evaporated (Roto-Vac) to dryness at room temperature whereupon it blackened. The ir spectrum of the crude product was different from the spectrum seen in a reaction performed with added pyridine. There was a notable OH band at 3546 cm^{-1}. This product was absorbed on a small amount of silica gel and eluted with benzene to yield a benzene soluble extract of a product which, after solvent evaporation, yielded 444 mg of a black tar-like product. The crude product was worked up by preparative tlc on silica gel using three plates 20 × 20 cm × 0.5 mm thick, eluting with benzene. A recovery of 46 mg of crystalline material was obtained which was sublimed at 90° (0.1 Torr). This produced 31 mg of a yellow solid 14 (5.6%), mp 78–81°, which was crystalline and showed one spot on tlc. When the above experiment was performed a second time, 24 mg of 14 was recovered (4.45%) after sublimation at 90° (0.1 Torr), mp 80–83°.

Synthesis of 14 *via* Hypochlorite–Hydrogen Peroxide Oxygenation.—In a 100-ml three-neck round-bottom reaction flask was placed 775 mg of 13 (5 mmol), 25 ml of DMF, and 3 ml of 30% hydrogen peroxide (18 mmol). The pyrrolo[1,2-*a*]indole (13) was shown to be stable to hydrogen peroxide in the cold. In a buret was placed 0.645 M sodium hypochlorite (Clorox) solution. The entire system was sealed and the gases generated were led to a eudiometer. The slow dropwise addition of 10 ml of hypochlorite solution to the mixture generated 5 ml of O_2 (0.225 mmol). After 15 ml of sodium hypochlorite (Clorox) was added, material appeared to crystallize from solution; 10 ml of additional DMF was added to affect resolution of this material. After 25 ml of Clorox (16 ml of O_2 generated) was added, tlc revealed no more 13.

Work-up yielded 2.005 g of black crude product which was chromatographed on 43 g of Florisil eluting with hexane, hexane–benzene, and chloroform. After combining fractions with the appropriate carbonyl band (1718 cm^{-1}) and sublimation at 30–35° (0.1 Torr), 18 mg of yellow product (14), mp 75–81 (2.14%), was recovered.

Synthesis of 14. Singlet Oxygen Generated *via* the Thermal Decomposition of 9,10-Diphenylanthracene *endo*-Peroxide.—In a 50-ml reaction flask was placed 155 mg of 13 (1 mmol), 724 mg of 9,10-DPA-O_2 (2 mmol), and 15 ml of benzene. The solution was kept under nitrogen and refluxed for 71 hr. The reaction was followed by tlc and ir. After 25 hr, a carbonyl band appeared in the ir. The reaction mixture was evaporated to dryness and column chromatographed on 30 g of silica gel. The column was eluted with benzene yielding 26 mg of amide which, after sublimation, yielded 18 mg of pure amide 14, mp 90–91° (10.6%).

Synthesis of 1,2-Dihydro-3*H*-pyrrolo[1,2-*a*]indol-3-one (17).—A mixture of 169 mg of 3*H*-pyrrolo[1,2-*a*]indol-3-one (14) (1 mmol), mp 90–93°, dissolved in 25 ml of absolute ethanol, and 40 mg of 10% palladium on carbon was hydrogenated at room temperature

and atmospheric pressure for 1 hr. The reaction mixture was then filtered yielding 156 mg (92%) of a white crystalline solid **17**, mp 150–151°, melting to a clear liqud. The material was recrystallized from methanol, mp 153–154°, and showed one spot on tlc: ir (chloroform) 1730 (C=O, s), 1570 (w), 1440 (m), 1380 (s), 1340 (m), 1310 (m), 1290 cm^{-1} (m); ir (potassium bromide) 2960 (w), 2940 (w), 2845 (w), 1735 (C=O, s), 1580 (m), 1470 (m), 1452 (s), 1390 (s), 1370 (m), 1330 (m), 1315 (m), 1290 (m), 1172 (m), 1158 (m), 1109 (m), 1055 (m), 820 (m), 785 (m), 760 (s), 750 cm^{-1} (m); uv (absolute ethanol) 238 nm (ϵ 25,400), 258 sh (11,900), 293 (2550), 300 (2350); nmr (deuteriochloroform) 3.02 (s, 4, CH_2CH_2), 6.29 (b s, 1, $W_{1/2}$ = 3 Hz, C-9), 7.23–7.70 (m, 3, H–$C_{6,7,8}$), 8.05–8.30 ppm (m, 1, C-5).

Anal. Calcd for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.4; H, 5.3; H, 8.1.

Synthesis of 1-Benzyl-3a,10b-dihydro-*v*-triazolo[4′,5:3,4]-pyrrolo[1,2-*a*]indol-4(1*H*)-one (21b).—In a 100-ml round-bottom reaction flask fitted with a water-cooled condenser was placed 349 mg of 3*H*-pyrrolo[1,2-*a*]indol-3-one (**14**) (2.06 mmol), mp 93–94°, 700 mg of benzyl azide (5.25 mmol), and 4 ml of benzene. The reaction was stirred under a nitrogen atmosphere at reflux temperature. After 24 hr, a precipitate was noted and an additional 1 ml of benzene was added. After 60 hr, the reaction was terminated and cooled, and hexane was added to the dark crude mixture. Additional precipitate formed. The mixture was filtered yielding a dark product. The product was crystallized twice from benzene yielding 331 mg (53.5%) of a crystalline white solid (**21b**) decomposing at 184–186° with apparent gas evolution, and then the material turned to a red liquid on the melting point block. The pure material **21b** showed one spot on a tlc plate: uv (ethanol) 217 nm (ϵ 26,600), 265 (9900), 290 sh (5200); ir (chloroform) 1748 (C=O, s), 1595 (w), 1445 (m), 1380 (m), 1351 (m), 1320 (m), 1166 (w), 1060 cm^{-1} (m); nmr (dimethyl sulfoxide) (DMSO reference) first half of AB quartet 4.91 (d, 1, J_{AB} = 16 Hz, benzyl CH_2), second half of AB quartet 5.08 (d, 1, J_{AB} = 16 Hz, benzyl CH_2), 5.05 (d, 1, J_{10b-3a} = 10 Hz showing additional apparent coupling $J_{10-10b} < 1$ Hz, C-10b), 5.98 (d, 1, J_{10b-3a} = 10 Hz, C-3a), 6.47 (b s, 1, $W_{1/2}$ = 2 Hz, $J_{10-10b} < 1$ Hz), 7.25–7.73 (m, 8, H–$C_{7,8,9}$ + 5 phenyl protons), 7.45 (b s, 5 phenyl protons), 7.85–8.05 ppm (m, 1, C-6). The analytical sample, prepared *via* benzene recrystallization, consisted of white needles which turn red at 175° and decomposed at 185° with apparent gas evolution.

Anal. Calcd for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.4; H, 4.8; N, 18.5.

Synthesis of 1-Phenyl-3a,10b-dihydro-*v*-triazolo[4′5′:3,4]pyrrolo[1,2-*a*]indol-4(1*H*)-one (21a).—In a 50-ml round-bottom flask under a nitrogen atmosphere was placed 507 mg of **14** (3 mmol), 714 mg of phenyl azide (6 mmol), and 5 ml of acetone. The stirred reaction mixture was kept at reflux for 24 hr. An ir spectrum indicated only small conversion to the triazoline **21a**. The solvent was blown off with a nitrogen stream, and then an additional 714 mg of phenyl azide (6 mmol) was added plus 1 ml of acetone. The mixture was held at 65–70° for an additional 12 hr and a precipitate was formed. The reaction mixture was evaporated under vacuum to dryness and washed with small portions of benzene, yielding 484 mg (56% yield) of slightly tan solid decomposing at 171–175° with apparent gas evolution and turning to red liquid. The material was recrystallized from THF–hexane yielding 464 mg (53.8%) of **21a**. In a separate experiment, 500 mg (2.96 mmol) of 3*H*-pyrrolo[1,2-*a*]indol-3-one (**14**) was mixed with 1.5 g of phenyl azide (13.4 mmol) and 1 ml of benzene, stirred under nitrogen between 70 and 75° for 24 hr yielding 871 mg (68% yield) of the phenyl triazolone **21a** crystallized from THF–hexane (we thank Mr. Robert Kempton for this result): uv (ethanol) end absorption 207 nm (ϵ 24,600), 238 (24,600), 290 (8800); ir (chloroform) 1745 (C=O, s), 1590 (m), 1440 (m), 1380 (s), 1340 (m), 1320 (m), 1170 (w), 1120 (w), 1055 cm^{-1} (m); ir (potassium bromide) 1740 cm^{-1} (C=O, s); nmr (deuteriochloroform) 5.63 and 6.02 (AB quartet, J_{10b-3a} = 10 Hz, C-10b, C-3a), 6.64 (b s, 1, $W_{1/2}$ = 2 Hz, C-10 showing apparent additional coupling to C-10b), 7.3–7.65 (m, 8, 5 phenyl protons +H–$C_{7,8,9}$), 7.5 (s, 5, phenyl protons of *N*-phenylaziridine), 8.0–8.33 ppm (m, 1, unique aromatic proton C-6). An analytical sample of **21a** was prepared by crystallizing from chloroform yielding a white solid which decomposed at 173–175° with apparent gas evolution.

Anal. Calcd for $C_{17}H_{12}N_4O$: C, 70.82; H, 4.20; N, 19.43. Found: C, 70.8; H, 4.3; N, 19.5.

Synthesis of 1a,8b-Dihydro-1-phenylazirino[2′,3′:3,4]pyrrolo-[1,2-*a*]indol-2(1*H*)-one (22).—In a 500-ml photochemical reaction vessel was placed 50 mg of 1-phenyl-3a,10b-dihydro-*v*-triazolo[4′,5′:3,4]pyrrolo[1,2-*a*]indol-4(1*H*)-one (0.174 mmol) and 300 ml of benzene. With a water-cooled immersion well inserted into the reaction vessel, the solution was purged with nitrogen gas for 10 min and the vessel was covered in the back with reflective foil. The stirred solution was irradiated (with a Sears Roebuck sun lamp no. 7081 held 1 in. from the reaction vessel) through two thicknesses of plate glass for 15 min. The solution color changed from clear to slight yellow. The solution was evaporated to dryness yielding a slightly yellow solid crude product **22**, mp 126–128°. The crude reaction mixture appeared to be quite pure by ir and tlc. The material was dissolved in benzene and filtered rapidly through a 9-in. Pasteur pipet packed with activity grade no. II neutral alumina to remove polar impurities, recovering after solvent removal 45 mg of material **22** (99.5%), which was crystallized from cyclohexane, mp 133–135°, to yield a white solid exhibiting one spot on tlc: ir (potassium bromide) 1739 cm^{-1} (C=O, s); ir (chloroform) 1739 (C=O, s), 1592 (m), 1445 (m), 1374 (m), 1318 (m), 1152 (w), 1075 (w), 1052 cm^{-1} (w); uv (ethanol) end absorption 206 nm (ϵ 22,000), 250 (22,000), 305 (5300); nmr (deuteriochloroform) 3.82, 4.02 (AB quartet, J_{8b-1a} = 3.7 Hz, C-8b, C-1a), 5.64 (s, 1, $W_{1/2}$ = 1.5 Hz, C-8), 6.95–7.61 (m, 8, H–$C_{5,6,7}$ + 5 phenyl protons), 7.75–8.0 ppm (m, 1, C-4); *m/e* 260 (molecular ion), 232 (M − CO), 169 (M − PhN<), 155 (M − PhNCH + H), 129 (?), 115 [M − Ph(C_3H_4N)C=O]. An analytical sample was obtained from material recrystallized from cyclohexane mp 136–137°.[19]

Anal. Calcd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.6; H, 4.8; N, 10.7.

Photolysis of Triazoline 21b.—In a quartz well photolysis apparatus with a water-cooled outer jacket was placed 100 mg of benzyltriazoline **21b** and 300 mg of benzene solvent. The benzene solution was purged for 15 min with dry N_2 gas. Photolysis of the stirred solution with a Hanovia No. 608A high-pressure mercury arc lamp (140 W) using a 2 mm 2800A cut-off filter proceeded for 85 min. Work-up of the reaction consisted of evaporation of the solvent *in vacuo* followed by preparative tlc using 10% ether chloroform as eluent. Two crystalline materials were isolated: 2 mg of material whose ir suggested it to be an imine, and 30 mg of starting benzyltriazoline **21b**. The remaining material on the plate was very complex in nature.

Registry No.—**8**, 26709-62-6; **11**, 26697-46-1; **12**, 26709-63-7; **14**, 24009-76-5; **17**, 26709-65-9; **21a**, 24009-77-6; **21b**, 26709-66-0; **22**, 24009-78-7.

(19) We thank Dr. Van Lear of Lederle Laboratories for the mass spectrum.

Synthesis and Properties of Fluorine-Containing Heterocyclic Compounds. VI. Reactions of Fluorinated 3-Keto Esters with Amines

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Received November 19, 1969

The reactions of fluorinated 3-keto esters with aliphatic primary amines and 1,2-diaminoethane have been studied. The factors which determined the preferential formation of five- or seven-membered rings, from 1,2-diaminoethane and ethyl 4,4,4-trifluoro-3-ketobutanoate (**1**), were established. Possible reaction paths for these cyclizations are proposed. The reactions of **1** with amines were extended to substituted 1,2-diamines, 1,3-diamines, 1,2- and 1,3-amino alcohols, and cysteine. The stereochemistry of some of the substituted imidazolidineacetic esters was investigated.

The reactions of aromatic 1,2-diamines and ethyl 3-ketobutanoate have been the subject of several publications.[1] The formation of various products under different reaction conditions has generated continued interest in this field. The condensation of ethyl 4,4,4-trifluoro-3-ketobutanoate (**1**) with various aromatic amines has been investigated in this laboratory.[2] More recently we became interested in the reactions of **1** with 1,2-diaminoethane.[3] The reactions of aliphatic 1,2-diamines with 3-ketobutanoates have received much less attention than those of their aromatic analogs.[4] Ethyl 3-phenyl-3-ketopropanoate and 1,2-diaminoethane were reported to give 7-phenyl-1,2,3,4-tetrahydro-1,4-diazepin-5-one in low yields.[5] When ethyl 3-ketobutanoate was treated with 1,2-diaminoethane, the expected 1,4-diazepin-5-one was not formed.[6] A product identified as diethyl 3,3′-(*N*,*N*′-diaminoethyl)bis-2-butenoate was isolated instead.

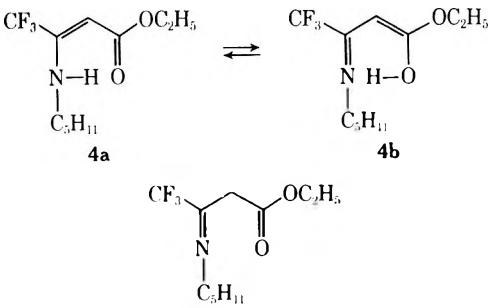
The reactions of fluorinated 3-ketobutanoates with aliphatic diamines proved to be more complex. Recently, we have reported the isolation of 1,2,3,4-tetrahydro-7-trifluoromethyl-1,4-diazepin-5-one (**2**) and ethyl 2-(trifluoromethyl)-2-imidazolidineacetate (**3**) from the reaction of 1,2-diaminoethane and **1**.[3] The yields of **2** and **3** were low (16 and 25%, respectively) and a large amount of undistillable tarry product was also obtained. The purpose of the present investigation was to establish favorable conditions for these condensations and to elucidate the mechanism of addition of 1,2-diamines to 3-keto esters.

Results and Discussion

The condensation of the keto ester, **1**, and 1,2-diaminoethane was conducted in different solvents and the order of addition of the reactants was varied. When **1** was added to the diamine, in refluxing benzene, the yield of imidazolidine, **3**, was increased to 36%, while the yield of diazepinone, **2**, decreased to 10%. In ethanol only the imidazolidine (18.5%) was obtained although the isolation of other diazepines has been reported under similar conditions.[7]

When 1,2-diaminoethane was added to **1**, in refluxing benzene, the yield of **3** increased to 81% but again no diazepinone could be isolated. The results obtained from various experiments pointed to the following trends: higher temperatures and a basic medium promoted diazepinone formation. An acidic medium increased the percentage of imidazolidine. Nonpolar solvents improved the yields of both **2** and **3**. This data suggested that the pH of the medium determined the initial site of attack. To differentiate between the two possible sites of attack in **1**, the keto carbonyl or the ester carbonyl, by the amine, the reaction of **1** with 1-aminopentane was investigated. It was expected that under acidic conditions an enamine, 3-(1-pentylamino)-4,4,4-trifluoro-2-butenoate (**4**) would be formed. In basic medium, an amide, *N*-(1-pentyl)-3-keto-4,4,4-trifluorobutanamide should be obtained.

When 1-aminopentane was added to a refluxing benzene solution of **1**, **4** was obtained in good yield. The ir spectrum of **4**, in carbon tetrachloride, showed two bands of about equal intensity in the carbonyl stretching region at 1670 and 1630 cm^{-1} and a weak (about 5%) band at 1740 cm^{-1}. Also two concentration-independent bands at 3280 and 3225 cm^{-1} were present. The higher carbonyl frequency band at 1670 cm^{-1} could be assigned to the hydrogen-bonded α,β-unsaturated ester carbonyl (**4a**), and the 1630-cm^{-1} band to the α,β-unsaturated imine (**4b**). The two bands in the 3200-



cm^{-1} region were assigned to the NH and -OH stretch of **4a** and **4b**, respectively. Further evidence for the existence of the tautomeric equilibrium **4a** ⇌ **4b** and the virtual absence of **4c** was supplied by the nmr spectrum of **4** which showed a broad peak at δ 8.27 (1 H) for the NH–OH proton and a sharp singlet at δ 5.04 (1 H) for the vinyl hydrogen but no absorption for the 2-methyl-

* To whom correspondence should be addressed.

(1) (a) J. Davoll, *J. Chem. Soc.*, 308 (1960); (b) A. Rossi, A. Hunger, J. Kebrle, and K. Hoffmann, *Helv. Chim. Acta*, **43**, 1298 (1960); (c) R. Barchet and K. W. Merz, *Tetrahedron Lett.*, **33**, 2239 (1964); (d) F. D. Popp and A. C. Noble in *Advan. Heterocycl. Chim.*, **8**, p 66 (1967).

(2) (a) F. B. Wigton and M. M. Joullié, *J. Amer. Chem. Soc.*, **81**, 5212 (1959); (b) A. S. Dey and M. M. Joullié, *J. Heterocycl. Chem.*, **2**, 113, 120 (1965).

(3) M. M. Joullié, G. M. J. Slusarczuk, A. S. Dey, P. V. Venuto, and R. H. Yocum, *J. Org. Chem.*, **32**, 4103 (1967).

(4) (a) W. Ried and W. Hohne, *Chem. Ber.*, **87**, 1811 (1954); (b) A. E. Martell, R. L. Belford, and M. Calvin, *J. Inorg. Nucl. Chem.*, **5**, 170 (1958); (c) G. O. Dudek and R. H. Holm, *J. Amer. Chem. Soc.*, **83**, 2099 (1961).

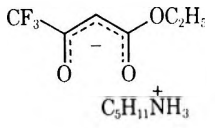
(5) W. Ried and P. Stahlhofen, *Chem. Ber.*, **90**, 828 (1957).

(6) C. M. Hofmann and S. R. Safir, *J. Org. Chem.*, **27**, 3565 (1962).

(7) D. Lloyd, R. H. McDougall, and D. R. Marshall, *J. Chem. Soc. C*, 780 (1966).

ene protons of **4c**. Similar results have been observed for the products of amines with 1,3-dicarbonyl compounds.[4b,5,8,9] The same type of tautomeric equilibrium has also been postulated for these products.

The addition of **1** to a refluxing benzene solution of 1-aminopentane afforded a waxy solid whose molecular formula was $C_{11}H_{20}F_3NO_3$. The same product could be formed by mixing the amine and **1** at room temperature, either neat or in carbon tetrachloride solution. The ir spectrum of this product showed broad bands in the 3300–2400-cm^{-1} region and a band at 1580 cm^{-1} typical of amine salts. Two relatively weak carbonyl bands at 1680 and 1640-cm^{-1} were also present. This data suggested **5**, a structure similar to that of metal chelates.

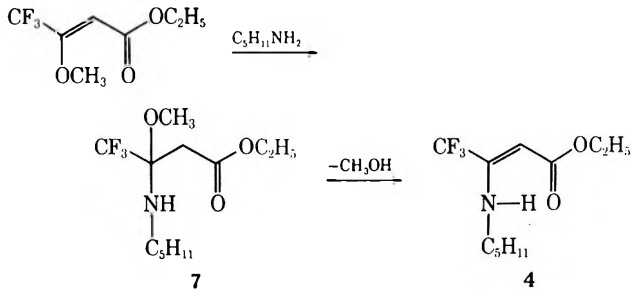


5

However, dicarbonyl chelates show only one carbonyl band with shoulders at higher and lower frequencies,[10] indicating a closer equivalence of the two carbonyls than that present in **5**. The nmr spectrum also supported this structure by showing the expected alkyl resonances and a singlet at δ 5.05 (1 H) assigned to the vinyl proton. A relatively sharp peak at δ 7.88 (3 H) was assigned to the alkyl ammonium ion. Its narrow half-width (3 Hz) indicated rapid exchange and equivalence of the three protons on the nmr time scale.

Compound **5** could be converted to **4** by heating **5** at 150° for a short period of time. Although these conditions were more drastic than those used in the original condensation of **1** with 1,2-diaminoethane, the isolation of **5** suggested the possibility of a similar salt as a precursor in the reaction of **1** with diamines.

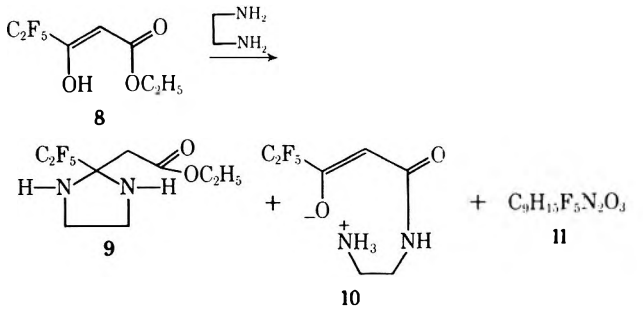
When ethyl 3-methoxy-4,4,4-trifluoro-2-butenoate (**6**) was treated with 1-aminopentane at 0°, ethyl 3-methoxy-3-(1-pentylamino)-4,4,4-trifluorobutanoate (**7**) was isolated. At room temperature **7** eliminated methanol and in about 3 days a quantitative conversion to **4** occurred. These results supported the possibility



7 **4**

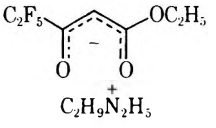
of an intermediate carbinolamine in the reaction of 1,2-diaminoethane and **1**.

The addition of 1,2-diaminoethane to a refluxing benzene solution of ethyl 3-keto-4,4,5,5,5-pentafluoropentanoate (**8**) yielded three products, ethyl 2-(perfluoroethyl)-2-imidazolidineacetate (**9**), *N*-(2-aminoethyl)-3-hydroxy-4,4,5,5,5-pentafluoro-2-pentenamide (**10**), and an addition compound of molecular formula $C_9H_{15}F_5$-



8 **9** **10**

N_2O_3 (**11**). The ir of **11**, in chloroform, showed a broad absorption band at 3400–2300 cm^{-1} and a band at 1570 cm^{-1} characteristic of amine salts. A single carbonyl absorption was seen at 1675 cm^{-1}. The nmr spectrum of **11** in deuteriochloroform showed a quartet at δ 4.04 (2 H, J = 7 Hz) and a triplet at 1.22 (3 H, J = 7 Hz) due to the ester methylene and methyl groups. A singlet at δ 2.90 (4 H) was assigned to the methylenes of the diamine. The area under the two remaining peaks at δ 5.07 and 5.37 integrated to six protons; by time-averaging, the ratio was shown to be exactly 1:5. The smaller peak was assigned to the vinyl proton (δ 5.07) and the larger one at 5.37 to the ammonium ion protons. The five protons formed a rather sharp peak 4 Hz wide at half-height, suggesting rapid exchange. Their position indicated that they were more shielded than those of **5**. A structure consistent with the above information is the 1,2-diaminoethane salt of **8**, which may be formulated as **11**. The structural assignment for this



11

compound is supported by its facile transformation into the amide salt **10**. This is in contrast with the behavior of **5**. When **5** is heated, the ammonium ion catalyzes the attack as the ketone carbonyl and **4** is formed exclusively. In compound **11**, one of the amino groups appears to be favorably located for nucleophilic attack at the ester carbonyl.

When 1,2-diaminoethane was added to an ice-cold solution of **1** in carbon tetrachloride, a salt (**12**) was obtained in almost quantitative yield. Although stable at room temperature when dry, this salt decomposed in solution making spectroscopic studies difficult. Its ir spectrum was similar to that of **11**. Its nmr spectrum, less than 1 min after solution, in deuteriochloroform, showed the same peaks as **11** and peaks due to the ammonium ion and vinyl proton at δ 5.12 and 5.04, respectively. Within 5 min the latter peaks coalesced into a broad peak and a new peak appeared at δ 2.75. Integration of this spectrum was not possible. When a chloroform solution of **12** was allowed to stand overnight at room temperature, it yielded the corresponding amide salt **13**. When this salt was heated at 170° for a short time, the diazepinone **2** was obtained.

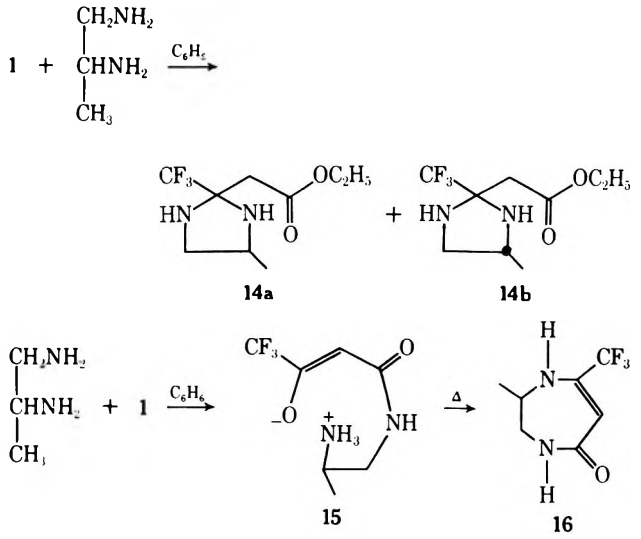
To extend the scope of this reaction, the condensation of **1** with substituted 1,2-diamines was studied. The addition of 1,2-diaminopropane to **1** afforded a good yield of the expected ethyl 4-methyl-2-(trifluoromethyl)-2-imidazolidineacetate (**14**). An isomeric mixture of two *dl* pairs in which the methyl and trifluoro-

(8) M. M. Joullié, S. Nasfay, and L. Rypstat, *J. Org. Chem.*, **21**, 1358 (1956).

(9) F. C. Pennington and W. D. Kehret, *ibid.*, **32**, 2034 (1967).

(10) R. L. Belford, A. E. Martell, and M. Calvin, *J. Inorg. Nucl. Chem.*, **2**, 11 (1956).

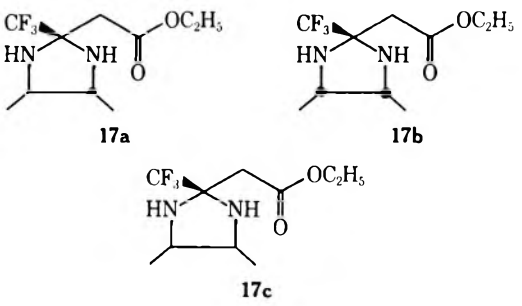
methyl groups may be cis or trans was expected (**14a**, **14b**).



Separation of the possible isomers could not be accomplished either by distillation on a spinning-band column or by vapor phase chromatography on a variety of columns. Evidence for an isomeric mixture was provided by the nmr spectrum. The peaks due to the ester methylene, ring methylene, α-methylene, and NH protons were found at δ 4.16 (2 H, J = Hz), ~3.2, 2.63, and 2.51, respectively. The ring methine proton was hidden under the α-methylene and NH protons (5 H). The peak due to the ester methyl at δ 1.28 (J = 7 Hz) was partly superimposed upon two doublets due to the methyl groups of the cis and trans forms at δ 1.14 (J = 6 Hz) and 1.11 (J = 6 Hz). The trans isomer would be expected to be somewhat less shielded although this assignment is not certain.[11]

When **1** was added to 1,2-diaminopropane, a solid was formed in addition to the imidazolidine mixture **14**. This solid was the amide salt, *N*-(2-aminopropyl)-3-hydroxy-4,4,4-trifluoro-2-butenamide (**15**) which was converted to 1,2,3,4-tetrahydro-2-methyl-7-trifluoromethyl-1,4-diazepin-5-one (**16**) by heating. The position of the methyl group in the compounds was not ascertained. It was assumed that the primary amino group would attack the ester carbonyl preferentially since it should be less sterically hindered.

The next substituted diamine used was 2,3-diaminobutane prepared by the reduction of dimethylglyoxime with Raney aluminum–nickel alloy in aqueous sodium hydroxide. A mixture of the *dl* and meso isomers was used; thus a mixture of three geometric isomers was expected, **17a**, **17b**, and **17c**.

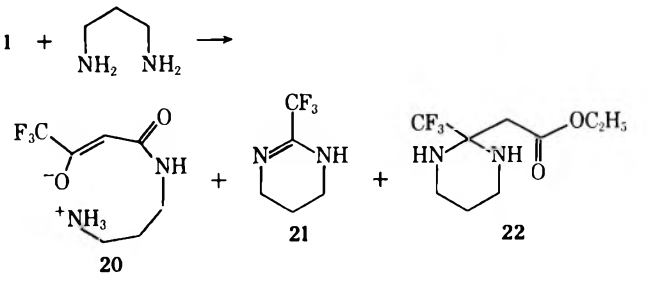


(11) G. J. Karabatsos, G. C. Sonnichsen, N. Hsi, and D. J. Fenoglio, *J. Amer. Chem. Soc.*, **89**, 5067 (1967).

Vapor phase chromatography of the product showed only two peaks of about equal area. These peaks appeared to be due to the reaction products of the two isomeric diamines, imidazoline **17a** from the *dl* isomer and a mixture of **17b** and **17c** from the meso isomer. The lower boiling material (A) was a solid at room temperature while the higher boiling material (B) was a liquid and probably a mixture of two isomers. The ir spectra of A and B were almost identical and very similar to the spectrum of **14**. The nmr spectra of A and B were, however, quite different.

The nmr spectra of both A and B showed the ester methylene peak at δ 4.16 (2 H, J = 7 Hz), the α-methylene peak at 2.61 (2 H), the NH protons at 2.74 (2 H), and the ester methyl group at 1.28 (3 H, J = 7 Hz). Isomer A exhibited a broad peak at δ 2.75 (2 H) which could be assigned to the ring methine protons and two doublets centered at 1.12 and 1.08 (6 H, J = 5.5 Hz) which could be assigned to the methyl side chains. The spectrum of B showed a multiplet centered at δ 3.45 (2 H) ascribed to the ring methine groups and a doublet at 0.97 (6 H, J = 6.3 Hz) assigned to the methyl side chains. These results are consistent with those obtained for 2,2,4,5-tetramethyl-1,3-dioxolane where the chemical shift of the ring methines in the trans isomer were 0.77 ppm upfield from the cis isomer and the methyl side chain in the trans isomer absorbed 0.10 ppm downfield from that of the cis isomer (J = 5.9 and 6.3 Hz, respectively).[12] These data appear to support the assignment of the cis–trans form **17a** to isomer A and that of cis–cis or trans–trans **17b** or **17c** to isomer B. Since no doubling of the methyl peaks is evident, only one isomer appears to be present. The assignment of the doubling of the methyl peaks in A to cis–trans isomerism was supported by the nmr spectrum of ethyl 4,4-dimethyl-2-(trifluoromethyl)-2-imidazolidineacetate (**18**). The peaks due to the ester methylene, α-methylene, and ester methyl are at δ 4.16 (2 H, J = 7 Hz), 2.61 (2 H), and 1.28 (3 H, J = 7 Hz), respectively. These chemical shifts are identical with those of the dimethylimidazolidine isomers. A peak at δ 2.87 (2 H) was assigned to the ring methylene protons and the NH proton absorption was a smeared out peak between δ 2.1 and 3.1 (2 H) which disappeared upon deuterium exchange with D_2O. The methyl side chains absorbed at δ 1.17 (3 H) and 1.22 (3 H). The difference in chemical shift between these two peaks, 3 Hz, is in good agreement with the values of 2 Hz for **14** and 2.5 Hz for **17a**.

Similarly, the addition of **1** to a refluxing benzene solution of 1,3-diaminopropane produced a mixture of at least three products, **20**, **21**, and **22**.



The most insoluble product precipitated from the reaction mixture and was formulated as the amide salt,

(12) F. A. L. Anet, *ibid.*, **84**, 747 (1962).

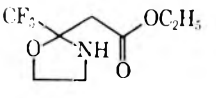
N-(3-aminopropyl)-3-hydroxy-4,4,4-trifluoro-2-butenamide (**20**), in agreement with the analytical and spectroscopic data. Attempts were made to convert **20** into the corresponding diazocinone. Although water was lost, only a polymer was obtained. Evaporation of the benzene afforded a semisolid mixture from which the known[13] 3,4,5,6-tetrahydro-2-(trifluoromethyl)pyrimidine (**21**) was isolated.

The third component of the mixture was ethyl 2-(trifluoromethyl)-2-perhydropyrimidineacetate (**22**) which was best obtained by inverting the addition sequence, that is, adding the diamine to the ester. The ir spectrum of **22** showed the carbonyl stretching at 1732 cm^{-1} with shoulders at 1738 and 1745 cm^{-1}. The NH stretching vibrations appeared at 3370 and 3350 cm^{-1} suggesting hydrogen bonding to the ester carbonyl. The nmr spectrum of **22** also supported its structure.

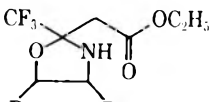
Since the reaction of 2-amino alcohols with carbonyl compounds is a well-known method for the synthesis of oxazolidines, it was of interest to explore the reaction of **1** with 2-aminoethanol. While the expected oxazolidine was obtained in good yield, the formation of an oxazepinone could not be detected. The ir spectrum of ethyl 2-(trifluoromethyl)-2-oxazolidineacetate (**23**) showed a great similarity to that of the imidazolidines: the ester carbonyl band at 1728 cm^{-1} with shoulders at 1735 and 1750 cm^{-1}, a region free of absorption between 1700 and 1500 cm^{-1}, and an intense peak of the $-CF_3$ group at 1172 cm^{-1}. The single NH stretching band at 3340 cm^{-1}, insensitive to dilution, indicated a stronger hydrogen bond to the ester carbonyl than is present in imidazolidines.

The nmr spectrum of **23** was quite complicated. Except for the ester methyl and methylene, all other protons were magnetically nonequivalent and contributed to the splitting. The α-methylene protons gave rise to an AB quartet centered at δ 2.77 (2 H, J = 15 Hz) and the ring methylenes absorbed between δ 3 and 4 giving rise to many poorly resolved peaks.

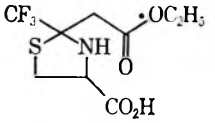
Several other commercially available amino alcohols were condensed successfully with **1** and esters related to **1** to yield the corresponding five-membered rings (**24**–**27**). Cysteine gave ethyl 4-carboxy-2-(trifluoromethyl)-2-thiazolidineacetate (**28**). The physical con-



23



24, $R_1 = CH_3$; $R_2 = H$
25, $R_1 = H$; $R_2 = CH_3$

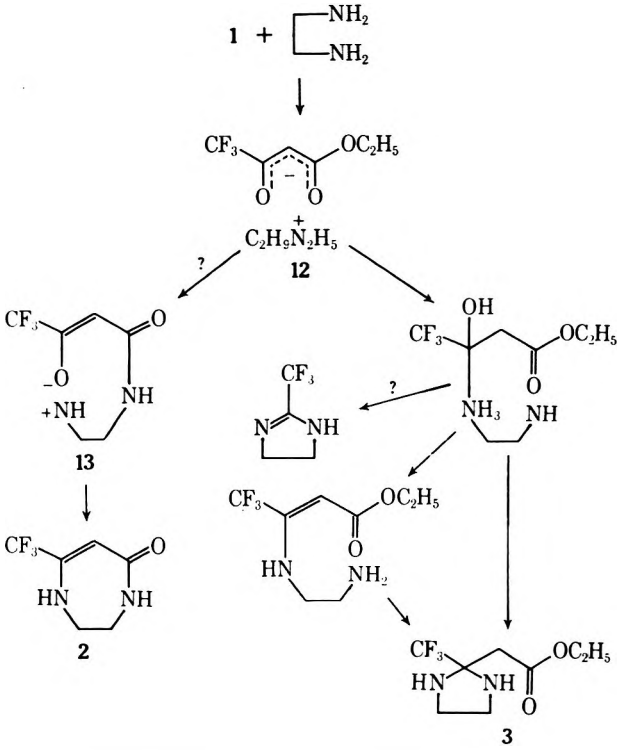


28

stants for these compounds are shown in Table I. 3-Aminopropanol reacted with **1** to yield ethyl 2-(trifluoromethyl)-2-(1,3-oxazine)acetate (**29**).

(13) R. N. Johnson and H. M. Woodburn, *J. Org. Chem.*, **27**, 3958 (1962).

A possible reaction sequence for the reaction of **1** with 1,2-diaminoethane is shown below.

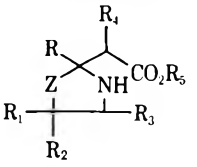


This reaction sequence is consistent with the available data. Since salt formation is the first step in the reaction, the ability of the ester to enolize is important. This reaction is rapid since only a proton transfer is involved. The salt may then react intramolecularly to form either the amide salt (thermodynamic control) or the carbinolamine (kinetic control). That the formation of the carbinolamine should be rapid is supported by the reaction of the enol ether with amines. The carbinolamine could undergo an intramolecular nucleophilic displacement to give directly the imidazolidine or the enamine. Although the enamine can cyclize to **3**, such a reaction might be predicted to be slower since cyclization of ethyl 3-(2-hydroxyethylamino)-4,4,4-trifluoro-2-butenoate to the corresponding oxazolidine (**22**) was shown to be much slower than the formation of **22** from **1** and 2-aminoethanol. Another possible product, 2-trifluoromethylimidazoline, was not found in the reaction mixture although it is a known compound.[13] However, an analogous compound was obtained in the reaction of **1** with 1,3-diaminopropane.

The proposed scheme for the reaction of **1** with 1,2-diaminoethane clarifies somewhat the results reported by previous workers for the condensation of ethyl 3-ketobutanoate and ethyl 3-phenyl-3-ketopropanoate with the same diamine.[4,6] The only product isolated from the first reaction was reported to be diethyl 3,3′-(*N*,*N*′-1,2-diaminoethyl)bis-2-butenoate. We repeated this condensation to investigate the presence of other products, but we were only able to obtain better yields (60%) of the bisenamine. The same result was obtained with *tert*-butyl 3-ketobutanoate. In both cases evolution of water was more rapid than in the case of **1** and 1,2-diaminoethane, suggesting fast dehydration to the enamine. With the more enolic 3-phenyl-3-ketopropanoate, the corresponding diazepinone and diamide were isolated. These could arise from a salt similar to

TABLE I

PHYSICAL CONSTANTS AND ANALYTICAL DATA FOR THE FIVE-MEMBERED RINGS[a]



Compd no.	R	R_1	R_2	R_3	R_4	R_5	Z	Bp (mm) or mp, °C	$n^{25}D$
3	CF_3	H	H	H	H	C_2H_5	NH	40.5–41.0	
9	C_2F_5	H	H	H	H	C_2H_5	NH	85–86 (3.5)	1.4035
14[b]	CF_3	CH_3	H	H	H	C_2H_5	NH	114.5– (20)	1.4173
17[b]	CF_3	CH_3	H	CH_3	H	C_2H_5	NH	93–97 (5)	
18	CF_3	CH_3	CH_3	H	H	C_2H_5	NH	120–120.5 (14.5)	1.4181
19	CF_3	H	H	H	H	$C(CH_3)_3$	NH	96–98 (4.8)	1.4247
23	CF_3	H	H	H	H	C_2H_5	O	108–109 (25)	1.4016
24	CF_3	CH_3	H	H	H	C_2H_5	O	100.5–101 (15)	1.4007
25	CF_3	H	H	CH_3	H	C_2H_5	O	99–99.5 (13)	1.4007
26	CF_3	H	H	H	H	$C(CH_3)_3$	O	92–92.5 (7.5)	1.4055
27	CF_3	H	H	H	CH_3	C_2H_5	O	84–85 (6.5)	1.4060
28	CF_3	H	H	CO_2H	H	C_2H_5	S	124.5–125.5	

[a] Satisfactory analytical values (±0.30% for C, H, N, F, and S) were reported for all compounds. [b] Mixture of isomers.

11 and 12. In the case of ethyl 3-ketobutanoate such a salt is not possible; thus no diazepinone is formed. Ethyl 4,4,4-trichloro-3-ketobutanoate, which is sufficiently enolic to form a salt, was reported to yield only a diazepinone.[14] In this case, the carbinolamine which would result from attack at the keto carbonyl could be expected to undergo a haloform-type of cleavage rather than forming the imidazolidine.

Experimental Section[15]

General.—Compound 1 was prepared by the procedure of McBee, *et al.*[16] However, if this procedure was followed exactly, an explosion occurred on three consecutive runs. Thus the conditions were modified as described for the preparation of ethyl 3-keto-4,4,5,5,5-pentafluoropentanoate (8). No accidents occurred in about 20 runs. Compound 1 was purified through its copper chelate.[17] 1,2-Diaminoethane (Fisher, 99%) was stored over calcium hydride and used without purification. Unless otherwise indicated the keto ester–amine condensations were conducted in a wide-mouth reaction flask with a four-necked head equipped with a Dean–Stark trap, an efficient condenser and a drying tube. The reactions were stirred magnetically and heated with a heating mantle. Reagents were added from a weighing buret that served as an addition funnel. After the reaction was completed, the solvent was removed under reduced pressure, and the residue distilled *in vacuo*, first on a short-path apparatus and then on a spinning-band column.

1,2,3,4-Tetrahydro-7-trifluoromethyl-1,4-diazepin-5-one (2).—A flask containing 1.98 g (0.01 mol of *N*-(2-aminoethyl)-3-hydroxy-4,4,4-trifluoro-2-butenamide (12) was heated in an oil bath at 160–170° for 0.5 hr. The reaction melted and foamed, and water vapor was evolved. After being heated for 15 min the melt solidified. The yield was almost quantitative. Recrystallization from methanol afforded 0.85 g (47%) of pure diazepinone 2: mp 191–192° (lit.[3] mp 191.5–192.5°); ir (KBr) 1650 and 1560 cm^{-1} (amide C=O); in dilute $HCCl_3$ solution 3424 cm^{-1} (*cis*-amide and *sec*-amide NH); nmr (in acetone-d_6) δ 7.33 (broad s, 1 H, amide NH), 6.92 (broad s, 1 H, amine NH), 4.93 (s, 1 H, vinyl), 3.48 (m, 4 H, ring methylene.)

Ethyl 2-(Trifluoromethyl)-2-imidazolidineacetate (3).—A solution of 6.0 g (0.1 mol) of 1,2-diaminoethane in 10 ml of benzene was added, over a period of 0.5 hr, to 18.4 g (0.1 mol) of 1 dissolved in 100 ml of refluxing benzene. The reaction mixture was refluxed for 5 hr. Water was collected in a Dean–Stark tube, the solvent was removed by distillation, and the residue distilled in a short-path apparatus at 15 mm to afford 18.3 g (81%) of 3, bp 110–113° (15 mm). The distillate solidified in the receiver and was recrystallized from CCl_4: mp 40.5–41° (lit.[3] mp 40.5–41°); ir 1729, 1735 (sh), 1745 cm^{-1} (sh) (NH); nmr δ 1.26 (t, 3 H, CH_2 ester), 4.15 (q, 2 H, J = 7 Hz, CH_2 ester), 2.61 (s, 2 H, α-methylene), 3.05 (s, 4 H, ring methylenes).

Reaction of 1-Aminopentane with 1. A. Addition of Amine to Keto Ester, in Benzene. Ethyl 3-(1-Pentylamino)-4,4,4-trifluoro-2-butenoate (4).—1-Aminopentane (4.35 g, 0.05 mol) in 10 ml of benzene was added over a period of 2 hr to a solution of 9.2 g (0.05 mol) of 1 in 100 ml of refluxing benzene and the mixture heated for an additional hour. The enamine 4 was obtained: 10.8 g (86%); bp 104° (10.0 mm); $n^{25}D$ 1.4375.

Anal. Calcd for $C_{11}H_{18}F_3NO_2$: C, 52.17; H, 7.16; F, 22.51; N, 5.53. Found: C, 52.33; H, 7.34; F, 22.38; N, 5.42.

B. Addition of Keto Ester to Amine, in Benzene.—To 4.35 g (0.05 mol) of 1-aminopentane dissolved in 100 ml of refluxing benzene was added 9.2 g (0.05 mol) of 1 over a period of 1 hr and the reaction refluxed for an additional hour. After the solvent and volatile substances were removed under reduced pressure, the residue, 12.5 g (83.5%), solidified upon standing overnight. It was a waxy solid, mp 76–80°. Distillation on a short-path apparatus, bp 88–89° (6.0 mm), gave a product that did not solidify completely, $n^{25}D$ 1.4355. This was a mixture of amine salt 5 and enamine 4. When the mixture was heated at 150°, the salt was converted to the enamine, $n^{25}D$ 1.4372. The ir of this product was identical with the ir of the material prepared by method A.

C. Addition of Amine to Keto Ester, Neat. Salt of Ethyl 3-Hydroxy-4,4,4-trifluorobutenoate with 1-Aminopentane (5).—

(14) D. K. Wald and M. M. Joullié, *J. Org. Chem.*, **31**, 3369 (1966).

(15) Melting points were determined on a calibrated Thomas–Hoover apparatus and are corrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. The infrared spectra were determined on a Perkin-Elmer 521 double-beam spectrophotometer either as potassium bromide pellets or as solutions in 0.2-mm sodium chloride cells. High dilution spectra were determined in 10-mm quartz cells. Nuclear magnetic resonance spectra were determined either on a Varian Associates HA-60-EL or A-60A spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane as internal standard (δ). All spectra are taken in CCl_4 unless otherwise noted. The ultraviolet spectra were obtained on a Cary 14 spectrophotometer in 1-cm quartz cells. Mass spectra were obtained on a Consolidated Electrodynamics Corp. 21-130 cycloidal mass spectrometer. Some mass spectra were recorded by the Morgan Schaffer Corp., Montreal, Canada. Vapor phase chromatographic analyses were carried out on a F & M Model 700 chromatograph with a thermal conductivity detector, helium carrier gas at a flow rate of 60 cc per min, using 6 ft long. 0.25 in. o.d. packed columns. The oven temperature was programmed at 10° per minute from 70° to the upper limit of the packing used. For preparative work, an Aerograph Autoprep A-700 instrument was employed. Solid samples were recrystallized to constant melting point and dried in an Abderhalden drying pistol *in vacuo*. Liquid samples were redistilled on a Nester–Faust NF-190 spinning-band column (6 × 450 mm, 23 theoretical plates).

(16) E. T. McBee, O. R. Pierce, H. W. Kilbourne, and E. R. Wilson, *J. Amer. Chem. Soc.*, **75**, 3152 (1953).

(17) A. L. Henne, M. S. Newman, L. L. Quill, and R. A. Staniforth, *ibid.*, **69**, 1819 (1947).

To 1.841 g (0.01 mol) of **1** in a serum-stoppered flask was added from a syringe, with stirring and cooling in ice, 0.872 g (0.01 mol) of 1-aminopentane. The reaction solidified almost immediately. Very rapid recrystallization from CCl_4 gave the pure salt **5**, mp 82.5–83.5°.

Anal. Calcd for $C_{11}H_{20}F_3NO_3$: C, 48.70; H, 7.43; F, 21.01; N, 5.16. Found: C, 48.74; H, 7.42; F, 20.89; N, 5.33.

Ethyl 3-Methoxy-4,4,4-trifluoro-2-butenoate (6).—A solution of 18.4 g (0.1 mol) of **1** in 50 ml of ether was treated with an excess of diazomethane prepared from 22 g of Du Pont ERX-101. The yellow solution was left standing overnight. The ether was removed by evaporation under nitrogen and the residue distilled, to give 16.7 g (85%) of **6**: bp 85–86° (90 mm); $n^{25}D$ 1.3834; vpc on SF-1265 column indicated 99+% purity; ir 1730 (C=O), 1667 (C=C), 1250, 1030 (CO vinyl ether), 1295 and 1155 (CO unsaturated ester), 1200 cm^{-1} (CF_3); nmr (neat) δ 5.78 (s, 1 H, vinyl) 4.05 (s, 3 H, OCH_3), 4.20 (2 H, J = 7 Hz, CH_2 ester), 1.28 (t, 3 H, J = 7 Hz, CH_3 ester).

Anal. Calcd for $C_7H_9F_3O_3$: C, 42.43; H, 4.58; F, 28.77. Found: C, 42.61; H, 4.75; H, 28.52.

Ethyl 3-Methoxy-3-(1-pentylamino)-4,4,4-trifluorobutanoate (7).—To 1.982 g (0.01 mol) of ice-cold **6**, 1-aminopentane (0.872 g, 0.01 mol) was added with stirring and cooling. The product formed was analyzed without any further purification: $n^{25}D$ 1.4222; ir 3370 (NH), 1730 cm^{-1} (C=O); nmr δ 3.28 (s, 3 H, OCH_3), 2.65 (s, 2 H, α-methylene).

Anal. Calcd for $C_{12}H_{22}F_3NO_3$: C, 50.52; H, 7.77; F, 19.98; N, 4.91. Found: C, 50.48; H, 7.49; F, 20.14; N, 4.97.

Upon attempted distillation or vapor phase chromatography, the compound lost methanol and was converted to **4**. Loss of methanol also occurred upon standing at room temperature for 2 or 3 days.

Ethyl 3-Keto-4,4,5,5,5-pentafluoropentanoate (8).—To a suspension of 0.5 mol of sodium hydride dispersion (in mineral oil) in 200 ml of anhydrous ether was added slowly, and with cooling, 96 g (0.5 mol) of ethyl perfluoropropanoate, followed by 44 g (0.5 mol) of ethyl acetate. The reaction was refluxed overnight, cooled, and poured onto a mixture of 300 g of ice and 30 ml of concentrated sulfuric acid. The ether layer was separated and the aqueous solution extracted three times with 100-ml portions of ether. The combined ether extracts were distilled (200 mm) to remove the ether; the residue was poured into a solution of 100 g of cupric acetate in 500 ml of water. The precipitated bis(ethyl pentafluoropropionoacetate)copper(II) was dried *in vacuo*, washed with petroleum ether to remove the mineral oil, and dried: yield, 100 g (76%); mp 154–155°.

Anal. Calcd for $C_{14}H_{12}CuF_{10}O_6$: C, 31.86; H, 1.91; F, 36.00. Found: C, 32.04; H, 2.25; F, 35.69.

The copper chelate was suspended in 200 ml of anhydrous ether, treated with hydrogen sulfide until all copper precipitated, and filtered through "Super Cel." The ether was evaporated and the residue distilled on a spinning-band column to yield 76.7 g (87%) of **8**: bp 142°; $n^{25}D$ 1.3630; ir 1670 and 1650 (sh) (C=O), also strong bands at 1250, 1220, and 1110 cm^{-1}.

Anal. Calcd for $C_7H_7F_5O_3$: C, 35.91; H, 3.02; F, 40.57. Found: C, 36.10; H, 3.08; F, 40.82.

Reaction of 1,2-Diaminoethane with Ethyl 3-Keto-4,4,5,5,5-pentafluoropentanoate. A. Addition of Amine to Keto Ester.—To a solution of 12.0 g (0.051 mol) of **8** in 80 ml of refluxing benzene was added dropwise, during 2 hr, 3.0 g (0.05 mol) of 1,2-diaminoethane dissolved in 20 ml of benzene. The reaction mixture was refluxed overnight and cooled to produce 5.9 g of a white solid which was redissolved in benzene, 1.2 g (9.7%) being insoluble. The insoluble material, *N*-(2-aminoethyl)-3-hydroxy-4,4,5,5,5-pentafluoro-2-pentenamide (**10**), was recrystallized from methanol: mp 202–206° dec; ir (KBr) 3400–2400 ($^+NH_3$), 3250 (amide ^+NH), 1645, 1630 (C=O), 1530 ($^+NH_3$), and also bands at 1565, 1250, and 740 cm^{-1}.

Anal. Calcd for $C_7H_9F_5N_2O_2$: C, 33.88; H, 3.65; F, 38.28; N, 11.29. Found: C, 34.04; H, 3.73; F, 38.32; N, 11.11.

The soluble part, 4.6 g (32%) of ethyl 3-hydroxy-4,4,5,5,5-pentafluoro-2-pentenoate salt with 1,2-diaminoethane (**11**), was again recrystallized from benzene, mp 117–117.5°.

B. Addition of Keto Ester to Amine.—To 3.0 g (0.05 mol) of 1,2-diaminoethane dissolved in 100 ml of refluxing benzene was added a solution of 12.0 g (0.051 mol) of **8** in 10 ml of benzene. A precipitate formed immediately upon addition of the first few drops of keto ester. The mixture was refluxed for 48 hr and cooled to afford 5.5 g of solid, which was separated with hot benzene into 4.0 g (32%) of **10** and 1.5 g (10%) of **11**. The benzene filtrate was evaporated and the residue distilled on a short-path apparatus, to yield 3.6 g (26%) of imidazolidine **9**.

Ethyl 3-Hydroxy-4,4,4-trifluoro-2-butenoate Salt with 1,2-Diaminoethane (12).—To a solution of 1.841 g (0.01 mol) of **1** in 10 ml of CCl_4 was added, with stirring and cooling in ice, 0.629 g (0.0105 mol) of 1,2-diaminoethane. The solid that formed was left in the ice bath for 1 hr, collected, washed with CCl_4, and dried. A salt (**12**) 2.24 g (91%), mp 84.5–86°, was obtained. The analytical sample was recrystallized from chloroform: mp 86.5–87.5°; ir (KBr) 3360, 3290 (bonded NH_2), 1700, 1660, 1630 (C=O, free and bonded), and also strong bands at 1270, 1180, and 1120 cm^{-1}; nmr ($DCCl_3$) δ 5.12 (s, 5 H, $^+NH_3$), 5.04 (s, 1 H, vinyl), 2.90 (s, 4 H, methylene), 4.04 (q, 2 H, J = 7 Hz, CH_2 ester), and 1.22 (t, 3 H, J = 7 Hz, CH_3 ester).

Anal. Calcd for $C_6H_{15}F_3N_2O_3$: C, 39.36; H, 6.19; F, 23.34; N, 11.46. Found: C, 39.56; H, 6.20; F, 23.18; N, 11.60.

***N*-(2-Aminoethyl)-3-hydroxy-4,4,4-trifluoro-2-butenamide (13).**—A solution of 4.6 g (0.025 mol) of **1** and 1.5 g (0.025 mol) of 1,2-diaminoethane in 25 ml of cold chloroform was allowed to stand at room temperature. A white crystalline precipitate began to form and continued to increase over a period of 2 weeks. The amide salt **13**, 3.55 g (72%), was collected in several crops. The analytical sample was recrystallized from methanol: mp 163–164° dec (with gas evolution); ir (KBr) 1630 (C=O) and strong bands at 1240, 1180, and 1105 cm^{-1}.

Anal. Calcd for $C_6H_9F_3N_2O_2$: C, 36.37; H, 4.58; F, 28.77; N, 14.44. Found: C, 36.61; H, 4.67; F, 28.69; N, 14.05.

Reaction of 1,2-Diaminopropane with 1. A. Addition of 1 to Amine.—To 7.4 g (0.1 mol) of 1,2-diaminopropane dissolved in 100 ml of refluxing benzene was added over a period of 1 hr a solution of 18.4 g (0.1 mol) of **1** in 15 ml of benzene. The reaction was refluxed overnight and during this time 3.0 ml of lower phase were collected. A white precipitate suspended in solution was recovered by filtration to afford 3.1 g (14.5%) of the amide salt **15**, mp 189.5–190.5°. The analytical sample was recrystallized from methanol, mp 190–190.5°.

Anal. Calcd for $C_7H_{11}F_3N_2O_2$: C, 39.63; H, 5.23; F, 26.86; N, 13.20. Found: C, 39.84; H, 5.43; F, 26.66; N, 13.42.

The benzene filtrate was distilled and the residual oil fractionated on a short-path distillation apparatus at 6-mm pressure; 9.7 g (40.5%) of **14** was collected, bp 91–97°. This compound was redistilled on a spinning-band column, bp 93–94° at 10-mm pressure, $n^{25}D$ 1.4172.

Anal. Calcd for $C_9H_{15}F_3N_2O_2$: C, 45.00; H, 6.29; F, 23.73; N, 11.66. Found: C, 45.09; H, 6.51; F, 23.48; N, 11.78.

B. Addition of Amine to 1. Preparation of Ethyl 4-Methyl-2-(trifluoromethyl)-2-imidazolidineacetate (14).—To a solution of 18.4 g (0.1 mol) of **1** in 90 ml of refluxing benzene was added over a period of 1 hr 7.4 g (0.1 mol) of 1,2-diaminopropane dissolved in 10 ml of benzene. The reaction was refluxed for 3 hr; 2.2 ml of lower phase were collected. The benzene was removed by distillation and the residue left standing overnight. A trace of amide salt **15** crystallized and was removed by filtration (200 mg). The filtrate was distilled on a short-path distillation apparatus at 6-mm pressure and 16.35 g (68%) of the imidazolidine **14**, bp 95–96°, was collected. This sample was redistilled on a spinning-band column.

Preparation of Ethyl 4,5-Dimethyl-2-(trifluoromethyl)-2-imidazolidineacetate (17).—The above compound was prepared from 8.8 g (0.1 mol) of 2,3-diaminobutane and 18.4 g of **1** according to procedure B.

Preparation of 1,2,3,4-Tetrahydro-2-methyl-7-trifluoromethyl-1,4-diazepin-5-one (16).—*N*-(2-Aminopropyl)-4,4,4-trifluoro-3-hydroxy-2-butenamide (**3**) 2.12 g (0.01 mol), was heated in an erlenmeyer flask at its melting point for 15 min. The mixture foamed and water vapor was evolved. It was cooled, dissolved in chloroform, and left to crystallize; 1.4 g (72.5%) of colorless crystals, mp 135–136°, were obtained. The analytical sample was recrystallized from chloroform, mp 135.5–136°.

Anal. Calcd for $C_7H_9F_3N_2O$: C, 43.30; H, 4.67; F, 29.36; N, 14.43. Found: C, 43.43; H, 4.75; F, 29.58; N, 14.33.

Reaction of 1,3-Diaminopropane with 1. A. Addition of Keto Ester to Amine.—To 7.4 g (0.1 mol) of 1,3-diaminopropane dissolved in 100 ml of refluxing benzene was added over a period of 2 hr 18.4 g (0.1 mol) of **1** dissolved in 15 ml of benzene. The reaction turned turbid and a white precipitate formed. The mixture was heated overnight. The solid formed was collected by filtration to give 5.4 g (25.4%) of **20**, mp 181–183°. The compound was recrystallized from methanol, mp 183–184°.

Anal. Calcd for $C_7H_{11}F_3N_2O_2$: C, 39.63; H, 5.23; F, 26.86; N, 13.20. Found: C, 39.88; H, 5.31; F, 26.91; N, 13.26.

The benzene filtrate was distilled and a semisolid was obtained, bp 74–80° (1.55 mm). This material was dissolved in CCl_4 and placed in a refrigerator to crystallize. A solid, **21**, was obtained, 5.5 g (36%), mp 110–111° (lit.[13] mp 110–111°).

Anal. Calcd for $C_5H_7F_3N_2$: C, 39.48; H, 4.64; F, 37.47; N, 18.41. Found: C, 39.50; H, 4.80; F, 37.25; N, 18.39.

The carbon tetrachloride filtrate was distilled. It contained ethyl 2-(trifluoromethyl)-2-perhydropyrimidineacetate (**22**) which could not be obtained analytically pure by this method.

Ethyl 2-(Trifluoromethyl)-2-perhydropyrimidineacetate (22).—To a solution of 18.4 g (0.1 mol) of **1** in 120 ml of refluxing benzene was added over a 1-hr period 7.4 g (0.1 mol) of 1,3-diaminopropane dissolved in 20 ml of benzene. The reaction was refluxed overnight. The benzene was removed by distillation and the residual oil was distilled on a short-path apparatus at 2-mm pressure to yield 13.45 g (56%) of **10**, bp 84–85° (2 mm), $n^{25}D$ 1.4285.

Anal. Calcd for $C_9H_{15}F_3N_2O_2$: C, 45.00; H, 6.29; F, 23.73; N, 11.66. Found: C, 44.75; H, 6.09; F, 23.66; N, 11.91.

Reaction of 2-Aminoethanol with 1. General Procedure. Ethyl 2-(trifluoromethyl)-2-oxazolidineacetate (23). A. Addition of Amine to Keto Ester.—To a solution of 18.4 g (0.1 mol) of **1** in 80 ml of refluxing benzene was added over a period of 1 hr 6.1 g (0.1 mol) of 2-aminoethanol. The reaction mixture was heated for 5 hr. The benzene was removed by distillation and the residue distilled on a short-path apparatus.

B. Addition of Keto Ester to Amine.—To 6.1 g (0 1 mol) of 2-aminoethanol was added slowly 2 ml of glacial acetic acid followed by 18.4 g (0.1 mol) of **1**. The mixture was heated at 130° for 2 hr and then distilled on a short-path apparatus to yield 9.7 g (43%) of **23**.

Procedure A was used to prepare the other oxazolidines shown in Table I (**23–27**). The yields obtained varied from 55 to 75%. Cysteine was condensed by the same procedure to yield 45% of ethyl 4-carboxy-2-trifluoromethyl-2-thiazolidineacetate (**28**, Table I).

Reaction of 1 with 3-Aminopropanol. Preparation of Ethyl 2-Trifluoromethyl-2-(1,3-oxazine)acetate (29).—To a solution of 18.4 g (0.1 mol) of **1** in 80 ml of refluxing benzene was added over a period of 1 hr 7.5 g (0.1 mol) of 3-aminopropanol. The reaction was refluxed overnight, the benzene removed by distillation, and the residue distilled on a short-path apparatus to yield 18.4 g (76%) of the oxazine **29**, bp 85–90° (3.5 mm). The compound was redistilled on a spinning-band column, bp 104–104.5° (15 mm), $n^{25}D$ 1.4117.

Anal. Calcd for $C_9H_{10}F_3NO_3$: C, 44.81; H, 5.85; F, 23.63; N, 5.81. Found: C, 44.59; H, 5.80; F, 23.72; N, 5.79.

Reaction of 23 with Methylmagnesium Iodide.—To a Grignard solution prepared from 4.8 g (0.2 g-atom) of Mg turnings and 28.4 g (0.2 mol) of iodomethane in 150 ml of anhydrous ether, a solution of 5.7 g (0.024 mol) of **23** in 15 ml of ether was added dropwise. The reaction was refluxed for 2 hr and allowed to stand overnight. The magnesium salt was decomposed with saturated ammonium chloride solution, and the ether layer separated and evaporated. The residue was distilled on a short-path apparatus to yield 13.5 g (89%) of ethyl 3-(2-hydroxyethylamino)-4,4,4-trifluoro-2-butenoate: bp 95–96° (1.5 mm); mp 23–24°; $\lambda_{max}^{C_6H_{14}}$ 285 mμ (log ε 4.18).

Anal. Calcd for $C_8H_{12}F_3NO_3$: C, 42.29; H, 5.33; F, 25.09; N, 6.17. Found: C, 42.47; H, 5.54; F, 24.92; N, 6.25.

A solution of 1.63 g (0.0072 mol) of ethyl 3-(2-hydroxyethylamino)-4,4,4-trifluoro-2-butenoate in 10 ml of benzene was refluxed and the progress of cyclization to **23** was followed. After 3 hr, only 5% of **23** was present, after 24 hr, 35% was observed. After 48 hr, about 60% of **23** was formed. This rate of formation of **23** is much slower than the rate observed for the condensation of **1** with 1-aminoethanol.

***tert*-Butyl 3-Keto-4,4,4-trifluorobutanoate (30).**—This ester was obtained by the method used for **1**, but as a hydrate, mp 69.5–70°, yield 56%. All attempts to dehydrate it resulted in decomposition. It was sublimed under reduced pressure to obtain an analytically pure sample.

Anal. Calcd for $C_8H_{11}F_3O_3H_2O$: C, 41.74; H, 5.69; F, 24.76. Found: C, 41.75; H, 5.89; F, 24.98.

The copper chelate of **30** was obtained in the usual manner, mp 141.5–142°.

Anal. Calcd for $C_{16}H_{20}F_6O_6Cu$: C, 39.55; H, 4.15; F, 23.46. Found: C, 39.80; H, 4.30; F, 23.34.

Ethyl 3-Keto-2-methyl-4,4,4-trifluorobutanoate (31).—This ester was also prepared by the method used for **1**: yield 50.2%; bp 85° (100 mm); $n^{25}D$ 1.3693 [lit.[18] bp 57.8 (26 mm); $n^{20}D$ 1.3650]. The copper chelate of **31** was obtained in the usual manner, mp 137–137.5°.

Anal. Calcd for $C_{14}H_{16}F_6O_6Cu$: C, 36.73; H, 3.52; F, 24.90. Found: C, 36.54; H, 3.54; F, 24.72.

Ethyl 2,2-Dimethyl-3-keto-4,4,4-trifluorobutanoate (32).—To a sodium amalgam, prepared from 14 g of sodium and 1 kg of mercury, was added under a stream of nitrogen, a solution of 70 g (0.25 mol) of triphenylchloromethane in 1.5 l. of anhydrous ether.[19] This mixture was shaken mechanically for 3 hr. The red solution was allowed to settle and was siphoned (under exclusion of air) into a nitrogen-swept erlenmeyer flask. Ethyl isobutyrate (24.0 g, 0.21 mol) and ethyl trifluoroacetate (28.4 g, 0.20 mol) were added and the solution was stirred magnetically for 1 hr. Glacial acetic acid (30 ml) and 100 ml of water were added to the solution. The ether layer was separated, washed, dried, and reduced in volume. The triphenylmethane formed was removed by filtration and the filtrate distilled on a spinning-band column to yield a pure sample of 32 g, bp 144.5–145.5°, $n^{25}D$ 1.3674.

Anal. Calcd for $C_8H_{11}F_3O_3$: C, 45.29; H, 5.23; F, 26.86. Found: C, 45.26; H, 5.19; F, 26.58.

When a solution of 10.3 g (0.0486 mol) of **32** in 100 ml of refluxing benzene was added dropwise to a solution of 3.0 g (0.05 mol) of 1,2-diaminoethane in 7 ml of benzene and the reaction mixture heated in the usual manner, no water separated. Evaporation of the benzene yielded a white solid identified as *N,N'*-bistrifluoroacetyl-1,2-diaminoethane, mp 202–202.5° (lit.[20] mp 201.5–202.5°). The presence of ethyl isobutyrate in this reaction and in the condensation of **20** with 2-aminoethanol indicated a reverse Claisen reaction.

Registry No.—**2**, 14120-51-5; **3**, 14120-52-6; **4**, 26717-82-0; **5**, 26717-83-9; **6**, 26717-84-0; **7**, 2617-85-1; **8**, 26717-86-2; **8** (copper chelate), 26785-67-1; **9**, 26717-87-3; **10**, 26717-88-4; **11**, 26717-89-2; **12**, 26717-90-8; **13**, 26717-91-9; **14**, 26717-92-0; **15**, 26717-93-1; **16**, 26717-94-2; **17**, 26717-95-3; **18**, 26717-96-4; **19**, 26717-97-5; **20**, 26717-98-6; **22**, 26717-99-7; **23**, 26718-00-3; **24**, 26718-01-4; **25**, 26717-71-5; **26**, 26717-72-6; **27**, 26717-73-7; **28**, 26717-74-8; **29**, 26785-70-6; **30**, 26717-75-9; **30** (copper chelate), 26736-15-2; **31** (copper chelate), 26736-16-3; **32**, 26717-76-0; ethyl 3-(2-hydroxyethylamino)-4,4,4-trifluoro-2-butenoate, 26717-77-1.

Acknowledgment.—The authors want to thank Mr. William B. Edwards, III, for his skillful assistance with the nmr spectra. Financial aid from the National Institute of Health (Research Fellowship 5-FI-GM-32,573-02) for the years 1966 and 1967 is gratefully acknowledged.

(18) E. T. McBee, C. E. Hathaway, and C. W. Roberts, *J. Amer. Chem. Soc.*, **78**, 4053 (1956).

(19) B. E. Hudson, Jr., and C. R. Hauser, *ibid.*, **63**, 3156 (1941).

(20) M. M. Joullié and A. R. Day, *ibid.*, **76**, 2990 (1954).

Chemistry of Imides. II. Cyclic Imides and Some Unusual Products from Some Diacid Chlorides and Lithium Nitride[1a]

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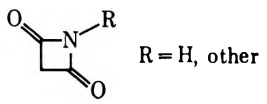
Received June 22, 1970

Diacid chlorides react with lithium nitride (Li_3N) under extremely mild conditions (in 1,2-dimethoxyethane at 0°). Phthaloyl chloride gives up to 70% phthalimide, 5% phthalic anhydride, and 10% *o*-cyanobenzamide, the result of an unusual deoxygenation. In a separate experiment, it was found that phthaloyl chloride reacts quantitatively with anhydrous Li_2O to form the anhydride. Succinyl chloride also reacts with Li_3N to give 35% succinimide, large amounts of a polyimide, and about 10% of a new compound, 4-(*N*-succinimidyl)-4-hydroxy-*cis*-2-butenoic acid lactone (**7**). It is noticed that the 4 proton in this and other α,β-unsaturated γ lactones are unusually deshielded ($\gtrsim$400 ppm from TMS) for an sp^3 CH. Malonyl chloride, even under high dilution conditions, fails to form the as yet unknown C-unsubstituted malonimide; only dark, resinous condensation polymers were recovered.

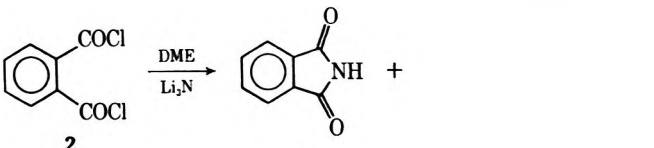
Synthesis of the as yet unknown C-unsubstituted malonimides (**1**) (2,4-azetidinediones)[2] has been under active investigation in our laboratories.[4] Baldwin and Koenig have reported[5] that lithium nitride (Li_3N) reacts at room temperature with aromatic acid chlorides to form triacyl amines[6] $(RCO)_3N$ in fair yield. It was thought that under suitable conditions diacid chlorides would react with Li_3N to form cyclic imides. The very mild reaction conditions would be of distinct advantage compared to the usual high temperature, acid- or base-catalyzed preparations, especially in view of the special problems associated with **1**.[4]



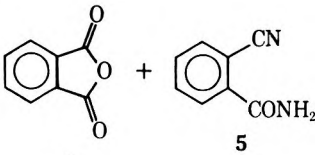
1

The reaction does indeed yield cyclic imides with succinyl and phathaloyl dichlorides in addition to other unusual products. The solvent used was 1,2-dimethoxyethane (DME); the nature of products from the heterogeneous reaction (Li_3N is insoluble) is independent of acid chloride concentration, avoiding the necessity of high dilution conditions. Equimolar amounts of reactants are stirred under N_2 at or near 0°, usually until the reddish Li_3N is consumed (see Experimental Section).

Phthaloyl chloride (**2**) reacts spontaneously and exothermically, yielding a white precipitate within a few minutes, which turns brown on standing. After quenching of the reaction with absolute ethanol and work-up of the residue, the following compounds are obtained (yields for a typical run, based on phthaloyl chloride): phthalimide, **3** (68%); phthalic anhydride, **4** (4%); 2-cyanobenzamide, **5** (10%); polymer (18%). Formation of imide **3** probably requires two steps: attack of a nucleophilic species $[Li_xN^{-(3-x)}]$[5] on one carbonyl, followed by intramolecular displacement of the second Cl. Formation of **4** and **5** was unexpected; a possible

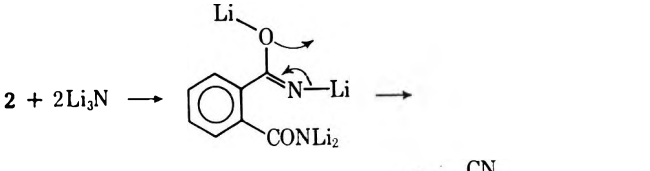


2 **3**



4 **5**

mechanism for **5** involves intermediate **6**. There is precedent in the formation of phenylacetonitrile from the reaction of phenylacetamide and butyllithium.[7] We also propose that the Li_2O formed with **6** reacts with unreacted **1** to yield **4**. In a separate experiment, anhydrous Li_2O was found to react with **1** quantitatively to give the anhydride.



6

The reaction with succinyl chloride was also rapid and exothermic, but the results differ considerably, due in part to the presence of α hydrogens. Succinimide was formed in 35% yield along with 3% succinic anhydride and a new compound **7** (7%); however, large amounts (54%) of a polyimide were also formed. The analog of **5**, *viz.* 3-cyanopropionamide, was not detected; this is not unexpected in view of the acidity of the α H's. Similar difficulties had been found in the reaction of Li_3N with acetyl chloride, from which only a very small amount of diacetamide could be recovered.[5] The new compound, **7**, had the following properties: *m/e* 181

(1) (a) Paper I: A. J. Gordon, *Tetrahedron*, **23**, 863 (1967). (b) Acknowledgment is made to the Research Corporation (N. Y.) and to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research. To whom correspondence should be addressed. (c) NDEA Fellow, 1968–1970.

(2) For reviews of the C-substituted compounds, see E. Testa, *Farmaco*, **17**, 168 (1962) and A. Ebnöther, *et al.*, *Helv. Chim. Acta*, **42**, 918 (1959). A reported[3] synthesis of *N*-phenylmalonimide has been shown to be incorrect.[4] The only C-unsubstitued malonimides known are the atypical *N*-sulfonyl derivatives [E. Mundlos and R. Graf, *Justus Liebigs Ann. Chem.*, **677**, 108 (1964)].

(3) W. H. Warren and R. A. Brigge, *Chem. Ber.*, **64**, 26 (1931).

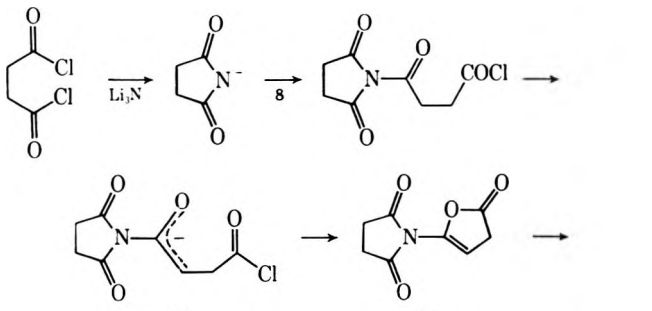
(4) A. J. Gordon and R. L. E. Ehrenkaufer, "Chemistry of Imides. III," in preparation.

(5) F. Baldwin and P. Koenig, *J. Org. Chem.*, **30**, 671 (1965).

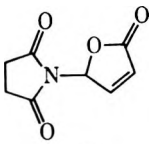
(6) May also be called *N,N*-diacylamides or *N*-acylimides; the recommended (IUPAC) term for such compounds (contrary to popular usage) is tertiary amide.

(7) E. Kaiser, R. Vaulx, and C. Hauser, *Tetrahedron Lett.*, 4833 (1965).

and analysis for $C_8H_7NO_4$; ir ($CHCl_3$) 3020 (w), 1800 (s), 1762 (w), 1730 (s), 1460 (m); nmr ($CDCl_3$–DMSO-d_6, internal TMS) δ 2.72 (s, 4 H), 6.39 (d of d, 1 H), 6.58 (multiplet, 1 H), 7.65 (d of d, 1 H); uv (CH_3CN) λ_{max} 219 (ϵ 3490). The assigned structure, **7** [4-(*N*-succinimidyl)-4-hydroxy-*cis*-2-butenoic acid lactone], and a possible mechanism for its formation are shown below.

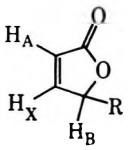


10 **11**



7

None of the unconjugated isomer **11** could be detected. The ir spectrum has the features of both an N-substituted succinimide and *cis*-4-hydroxy-2-butenoic acid lactone;[8] the uv spectrum is in agreement with that for the unsubstituted lactone [λ_{max} (heptane) 220 (ϵ 1670)].[8] The nmr spectrum shows an ABX pattern for the lactone ring, **12**. Assignments are in agreement with those



12

R = *N*-succinimidyl

δ_{H_A} 6.39, δ_{H_B} 6.58, δ_{H_X} 7.65
(J_{AX} = 5.8, J_{AB} = 2.0, J_{BX} = 1.4 Hz)

of the parent compound (**12**, R = H),[9] and the spectrum is in accord with a theoretical example given by Bovey.[10] The chemical shift of H_B is extremely low for an sp^3 C (395 Hz from TMS), even one containing two (or three) heteroatoms; however, this behavior appears to be typical of this lactone system.[11] The succinimide ring protons (δ 2.72) are typical (succinimide itself, δ 2.83); although **7** is a chiral molecule, no diastereotopic splitting was detected for the methylene protons.

In the reaction with malonyl chloride, anhydrous NH_4Cl or CH_3I were used in the work-up to avoid possible solvolysis of the desired **1** (R = H or CH_3), were it present. However, even under conditions of high dilution, only a dark resinous solid was obtained. Other approaches to the malonimide system will be discussed in another publication.[4]

(8) R. Smith and R. Jones, *Can. J. Chem.*, **37**, 2092 (1959).

(9) R. Freeman, *Mol. Phys.*, **5**, 499 (1962).

(10) F. Bovey, "NMR Spectroscopy," Academic Press, New York, N. Y., 1969, p 286.

(11) *E.g.*, P. Steyn, *et al.*, *J. Chem. Soc.*, 3075 (1965), report for **12** (R = Br, 2-phenyl derivative) δ, for H-4, 7.33 in $CDCl_3$.

Experimental Section[12]

Phthaloyl Chloride Reaction.—Phthaloyl chloride (Eastman) (2.03 g, 0.01 mol) in a few milliliters of 1,2-dimethoxyethane (distilled from Na–benzophenone) was added under N_2 to a suspension of Li_3N (Alfa Inorganics) (0.35 g, 0.01 mol) in 25 ml of DME at 0°. Reaction was spontaneous and exothermic, with a white precipitate (LiCl) forming within a few minutes. After stirring overnight, the darkened mixture was quenched with absolute ethanol (2 ml in 2 ml of Et_2O) at 0° and then filtered to remove LiCl. The following work-up simplified quantitative analysis. The filtrate was divided into two equal portions and solvent was removed from both to leave a dark brown residue. One portion was dissolved in 25 ml of 10% KOH (aqueous) and rapidly extracted with cold EtOAc; acidification of the aqueous layer, followed by $CHCl_3$–EtOAc extraction, gave, after removal of solvent, phthalimide **3** (0.50 g, 68% total yield) identified by mp and mmp 234° and superimposability of the ir spectrum with that of an authentic sample. The second portion was sublimed *in vacuo* at 200°; the sublimate was analyzed by vpc (2-m column, 15% SE-30/Chromsorb W, 65 cc He/min, column temperature 240°) which showed (retention time in minutes and yield based on starting material in parentheses) phthalic anhydride **4** (1.25, 4%), phthalimide **3** (1.75, 68%, from above recovery), *o*-cyanobenzamide **5** (2.30, 10%). The sublimation residue contained only polymeric material (ir) (18%). For a preparative run, the products could be separated on a silica gel column [benzene–petroleum ether (30–60°), benzene–$CHCl_3$, $CHCl_3$, EtOAc]. *o*-Cyanobenzamide (**5**) was identified by mp 173° (lit.[13] mp 173°) (compound recrystallizes and remelts at 190–194°): mass spectrum *m/e* 146; ir (KBr) 3360 and 3180 (s), 2230 (m), 1650 (s), 1630 (m), 1400 cm^{-1} (s). In addition, hydrolysis (75% H_2SO_4) of **5** at 150° gave a mixture of phthalamide (mp 219–220°) and phthalamic acid (148–149°), separated by fractional sublimation. Phthalic anhydride (**4**) was identified by its mp and mmp 131–132°, glc retention time, and comparison of its ir spectrum with authentic material; the same applies to phthalimide. To ensure that phthalic anhydride (**4**) was not an impurity in starting material, or did not come from unreacted **2** during work-up, glc analysis was performed on both starting **2**, which showed evidence for only a trace of **4**, and on the reaction mixture (under N_2) before work-up.

Succinyl Chloride Reaction.—Reaction conditions were identical with those of the phthaloyl chloride reaction, using 1.55 g (0.01 mol) of succinyl chloride (**8**) and 0.35 g (0.01 mol) of Li_3N. After stirring for 24 hr, the mixture was quenched as above and the solvent removed to yield a dark, sticky residue, which was chromatographed on silica gel to give **7** [mp 157° (sharp) (75:25 $CHCl_3$–C_6H_6) (0.13 g, 7%)], succinimide, and succinic anhydride ($CHCl_3$), separated by preparative vpc (same conditions as above, column temperature 150°) (anhydride, 2.20 min, 3%; imide, 4.70 min, 35%). Compound **7**, a new compound, had the following properties: mass spectrum *m/e* 181, 153, 109, 83, 82 (base), 70, 56, 55; ir ($CHCl_3$) 3020 (w), 1800 (s), 1762 (w), 1730 (s), 1460 cm^{-1} (m); uv (CH_3CN) λ_{max} 219 (ϵ 3490); nmr ($CDCl_3$–DMSO-d_6) δ 2.72 (s, 4 H), 6.39 (d of d, 1 H), 6.58 (m, 1 H), 7.65 (d of d, 1 H).

Anal. Calcd for $C_8H_7NO_4$: C, 53.04; H, 3.87; N, 7.73; O, 35.36. Found: C, 53.02; H 3.86; N, 7.58.

Malonyl Chloride Reaction.—The reaction was run as above; work-up was with anhydrous NH_4Cl or CH_3I. In addition, high dilution runs were made (0.01 mol in 500 ml of DME added dropwise to Li_3N in 100 ml of DME). In all cases, only dark, resinous solid was obtained, which is probably a mixture of polyimides and other condensation polymers [ir ($CHCl_3$) 2900–3000 (w), 1750 (br, s), 1610 (m), 1520 cm^{-1} (m)].

Registry No. —**7**, 26893-44-7; lithium nitride, 26134-62-3; phthaloyl chloride, 88-95-9; succinyl chloride, 543-20-4.

(12) All melting points are uncorrected. Yields in mole per cent are based on starting material. Ir spectra were recorded on a Beckman IR-8, mass spectra with a Varian-Mat CH-5, uv spectra on a Beckman DB-G, and nmr spectra with a Varian A-60. Combustion analyses from MHW Laboratories, Garden City, Mich.

(13) "Handbook of Tables for Organic Compound Identification," 3rd ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1967, p 205.

Synthesis of Cyclic Guanidines[1]

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Received June 29, 1970

A method is described whereby a variety of cyclic guanidines may be prepared *via* the intermediacy of tosyl-protected cyclic guanidines; the latter compounds are easily available from the reactions of both aliphatic and aromatic diamines with *S,S*-dimethyl-*N*-tosyliminodithiocarbonimidate. The detosylation reaction which results in guanidine formation proceeds quantitatively in anhydrous hydrogen fluoride.

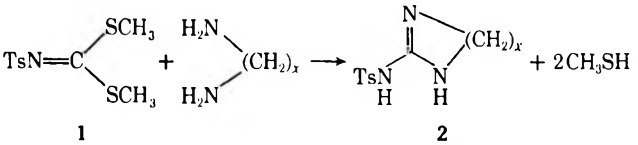
The observation that *S,S*-dimethyl-*N*-tosyliminodithiocarbonimidate (1) reacts with ethylenediamine and *o*-phenylenediamine to give high yields of the *N*-tosyl cyclic guanidines 2a and 3[3] prompted us to examine the possible general usefulness of this reagent for the generation of cyclic guanidines. This approach appeared to be especially attractive in view of a recent report from the peptide field which described the removal of the tosyl group from the guanido group of arginine using anhydrous hydrogen fluoride.[4] We now report that 1 reacts with a variety of aliphatic and aromatic diamines to give easily isolable tosyl-protected cyclic guanidines and that the usually difficult detosylation process[5] can be carried out in anhydrous hydrogen fluoride to give cyclic guanidines; the detosylation step is quantitative.

There are methods available for the synthesis of cyclic guanidines from diamines, both aliphatic and aromatic. Thus 2-amino-2-imidazoline and 2-aminobenzimidazole can be obtained as their salts by the action of cyanogen bromide on ethylenediamine and *o*-phenylenediamine, respectively,[9-11] and 2-amino-2-imidazoline is also available by the action of cyanamide or dimethylcyanamide on ethylenediamine monotoluene-*p*-sulfonate.[12] The latter method has also been extended to the preparation of the six-membered cyclic guanidine, 2-amino-3,4,5,6-tetrahydropyrimidine.[12] A second approach to cyclic guanidines in wide use involves the reaction of amines with 2-methylthio-1,3-diazines (available in two steps from diamines); this procedure has been used to prepare *N*-alkylguanidines of a wide variety.[13-15] Two other routes into the cyclic guanidine system, which have limited applicability, are hydrogenation of a 2-aminopyrimidine to obtain a 2-amino-3,4,5,6-tetrahydropyrimidine[16] and the fusion of guanidine with 4,5-diamino-6-hydroxypyrimidine to afford 8-amino-6-hydroxypurine.[17] We now report a synthesis *via* *S,S*-dimethyl-*N*-tosyliminodithiocarbonimidate as an alternative to the above. Inherent in this approach is the attractiveness of the intermediacy of the tosyl-protected guanidine which conceivably could be subjected to further chemical operations before the detosylation step required to generate a free guanidine.[18]

Synthesis of Tosyl-Protected Cyclic Guanidines.—*S,S*-Dimethyl-*N*-tosyliminodithiocarbonimidate (1) is a stable compound which can be easily prepared in high yield.[1] The reaction of 1 with aliphatic diamines proceeds readily in refluxing aqueous ethanol to give cyclic tosylguanidines in high yields. In addition to the guanidine a second product is produced which is insoluble in the hot reaction medium and which can be removed from the tosylguanidine by filtration; mass spectral data indicate these second products are compounds of high molecular weight and thus are probably polymeric in nature. In Table I are given the details of the reaction of 1 with four aliphatic diamines. The diamines were used directly or were generated *in situ* from their dihydrochlorides; the "polymeric" side products were removed by filtration of the hot reaction solution.

TABLE I

REACTION OF *S,S*-DIMETHYL-*N*-TOSYLIMINODITHIOCARBONIMIDATE (1) WITH ALIPHATIC DIAMINES



1 2

Diamine, X	Time, hr	Yield, % "Polymer"	Yield, % Tosylguanidine, 2
2	4	0	a, 87
3	9	6	b, 79
4	24	16	c, 76
6	48	100	d, 0

An unsymmetrical (*i.e.*, substituted) aliphatic diamine was next chosen for investigation. With the aim of preparing an optically active intermediate which might be potentially useful for the synthesis of the novel guanido amino acid capreomycidine (5),[16] we prepared the op-

* To whom correspondence should be addressed.

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(2) On special assignment from the U. S. Food and Drug Administration.

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(4) R. H. Mazur and G. Plume, *Experientia*, **24**, 661 (1968).

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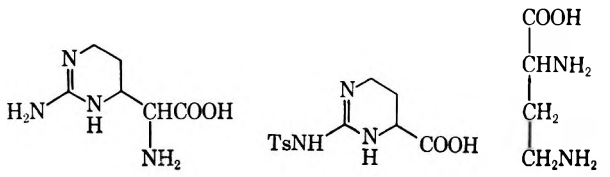
(18) The presence of the tosyl group on the guanidine moiety considerably reduces the basicity of this ordinarily strongly alkaline group. We have found that tosyl-protected guanidines do not form salts in the presence of HCl, whereas guanidines and acylguanidines do.

tically active tosylguanidine **6**. The required optically active 2,4-diaminobutyric acid (**7**) was available from



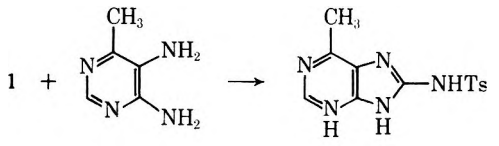
5 **6** **7**

L-(+)-glutaminc acid *via* a Schmidt rearrangement.[19] The unsymmetrical tosyl-protected cyclic guanidine was obtained in 83% yield by the reaction of the sodium salt of (+)-2,4-diaminobutyric acid (**7**) with **1** in refluxing aqueous ethanol followed by acidification of the reaction medium to regenerate the acid. Due to the low solubility of the tosyltetrahydropyrimidine **6**, optical rotation was not measured; however, the detosylated guanidine (see below) proved to be optically active.

No attempts were made to prepare *N*-alkylguanidines by this method since other work with **1** has shown that it is unreactive toward secondary amines. However, **1** can easily be converted to the dichloro compound;[20] the latter has been demonstrated to be highly reactive to secondary amines[21] and thus could conceivably be a useful reagent for the generation of *N*-alkyl cyclic guanidines corresponding to *N*-alkyl derivatives of **2**.

The general usefulness of the *N*-tosyldichlorocarbonimidate for the preparation of cyclic guanidines is, however, limited by the fact that an extra equivalent of the diamine (or some other base) is required in the reaction medium to neutralize the released acid. Dithio compound **1** requires, of course, only 1 equiv of diamine since the weak and volatile conjugate acid of CH_3S^- is released during the reaction.

The reactivity of **1** toward aromatic diamines is reduced considerably from that observed for its reaction with aliphatic diamines. Thus the tosylguanidine 2-*p*-tosylaminobenzimidazole (**3**) can be obtained in 72% yield from the reaction of **1** with *o*-phenylenediamine in DMF at 150–160° for 12–16 hr.[1] This procedure is quite similar to that[22] in which 2-benzenesulfonylaminobenzimidazole could be obtained by fusing *o*-phenylenediamine with benzenesulfonylguanidine. We have extended the reaction of **1** with aromatic diamines to the case of 6-methyl-4,5-diaminopyrimidine and have found that, at 150° in DMF for 16 hr, a 58% yield of 6-methyl-8-tosylaminopurine (**8**) is obtained.

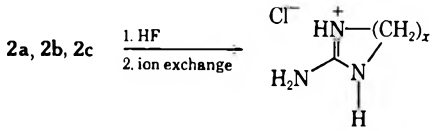


8

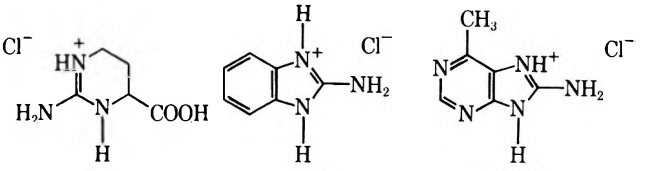
Detosylations Using Anhydrous Hydrogen Fluoride.—Detosylations of the six tosylguanidines described above were effected in anhydrous HF in a system similar to that diagrammed by Lenard.[23] Liquid HF was dried over cobalt fluoride, distilled into the reaction vessel, and subsequently removed without exposure to air or moisture. The residue was partitioned between benzene and water and the benzene extract contained the removed tosyl portion of the reaction mixture, which was characterized as tosyl fluoride.

The cyclic guanidines, as HF salts in water, were applied to an ion-exchange column, the HF was eluted with water, and the guanidine (as its hydrochloride) was removed with 4 *N* HCl. Evaporation left the guanidine salts which could be crystallized from isopropyl alcohol–ether. The products were quite hygroscopic and in all cases the yields were essentially quantitative (97–100%). The carboxy-substituted cyclic guanidine (**10**) proved to be optically active ($[\alpha]^{25}D$ +144°) and thus of potential value as an asymmetric intermediate in the synthesis of capreomycidine (**5**).

There seems to be no doubt as to the usefulness of anhydrous HF as a detosylating reagent for tosyl-protected guanidines. However, it is known that *p*-toluenesulfonamides are inert to this reagent. Sakakibara, *et al.*,[24] have reported that the tosyl group



9a, $x = 2$
9b, $x = 3$
9c, $x = 4$



10 **11** **12**

is not removed from tosyl-protected peptides under conditions in which a large number of protective groups can be removed from peptides (20° for periods of 30 min to 2 hr). We have found that *p*-toluenesulfonamide and tosylglycine are recovered completely intact after 24 hr exposure to anhydrous HF. Thus the applicability of the HF detosylation procedure is limited, but the bounds of its limitations have yet to be defined.

Experimental Section[25]

2-*p*-Toluenesulfonylamino-2-imidazoline (**2a**).—Ethylenediamine dihydrochloride (951 mg, 7.15 mmol) was dissolved in 5 ml of water and 14.3 ml of 1 *N* NaOH was added. Ethanol (75 ml) was added along with *S,S*-dimethyl-*N*-tosyliminodithiocarbonimidate[1] (**1**) (1.94 g, 7.15 mmol). The mixture was refluxed for 4 hr and then filtered, and the filtrate was taken to one-third of the original volume. Water was added to cloudiness, the solution was cooled, and the product crystallized as colorless

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needles, mp 224–227.5°. Recrystallization from acetone gave material of mp 227–227.5° (lit.[3] mp 230–32°) in 1.47 g, 87% yield, mass spectrum *m/e* 239 (M^+), *m/e* 175 ($M^+ - 64$).[26]

2-*p*-Toluenesulfonylamino-3,4,5,6-tetrahydropyrimidine (2b).—The procedure was the same as that used for **2a** except that the diamine used was freshly distilled 1,3-diaminopropane, the reaction solvent was 95% ethanol, and the reaction time was 9 hr. The product was obtained as colorless needles from acetone: mp 264–267 (79% yield); mass spectrum *m/e* 253 (M^+) *m/e* 189 ($M^+ - 64$).

Anal. Calcd for $C_{11}H_{15}N_3O_2S$: C, 52.2; H, 6.0; N, 16.6; S, 12.7. Found: C, 52.2; H, 5.9; N, 16.7; S, 12.6.

2-*p*-Toluenesulfonylamino-4,5,6,7-tetrahydro-1,3-diazepine (2c).—The procedure, using 1,4-diaminobutane dihydrochloride, was identical with that used for **2a** except that the reaction time was 24 hr. The colorless crystals from acetone (76% yield) had mp 221–233°, mass spectrum *m/e* 267 (M^+), 203 ($M^+ - 64$).

Anal. Calcd for $C_{12}H_{17}N_3O_2S$: C, 53.9; H, 6.4; N, 15.7; S, 12.0. Found: C, 54.0; H, 6.3; N, 15.8; S, 11.8.

2,4-Diaminobutyric Acid Dihydrochloride (7).—The procedure used was that of Adamson,[18] with an improvement in the work-up. Sodium azide (4 g, 0.062 mol) was added in small portions to L-(+)-glutamic acid (7.35 g, 0.050 mol), 25 ml of concentrated sulfuric acid, and 15 ml of chloroform and the mixture was stirred at 45°. After 3 hr, the reaction mixture was poured onto 200 ml of ice and the resulting aqueous solution was treated with hot saturated barium hydroxide solution until no longer acid to congo red. Barium sulfate was removed by centrifugation and the aqueous solution was reduced to 100 ml by reduced pressure distillation and then applied to a 100-ml Bio-Rad AG 50W-X (50–100 mesh) ion-exchange column. The column was eluted with 300 ml of 0.1 *N* HCl which removed all of the unreacted glutamic acid as its hydrochloride (4.30 g, 58% recovery). The product was eluted with 1 l. of 1 *N* HCl, the water was removed at reduced pressure, and the residue was ground with absolute ethanol, collected by filtration and dried, mp 199–201° dec. The yield was 3.70 g (91% based on consumed glutamic acid): $[\alpha]^{25}D$ +15.0° (*c* 3.50, water) [lit.[18] mp 195–196, $[\alpha]^{18}D$ +14.6° (c 3.67, water)] [lit.[28] mp 204°, $[\alpha]^{25}D$ +15.1° (*c* 3.82, water)].

2-*p*-Toluenesulfonylamino-4-carboxy-3,4,5,6-tetrahydropyrimidine (6).—(+)-2,4-Diaminobutyric acid dihydrochloride (**7**) (1.09 g, 5.70 mmol) was dissolved in 17.1 ml of 1 *N* NaOH. Ethanol (75 ml) and *S,S*-dimethyl-*N*-tosyliminodithiocarbonimidate (**1**) (1.57 g, 5.70 mmol) were added and the reaction mixture was refluxed for 12 hr and cooled, and 5.7 ml of 1 *N* HCl was added to the solution. The solution was evaporated under reduced pressure to the cloud point and allowed to stand overnight in the cold. The product was collected as colorless plates, mp 202–204° (1.42 g, 83% yield).

Anal. Calcd for $C_{12}H_{15}N_3O_4S$: C, 48.5; H, 5.1; N, 14.1; S, 10.8. Found: C, 48.7; H, 5.3; N, 13.9; S, 10.7.

6-Methyl-8-*p*-toluenesulfonylaminopurine (8).—The procedure was similar to that used for 2-*p*-toluenesulfonylaminobenzimidazole.[1] 4,5-Diamino-6-methylpyrimidine[27] (25.8 mg, 0.208 mmol) was heated at 150° in 6 ml of DMF under a nitrogen atmosphere with *S,S*-dimethyl-*N*-tosyliminodithiocarbonimidate (**1**) (57.2 mg, 0.208 mmol) for 16 hr. The reaction mixture was cooled to 5° and stored overnight forming pale yellow crystals which were collected and washed with water and dried. The compound was characterized after detosylation (see below).

2-Amino-1,3-imidazolidine Hydrochloride and Isolation of *p*-Toluenesulfonyl Fluoride.—2-*p*-Toluenesulfonylamino-1,3-imidazolidine (**2a**) (716 mg, 3.00 mmol) was stirred at room temperature for 2 hr in *ca.* 3 ml of anhydrous HF in a sealed Kel-F vessel.[23,24] The HF was evaporated and the reaction mixture dried over KOH pellets under high vacuum. The residue was washed into a separatory funnel with three 5-ml portions each of water and benzene, alternatively, the layers were separated, and the water was washed with two 10-ml portions of benzene.

The total benzene extract was dried over Na_2SO_4, evaporated under reduced pressure, and dried in a desiccator overnight giving a residue of *p*-toluenesulfonyl fluoride which crystallized as colorless plates (518 mg, 100%), mass spectrum *m/e* 174 (M^+).

Anal. Calcd for $C_7H_7FO_2S$: C, 48.3; H, 4.1; S, 18.4. Found: C, 48.1; H, 4.2; S, 18.3.

The aqueous layer was reduced to 5 ml and added to a 100-ml Bio-Rad AG 50W-X (50–100 mesh) ion-exchange column. Elution with water until the eluate was neutral (after an initial period when the eluate was acid) was followed by washing with 300 ml of 4 *N* HCl, and the latter eluate was taken to dryness and the residue dried at reduced pressure overnight. The residue was crystallized from isopropyl alcohol–ether as colorless needles of **9a**, mp 118–121°, yield 330 mg (98%).

Anal. Calcd for $C_3H_8N_3Cl \cdot {}^1/_2H_2O$: C, 27.7; H, 6.8; N, 32.0. Found (hygroscopic): C, 28.2; H, 6.5; N, 31.6.

2-Amino-3,4,5,6-tetrahydropyrimidine Hydrochloride (9b).—2-*p*-Toluenesulfonylamino-3,4,5,6-tetrahydropyrimidine (**2b**, 330 mg, 1.30 mmol) was treated with anhydrous HF as described above. The residue, after ion-exchange chromatography, was recrystallized from isopropyl alcohol–ether and gave colorless needles of **9b** (177 mg, 101%), mp 127–129.5°.

Anal. Calcd for $C_4H_{10}N_3Cl$: C, 35.4; H, 7.4; N, 31.0. Found (hygroscopic): 35.2; H, 7.4; N, 30.8.

2-Amino-4,5,6,7-tetrahydro-1,3-diazepine Hydrochloride (9c).—2-*p*-Toluenesulfonylamino-4,5,6,7-tetrahydro-1,3-diazepine (**2c**) (267 mg, 1.0 mmol) was treated with anhydrous HF as described above. The residue, after ion-exchange chromatography, was recrystallized from isopropyl alcohol–ether and gave colorless needles of **9c** (149 mg, 98%), mp 129–132°.

Anal. Calcd for $C_5H_{12}N_3Cl$: C, 40.1; H, 8.1; N, 28.1. Found: C, 39.9; H, 8.2; N, 27.9.

2-Amino-4-carboxy-3,4,5,6-tetrahydropyrimidine Hydrochloride (10).—4-Carboxy-2-*p*-toluenesulfonylamino-3,4,5,6-tetrahydropyrimidine (**6**) (672 mg, 22.4 mmol) was treated with anhydrous HF as described above. The residue, after ion-exchange chromatography, was recrystallized from isopropyl alcohol–ether and gave colorless needles of **10**: mp 210–211° dec; 383 mg, 95% yield; $[\alpha]^{25}D$ +144° (c 1.08, water); nmr δ 4.31 (t, 1 H), 3.32 (m, 2 H), 2.24 (t, 2 H).

Anal. Calcd for $C_5H_{10}N_3O_2Cl$: C, 33.4; H, 5.8; N, 23.4. Found (hygroscopic): C, 33.7; H, 6.1; N, 23.4.

2-Aminobenzimidazole Hydrochloride (11).—2-*p*-Toluenesulfonylaminobenzimidazole (**6**) (322 mg, 1.34 mmol, prepared as described by Gompper and Hagele[3]) was treated with anhydrous HF as described above. The residue, after ion-exchange chromatography, was recrystallized from isopropyl alcohol–ether and gave colorless crystals of **11** (177 mg, 91% yield): mp 209–210°; high resolution mass spectrum *m/e* 133.0643 (M^+ – HCl) (calcd $C_7H_7N_2$: 133.0639).

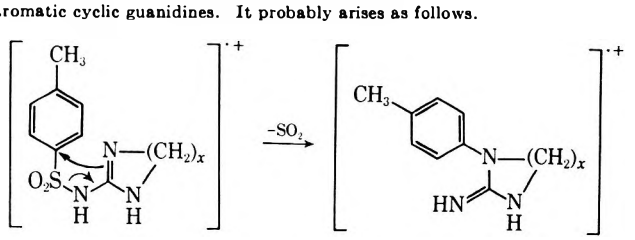
Anal. Calcd for $C_7H_8N_3Cl \cdot {}^1/_2H_2O$: C, 47.2; H, 5.1; N, 23.4. Found (hygroscopic): C, 47.2; H, 5.2; N, 23.2.

8-Amino-6-methylpurine Hydrochloride (12).—6-Methyl-8-*p*-toluenesulfonylaminopurine (**8**, total crude from above) was treated with anhydrous HF as described above. The residue, after ion-exchange chromatography, was recrystallized from isopropyl alcohol–ether to give pale yellow plates: mp 314–317° dec; 21.0 mg, 58% yield based on starting diamine; mass spectrum *m/e* 149 (M^+ – HCl); uv $\lambda_{max}^{H_2O,\ pH\ 2.4}$ 285 nm (ε 17,000); $\lambda_{max}^{H_2O,\ pH\ 7.0}$ 239 nm (ε 3800), 280 (15,100) [lit.[29] for 8-aminopurine; $\lambda_{max}^{H_2O,\ pH\ 2.4}$ 288 nm (ε 15,800); $\lambda_{max}^{H_2O,\ pH\ 7}$ 241 nm (ε 3200), 283 (14,400)].

Anal. Calcd for $C_6H_8N_5Cl \cdot H_2O$: C, 35.4; H, 4.9. Found (hygroscopic): C, 35.9; H, 4.6.

Registry No.—**2a**, 13111-53-0; **2b**, 26893-35-6; **2c**, 26893-36-7; **6**, 26893-37-8; **7**, 26889-08-7; **9a**, 26893-38-9; **9b**, 26893-39-0; **9c**, 26893-40-3; **10**, 26889-09-8; **11**, 26893-41-4; **12**, 26893-42-5; *p*-toluenesulfonyl fluoride, 455-16-3.

(26) The ($M^+ - 64$) peak appears in the mass spectra of all of the nonaromatic cyclic guanidines. It probably arises as follows.



This rearrangement is analogous to that found for sulfonylureas.[27]

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The Synthesis of Peptides in Aqueous Medium. VII. The Preparation and Use of 2,5-Thiazolidinediones in Peptide Synthesis

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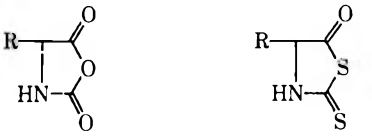
Received May 4, 1970

Optically active *N*-thiocarboxyamino acid anhydrides, NTA's (**4**), have been prepared and used for the stepwise synthesis of peptides in aqueous solution. Generally thiocarboxyanhydrides of good optical purity were obtained by the recrystallization of products from the reaction of alkoxythiocarbonyl L-amino acids (**3**) with phosphorus tribromide. Alternative syntheses of these anhydrides were provided by the cyclization of L-amino acid and L-amino thio acid thio carbamates, or by the reaction of an L-amino thio acid, L-thioproline, with phosgene. Salts of amino acid thiocarbamates were stable to electrophoresis at pH 11, whereas the carbamate salts decomposed. Using conditions similar to those reported for *N*-carboxyanhydrides (NCA's), addition of an NTA to an aqueous solution of an amino acid or peptide at pH 9–9.5 at 0–4° led to high yields of the peptide homolog. The increased stability of the thiocarbamates permitted the reaction to be carried out at a lower pH than was the case with the NCA's, generally affording higher yields but still leading to by-products analogous to those observed with the NCA's. In contrast to the NCA's, the NTA's led to 1–20% of epimeric peptide in the product. Quantitation of small amounts of racemate derived from alanine NTA was made by nmr spectral comparison of the low intensity peaks in the alanine *C*-methyl doublet in a diastereomeric by-product with the ^{13}C-satellite peaks of the *C*-methyl doublet of the major product. Racemization occurring during reaction of proline NTA was estimated using a previously reported method in which the incorporation of tritium from labeled water was measured. The NTA's which should prove most useful in peptide synthesis are those of glycine and alanine which gave significantly higher yields of product than the NCA's, and histidine NTA which, in contrast to the NCA, was used successfully for controlled peptide synthesis.

The use of the α-amino acid *N*-carboxyanhydrides (NCA's), **1**, in the synthesis of peptides in aqueous solution is complicated by the fact that below pH 11 the instability of peptide carbamates leads to overreactions *via* decarboxylation, whereas at pH 11 overreaction *via* the NCA anion, formation of hydantoic acids, and hydrolysis become troublesome side reactions.[1] Hydantoic acid formation was a problem even at pH 10.2 with the NCA of glycine and occasionally with that of alanine. Further, histidine NCA rearranged to a fused imidazolone. A more stable carbamate analog would permit peptide condensation to be carried out at lower pH and this, in turn, would suppress those side reactions arising from reactions of the anhydride with base. Moreover, the production of a more stable carbamate ion should suppress the acid-catalyzed formation of overreaction products.

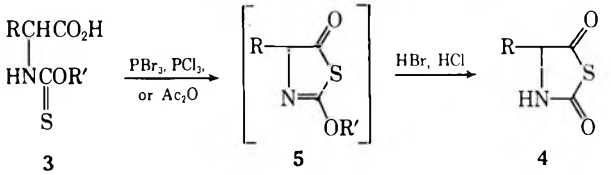
It was thought that analogs of the NCA's in which the ether oxygen is replaced by sulfur might solve some of these problems because the related thiocarbamates could be expected to show a greater stability at a given pH than would the carbamates. A few free dithiocarbamic acids were known,[2] and although the free monothiocarbamic acids had not been reported,[3] we assumed that they would have a stability intermediate between the carbamates and dithiocarbamates. Therefore, it should be possible to carry out peptide syntheses at a lower pH with NTA's than with the NCA's. The use of 2-thiono-5-thiazolidinones, **2**, in peptide synthesis has been reported,[4,5] but a considerable amount of racemization accompanied peptide formation.[5] The present



1 2

paper describes the synthesis of optically active *N*-thiocarboxyanhydrides (NTA's), *i.e.*, derivatives of 2,5-thiazolidinedione (**4**, R = H), and their use in stepwise peptide synthesis in aqueous solutions.[6]

The *N*-thiocarboxyanhydride of glycine has been prepared by the reaction of the thionourethan, *N*-(ethoxythiocarbonyl)glycine (**3**, R = H; R′ = Et), with phosphorus tribromide or trichloride.[7-9] Recently, the syn-



3 5 4

(1) R. Hirschmann, R. G. Strachan, H. Schwam, E. F. Schoenewaldt, H. Joshua, H. Barkemeyer, D. F. Veber, W. J. Paleveda, Jr., T. A. Jacob, T. E. Beesley, and R. G. Denkewalter, *J. Org. Chem.*, **32**, 3415 (1967).

(2) (a) A. Y. Yakubovich and V. A. Klimova, *J. Gen. Chem. USSR*, **9**, 1777 (1939); *Chem. Abstr.*, **34**, 3685 (1940). (b) H. Korner, *Chem. Ber.*, **41**, 1901 (1908).

(3) E. E. Reid, "The Chemistry of Bivalent Sulfur," Vol. IV, Chemical Publishing Co., New York, N. Y., 1962, p 196.

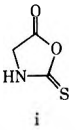
(4) (a) J. D. Billimoria and A. H. Cook, *J. Chem. Soc.*, 2323 (1949); (b) A. C. Davis and A. L. Levy, *ibid.*, 2419 (1951).

(5) A. H. Cook and A. L. Levy, *ibid.*, 651 (1950).

(6) (a) For a preliminary communication, see R. S. Dewey, E. F. Schoenewaldt, H. Joshua, W. J. Paleveda, Jr., H. Schwam, H. Barkemeyer, B. H. Arison, D. F. Veber, R. G. Denkewalter, and R. Hirschmann, *J. Amer. Chem. Soc.*, **90**, 3254 (1968). (b) We are grateful to Dr. Dieter Ziebarth of the Institute für Krebsforschung of the Deutsche Akademie der Wissenschaften zu Berlin for making available a copy of his recent thesis, "Uber 2,5-Dioxothiazolidine. Ein Beitrag zur Peptidsynthese," Humbolt Universität, Berlin, 1968, in which he describes the preparation of some NTA's and the formation of racemic peptides when the NTA's were condensed in basic aqueous solution.

(7) (a) P. Aubert and E. B. Knott, *Nature*, **166**, 1039 (1950); (b) P. Aubert, R. A. Jeffreys, and E. B. Knott, *J. Chem. Soc.*, 2195 (1951).

(8) J. L. Bailey, *ibid.*, 3461 (1950). **4** was formulated as the isomeric 2-thiono-5-oxazolone, i, a structure which was implicated in the formation of polyalanine by the thermal decomposition of lead alanine dithiocarbamate [G. Losse and H. Weddige, *Justus Liebigs Ann. Chem.*, **636**, 144 (1960)].



i

(9) (a) H. G. Khorana, *Chem. Ind. (London)*, 129 (1951); (b) G. W. Kenner and H. G. Khorana, *J. Chem. Soc.*, 2076 (1952). Khorana proposed an NTA as a product in the acid cleavage of a peptide N-terminal alkoxythiourethan.

TABLE I

N-(ALKOXYTHIOCARBONYL) AMINO ACIDS, ROCHNCHRCO$_2$H

Amino acid	L-Ala	D-Allo-isoleu	L-Arg	Gly	L-His	L-Ileu	L-Leu	L-Phe	L-Pro	L-Val
R′	CH_3	CH_3	CH_3	CH_3	C_2H_5	C_2H_5	CH_3	C_2H_5	CH_3	CH_3
Mp, °C	114–115	44–52	212–220 dec	80–82	212 dec	67–69	68–70	85–88	93–94	63–66
$[\alpha]^{25}_{589}$[a]	−19.3	−66			+24	+15.9	−31.3	+80.8	−126[b]	−8.35
Calcd, %										
C	36.81	46.80	38.70	32.20	44.44	49.29	46.80	56.89	44.44	46.80
H	5.56	7.37	6.50	4.73	5.39	7.81	7.37	5.97	5.82	7.36
N	8.58	6.82	22.57	9.38	17.28	6.39	6.82	5.53	7.41	6.82
S	19.64	15.62	12.90		13.19	14.62	15.62	12.66	16.92	15.63
Found, %										
C	37.32	46.96	38.89	32.50	44.56	49.43	46.71	56.85	44.49	47.02
H	5.64	7.45	6.31	4.75	5.47	7.76	7.26	6.14	5.68	7.40
N	8.43	7.05	22.61	9.36	17.58	6.68	5.93	5.81	7.37	6.82
S	20.27	16.03	13.20		13.49	13.76	16.17	12.35	17.03	15.52

[a] *c* 1 (CH_2Cl_2) except as otherwise noted. [b] *c* 1 ($CHCl_3$).

thesis of DL-phenylalanine NTA (**4**, R = $C_6H_5CH_2$) was reported.[10] Glycine or DL-alanine thioanhydride has been used to prepare glycylglycine ethyl ester,[8] DL-alanylglycine,[9a] and a glycine polymer.[11] The thioanhydride has also been postulated as the intermediate in the hydrogen chloride catalyzed cleavage of the N-terminal amino acid of a *N*-(ethoxythiocarbonyl)peptide in analogy with the Edman degradation.[9]

Greater stability of amino acid thiocarbamates compared to carbamates was indeed indicated by electrophoresis. The electrophoretic behavior of glycine carbamate[12] (see below) at pH 11 at room temperature is that of glycine indicating decomposition of the carbamate while glycine thiocarbamate moved with about twice the mobility of glycine indicating the greater stability of the thiocarbamate. Phenylalanine thiocarbamate showed a similar stability at pH 11, but when the electrophoresis was carried out at pH 9 at room temperature streaking was observed, suggesting thiocarbamate decomposition during the electrophoresis at the lower pH.

Preparation of the NTA's.—Because optically active NTA's had not heretofore been prepared, a variety of methods were explored for the synthesis of NTA's of L-amino acids. Of the methods outlined below, cyclization of the thionourethan **3** (method A) was the most convenient,[7] and could in several instances be used to give material of good optical purity. Methods B and C also gave NTA's of good optical purity, but the preparations involved more steps and led to lower yields. The peptides reported in this paper were synthesized with NTA's prepared *via* method A unless otherwise specified.

1. Cyclization of *N*-Alkoxythiocarbonyl Amino Acids. Method A.—A number of optically active *N*-alkoxythiocarbonyl amino acids were prepared by the reaction of xanthate esters and L-amino acids in alcoholic base (Table I). Generally these derivatives could be crystallized except as noted. The optical purity of the *N*-alkoxythiocarbonyl derivatives of the amino acids was investigated in three cases. The preparation of *N*-ethoxythiocarbonylproline was carried out in ethanol-tritiated water. Examination of the recovered crystalline derivative for nonexchangeable tritium showed that less than 0.006% racemization had taken place. When *N*-(ethoxythiocarbonyl)phenylalanine was treated with sodium methoxide in methanol under the conditions of synthesis, the optical rotation of the compound remained unchanged. Finally, repeated recrystallization of *N*-(ethoxythiocarbonyl)-L-leucine as the quinine salt led to no change in rotation of the recovered compound. Therefore, the crystalline alkoxycarbonyl amino acids are thought to be of excellent optical purity.

Aubert reported that alkoxythionocarbonylglycines (**3**, R = H) could be cyclized to the 2-alkoxy-5-thiazolone **5** with acetic anhydride.[13] Application of this reaction to *N*-(methoxythiocarbonyl)-L-leucine led to an oil which differed in its chromatographic behavior from both the thionourethan and the NTA. The infrared spectrum was consistent with the 5-thiazolone structure **5** (R = Me, R′ = *i*-Bu). Exposure of this oil to hydrogen chloride led to the formation of largely racemized leucine NTA. On the other hand, the rotation of phenylalanine NTA was essentially unchanged after treatment in THF with hydrogen chloride or phosphorus trichloride for 1 hr at room temperature. These results suggested that the racemization observed in the above leucine NTA occurred at the intermediate 5-thiazolone stage. Indeed, the thiazolone **5** is analogous to the azlactones, which have been cited as a major pathway for racemization of *N*-acyl amino acid derivatives.[14] Reaction of *N*-(methoxythiocarbonyl)-L-leucine with phosphorus tribromide at −30° led to a mixture from which the related 5-thiazolone and a partially racemized NTA could be isolated by silica gel chromatography.

The *N*-(alkoxythiocarbonyl) amino acids were best cyclized to the NTA's **4** by reaction with phosphorus tribromide for 5–10 min at 0°. In general, these conditions led to crystalline NTA's of relatively high optical purity. Addition of nucleophiles which should acceler-

(10) I. Z. Siemion, D. Konopińska, and A. Dżugaj, *Rocz. Chem.*, **43**, 989 (1969).

(11) J. H. Bradbury and J. D. Leeder, *Text. Res. J.*, **30**, 118 (1960); *Chem. Abstr.*, **54**, 8092*d* (1961).

(12) A. C. Farthing, *J. Chem. Soc.*, 3213 (1950).

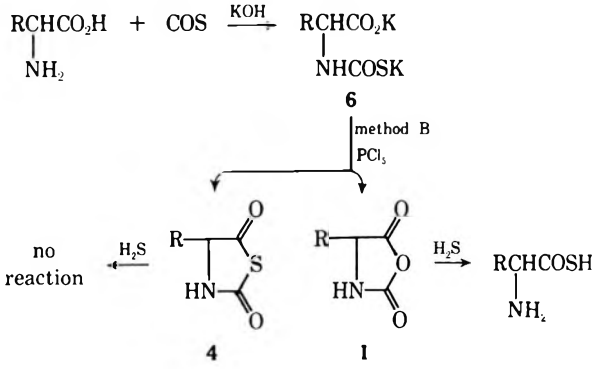
(13) P. Aubert, E. E. Knott, and L. A. Williams, *ibid.*, 2185 (1951).

(14) (a) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. II, Wiley, New York, N. Y., 1961, pp 832–836, and references therein; (b) I. Antonovics and G. T. Young, *Chem. Commun.*, 398 (1965).

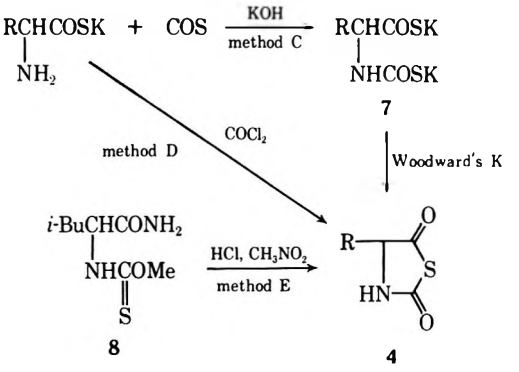
ate the cleavage of the intermediate oxazolone, such as sodium iodide, imidazole, or 1,2,4-triazole,[15] showed slight improvements in the yield and optical rotation of the NTA.

Although hydrogen chloride in the previously cited experiment did not racemize a preformed NTA, treatment of NTA with hydrogen bromide at room temperature led to a drop in optical activity in the product. Nevertheless, the use of PBr_3 proved to be advantageous because the greater reactivity of phosphorus tribromide permitted NTA formation to be carried out for a shorter period of time, thus reducing exposure to acidic conditions. The overall advantage of the use of phosphorus tribromide may be attributed to the greater nucleophilic activity of bromide ion in the cleavage of the thiazolone ether **5**. In an attempt to circumvent some of the above problems in the preparation of the NTA's, other methods of synthesis were examined.

2. From the Amino Acid Thiocarbamate. Method B.—Amino acid carbamates have been converted to NCA's with thionyl chloride.[12] Reaction of phenylalanine with carbonyl sulfide in a basic medium led to the salt of the amino acid thiocarbamate (**6**, R = $C_6H_5CH_2$).[16] Treatment of a suspension of this salt in tetrahydrofuran with phosphorus pentachloride gave a mixture of phenylalanine NCA (**1**, R = $C_6H_5CH_2$) and NTA (**4**, R = $C_6H_5CH_2$). Addition of hydrogen sulfide rapidly cleaved the NCA, thus permitting the isolation of the unchanged NTA by extraction with ethyl acetate. The products had an optical purity comparable to those prepared by route A.



3. Other Routes.—The problem of contamination of the NTA with NCA in method B could be avoided by use of an amino thio acid. Optically active thioleucine was prepared from the NCA with hydrogen sulfide and then converted to the potassium salt of thioleucine thiocarbamate (**7**, R = *i*-Bu) in analogy to method B. The salt was cyclized directly in aqueous solution with Woodward's Reagent K to the NTA (method C). Alternatively, the amino thio acid thiophenylalanine was converted to the NTA of good optical purity with phosgene (method D).



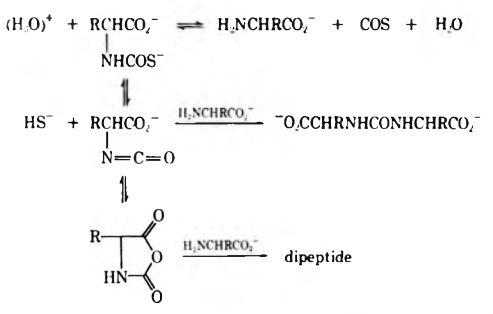
Finally, in analogy with a known scheme[9] for peptide degradation, *N*-methoxythiocarbonylleucine amide (**8**) was cyclized to the NTA with hydrogen chloride (method E). The anhydride was, however, largely racemized. The results of these methods are outlined in Table II.

Optical Purity.—The optical purity of selected NTA's was estimated by hydrolysis to the amino acid and determination of the amount of the D isomer present in the product. In general, the crystallization of the NTA's permitted the isolation of anhydrides with an optical purity ≧98%. This was not true of the NTA of leucine. Rotations of samples of the latter varying from $[\alpha]^{25}_{589}$ −30 to −55° remained essentially unchanged upon crystallization. To determine the optical purity of the NTA of leucine, $[\alpha]_{589}$ −57.4°, a sample was treated with silver nitrate to give silver sulfide and leucine. The crude product was treated with phenylalanine NCA. The resulting dipeptide contained 3% LD isomer by comparison on tlc[17] with dipeptide similarly prepared from DL-leucine and spotted at various concentrations. In the case of the NTA of proline, acid hydrolysis gave a quantitative yield of proline. The crude reaction product was assayed with D-amino acid oxidase and was found to contain about 2% D-proline.

Use of NTA's in Peptide Synthesis.—The reaction of *N*-thiocarboxyanhydrides with amino acids and peptides in aqueous solution was examined to determine yields and extent of racemization in peptide formation. The experimental conditions were similar to those used for the stepwise synthesis of peptides with NCA's,[1] (Scheme I) except that the pH was lower. After

(15) The addition of nucleophiles has catalyzed amino acid active ester condensations in some solvents: H. C. Beyerman and W. M. van den Brink, *Proc. Chem. Soc.*, 266 (1963); T. Wieland and W. Kahle, *Justus Liebigs Ann. Chem.*, **691**, 212 (1966).

(16) An aqueous solution of phenylalanine thiocarbamate gave rise to phenylalanine and a trace of phenylalanylphenylalanine on standing, which was detected by electrophoresis at pH 11. Upon tlc the dipeptide resolved into two spots corresponding to LL- and DL-phenylalanylphenylalanine. Phenylalanine carbamate did not give rise to peptide formation under these conditions, whereas phenylalanine dithiocarbamate, which was prepared from phenylalanine and carbon disulfide, did form the dipeptide. Further, a solution of phenylalanine thiocarbamate and radioactive phenylalanine in addition gave rise to a ninhydrin negative spot on tlc corresponding to hydantoic acid. A possible mechanism for the formation of these products is as follows.



This type of ring formation has been suggested previously by T. Wieland, R. Lambert, and H. U. Land, *ibid.*, **597**, 181 (1956). It may be noted that this route would seem to offer another pathway to peptide formation under prebiotic conditions.

(17) E. Taschner, J. F. Biernat, and T. Sokolowski, *Peptides, Proc. Eur. Symp.*, 5th, 1962 (1963).

TABLE II
AMINO ACID N-THIOCARBOXYANHYDRIDES[a]

Amino acid	Method	Yield, %	Mp, °C	$[\alpha]^{25}_{589}$[b]	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Found, % C	Found, % H	Found, % N	Found, % S
L-Ala[c]	A	47	91–93	−164	36.62	3.81	10.68		36.50	3.61	10.65	
L-Arg[d]	A	62.5	115–117	−124.5[f]	28.29	4.41	18.85	10.79	28.57	4.40	18.99	10.73
Gly[e]	A	66	108–109		30.77	2.58	11.96	27.38	30.96	2.61	11.99	27.57
L-His[d,e]	A	72.5		−7.0[g]	30.20	2.90	15.10		30.16	3.00	14.76	
L-Leu	A	68	77–78	−57.2	48.53	6.40	8.09	18.51	48.67	6.34	8.02	18.80
	B	13		−56.0								
	C	45	76–77	−56.7								
	E	28		−34.5								
L-Phe[e]	A	47	109–111	−154	57.94	4.37	6.75	15.46	58.10	4.31	6.67	15.70
	B	25	111–112	−153								
	D	29[h]		−155, −154								
L-Pro	A	21	44.5–45	−157[i]	45.80	4.55	8.96	20.40	45.96	4.43	8.90	19.71
L-Val[e]	A	67	80–82	−82	45.26	5.70	8.80	20.14	45.09	5.83	8.93	20.44

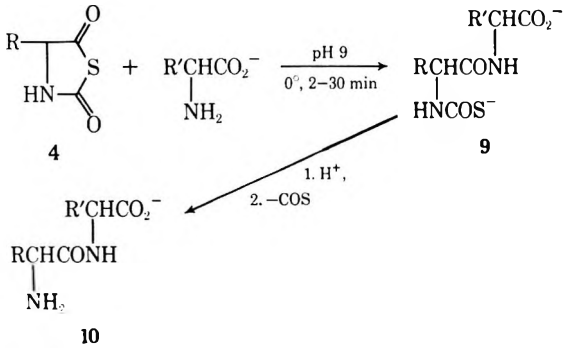
[a] The anhydrides were prepared from the methyl thionourethans unless otherwise indicated. [b] c 1 (CH_2Cl_2) unless otherwise indicated. [c] Prepared in the presence of added imidazole. [d] As the N-thiocarboxyanhydride hydrobromide. [e] Prepared from the ethyl thionourethan. [f] c 2 (DMSO). [g] c 2 (methyl carbitol) at 365 nm. [h] Two crops of 9.2 and 22%. [i] c 1 ($CHCl_3$, EtOH free).

TABLE III
PEPTIDES, PREPARED WITH NTA'S IN COMPARISON WITH OTHER METHODS

Reactants: Carboxyanhydride	Reactants: Nucleophile	pH: NTA[a]	pH: NCA[a]	Product	Isolated yield: NTA, %	Isolated yield: NCA, %
Gly	Phe	9.5	10.5	Gly-Phe	93	50[b]
Gly	Phe-Leu	9.0	10.2	Gly-Phe-Leu	75[c]	37
Ala	Leu-Phe	9.5	10.2	Ala-Leu-Phe	92	70
Ala	Ser-Val (Bzl)	9.15	10.1	Ala-Ser-Val (Bzl)	68[d]	55[d]
His	Phe-Asp-Ala-Ser-Val (Bzl)	9.0		His-Phe-Asp-Ala-Ser-Val (Bzl)	24[e]	
Boc-His·N_3	Phe-Asp-Ala-Ser-Val[f]			Boc-His-Phe-Asp-Ala-Ser-Val	79[d]	

[a] The NCA or NTA was used in 10% excess unless otherwise specified. [b] Disappearance yield. More than 20% of the hydantoic acid was indicated by tlc. [c] The NTA was used in 20% excess. [d] Small amounts of impurities were indicated. [e] 3.8 equiv of the NTA were used. [f] The reaction was run in DMF–Et_2O.

SCHEME I
STEPWISE SYNTHESIS OF PEPTIDES WITH NTA'S



cessation of a rapid uptake of base (2–30 min), the solution was acidified to cleave the carbonyl sulfide protecting group. The carbonyl sulfide was swept from the reaction mixture with nitrogen. Representative reactions of NTA's and NCA's with amino acid or peptide nucleophiles are compared in Table III. The yields refer to isolated products unless otherwise indicated. Alanine NTA and, especially, glycine NTA gave higher yields of the desired peptides than did the NCA's.

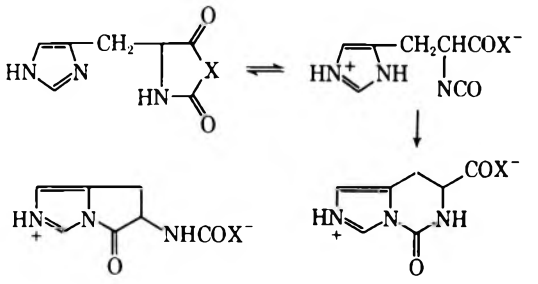
A comparison of the products from the reaction of phenylalanine NCA and of NTA with ^{14}C-arginine is given in Table IV. The reactions were evaluated by paper-strip electrophoresis as previously described.[1] A higher yield of peptide was obtained with the NTA at pH 9.5 than with the NCA at pH 10. Furthermore, the NTA left less unchanged arginine and afforded less of the overreaction product, Phe-Phe-Arg. The amount of hydantoic acid formed was not changed significantly. The yields in Tables III and IV support the expectation that a greater stability of the thiocarbamate should permit efficient peptide condensation to be carried out at a lower pH.

TABLE IV
REACTION PRODUCTS FROM PHE NTA AND PHE NCA WITH LABELED ARGININE

Reactants	pH, NTA	Product	Yield,[a] %
Phe-NCA + ^{14}C-Arg	10.0	Phe-Arg	89.2
		Arg	3.5
		Phe-Phe-Arg	4.0
		Hydantoic acid[b]	2.8
Phe-NTA + ^{14}C-Arg	9.5	Phe-Arg	94.2
		Arg	2.2
		Phe-Phe-Arg	0.3
		Hydantoic acid[b]	2.7

[a] Yields based on radioactivity counts from fractions from paper electrophoresis. [b] $HO_2CCH(CH_2C_6H_5)NHCO\cdot Arg\cdot OH$.

A striking difference was noted between the NCA and the NTA of histidine. The former failed to yield histidyl peptides at pH 10.2, whereas the NTA was used, for example, to prepare the C-terminal hexapeptide of ribonuclease[18] (Table III). Inspection of molecular models suggested that the imidazole nitrogen is in an ideal position to abstract the NH proton from the nitrogen of the anhydride ring. This intramolecular, base-catalyzed ring opening which would lead to an isocyanate parallels the mechanism for isocyanate formation which had been proposed[1] to explain the hydantoic acid by-products in NCA reactions. In the case of the NCA and NTA derived from histidine, the intermediate isocyanate can be expected to undergo further intramolecular reaction to form the imidazopyrimidine **11** (X = O or S, respectively), and indeed the NCA gave a noncrystalline product which was formulated as **11** (X = O) on the basis of its ir and nmr spectra. When the NTA of histidine was treated with aqueous alkali a crystalline product was obtained after acidification which had an elemental analysis and ir spectrum consistent with structure **11** (X = S). An alternate structure, **12**, was discarded on the basis of its infrared spectrum and of its expected ease of decarboxylation. We believe that the NTA, unlike the NCA, of histidine is useful in controlled peptide synthesis because the equilibrium be-



12 **11**

tween anhydride and isocyanate is shifted to the left when X = S. It was also possible to prepare histidyl peptides using compound **11** (X = S). The reaction proceeded slowly at room temperature but **11**, unlike the NTA, failed to give histidyl peptides at an appreciable rate at 0°.

In the reaction of glycine NTA with L-phenylalanyl-L-leucine a 75% yield of the isolated tripeptide (Table III) was obtained whereas the NCA gave about half that amount. In Table V, the distribution of products is shown for the reaction carried out between the ^{14}C-labeled dipeptide used in 5% excess and glycine NTA. Although the yield in NCA reactions decreases sharply when the reaction was carried out at a pH below 10,[1] the NTA reaction is optimal either below the pH range studied or between 8.5 and 9.2 (see Table V). The data are consistent with the results expected for the greater stability of the thiocarbamate. Thus, overreaction is suppressed even at pH 8.5 as judged by the lack of a substantial increase in the amount of unchanged nucleophile (Phe-Leu) indicating that it is not being inactivated by reaction with any carbonyl sulfide derived from the decomposition of the product thiocarbamate. The increase in residual nucleophile at pH 10 can be ascribed to the loss of NTA *via* hydrolysis and polymerization. In the NCA reaction, the yield of hydantoic acid rose with pH.[1] In the pH range examined for the NTA case (Table V), the yield of hydantoic acid remained essentially unchanged. That the NTA does form the anion is suggested by the increase in overreaction products at high pH due to anionic oligomerization of the NTA. However, ring opening may be less favored for the reasons discussed in the case of NTA histidine. If it is assumed that the NTA has about the same solubility at the pH's studied and that the nucleophile competes relatively effectively against hydroxide ion for any isocyanate, a second mechanism for hydantoic acid formation may be required.[19]

In stepwise peptide condensation, the NTA's gave a significant amount of the epimeric product,[20] whereas the NCA's had given optically pure products. Using the NTA's in aqueous solutions, from less than 1 to as high as 20% of the D isomer appeared in the resulting peptide. The reaction of L-histidine NTA hydrobromide with L-alanylglycine led to a mixture which was analyzed directly by nmr. The analysis of D-His-L-Ala-Gly in L-His-L-Ala-Gly could be made by comparison of the separated alanine methyl doublets of the two diastereomeric products using 100-MHz nmr.[21] The product contained 75% of His-Ala-Gly, which consisted of 93% of the LL isomer and 6.7% of the DL isomer based on nmr examination of the freeze-dried crude product. Similarly, reaction of L-histidine NTA with D-alanylglycine gave a 58% yield of tripeptide, 83% of which was the LD isomer and 17% of which was the DD isomer. The

Table V
Products from the Reaction Glycine NTA with L-Phenylalanyl-^{14}C-L-Leucine[a]

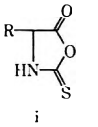
Product	At pH 8.5 (%)	At pH 9.2 (%)	At pH 10.0 (%)
Gly-Phe-Leu	78.9	76.3	50.0
Hydantoic acid[b]	5.95	5.55	5.15
Phe-Leu	12.28	11.64	33.7
Gly-Gly-Phe-Leu	3.03	6.33	8.47
(Gly)$_3$Phe-Leu	0.07	0.34	2.14

[a] The reaction was carried out with a 5% deficiency of Gly NTA. [b] HSOCCH$_2$NHCO-Phe-Leu·OH.

(18) S. R. Jenkins, R. F. Nutt, R. S. Dewey, D. F. Veber, F. W. Holly, W. J. Paleveda, Jr., T. Lanza, Jr., R. G. Strachan, E. F. Schoenewaldt, H. Barkemeyer, M. J. Dickinson, J. Sondey, R. Hirschmann, and E. Walton, *J. Amer. Chem. Soc.*, **91**, 505 (1969).

(19) Possibly the hydantoic acid is formed by direct attack of the nucleophile on the carbamate carbonyl. Alternatively, the hydantoic acid could be formed *via* the isocyanate if the ring opening were catalyzed by the solvent.

(20) The late Professor Weygand had kindly offered the interesting suggestion that the racemization might be attributed to the presence of a 2-*thiono*-5-oxazolone, i, as an isomeric impurity in the NTA. Although we have no reference sample, two considerations argue against the presence of i in our cyclic anhydrides. It should be detectable by nmr or uv spectroscopy.



i

For example, a marked difference in the anisotropic magnetic field around the C=S bond compared to that around the C=O bond has been reported for thioamides and amides [H. Paulsen and K. Todt, *Angew. Chem. Int. Ed. Engl.*, **5**, 899 (1966)]. Histidine NTA shows only the expected peaks although it gives rise to 10% of the D epimer on reaction. Further, whereas the uv of glycine NTA shows only end absorbtion, that of glycine thionourethan, which would contain the major chromophore of a 2-thiono-5-oxazolone system, shows $\lambda_{max}^{0.01\ N\ HCl}$ 240 mμ (ε 12,000).

(21) B. Halpern, D. E. Nitecki, and B. Weinstein, *Tetrahedron Lett.*, 3075 (1967).

identification of the peaks could be determined by comparison of the positions of the methyl doublets of the diastereomers in the two preparations.

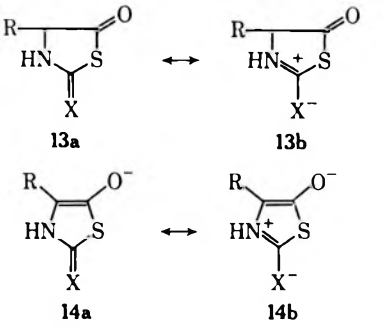
In contrast to the racemization found in the above crude tripeptide, that in the *purified* form of the C-terminal hexapeptide of ribonuclease prepared using histidine NTA was considerably lower. This hexapeptide was also prepared using *α-tert*-butyloxycarbonyl histidine azide. In both cases these intermediates were converted to the N-terminal heptapeptide at which point they were purified by chromatography on silica gel. Enzymatic hydrolysis of the purified heptapeptide with aminopeptidase M showed only about 2% residual peptide and similar amino acid analyses in either case. The fact that the above histidine containing heptapeptide appears to be of good optical purity may be due to purification effected in its isolation or it may indicate that polypeptides react appreciably faster with the L than with a D anhydride. A greater reactivity of L-amino acid NCA's with amino acids or peptides of like configuration has been observed previously.[22,23]

Far less racemization was observed with alanine NTA. Reaction of L-alanine NTA with L-phenylalanine led to a crude dipeptide which by nmr analysis contained 1.4% of the DL isomer. In this case, the peak areas of the alanine methyl doublet of the low intensity epimeric product were compared with the methyl doublets in the ^{13}C satellites of the major product. The satellite peaks provided an internal standard which was directly available for the comparison of the low intensity peaks.[24]

Reaction of L-arginine NTA hydrobromide with L-phenylalanine led to diastereomeric dipeptides which could be separated by chromatography on silica gel. The amounts of the fractionated products were then determined by means of their ultraviolet absorption. The ratio of L-Arg-L-Phe to D-Arg-L-Phe was 95:5. A similar experiment with D-phenylalanine led to a ratio of L-Arg-D-Phe to D-Arg-D-Phe of 84:16. Again these results suggest a preferred reaction between amino acids and NTA's of like configuration.

To estimate the extent of racemization occurring during the peptide forming reaction only, our previously described[25] hydrogen isotope exchange method was employed. The reaction of L-proline NTA with L-phenylalanine was carried out in tritiated water, and a sample of the dipeptide was examined for uptake of "permanently bound" tritium. A reaction carried out at pH 9.35 gave 0.114% of one tritiated hydrogen in the dipeptide and a reaction at pH 10.0 gave 0.129%. A similar reaction carried out in D_2O gave a dipeptide with 0.495% excess of one deuterium in the dipeptide indicating a H/T isotope effect of 4.6. Since it is possible that hydrogen exchange could occur in part with retention, the figures represent the maximum racemization that occurred during the condensation step. Proline NTA appeared to give rise to the lowest level of racemization of the NTA's studied. A sample of L-proline NTA (Table II) which had shown 2.9% of D-proline after acid hydrolysis, therefore, on the basis of the above isotope exchange experiment, might be expected to yield a maximum of 3.2% of a D-prolyl peptide.

Some explanation for the difference between the levels of racemization of the NTA's and NCA's is in order. Tyrosine NCA has been reported to show less than 0.004% racemization when the condensation was carried out in aqueous solution at pH 10.[25] At the other extreme, the tyrosine cyclic anhydride containing two sulfur atoms, the 2-thiono-5-thiazolidine-2,5-dione **2** (R = p-$HOC_6H_4CH_2$), was completely racemized in a reaction with glycine.[4] In this case the high level of racemization could be attributed to an expected greater



double bond character of structure **13b** where X = S than for X = O.[26-28] Systems having such increased urethan C–N double bond character would show a greater tendency to racemize at the 4 position giving rise to the hydroxythiazole anion ring system **14** (X = S). In the NTA's no such C–S double bond can occur. However, two reasons can be offered for the relative case of enolization in the thiazolidine system of the NTA's *vs.* the oxazolidine system of the NCA's. It has been postulated that the larger delocalization energy of thiophene relative to furan can be attributed to sulfur d-orbital participation and to differences in oxygen and sulfur electronegativities.[26] Furthermore, some decrease in bond angle strain of sp^2 carbon in a five-membered ring could be attained by the change of the heteroatom from oxygen to sulfur.[26] In the present case the thiazole system should similarly be favored over the oxazole analog by sulfur d-orbital participation and by the possibility of formation of a slightly less strained anion. That the observed racemization in the NTA's cannot be attributed to bond angle strain alone is indicated by the fact that N-protected amino acid thio esters exhibit racemization in peptide synthesis[29] and in fact the blocked amino acid esters of thiophenol show higher rates of racemization in the presence of triethylamine than do the corresponding esters of the more acidic p-nitrophenol.[30]

In view of these studies, the usefulness of the NTA's in controlled peptide synthesis is restricted to the NTA of glycine, of alanine, which affords products of good optical purity, and of histidine. In addition, the method

(22) P. D. Bartlett and R. H. Jones, *J. Amer. Chem. Soc.*, **79**, 2153 (1957).

(23) M. Idelson and E. R. Blout, *ibid.*, **80**, 2387 (1958).

(24) The use of the ^{13}C satellites as an internal standard has been employed to relate aromatic hydrocarbons of greatly different concentrations: F. F. Caserio, *Anal. Chem.*, **38**, 1802 (1966).

(25) R. G. Denkewalter, H. Schwam, R. G. Strachan, T. E. Beesley, D. F. Veber, E. F. Schoenewaldt, H. Barkemeyer, W. J. Paleveda, Jr., T. A. Jacob, and R. Hirschmann, *J. Amer. Chem. Soc.*, **88**, 3163 (1966).

(26) E. Kooyman in "Organosulfur Chemistry," M. J. Janssen, Ed., Interscience, New York, N. Y., 1967, Chapter 1.

(27) This sulfur probably exists in the thiono form: A. R. Katritsky and J. M. Lagowski, *Advan. Heterocycl. Chem.*, **2**, 61 (1964).

(28) Hindered rotation in simple thionocarbamate esters has been observed by R. A. Bauman, *J. Org. Chem.*, **32**, 4129 (1967).

(29) In peptide synthesis varying levels of racemization have been seen with thiol esters: H. Determann and T. Wieland, *Justus Liebigs Ann Chem.*, **670**, 136 (1963); F. Weygand, A. Prox, and W. König, *Chem. Ber.*, **99**, 1451 (1966).

(30) B. Liberek and Z. Grzonka, *Tetrahedron Lett.*, 159 (1964).

should prove useful in situations when the purification of a desired diastereoisomer is readily accomplished or when optical purity is relatively unimportant as in the preparation of a reference compound in connection with sequence studies.[31]

Experimental Section

Methoxythiocarbonyl-L-alanine (Alanine Thionourethan), 3 (R, R′ = Me).—A solution of 71.5 g (0.80 mol) of L-alanine in 69 ml (0.80 mol) of a 45% solution of aqueous potassium hydroxide was stirred under nitrogen at 25° while 97.5 g (0.80 mol) of *O,S*-dimethyl dithiocarbonate (dimethyl xanthate)[32,33] in 90 ml of methanol was added. The mixture was held at 45° while nitrogen was passed through the mixture to remove methyl mercaptan. The exit gas was passed through a scrubber containing potassium hydroxide in aqueous ethanol until after 1 hr the exit gas gave only a weak test for mercaptan (yellow precipitate with aqueous lead acetate). The reaction mixture was concentrated and the syrup was taken up in water and extracted with ether. The aqueous layer was acidified with 6 *N* HCl and extracted with ethyl acetate. The extract was washed with saturated aqueous NaCl, dried with Na_2SO_4, and concentrated to an oil which solidified to give 118 g of the urethan. Recrystallization from ethyl acetate and hexane afforded 74 g (56.7%) of methoxythiocarbonyl-L-alanine: ir (CH_2Cl_2) 3534 (NH), 1724 (-CO_2H), 1528 cm^{-1} (NH); mp 114–115° (Table I).

Alkoxythiocarbonyl derivatives of other amino acids were prepared in a similar manner (Table I). The ethoxythiocarbonyl derivatives were prepared using *O,S*-diethyl dithiocarbonate (Eastman Organic Chemicals).

Optical Purity of Ethoxythiocarbonyl-L-leucine 3 (R = *i*-Bu; R′ = Et).—The salt prepared from 2.19 g (10 mmol) of L-ethoxythiocarbonyl-L-leucine, $[\alpha]^{25}_{589}$ −27.9° (*c* 1, CH_2Cl_2), and 3.24 g (10 mmol) of quinine was fractionally crystallized from benzene–hexane to yield three crops: A, 1.76 g; B, 1.475 g; C, 0.925 g. The three fractions were individually dissolved in ethyl acetate and washed with dilute hydrochloric acid. Concentration of the ethyl acetate extracts led to crystalline residues with the following properties.

Sample	Mp, °C	$[\alpha]^{25}_{589}$ (*c* 1, CH_2Cl_2)
Starting material	79–81	−27.9 ± 0.4°
A	79–80	−27.5
B	79–80	−28.2
C	79–80	−28.3

Stability of Ethoxythiocarbonyl-L-phenylalanine, 3 (R = $C_6H_5CH_2$; R′ = Et), in Alkali.—A solution of 5.0 g of ethoxythiocarbonyl-L-phenylalanine, mp 85–88°, $[\alpha]^{25}_{589}$ +80.8° (*c* 1, CH_2Cl_2), in 20 ml of ethanol and 10 ml of water was brought to pH 10 with a 50% solution of NaOH and heated under reflux in a nitrogen atmosphere for 18 hr. The solution was concentrated *in vacuo* and diluted with 25 ml of water, acidified, and extracted twice with ethyl acetate. The combined extract was washed with saturated NaCl, dried, and concentrated to an oil which crystallized. Trituration with hexane gave 4.16 g (83%) of ethoxythiocarbonyl-L-phenylalanine, mp 82–85°, $[\alpha]^{25}_{589}$ +77.8° (*c* 1, CH_2Cl_2). Recrystallization from benzene–hexane gave the thionourethan, $[\alpha]^{25}_{589}$ +81.3° (*c* 1, CH_2Cl_2).

Preparation of Ethoxythiocarbonyl-L-proline in Tritiated Aqueous Ethanol.—A solution of 5.75 g of L-proline was prepared in 5 ml of tritiated water containing 3.3 g of 85% potassium hydroxide. To this was added 7.5 g of *O,S*-diethyl dithiocarbamate along with 5 ml of ethanol. The mixture was stirred for 2 hr at 65–75° and overnight at room temperature. The mixture was concentrated to dryness *in vacuo* and reconcentrated four times with H_2O (in order to exchange labile hydrogen). This residue was taken up in 60 ml of water, extracted three times with ether, acidified with HCl, and extracted three times with ethyl acetate. The ethyl acetate extract was washed three times with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated to an oil, which was triturated to give 7.4 g of solid. This material was recrystallized from ethyl acetate and hexane to give 5.2 g of thionourethan. The specific activity of the tritiated solvent after dilution by exchangeable hydrogen was 7.55 × 10^6 cpm/mg-atom H. The specific activity of hydrogen in the product corresponded to 2.44 × 10^2 cpm/mmol of thionourethan.

Preparation of L-Alanine NTA, 4 (R = Me).—A solution of 26.12 g (0.16 mol) of methoxythiocarbonyl-L-alanine and 10.92 g (0.16 mol) of imidazole in 200 ml of THF was stirred under nitrogen. Phosphorus tribromide (18.2 ml, 0.19 mol) from a freshly opened bottle was added over 2–3 min while the reaction temperature was held at 25–35°. Initially, a strong exothermic reaction occurred and a thick precipitate formed which made temperature control difficult. The mixture thinned considerably as the last two thirds of the phosphorus tribromide was added. The reaction mixture was then poured into an ice cold mixture of 800 ml of a saturated solution of $NaHCO_3$ and 800 ml of ethyl acetate. The organic layer was washed successively with 1 *N* hydrochloric acid, 10% $NaHCO_3$, and saturated NaCl, dried over Na_2SO_4, and concentrated to an oil. The oil was crystallized from ethyl acetate hexane to give 9.85 g (47%) of L-alanine NTA: mp 91–93° (Table II); ir (CH_2Cl_2) 3559 (NH), 1758, 1718 cm^{-1}. A number of the other thiocarboxyanhydrides were similarly prepared (Table II).

L-Histidine NTA Hydrobromide, 4 (R = $C_3H_3N_2CH_2$·HBr).—Ethoxythiocarbonylhistidine was prepared by the procedure used for the alanine derivative. A slurry of 10 g (0.041 mol) of ethoxythiocarbonyl-L-histidine in 250 ml of THF was stirred at room temperature while a freshly prepared ice cold solution of 5 ml (0.052 mol) of phosphorus tribromide in 50 ml of THF was added rapidly. The ethoxythiocarbonylhistidine dissolved and a precipitate separated. After an additional 3 min this was collected and washed with ether in a drybox. Some residual material which remained on the flask walls was stirred with 3 ml of phosphorus tribromide in 300 ml of THF, and the resulting precipitate brought the yield of crude NTA to theory (15 g). The NTA was dissolved in 125 ml of methyl carbitol and 375 ml of ethyl acetate was added to give 10.5 g (72% recovery) of histidine NTA hydrobromide, $[\alpha]^{25}_{589}$ −7.0° (c 2, methyl carbitol).

Histidine NTA By-product 11.—The NTA of histidine hydrobromide (2.80 g) was added over 2 min at 0° to 100 ml of a 0.2 *M* solution of potassium borate at pH 10.2 with magnetic stirring. Stirring was continued for 10 min more after the addition was complete and the mixture was brought to pH 4 with sulfuric acid at 0°. The product (1.6 g) was removed by filtration and washed with water. An aliquot was crystallized for analysis by purification *via* the sodium salt, ir (methyl carbitol) 1705 cm^{-1} (NCONH).

Anal. Calcd for $C_7H_7O_2N_3S$: C, 42.64; H, 3.58; N, 21.32; S, 16.26. Found: C, 42.43; H, 3.34; N, 21.46; S, 16.82.

L-Arginine NTA Hydrobromide, 4 [R = $(CH_2)_3NHC(NH_2)_2^+$].—Methoxythiocarbonyl-L-arginine was prepared from the free base by the usual procedure and the crude concentrate from this reaction could be crystallized from water. A suspension of 10 g of methoxythiocarbonyl L-arginine in 240 ml of THF was stirred and a cold solution of 15 ml of phosphorus tribromide in 35 ml of THF was added rapidly. An oil separated which crystallized and was collected after 3 hr. Recrystallization from 2-propanol and ether led to 7.5 g of a hygroscopic white solid, $[\alpha]^{25}_{589}$ −18.7° (*c* 1, CH_2Cl_2), mp 115–117°.

L-Leucine NTA, 4 [R = $(CH_3)_2CHCH_2$], *via* the Methyl Enol Ether, Isobutyl-2-methoxy-5-thiazolone.—A solution of 4.11 g (0.020 mol) of the methoxythiocarbonyl-L-leucine in 15 ml of benzene was stirred with 1.9 ml (0.020 mol) of acetic anhydride for 5 hr at room temperature. The solution was diluted with 20 ml of ethyl acetate and washed with 20 ml of water, twice with 20-ml portions of 5% $NaHCO_3$, and with 10 ml of saturated aqueous NaCl. The organic phase was dried over Na_2SO_4 and con-

(31) T. E. Beesley, R. E. Harman, T. A. Jacob, C. F. Hornick, R. A. Vitali, D. F. Veber, F. J. Wolf, R. Hirschmann, and R. G. Denkewalter, *J. Amer. Chem. Soc.*, **90**, 3255 (1968).

(32) M. Delepine, *Bull. Soc. Chim. Fr.*, **7**[4], 404 (1910).

(33) *O,S*-Dimethyl dithiocarbonate prepared from dimethyl sulfate and potassium *O*-methyl dithiocarbonate occasionally developed a band in its ir spectrum at 5.90 μ. This decomposition could be avoided if the xanthate ester were stirred with a small amount of triethylamine for 1 hr. The decomposition was attributed to the following rearrangement catalyzed by a trace of methyl sulfate.

$$(CH_3O)_2SO_2 + CH_3\overset{S}{\overset{\|}{S}}COCH_3 \longrightarrow [CH_3\overset{SCH_3}{\overset{|}{S}}COCH_3]^+CH_3OSO_3^-$$

$$[CH_3\overset{SCH_3}{\overset{|}{S}}COCH_3]^+ + CH_3\overset{S}{\overset{\|}{S}}COCH_3 \longrightarrow CH_3\overset{O}{\overset{\|}{S}}CSCH_3 + [CH_3\overset{SCH_3}{\overset{|}{S}}COCH_3]^+ \text{ etc.}$$

A similar observation was made for thioglycolic acid by E. Bülmann, *Justus Liebigs Ann. Chem.*, **364**, 314 (1909).

centrated to give 0.42 g of an oil, ir (CH_2Cl_2) 1730 (s, C=O), 1631 cm^{-1} (N=C). Tlc revealed one component as detected by iodine vapor with an R_f 0.46 (benzene), whereas leucine NTA showed an R_f of 0.09 and methoxythiocarbonyl-L-leucine remained at the origin.

The enol ether (0.16 g, 0.855 mmol) prepared above was allowed to react with 1.0 ml of 1.7 *N* HCl in THF at room temperature for 20 min. The solution was then diluted with 5 ml of ethyl acetate and washed successively with water, aqueous $NaHCO_3$, and saturated NaCl. From the organic layer was obtained 0.067 g (45% yield) of leucine NTA, mp 79.5–81° (ethyl acetate–hexane), $[\alpha]^{25}_{589}$ −27° (*c* 1, CH_2Cl_2). The ir spectrum of this product was identical with that of a specimen prepared from methoxythiocarbonyl-L-leucine with phosphorus tribromide.

L-Leucine NTA. Direct Preparation from *N*-Methoxythiocarbonyl-L-leucine.—A solution of 8.12 g (39.6 mmol) of *N*-methoxythiocarbonyl-L-leucine and 2.72 g (40 mmol) of imidazole in 32 ml of THF was treated with 4.56 ml (48 mmol) of phosphorus tribromide with ice bath cooling such as to keep the reaction temperature below 40°. A precipitate formed, and after about 10-sec reaction time the product was quenched into an ice-cold stirred mixture of 200 ml of ethyl acetate and 200 ml of 10% aqueous $NaHCO_3$. The organic layer was washed with cold 1 *N* HCl, 5% aqueous $NaHCO_3$, and with saturated aqueous NaCl. The organic layer was dried and concentrated to yield 6.45 g (93.4%) of a colorless oil which rapidly crystallized. This product showed a strong spot for leucine NTA (R_f 0.25) and a smaller spot (R_f 0.80) corresponding to the 2-methoxythiazolone upon tlc on silica gel in chloroform–methanol (9:1). Recrystallization from 7 ml of ethyl acetate and 80 ml of hexane gave 4.67 g (68%) of L-leucine NTA, mp 77–78°, $[\alpha]^{25}_{589}$ −57.2° (*c* 1.035, CH_2Cl_2).

When a similar reaction was carried out at −30° for 0.5 hr, an oil was obtained which showed the thiazolone and the NTA by tlc. The product mixture was chromatographed on silica gel in benzene to give 230 mg of an oil which corresponded in its R_f to that of the thiazolone. A second fraction (160 mg) was obtained which when rechromatographed gave 22 mg of leucine NTA $[\alpha]^{25}_{589}$ −34.5 (*c* 0.345, CH_2Cl_2), mp 73.5–75°. Another reaction was performed at 4–10° for 20 min, and gave the crude NTA in 85% yield, $[\alpha]^{25}_{589}$ −52.4 (*c* 1, CH_2Cl_2). Repeated recrystallizations from ethyl acetate–hexane gave successive rotations of −54.0 and −52.7° (*c* 1, CH_2Cl_2). A similar difficulty in obtaining optically pure NTA by recrystallization was observed in other experiments.

Leucine NTA [1.73 g, 10 mmol, $[\alpha]^{25}_{589}$ −57.4° (*c* 1, CH_2Cl_2)] was added to a solution of silver nitrate (5.1 g, 30 mmol) in 10 ml of water and 10 ml of dioxane. The mixture was stirred overnight at room temperature and filtered to remove the precipitate of silver sulfide. The filtrate was adjusted to pH 6 with triethylamine and concentrated to a semisolid. The residue was triturated with ethanol and the resulting white crystals (0.63 g, 4.8 mmol) were collected after 1.5 hr. The filtrate was made alkaline with NaOH and concentrated to remove triethylamine.

A portion of the above crystalline leucine (131 mg, 1.00 mmol) was treated with 210 mg (1.10 mmol) of L-phenylalanine NCA under the usual conditions for controlled peptide synthesis.[1] The product was examined by tlc on silica gel in butyl alcohol–acetic acid–water (10:1:3) for the presence of L-phenylalanyl-D-leucine in addition to the major product, L-phenylalanyl-L-leucine. No LD-dipeptide (<1%) was detected. Comparison standards were made from the dipeptide obtained from the reaction of L-phenylalanine NCA with DL-leucine to give the LL-dipeptide (R_f 0.62) and the LD-dipeptide (R_f 0.46).

A similar experiment was carried out on the above filtrate from the hydrolysis. One half of the filtrate was made up to 10 ml. Comparison by tlc with standard solutions showed a concentration of leucine of 0.037 ± 0.012 *M*. Reaction with phenylalanine NCA led to a dipeptide mixture showing 15% L-phenylalanyl-D-leucine in the mother liquors. This amount would correspond to 3 ± 1% D-leucine of the leucine in the hydrolysate.

Preparation of Amino Acid Thiocarbamates, Dipotassium Phenylalanine Thiocarbamate (9, R = $C_6H_5CH_2$).—To a suspension of 33 g of L-phenylalanine in 50 ml of methanol was added 50 ml of a 4 *N* solution of methanolic potassium hydroxide. The resulting solution was cooled to 0° and 15 ml of carbonyl sulfide (The Matheson Co., Rutherford, N. J.) which had been condensed at −80°, was distilled into the solution while a second portion (53 ml) of methanolic potassium hydroxide was added. After 1 hr, the solution was concentrated *in vacuo* to give a syrup, which was taken up in anhydrous ethanol and concentrated to dryness *in vacuo*. This operation was repeated to remove traces of water, which inhibited crystallization. The residue was then taken up in 150 ml of methanol and filtered and 200 ml of 2-propanol was added slowly to give 59.4 g (48.6%) of a white granular precipitate. Electrophoresis at pH 11 in 0.1 *N* phosphate buffer on S & S 598 paper at 600 V showed a strong spot (ninhydrin) migrating toward the anode with about twice the mobility of phenylalanine as well as a weak spot corresponding to phenylalanine itself. A sample was recrystallized for analysis from hot ethanol with 2-propanol added.

Anal. Calcd for $C_{10}H_9K_2NO_3S$: C, 39.85; H, 3.01; K, 25.94; N, 4.65; S, 10.60. Found: C, 39.08; H, 3.68; K, 23.46; N, 4.22; S, 9.12.

The electrophoresis of the disodium salt of glycine thiocarbamate which was similarly prepared was carried out as above and showed a single spot by ninhydrin at 17.2 cm while glycine and disodium glycine carbamate showed spots at 6.8 cm.

L-Leucine NTA [4, R = $(CH_3)_2CHCH_2$–] *via* Leucine Thiocarbamate. Method B.—Dipotassium leucine thiocarbamate (5.34 g, prepared in analogy with phenylalanine thiocarbamate), 40 ml of THF, and 4.4 g of phosphorus pentachloride were stirred at 0° under nitrogen to give a translucent gel. After 5 min hydrogen sulfide was bubbled through the mixture while the temperature was raised to 25°. After 1 hr, 25 ml of ethyl acetate and 25 ml of water were added to the opaque mixture. The organic layer was washed with water and sodium bicarbonate, dried over $MgSO_4$, and concentrated to give 2.04 g of a syrup. Silica gel chromatography led to 0.45 g (13%) of crystalline leucine NTA (see Table II).

L-Leucine NTA *via* Thioleucine Thiocarbamate. Method C.—A solution of 20 ml of 2,6-lutidine in 200 ml of THF was saturated with hydrogen sulfide at −10°, and leucine NCA (7.9 g) was added with stirring. A heavy precipitate developed after 3 hr. The solid was collected, washed with ethanol and ether, and then dried *in vacuo* to give 6.63 g (90%) of thioleucine. A sample was recrystallized from water.

Anal. Calcd for $C_6H_{13}NOS$: C, 48.95; H, 8.90; N, 9.52; S, 21.78. Found: C, 49.10; H, 9.15; N, 9.55; S, 22.24.

A solution of 0.43 g (2.9 mmol) of the above thioleucine in 5 ml of water was stirred at 0–5°, and a slight excess of carbonyl sulfide was passed into the solution while 2.5 ml of a 2.5 *N* sodium hydroxide solution was added dropwise so as to maintain the pH at 10. The solution was stirred 2 hr at ambient temperature, and the resulting crude thiocarbamate solution was used directly in the following step.

The solution (pH 8.8) was cooled to 0°, and 5 ml of ethyl acetate was added. Then 0.76 g (3.0 mmol) of *N*-ethyl-5-phenylisoxazolium-3-sulfonate (Woodward's reagent K) was added with rapid stirring. The mixture showed a pH of 8. After 10 min the organic layer was separated, washed with water, and dried to give an oil which crystallized upon the addition of hexane to give 0.23 g (45%) of leucine NTA, $[\alpha]^{25}_{589}$ −56.7° (*c* 0.96, CH_2Cl_2) (Table II).

Dipotassium thioleucine thiocarbamate was also prepared and isolated from alcohol in a manner similar to the preparation of phenylalanine thiocarbamate. Upon electrophoresis at pH 11 the product showed a single fast moving spot relative to thioleucine. However, when the reaction with Woodward's K was carried out upon isolated thioleucine thiocarbamate, only a 29% yield of NTA was obtained, $[\alpha]^{25}_{589}$ −28.9° (*c* 1, CH_2Cl_2).

A reaction of the thiocarbamate with phosphorus pentachloride in THF gave a 23% yield of NTA, $[\alpha]^{25}_{589}$ −1.9° (*c* 1, CH_2Cl_2).

Leucine NTA *via* Leucine Amide. A. From Leucine Amide.—A solution of 2.6 g (20 mmol) of L-leucine amide and 2.17 ml (23 mmol) of *O*,*S*-dimethyl dithiocarbonate in methanol (5 ml) was stirred under nitrogen at room temperature for 3.5 hr and then heated to 50° for 0.5 hr. Evolution of methyl mercaptan as detected by a yellow precipitate with lead acetate had virtually ceased. The reaction mixture was taken up in ethyl acetate (10 ml), washed with 10% NaCl solution, dried over Na_2SO_4, and concentrated to a tacky noncrystalline residue of the thionourethan amide, ir (CH_2Cl_2) 1689 cm^{-1} (amide C=O).

Hydrogen chloride was bubbled through a solution of crude thiourethan derived from leucine amide (0.45 g) in nitromethane (5 ml) for 1 hr at room temperature. After 2 hr the mixture was partitioned between ethyl acetate (5 ml) and water (5 ml). The organic layer was separated, washed with water (5 ml), dried over sodium sulfate, and concentrated. The residue was crystal-

lized from cyclohexane to give 0.17 g of leucine NTA as colorless needles, mp 74–75°, $[\alpha]^{25}_{589}$ −35.4° (*c* 1.06, CH_2Cl_2). Its infrared spectrum was identical with that of leucine NTA prepared *via* the thionourethan.

B. From Methoxythiocarbonylleucine Amide.—In an alternate route, 2.05 g (10 mmol) of L-methoxythiocarbonylleucine was dissolved in ether (15 ml) and ammonia was bubbled through the solution for a few minutes. An oil separated. The mixture was concentrated *in vacuo*. Acetonitrile (10 ml) and 2.06 g (10 mmol) of dicyclohexylcarbodiimide were added, and the mixture was stirred overnight at room temperature. The mixture was concentrated and the residue was extracted with three 10 ml portions of ether. The ether extract was filtered and concentrated to give an oil, 2.08 g.

The above thiourethan (1.0 g) was treated with HCl to give 0.29 g of leucine NTA, mp 81–82°, $[\alpha]^{25}_{589}$ 0.0° (c 1.02 CH_2Cl_2). Its infrared spectrum was identical with that of leucine NTA prepared as described above.

Phenylalanine NTA (4, R = $PhCH_2$–) from Thiophenylalanine and Phosgene. Method D.—A suspension of thiophenylalanine (5.44 g, 0.030 mol) in dioxane (125 ml) was stirred at room temperature while phosgene (0.031 mol) was introduced below the surface of the slurry to yield a clear solution after 15 min. After 1 hr the solution was concentrated, and ethyl acetate (75 ml) and hexane (150 ml) were added to give a solution which was decanted from a small amount of oil and concentrated. The solid residue was crystallized from ethyl acetate (17 ml) and hexane (17 ml) to give 0.50 g (81%) of the NTA, $[\alpha]^{25}_{589}$ −155° (*c* 1, CH_2Cl_2). Addition of further hexane (20 ml) gave a further 1.36 g, $[\alpha]^{25}_{589}$ −154° (c 1, CH_2Cl_2).

Peptide Syntheses Using NTA's.—In general the reactions were carried out in a Waring Blendor as previously described for the reaction of NCA's,[1] but with the following modifications. The amino acid or peptide was dissolved in 0.45 *M* boric acid, and the solution was adjusted to pH 9.5 in the case of amino acids and to pH 9.0 for peptides. In some of the earlier runs, standard glass equipment was used. The powdered NTA was added over a 15–60-sec period at 0° while concentrated aqueous potassium or sodium hydroxide was added subsurface in order to maintain the initial pH. At the end of the reaction, which was ascertained by the cessation of a significant uptake of base (generally 5–20 min), the pH was lowered to 3–5, and the mixture was swept with nitrogen to remove carbonyl sulfide.

Glycyl-L-phenylalanine.—An aqueous solution of 0.181 g (1.1 mmol) of L-phenylalanine was treated with 0.131 g (1.5% excess) of glycine NTA in a blender while the pH was maintained with saturated barium hydroxide. The solution was neutralized with sulfuric acid, and the precipitate was filtered. An aliquot of the filtrate was placed directly on a Beckman amino acid analyzer and the peaks were compared with those of glycylphenylalanine and of phenylalanine. The intensity of the peaks indicated Gly-Phe, 92.5%, Phe, 2.25%, and a third peak presumed to be Gly-Gly-Phe, about 2%. Residual phenylalanine was thought to have been converted to the hydantoic acid by-product. The solution was concentrated and the residue was crystallized from aqueous ethanol to give 1.49 g (74.5%) of dipeptide.

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.46; H, 6.35; N, 12.61. Found: C, 59.08; H, 6.60; N, 12.54.

A second crop of 0.23 g (11.5%) was obtained which showed a second but weak spot by tlc corresponding to a trace of Gly-Gly-Phe.

Glycyl-L-phenylalanyl-L-leucine. A. *Via* Glycine NTA.—In a three-necked flask equipped with a paddle stirrer, combination pH electrode, and a nitrogen inlet was placed 10 ml of 0.45 *M* boric acid and 0.556 g (1.9 mmol based on 95% peptide content by amino acid analysis) of L-Phe-L-Leu. The solution was cooled to 4° and adjusted to pH 9.5 with 45% potassium hydroxide. The solution was stirred vigorously while 0.246 g (2.1 mmol) of glycine NTA was added. The pH was held at 9.5 with potassium hydroxide. After the reaction was complete (about 5 min), the mixture was brought to room temperature and filtered. The filtrate showed a disappearance yield[1] by tlc on silica gel of 90–95% in butyl alcohol–acetic acid–water (10:1:3). The solution was brought to pH 5.5 with 50% H_2SO_4 and the resulting precipitate was collected to give 0.430 g (64%) of the tripeptide, R_f 0.45 (10:1:3), $[\alpha]^{25}_{589}$ −12.5° (*c* 1.04, HOAc). An amino acid analysis showed a ratio of $Gly_{1.00}Phe_{0.99}Leu_{1.00}$.

Anal. Calcd for $C_{17}H_{25}N_3O_4$: C, 60.88; H, 7.51; N, 12.53; neut equiv, 335. Found: C, 60.95; H, 7.40; N, 12.76; neut equiv, 323.

B. *Via* Glycine NCA.—A solution of 1.112 g (4 mmol) of L-phenylalanyl-L-leucine was treated with 0.424 g (4.2 mmol) of glycine NCA in a blender under the usual conditions. The crude product showed a disappearance yield of about 85%. Acidification of the solution led to precipitation of 0.450 g (35.4%) of the tripeptide, which corresponded in R_f to that prepared above.

C. *Via* Glycine NTA (Variation of By-products with pH).—A series of reactions were carried out similar to the above but at various pH levels. Visual comparison of the spot intensities of the products by tlc (10:1:3) indicated the following by-products along with glycine and the tripeptide. The sample of the overreaction product, Gly-Gly-Phe-Leu was prepared by a reaction of glycine NTA with the above tripeptide. A solution of this product was then diluted to the appropriate concentration for comparisons.

pH	Phe-Leu, %	Gly-Gly-Phe-Leu, %
8.5	<2	>10, <20
9.0	2	<10
9.5	>5, <10	>10
10.0	>10, <20	>10, <20

D. Glycyl-L-phenylalanyl-^{14}C-L-leucine.—Glycine NTA (0.95 equiv) was added to a stirred solution of L-phenylalanyl-^{14}C-L-leucine at a concentration of 1 mmol in 5 ml of 0.4 *N* borate buffer at 0–2°. The reaction was carried out at pH 8.5, 9.2, and 10.0. The product was examined by tlc on silica gel in the butyl alcohol–acetic acid–water system (10:1:3). The plates were scanned directly and the spots on the plates were extracted and their radioactivity was redetermined by means of a scintillation counter, by a previously outlined procedure.[1] The assays determined by the use of the scintillation counter are summarized in Table V.

L-Alanyl-L-phenylalanyl-L-leucine. A. *Via* Alanine NTA.—In the apparatus described for the preparation of glycylphenylalanylleucine, a mixture of 0.556 g (2.0 mmol) of L-phenylalanyl-L-leucine and 10 ml of 0.45 *M* aqueous boric acid was chilled to 4° and adjusted to pH 9.05 by addition of 0.106 ml of 50% aqueous sodium hydroxide. L-Alanine NTA (0.276 g, 2.1 mmol) was added in one portion with vigorous stirring along with addition of 0.294 ml of 50% aqueous sodium hydroxide as required to maintain the pH in the range 9.05 ± 0.05. Thin layer chromatography of the reaction mixture showed a "disappearance yield"[1] of 98%. Acidification to pH 5.1 with 50% aqueous sulfuric acid yielded a solid product (0.510 g). This was dissolved in 5 ml of water by addition of 2.5 *N* sodium hydroxide and then acidified with acetic acid. The crystalline precipitate was collected, washed with water, and dried to give 0.420 g (63.4%) of L-alanyl-L-phenylalanyl-L-leucine which moved as a single spot component upon tlc (R_f 0.54, 10:1:3), amino acid analysis, $Ala_{0.98}Phe_{0.97}Leu_{1.00}$.

Anal. Calcd for $C_{18}H_{27}N_3O_4$: C, 61.87; H, 7.79; N, 12.03; neut equiv, 349. Found: C, 62.14; H, 7.70; N, 12.29; neut equiv, 347.5, pK_2 = 7.4.

The optical purity of the crude tripeptide was examined in another experiment carried out essentially as described above; tlc analysis again showed a 98% disappearance yield. A sample of the filtrate prior to acidification (0.04 ml, corresponding to 8 μmol) in 0.1 ml of a solution of 1.0 mg of leucine aminopeptidase in 0.5 ml of tris buffer was held at 37° for 18 hr. Comparison with standard solutions showed that 1% of the tripeptide in the sample remained unhydrolyzed. A sample of D-alanyl-L-phenylalanyl-L-leucine (prepared by reaction of D-alanine NCA with the dipeptide) showed little or no hydrolysis with the enzyme under the same conditions.

B. *Via* Alanine NCA.—Reaction of a 10% excess of L-alanine NCA with L-phenylalanyl-L-leucine at pH 10.2 under the usual conditions[1] gave 52% of a product which upon reprecipitation as above led to a 36% yield of a single spot tripeptide with an amino acid analysis of $Ala_{1.00}Phe_{1.00}Leu_{0.98}$: equiv wt, found 338; pK_2 = 7.3.

Comparison of L-Alanine NCA and NTA in a Reaction with *O*-Benzyl-L-seryl-L-valine. Formation of L-Alanyl-*O*-benzyl-L-seryl-L-valine.—Reaction of *O*-benzylserine NCA with a 0.2 *M* solution of valine in 0.45 *M* borate buffer led to a solution of crude *O*-benzyl-L-seryl-L-valine which was used directly for the following experiments. In two other runs the disappearance yields of the dipeptide were 88 and 95%.

A. With L-Alanine NCA.—A 20-ml aliquot (3.7 mmol) of the above solution of crude *O*-benzyl-L-seryl-L-valine was treated with 459 mg (3.99 mmol) of alanine NCA at pH 10.1. The resulting solution showed a 90% disappearance yield by tlc (10:1:3). The solution was filtered and acidified to pH 5.9. The precipitate was collected, washed with water, and dried to give 748 mg (55%) of crude tripeptide. Reprecipitation of this product from a sodium hydroxide solution with acetic acid gave 673 mg (49%) of the tripeptide, R_f 0.44 (10:1:3), amino acid analysis, $Ala_{0.99}Ser_{1.00}Val_{1.00}$.

Anal. Calcd for $C_{18}H_{27}N_3O_5$: C, 59.16; H, 7.45; N, 11.50; neut equiv, 365. Found: C, 58.96; H, 7.51; N, 11.39; neut equiv, 347, $pK_2 = 7.6$ (in 50% v/v aqueous methanol).

B. With L-Alanine NTA.—A similar experiment was carried out between another 20-ml aliquot of the dipeptide solution and 512 mg (3.91 mmol) of alanine NTA at pH 9.15 to give a 95% disappearance yield, and precipitation with acetic acid led to 923 mg (67.8%) of the crude tripeptide. Reprecipitation led to 830 mg (61%) of the tripeptide, R_f 0.44 (10:1:3), amino acid analysis, $Ala_{1.02}Ser_{0.99}Val_{1.00}$.

Anal. Found: C, 59.28; H, 7.73; N, 11.44; neut equiv, 354, $pK_2 = 7.6$.

Formation of L-Valyl-L-histidyl-L-phenylalanyl-L-aspartyl-L-alanyl-*O*-benzyl-L-seryl-L-valine. A. *Via* **Histidine NTA.**—A solution of crude pentapeptide prepared by the reaction of phenylalanine NCA on 10.1 g (20 mmol) of aspartylalanyl-*O*-benzylserylvaline was treated with an excess of histidine NTA hydrobromide (21.45 g, 77.3 mmol) in 100 ml of borate buffer at pH 9. The product showed a disappearance yield of 92% (10:1:3). The mixture was extracted with butyl alcohol at pH 3.5, and the residue (14.15 g) from the organic extract was fractionated on a dry silica gel column in 1-propanol–water (71:29) to give 2.41 g of starting pentapeptide and 3.62 g (23.7%) of the product hexapeptide, R_f 0.24 in ethyl acetate–pyridine–acetic acid–water (10:5:1:3).

The above hexapeptide (3.06 g, 4.0 mmol) was treated with 0.63 g (4.4 mmol) of valine NCA in 20 ml of 0.45 *M* borate buffer in the usual manner. The crude heptapeptide was reprecipitated from a basic solution with acetic acid. Hydrogenation in 75% acetic acid with 10% Pd-C led to the unprotected peptide,[34] amino acid analysis, $Val_{2.02}His_{0.99}Phe_{0.99}Asp_{1.01}Ala_{1.01}Ser_{1.00}$.

Anal. Calcd for $C_{35}H_{51}N_9O_{11}\cdot 4H_2O$: C, 49.70; H, 7.03; N, 14.90; equiv wt 423. Found: C, 49.37; H, 6.41; N, 14.37; equiv wt, 418.

Enzymatic cleavage of the peptide with aminopeptidase M (Rohm and Haas GmbH, Darmstadt) was carried out analogous to a reported procedure.[35] The reaction mixture was compared with standards of diluted peptide solution by tlc in butyl alcohol–acetic acid–water (10:2.5:6) and showed 2% residual peptide, amino acid analysis, $Val_{1.98}His_{0.95}Phe_{1.01}Asp_{1.04}Ala_{1.02}Ser_{1.00}$.

B. *Via tert*-**Butoxycarbonyl-L-histidine Azide.**—A solution of 54 mg (0.20 mmol) of *tert*-butoxycarbonyl-L-histidine hydrazide[36] in 2 ml of DMF was cooled to −30° and 0.4 ml of 2 *N* hydrogen chloride in THF was added. Isoamyl nitrite (0.026 ml, 0.20 mmol) was added and the solution was stirred at −20° for 30 min. Complete disappearance of the starting hydrazide was evident by tlc in methanol. The solution was cooled to −40° and adjusted to an apparent pH of 8 with triethylamine. A solution of 107 mg (0.20 mmol) of the free seryl pentapeptide, which had been deblocked by the above hydrogenation procedure, was added at −20° in 1.5 ml of DMF. The pH was brought to 8 and the mixture was stored at −10° for 3 days with an occasional readjustment of the pH to 8. The reaction mixture was filtered, the filtrate was concentrated *in vacuo*, and the residue was triturated with ethanol to give 79% of the crude hexapeptide.

The crude *N*-*tert*-butoxycarbonyl hexapeptide (100 mg) was suspended in ethyl acetate in an ice bath and hydrogen chloride was passed through the mixture for 10 min. The mixture was allowed to stand for 30 min and then was swept with nitrogen. The precipitate was collected to give an 86% yield of the deblocked hexapeptide. Peptide (149.2 mg) prepared in this manner was treated with a 50% excess of *tert*-butoxycarbonyl valine *N*-hydroxysuccinimide (93.6 mg) in DMF. The reaction was kept slightly alkaline by small additions of triethylamine for 2 days. The product was isolated by silica gel chromatography in 32% yield. The *tert*-butoxycarbonyl group was removed with HCl in ethyl acetate under conditions similar to the above to give the deblocked heptapeptide, amino acid analysis, $Val_{2.03}His_{0.97}Phe_{1.01}Asp_{1.03}Ala_{1.00}Ser_{0.97}$.

A sample of this heptapeptide was cleaved by aminopeptidase M according to the procedure that was used for the peptide prepared *via* histidine NTA. Residual peptide amounting to about 2% remained after incubation, amino acid analysis, $Val_{2.07}His_{0.94}Phe_{0.97}Asp_{0.98}Ala_{1.02}Ser_{1.02}$.

Histidylalanylglycine. Racemization in the Use of L-Histidine NTA Hydrobromide. A.—Reaction of L-alanyl-glycine with 2 equiv of L-histidine NTA hydrobromide ($[\alpha]^{25}_{589}$ −7.7°) at pH 9.4–9.55 at 4° led to a crude product which was examined directly by 100-MHz nmr. The alanine methyl doublet peaks of L-alanylglycine at τ 8.40 (d, J = 7.3 Hz), of L-histidyl-L-alanylglycine at 8.53 (d, J = 7.1 Hz), and of D-histidyl-L-alanylglycine, at 8.66 (d, J = 7.2 Hz) were found in the ratios of 25:70:5. The ratios of the peak areas were determined from a spectrum of C.A.T. of 27 scans in this region at 100 ml in D_2O. The peaks at τ 8.66 were attributed to the methyl doublet of D-histidyl-L-alanyl-glycine, and this position corresponded to the doublet of L-histidyl-D-alanyl-glycine below.

B. With D-Alanyl-glycine.—A similar reaction was carried out on D-alanylglycine. Here the alanine methyl doublets were in the ratios: D-alanylglycine, 42; D-histidyl-D-alanyl-glycine, 10; L-histidyl-D-alanyl-glycine, 48.

Alanylphenylalanine. Determination of the Racemization with L-Alanine NTA.—A reaction was carried out similar to the above using L-phenylalanine and a 10% excess of L-alanine NTA at pH 9.5. The freeze-dried crude product was examined by nmr in D_2O. The product showed the doublet of the alanine methyl group at τ 8.16 (J_{HH} = 7, $J_{^{13}CH}$ = 132 Hz) attributed to L-alanyl-L-phenylalanine and at τ 8.42 (J_{HH} = 7 Hz) attributed to D-alanyl-L-phenylalanine. The intensities of the alanine methyl doublets for the dipeptide and its epimer were determined from a C.A.T. of 1660 scans of this region in a 100-MHz nmr spectrum. The ratio of the upfield ^{13}CH satellite doublet[24] of the methyl doublet of the LL isomer to the central methyl doublet of the DL-isomer was 1:2.5, which would indicate a ratio of LL to DL peptide of 98.6 to 1.4.

Arginylphenylalanine. Determination of Racemization in the Reaction of L-Arginine NTA Hydrobromide with L- and D-Phenylalanine. A. With L-Phenylalanine.—A reaction of L-phenylananine with a 23% excess of arginine NTA hydrobromide was run at pH 9.5 as above, but in this case the diastereomeric dipeptides were separated by dry column chromatography[1] on silica gel H (E. Merck, Darmstadt) in chloroform–methanol 9:1, and the ultraviolet spectra of aliquots of the total fractions were compared at 258 mμ. The ratio of L-Arg-L-Phe to D-Arg-L-Phe was 95:5. A third fraction corresponded to phenylalanine and represented 2% of the total dipeptide fraction.

B. With D-Phenylalanine.—An identical experiment with D-phenylalanine gave a ratio for L-arginyl-D-phenylalanine to D-arginyl-D-phenylalanine of 84:16. A third fraction, phenylalanine, was obtained, which represented 5% of the dipeptide fractions.

Phenylalanylarginine from Phenylalanine NTA and ^{14}C-Arginine.—A stock solution of ^{14}C-labeled L-arginine was prepared by dissolving 3.484 g of L-arginine (20 mmol, 0.5 mCi) in 80 ml of water, adjusting the pH to 3 with 10 *N* H_2SO_4, and making up the solution to 100 ml with water. A 10-ml aliquot of the arginine stock solution (2 mmol, 50 μCi) was pipetted into a Waring Blendor along with 8 ml of water. The solution was stirred under N_2 at 24.5° and the pH was adjusted to 9.5 with saturated barium hydroxide solution. Phenylalanine NTA (456 mg, 2.2 mmol) was added while the pH was maintained at 9.5. After 20 min the pH was raised to 10.6. The solution was filtered and made up to 50 ml. Electrophoresis at pH 2 separated the peptides and the hydantoic acid derived from phenylalanine NTA and arginine. The paper strip was cut into sections and the radioactivity was determined as per cent of total on the strip. For details see ref 1. A similar reaction was run with phenylalanine NCA at 0–2°, pH 10.0. The results are outlined in Table VI.

L-Proline NTA.—A solution of 94.6 g (0.50 mol) of methoxythiocarbonyl-L-proline, $[\alpha]_{589}$ −126° (c 1, $CHCl_3$), which was prepared by the usual procedure, in 350 ml of THF was cooled to −35° and 270.7 g (1.00 mol) of phosphorus tribromide was added. After 4 hr at −35° the reaction was diluted with ethyl acetate and extracted at 0° with 375 ml of ice water. The organic

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TABLE VI
DISTRIBUTION OF PRODUCTS IN THE PHE-ARG REACTION[a]

Product	From Phe-NTA, %	From Phe-NCA, %
Arginine	2.2	3.5
H-Phe-Arg·OH	94.2	89.2
H-Phe-Phe-Arg·OH	0.3	4.0
Hydantoic acid	2.7	2.8

[a] Traces of radioactivity between these spots bring the total to 100%.

layer was washed three times with 5% aqueous $NaHCO_3$, three times with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated to give 33 g (21%) of crude proline NTA. One recrystallization from ether gave material with a rotation of $[\alpha]_{589}$ $-155.1°$ (c 1, $CHCl_3$) and three further crystallizations gave proline NTA of constant rotation, $[\alpha]_{589} -157 \pm 0.5°$ (c 1, $CHCl_3$). The final recrystallized proline NTA was used for the following racemization study.

Racemization in the Preparation of Prolylphenylalanine. A. In Tritiated Water.—A solution of 0.826 g (5.0 mmol) of phenylalanine in 50 ml of 0.5 *M* potassium borate in tritiated water was adjusted to pH 9.35 at 0°. Proline NTA (0.807 g, 5.8 mmol) was added while the pH was maintained at 9.35. The peptide was precipitated at pH 4.5 and recrystallized from water to constant activity. This product corresponded by tlc to peptide prepared *via* proline NCA.[1] A similar experiment was carried out at pH 10.0. At pH 9.35, 0.114% of 1 equiv of tritium was incorporated, and at pH 10.0, 0.129%.

B. In D_2O.—A solution of 0.66 g (4.0 mmol) of phenylalanine in 40 ml of 0.5 *M* borate buffer in D_2O which was prepared from boric acid anhydride and sodium deuterioxide was adjusted to a pH of 10.0 using a combination glass–calomel electrode set for a meter reading of 9.6.[37] A sample of the dipeptide was repeatedly recrystallized to free it of labile deuterium. This product was burned, and the water was reduced to hydrogen and then examined by mass spectroscopy.[38] Deuterium appeared at 0.0275% above natural abundance, which would correspond to an excess of 0.495% deuterium for one hydrogen position in the dipeptide.

A sample of L-proline NTA was hydrolyzed in dilute hydrochloric acid to proline, which was identified by tlc. The solution was concentrated and the product was assayed for D-proline by D-amino acid oxidase using a Warburg manometric technique[39] with an increased ratio of enzyme to substrate. Controls containing 0.5, 1.0, and 2.9% D-proline showed 0.34, 0.94, and 2.88% D-proline, whereas the above sample showed 2.08% D-proline (each an average of two runs).

Registry No.—Table I—L-Ala, 19777-64-1; D-alloisoleu, 26686-26-0; L-Arg, 26686-27-1; Gly, 26686-28-2; L-His, 19777-65-2; L-Ileu, 26686-30-6; L-Leu, 26686-31-7; L-Phe, 26686-32-8; L-Pro, 26686-33-9; L-Val, 26686-34-0; Table II—L-Ala, 16964-94-6; L-Arg, 26731-59-9; Gly, 16874-97-8; L-His, 26731-60-2; L-Leu, 26607-56-7; L-Phe, 26686-38-4; L-Pro, 26686-39-5; L-Val, 26731-61-3; **3** (R = *i*-Bu; R′ = Et), 26686-40-8; **9** (R = $C_6H_5CH_2$), 26686-41-9; **11**, 26686-47-5; glycyl-L-phenylalanyl-L-leucine, 15373-56-5; L-alanyl-L-phenylalanyl-L-leucine, 26686-43-1; L-Ala-*O*-benzyl-L-Ser-L-Val, 26731-62-4; L-Val-L-His-L-Phe-L-Asp-L-Ala-*O*-benzyl-L-Ser-L-Val, 6169-58-0; L-histidyl-L-alanylglycine, 26731-63-5; L-alanyl-L-phenylalanine, 3061-90-3; L-Arg-L-Phe, 2047-13-4.

Acknowledgments.—We wish to acknowledge the capable technical assistance of Messrs. James E. Deak, Victor Garsky, and John Sondey. We are indebted to Mr. R. Boos and associates for the elemental analyses, Mr. C. Homnick for the amino acid analyses, Dr. C. Rosenblum and his associates for assistance with the radiochemical measurements, and Miss D. L. Keller and Dr. T. Devlin for the D-amino acid oxidase studies.

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Steroidal β-Lactams.[1] II. Synthesis of Pregnane and *D*-Homo Compounds

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Received June 2, 1970

The conversion of *A*-norprogesterone (1) into 3,4-dinor-5-aza-*B*-homopregnane-2,20-dione (20) and its *D*-homo isomer, 17α-methyl-3,4-dinor-*B*-homo-*D*-homo-5-azaandrostane-2,17a-dione (16) is described.

The synthesis of a new steroidal ring system possessing a fused β-lactam as ring A has been recently described.[1] In that case, the substituent at C_{17} was a hydroxyl group, and we then became interested, from both the chemical and biological points of view, in the synthesis of a steroidal β-lactam bearing a pregnane side chain at C-17.[2] In this paper, we wish to describe the results of our efforts to convert *A*-norprogesterone (**1**)[3] into such a compound.

Our initial step in the synthesis was protection of the C-20 carbonyl of **1** as a hydroxyl function. We expected that treatment of **1** with sodium borohydride would lead to selective reduction at C-20, since α,β-unsaturated ketones reduce more slowly than saturated ketones (unhindered).[4] Indeed, reduction of **1** with sodium borohydride in methanol at 0° gave **2** in 80–90% yield. This compound has been previously prepared during the synthesis of **1**, by the ring A contraction method starting with 20β-hydroxy-4-pregnen-3-one.[3] Treatment of **2** with the permanganate–periodate combination[5] transformed the ring A α,β-unsaturated ketone system into a keto acid that cyclized and was isolated as the lactonol **3**. Room temperature acetylation selectively esterified the 20β-hydroxy group to give **4**. The methyl ester **5**, prepared by treatment of **4** with

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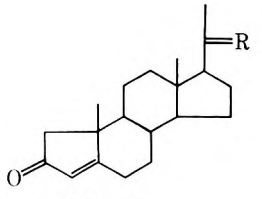
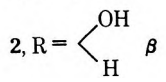
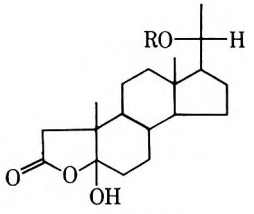
diazomethane, was reacted with hydroxylamine hydrochloride in pyridine to prepare the 5-oximino derivative. This oxime was not obtained in crystalline form, but was treated directly with thionyl chloride in dioxane to effect the ring B Beckmann rearrangement and give, after hydrolysis with base, the high-melting, very insoluble lactam acid **6**. Esterification with diazomethane gave the methyl ester **7**, which was reduced with lithium aluminum hydride in tetrahydrofuran to the amino diol **8**. Reaction of **8** with acetic anhydride in pyridine and purification of the product by alumina chromatography gave the *N*-acetyl diacetate **9** as an oil, which was characterized by its nmr spectrum.



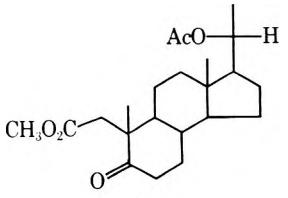
1, R = O



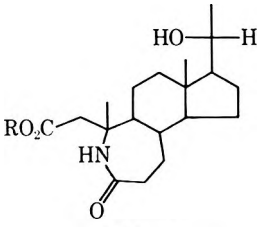
2, R = 17β-OH



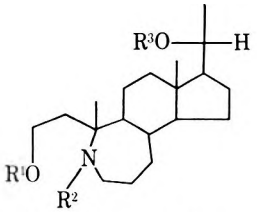
3, R = H
4, R = Ac



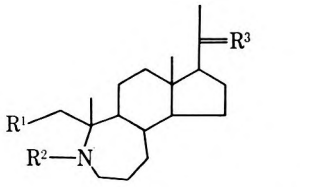
5



6, R = H
7, R = CH_3



8, $R^1 = R^2 = R^3 = H$
9, $R^1 = R^2 = R^3 = Ac$
10, $R^1 = H$; $R^2 = R^3 = Ac$
17, $R^1 = R^3 = H$; $R^2 = Ac$



11, $R^1 = CHO$; $R^2 = Ac$; $R^3 = 17\beta$-OAc
12, $R^1 = CO_2H$; $R^2 = Ac$; $R^3 = 17\beta$-OAc
18, $R^1 = CHO$; $R^2 = Ac$; $R^3 = O$
19, $R^1 = CO_2H$; $R^2 = Ac$; $R^3 = O$

We next sought to hydrolyze the C-2 and C-20 acetates in **9** to provide an *N*-acetyl diol that would, upon Jones oxidation, provide the C-17 progesterone side chain and an aldehyde at C-2, which could then be transformed into the desired β-lactam by following the same route employed in the androstane series.[1] Hydrolysis of **9** with refluxing methanolic potassium hydroxide solution for a few minutes gave, however, a product that contained only one hydroxyl group. An examination of the nmr spectrum of the product demonstrated that it was the C-2 alcohol. The signals for the C-18 Me, C-21 Me, and the 20α H were almost the same as those in **9**; therefore, the product was assigned structure **10**. At this stage, we decided to continue the synthesis as outlined above, because we felt that we could hydrolyze the 20β-acetate later, during the acid hydrolysis of the *N*-acetyl function. The desired ring A β-lactam, with a 17β-acetyl side chain, could then be prepared by cyclization to the β-lactam, followed by Jones oxidation of the 20β-ol.

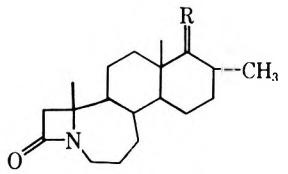
Stepwise oxidation at C-2 of **10**, first to the aldehyde **11** with Jones reagent at low temperature, and then to the carboxylic acid **12** with silver oxide proceeded uneventfully. Acid hydrolysis of **12** gave the crude amino acid that was cyclized with dicyclohexylcarbodiimide (DCC) in methylene chloride–nitromethane to provide a steroidal β-lactam having the expected molecular formula, $C_{19}H_{31}NO_2$. An inspection of the nmr spectrum of the product, however, revealed that we were no longer dealing with a 20β-hydroxypregnane derivative. This β-lactam has been assigned the *D*-homo structure **13** resulting from a uranediol type rearrangement.[6] The relevant nmr signals that enabled us to make the structural and stereochemical assignment are shown for **13**, uranediol **14**, and 17a-epiuranediol **15** in Table I.

TABLE I
NMR SIGNALS

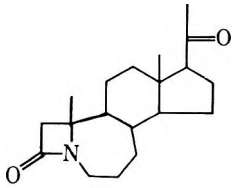
Compd	18-Me	17α Me	17α H
13	9.15	9.03 d, J = 5.5 Hz	7.28 d, J = 9 Hz
14[a]	9.19	9.06 d, J = 5 Hz	7.30 d, J = 9 Hz
15[a]	9.19	9.08 d, J = 7 Hz	6.69, W_H = 5 Hz

[a] See ref 6.

The rearrangement of the 20β-hydroxypregnane to the *D*-homo structure no doubt took place during the acid hydrolysis of **12**. The mechanism of this reaction has been discussed previously in detail[6] and will not be dealt with here. Jones oxidation of **13** provided the 17a-keto compound **16**.

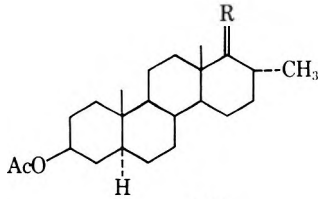


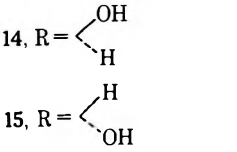
13, R = 17β-OH



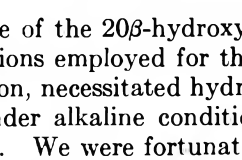
20

16, R = O





14, R = 17β-OH



15, R = 17β-OH

The unstable nature of the 20β-hydroxy side chain, under the acid conditions employed for the hydrolysis of the *N*-acetyl function, necessitated hydrolysis of the 20β-acetoxy group under alkaline conditions at some point in the synthesis. We were fortunate to observe that the 20β-acetoxy function could be slowly hydro-

(6) H. Hirschmann, F. B. Hirschmann, and A. P. Zala, *J. Org. Chem.*, **31**, 375 (1966), and references contained therein.

lyzed when the alkaline treatment of **9** was allowed to proceed at room temperature for an extended period of time (4–6 days). In this manner, we were able to obtain the desired *N*-acetyl diol **17**. Jones oxidation of **17** to the 2-aldehydo compound **18**, followed by further oxidation with silver oxide, afforded the *N*-acetyl acid **19**. The synthesis of the β-lactam bearing a 17β-acetyl side chain **20** was completed by acid hydrolysis of the *N*-acetyl group and cyclization of the resulting crude amino acid with DCC in nitromethane and chloroform.

Experimental Section

Melting points were determined in a Thomas–Hoover capillary melting-point apparatus and are uncorrected. Values of $[\alpha]D$ have been approximated to the nearest degree and were taken on a Perkin-Elmer 141 polarimeter in 95% EtOH. Ir spectra were determined on a Perkin-Elmer 21 spectrometer in pressed KBr pellets (unless otherwise indicated), and nmr spectra on a Varian A-60 spectrometer, employing TMS as the internal standard. The organic solutions were dried over sodium sulfate and all evaporations were carried out *in vacuo*. Alumina refers to neutral alumina, activity V, and silica gel refers to silica gel $HF_{254+366}$. Compounds were detected on the plates with iodine vapor. IPE stands for isopropyl ether.

20β-Hydroxy-*A*-nor-3-pregnen-2-one (2).—A solution of *A*-norprogesterone (2.0 g) in MeOH (200 ml) was treated at 0° with $NaBH_4$ (380 mg) and stirred at that temperature for 1 hr. Acetic acid (3 drops) was added and the solution was evaporated, diluted with H_2O, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with 8% NaCl solution, dried, and evaporated. Crystallization from $CHCl_3$–IPE gave **2** [1.68 g, mp 210–212° (lit.[3] mp 213–214°)].

5β,20β-Dihydroxy-3-oxa-*A*-norpregnan-2-one (3).—A solution of **2** (1.0 g) in *tert*-BuOH (150 ml) was treated with a suspension of K_2CO_3 (1.38 g), $KMnO_4$ (0.18 g), and $NaIO_4$ (5.72 g) in H_2O (150 ml) and stirred overnight at room temperature. The mixture was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with 8% NaCl solution, dried, and evaporated. Crystallization of the residue from $CHCl_3$–acetone gave **3** (413 mg, mp 192–193°). Recrystallization from $CHCl_3$ gave the analytical sample: mp 192–193°; $[\alpha]D$ +29°; ir 2.79, 2.82, 2.95, 5.64, and 5.79 μ; nmr ($CDCl_3$) τ 9.21 (s, 18-Me), 8.89 (s, 19-Me), 8.86 (d, J = 6 Hz, 21-Me), and 6.28 (m, 20α H).

Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.67; H, 9.15.

3-Oxa-5β-hydroxy-20β-acetoxy-*A*-norpregnan-2-one (4).—A solution of **3** (10.0 g) in Ac_2O (13 ml) and pyridine (25 ml) was left at room temperature for 4 hr. The mixture was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with 2 *N* HCl and 8% NaCl solution, dried, and evaporated. Crystallization of the residue from $CHCl_3$–IPE gave **4** (9.4 g, mp 167–168°). Recrystallization from acetone–IPE gave the analytical sample: mp 168–169°; $[\alpha]D$ +57°; ir 2.97, 5.71, and 5.79 μ; nmr ($CDCl_3$) τ 9.33 (s, 18-Me), 8.87 (s, 19-Me), 8.85 (d, J = 6 Hz, 21-Me), 7.97 (s, 20β-OAc), and 5.11 (m, 20α H).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.09; H, 8.69.

5-Oxo-20β-acetoxy-3,4-dinor-2,5-secopregnan-2-oic Acid 2-Methyl Ester (5).—A solution of **4** (3.57 g) in MeOH (8 ml) and ether (8 ml) was treated with an excess of diazomethane in ether at room temperature for 12 min. Acetic acid was added and the solvents were evaporated. The residue was dissolved in $CHCl_3$ and this solution was washed with 8% NaCl solution, dried, and evaporated to afford **5** (3.85 g) as a homogeneous oil (tlc): nmr ($CDCl_3$) τ 9.29 (s, 18-Me), 8.84 (d, J = 6 Hz, 21-Me), 8.83 (s, 19-Me), 7.99 (s, 20β-OAc), 6.34 (s, 2-CO_2CH_3), and 5.10 (m, 20α H).

6-Oxo-20β-hydroxy-3,4-dinor-2,5-seco-5-aza-*B*-homopregnan-2-oic Acid (6).—A solution of **5** (3.85 g) and $NH_2OH \cdot HCl$ (4 g) in pyridine (40 ml) was left at room temperature for 40 hr. The mixture was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with 2 *N* HCl and 8% NaCl solution, dried, and evaporated to give the crude oxime (3 6 g).

The oxime (3.6 g) in dioxane (60 ml) was cooled to 12° in an ice bath. Thionyl chloride (4 ml) was added, the ice bath was removed, and the mixture was stirred for 9 min. The reaction mixture was then added to 25% KOH solution (170 ml) and heated to 80°. After cooling, the mixture was extracted with ether. The aqueous portion was acidified and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with 8% NaCl solution, dried, and evaporated, Crystallization of the residue from MeOH–IPE gave **6** (1.39 g, mp 266–267.5°). Recrystallization from MeOH gave the analytical sample: mp 270–271.5°; ir 2.86, 3.04, 3.11, 5.83, and 6.16 μ.

Anal. Calcd for $C_{19}H_{31}NO_4$: C, 67.62; H, 9.26; N, 4.15. Found: C, 67.84; H, 9.59; N, 4.09.

6-Oxo-20β-hydroxy-3,4-dinor-2,5-seco-5-aza-*B*-homopregnan-2-oic Acid 2-Methyl Ester (7).—Methylation of **6** (370 mg) by the procedure described for **5** gave **7** (277 mg, mp 151.5–152.5°) from EtOAc–IPE. Recrystallization from EtOAc–IPE gave the analytical sample: mp 154–155°; $[\alpha]D$ +22°; ir 2.87, 2.97, 5.81, and 6.10 μ; nmr ($CDCl_3$) τ 9.20 (s, 18-Me), 8.87 (d, J = 6 Hz, 21-Me), 8.58 (s, 19-Me), 6.3 (m, 20α H), and 6.27 (s, 2-CO_2CH_3).

Anal. Calcd for $C_{20}H_{33}NO_4$: C, 68.34; H, 9.46; N, 3.99. Found: C, 68.21; H, 9.36; N, 3.80.

2,20β-Dihydroxy-3,4-dinor-2,5-seco-5-aza-*B*-homopregnane (8).—A solution of **7** (2.5 g) in THF (250 ml) was treated with $LiAlH_4$ (2.6 g) for 67 hr. The cooled mixture was treated with EtOAc and H_2O and the organic layer separated. The aqueous layer was extracted with $CHCl_3$. The combined organic fractions were washed with 8% NaCl solution, dried, and evaporated. Crystallization of the residue from EtOAc–IPE gave **8** (1.05 g, mp 158–159°). Recrystallization from EtOAc–IPE gave the analytical sample: mp 159–160.5°; $[\alpha]D$ −20°; ir 2.96 and 3.03 μ; nmr ($CDCl_3$) τ 9.24 (s, 18-Me), 8.87 (d, J = 6 Hz, 21-Me), and 8.81 (s, 19-Me).

Anal. Calcd for $C_{19}H_{35}NO_2$: C, 73.73; H, 11.40; N, 4.53. Found: C, 73.94; H, 11.45; N, 4.37.

***N*-Acetyl-2,20β-diacetoxy-3,4-dinor-2,5-seco-5-aza-*B*-homopregnane (9).**—A solution of **8** (0.9 g) in Ac_2O (9 ml) and pyridine (9 ml) was left at room temperature overnight. The mixture was diluted with H_2O and extracted with ether. The ether extracts were washed with 8% NaCl solution, dried, and evaporated. Plate chromatography of the residue on alumina, using $CHCl_3$–hexane (5:1) as the developing solvent, and elution of the major band with EtOAc gave **9** (0.9 g) as an oil: nmr ($CDCl_3$) τ 9.33 (s, 18-Me), 8.87 (d, J = 6 Hz, 21-Me), 8.63 (s, 19-Me), 7.98 (s, 2 and 20β-OAc), 7.93 (s, 5-NAc), and 5.13 (m, 20α H).

***N*-Acetyl-2-hydroxy-20β-acetoxy-3,4-dinor-2,5-seco-5-aza-*B*-homopregnane (10).**—A solution of **9** (1.4 g) in 12.5% KOH solution (4 ml) and MeOH (40 ml) was refluxed for 8 min and then left at room temperature for 0.5 hr. The mixture was concentrated and diluted with H_2O. The precipitate was collected by filtration to give **10** (1.07 g, mp 167–168.5°). Recrystallization from ether–IPE gave the analytical sample: mp 169.5–170.5°; $[\alpha]D$ −9°; ir 2.83, 2.84, 5.84, and 6.12 μ; nmr ($CDCl_3$) τ 9.35 (s, 18-Me), 8.85 (d, J = 6 Hz, 21-Me), 8.6 (s, 19-Me), 7.99 (s, 20β-OAc), 7.92 (s, 5-NAc), and 5.15 (m, 20α H).

Anal. Calcd for $C_{23}H_{39}NO_4$: C, 70.19; H, 9.99; H, 3.56. Found: C, 70.06; H, 10.04; H, 3.41.

***N*-Acetyl-20β-acetoxy-3,4-dinor-2,5-seco-5-aza-*B*-homopregnan-2-al (11).**—A solution of **10** (535 mg) in acetone (40 ml) at 3° was treated with an excess of Jones reagent and stirred at 3° for 1.75 hr. The mixture was treated with MeOH, filtered through Hy-flo, and evaporated. Plate chromatography of the residue on alumina, using $CHCl_3$–hexane (4:1) as the developing solvent, gave a major band which was eluted with EtOAc. Evaporation gave a residue (367 mg) that was crystallized from acetone–IPE to give **11** (75 mg, mp 159.5–160.5°). Recrystallization from acetone–IPE gave the analytical sample: mp 159.5–160.5°; $[\alpha]D$ +19°; ir 5.79, 5.84, and 6.09 μ; nmr ($CDCl_3$) τ 9.36 (s, 18-Me), 8.85 (d J = 6 Hz, 21-Me), 8.59 (s, 19-Me), 8.01 (s, 20β-OAc), 7.94 (s, 5-NAc), 5.16 (m, 20α H), and 0.27 (t, J = 1.6 Hz, 2-CHO).

Anal. Calcd for $C_{23}H_{37}NO_4$: C, 70.55; H, 9.53; N, 3.58. Found: C, 70.75; H, 9.49; N, 3.60.

***N*-Acetyl-20β-acetoxy-3,4-dinor-2,5-seco-5-aza-*B*-homopregnan-2-oic Acid (12).**—A solution of $AgNO_3$ (2.2 g) in H_2O (23 ml) was added to a solution of **11** (2.1 g) in EtOH (45 ml). A solution of NaOH (2.2 g) in H_2O (45 ml) was then added to the reaction mixture and the resulting suspension was stirred in the dark for 4 hr. The mixture was filtered and the solid was washed with H_2O. The filtrate was extracted with $CHCl_3$ and then acidified with 2 *N* HCl. The acidic phase was extracted with

$CHCl_3$ and the $CHCl_3$ extracts were washed with 8% NaCl solution, dried, and evaporated. Crystallization of the residue from acetone–IPE gave **12** (957 mg, mp 172–173°). Recrystallization from acetone–IPE gave the analytical sample: mp 177–177.5°; $[\alpha]D$ −21°; ir 5.80 and 6.30 μ; nmr ($CDCl_3$) τ 9.35 (s, 18-Me), 8.86 (d, J = 6 Hz, 21-Me), 8.47 (s, 19-Me), 7.99 (s, 20β-OAc), 7.91 (s, 5-NAc), and 5.17 (m, 20α H).

Anal. Calcd for $C_{23}H_{37}NO_5$: C, 67.78; H, 9.15; N, 3.44. Found: C, 67.82; H, 9.12; N, 3.40.

17α-Methyl-17a,β-hydroxy-3,4-dinor-*B*-homo-*D*-homo-5-aza-androstan-2-one (13).—A solution of **12** (1 g) in H_2O (1 ml), concentrated HCl (10 ml), and dioxane (80 ml) was refluxed overnight. Evaporation of the solvents gave a residue that was dissolved in H_2O; the pH was then adjusted to 5.1 The aqueous solution was extracted with $CHCl_3$. The aqueous phase was then adjusted to pH 5.1, 8% NaCl solution was added, and the solution was evaporated. The residue was extracted with warm $CHCl_3$ which was then evaporated to yield the crude amino acid (507 mg).

The amino acid was dissolved in CH_2Cl_2 (20 ml) and CH_3NO_2 (80 ml), treated with DCC (340 mg), and stirred at room temperature for 72 hr. The precipitate was removed by filtration and the filtrate was evaporated. The residue (496 mg) was plate chromatographed on silica gel, using $CHCl_3$–EtOAc (1:1) as the developing solvent. Elution of the major band with EtOAc–MeOH (3:1) gave a residue that was crystallized from acetone–IPE to give **13** (163 mg, mp 155–157°). Recrystallization from acetone–IPE gave the analytical sample: mp 158–159.5°; $[\alpha]D$ +27°; ir ($CDCl_3$) 2.87 and 5.79 μ; nmr ($CDCl_3$) τ 9.15 (s, 18-Me), 9.03 (d, J = 6 Hz, 17α-Me), 8.59 (s, 19-Me), and 8.22 (s, 17a β-OH).

Anal. Calcd for $C_{19}H_{31}NO_2$: C, 74.71; H, 10.23; N, 4.99. Found: C, 74.49; H, 10.29; N, 4.89.

17α-Methyl-3,4-dinor-*B*-homo-*D*-homo-5-aza-androstane-2,-17a-dione (16).—A solution of **13** (150 mg) in acetone (10 ml) was treated with a slight excess of Jones reagent while stirring at room temperature. Methanol was added and the mixture was filtered through Hy-flo. The filtrate was concentrated and then diluted with H_2O, and the precipitate was collected by filtration to obtain **16** (41 mg, mp 193.5–195.5°). Recrystallization from acetone–IPE gave the analytical sample: mp 199–201°; $[\alpha]D$ −12°; ir 5.73 and 5.90 μ; nmr ($CDCl_3$) τ 9.02 (d, J = 6 Hz, 17α-Me), 8.88 (s, 18-Me), 8.60 (s, 19-Me), and 7.37 (s, 1-CH_2).

Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63; N, 4.62. Found: C, 75.48; H, 9.83; N, 4.53.

***N*-Acetyl-2,20β-dihydroxy-3,4-dinor-2,5-seco-5-aza-*B*-homopregnane (17).**—A solution of **9** (4.9 g) in MeOH (125 ml) containing 12.5% KOH solution (20 ml) was refluxed for 15 min and then stirred at room temperature for 6 days. The mixture was concentrated, diluted with H_2O, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with 8% NaCl solution, dried, and evaporated to give crude **17** (4.07 g).

A sample of **17** (276 mg) was plate chromatographed on alumina, using $CHCl_3$–MeOH (97:3) as the developing solvent. The major band was eluted with EtOAc, evaporated, and the residue was crystallized from acetone–IPE to give **17** (81 mg, mp 179–181.5°). Recrystallization from acetone–IPE gave the analytical sample: 184.5–185°; $[\alpha]D$ −51°; ir 2.90, 2.98, and 6.23 μ; nmr ($CDCl_3$) τ 9.24 (s, 18-Me), 8.87 (d, J = 6 Hz, 21-Me) 8.59 (s, 19-Me), and 7.92 (s, 5-NAc).

Anal. Calcd for $C_{21}H_{37}NO_3$: C, 71.75; H, 10.61; N, 3.99. Found: C, 71.71; H, 10.63; N, 3.96.

***N*-Acetyl-20-oxo-3,4-dinor-2,5-seco-5-aza-*B*-homopregnan-2-al (18).**—A solution of **17** (489 mg) in acetone (50 ml) at 3° was treated with an excess of Jones reagent and stirred at 3° for 1.75 hr. The mixture was treated with MeOH, concentrated, diluted with H_2O, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with 8% NaCl solution, dried, and evaporated. The residue was plate chromatographed on alumina, using $CHCl_3$ as the developing solvent. Elution of the major band with EtOAc and evaporation, gave **18** (221 mg) as an oil: nmr ($CDCl_3$) τ 9.38 (s, 18-Me), 8.59 (s, 19-Me), 7.94 (s, 5-NAc), 7.91 (s, 21-Me), and 0.34 (t, J = 1.6 Hz, 2-CHO).

***N*-Acetyl-20-oxo-3,4-dinor-2,5-seco-5-aza-*B*-homopregnan-2-oic Acid (19).**—A sample of **18** (220 mg) was oxidized as previously described for the preparation of **12**. Crystallization of the residue from acetone–IPE gave **19** (52 mg, mp 174–175°). Recrystallization from acetone–IPE gave the analytical sample: mp 176–177°; $[\alpha]D$ +1°; ir 5.78, 5.89, and 6.25 μ; nmr ($CDCl_3$) 9.35 (s, 19-Me), 8.46 (s, 18-Me), 7.88 (s, 5-NAc and 21-Me).

Anal. Calcd for $C_{21}H_{33}NO_4$: C, 69.39; H, 9.15; N, 3.85. Found: C, 69.72; H, 9.39; N, 3.75.

3,4-Dinor-5-aza-*B*-homopregnane-2,20-dione (20).—A solution of **19** (380 mg) in H_2O (0.4 ml), concentrated HCl (7 ml), and dioxane (20 ml) was refluxed overnight. Evaporation of the solvents gave a residue that was dissolved in water; the pH was then adjusted to 5.1. After the aqueous solution had been extracted with $CHCl_3$, the aqueous phase was adjusted to pH 5.5, 8% NaCl solution was added, and the solution was evaporated. The residue was extracted with warm $CHCl_3$, and the $CHCl_3$ evaporated to yield the crude amino acid (75 mg).

The amino acid was dissolved in CH_2Cl_2 (2 ml) and CH_3NO_2 (5 ml), treated with DCC (50 mg), and stirred at room temperature for 67 hr. The precipitate was removed by filtration and the filtrate was evaporated. The residue was chromatographed on silica gel, using EtOAc–$CHCl_3$ (1:1) as the developing solvent. Elution of the major band with EtOAc gave a residue which was crystallized from acetone–IPE to give **20** (17 mg, mp 169–170°). Recrystallization from acetone–IPE gave the analytical sample: mp 169.5–170.5°; $[\alpha]D$ +120°; ir 5.75 and 5.93 μ; nmr ($CDCl_3$) τ 9.34 (s, 18-Me), 8.61 (s, 19-Me), 7.89 (s, 21-Me), and 7.38 (s, 1-CH_2).

Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63; N, 4.62. Found: C, 75.20; H, 9.68; N, 4.60.

Registry No.—**3,** 26527-03-7; **4,** 26527-04-8; **5,** 26527-05-9; **6,** 26527-06-0; **7,** 26527-07-1; **8,** 26527-08-2; **9,** 26527-09-3; **10,** 26527-10-6; **11,** 26527-11-7; **12,** 26599-14-4; **13,** 26527-12-8; **16,** 26527-13-9; **17,** 26527-14-0; **18,** 26527-15-1; **19,** 26599-15-5; **20,** 26527-16-2.

Acknowledgment.—The authors wish to thank Dr. A. I. Cohen for the nmr spectra and Mr. J. Alicino and his staff for the microanalyses.

Synthesis and Crystal Structure of *trans*-2,8-Dihydroxy-1(7)-*p*-menthene, a New Terpenoid Diol*[1]

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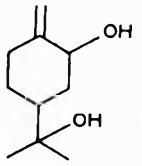
Received October 6, 1969

The crystal structure of a new terpenoid diol, *trans*-2,8-dihydroxy-1(7)-*p*-menthene, has been determined from three-dimensional X-ray data obtained near the temperature of liquid nitrogen. The structure was solved by application of the symbolic addition method for noncentrosymmetric crystals. It refined to an R index of 0.083. The methylenecyclohexane ring took on the ordinary chair conformation with the ring hydroxyl group axial and the 2-hydroxyisopropyl group equatorial. As indicated by the dihedral angles, 45.5 and 52.6°, the ring is flatter than that of cyclohexane. The molecules are held together in the crystal by a network of hydrogen bonds in which each hydroxyl participates in linkages with two other molecules.

The reaction between lead tetraacetate and β-pinene in glacial acetic acid has been shown to produce a complex mixture of monoacetate and diacetate products.[2-5] In the course of investigating the reaction in this laboratory a white, crystalline material was isolated from the transesterified product mixture. The infrared and nuclear magnetic resonance spectra of the material suggested the presence of a double bond exocyclic to a six-membered ring. Structure I was compatible with



I

the evidence. No reference to any such compound was found in the literature. A single-crystal X-ray analysis of the material was undertaken in order to establish its correct structure and to provide information on the effect substituents have in distorting the cyclohexane ring from the ideal chair conformation.

Experimental Section

Synthesis of *trans*-2,8-Dihydroxy-1(7)-*p*-menthene.—β-Pinene (75 g, 0.55 mol), glacial acetic acid (707 ml), and acetic anhydride (280 ml) were mixed together in a three-necked, 2-l. flask which was fitted with a condenser and stirrer. Lead tetraacetate (331 g of 85% slurry in acetic acid, 0.65 mol) was added to the stirred mixture (55–65°) over a period of 2 hr, and then the reaction solution was poured into cold water and allowed to remain overnight. After extracting this mixture with three 600-ml portions of ether, the combined extracts were neutralized with saturated sodium bicarbonate, washed with three 1000-ml portions of water, and dried over anhydrous magnesium sulfate. Removal of the ether by distillation left a yellow, sweet-smelling oil, yield 101.8 g.

The oil was distilled using a spinning-band column operating at a pressure of 0.15 mm. The fraction boiling at 77–85° (11.2 g) was collected. This fraction, whose ir spectrum contained bands (906 and 1654 cm^{-1}) indicative of a disubstituted alkene, was deesterified with sodium methoxide in methanol. The product was isolated in the usual manner, and the light yellow, crystalline solid (3.8 g) was recrystallized from benzene to give 2.8 g of needle-like crystals, mp 129.5–130.0°.

Anal. Calcd as $C_{10}H_{18}O_2$: C, 70.53; H, 10.68; O, 18.79. Found: C, 70.85; H, 10.58; O, 18.57.

The infrared spectrum (Perkin-Elmer 21) showed bands at 3360 (s), 3300 (s), 3060 (w), 2960 (s), 2925 (s), 1820 (w), 1654 (w), 906 (s), 875 (m), 829 (m), 785 (w), 768 (w), 725 (w), and 670 cm^{-1} (m). Bands from the nmr spectrum (Varian A-60A, $CDCl_3$) were centered at δ 4.75 (2 H), sextet (ethylenic hydrogens), 4.37 (1 H), triplet (carbinol proton), 2.23–1.75 (7 H), multiplets, 1.58 (2 H), singlet (hydroxyl), and 1.17 (6 H), singlet (methyl groups).

The crystals obtained from benzene were unsuitable for X-ray studies. Water was found to be a more suitable recrystallization solvent, producing prisms having approximately uniform dimensions.

X-Ray Data.—Three-dimensional data were obtained at approximately liquid nitrogen temperature using the multiple film equiinclination Weissenberg technique and a previously described gas flow cryostat[6] (Cu Kα radiation). Two crystals were used: one, 0.58 × 0.41 × 0.20 mm ($\mu R \simeq 0.18$) to obtain ($hk0$) to ($hk5$) and the other, 0.50 × 0.30 × 0.20 mm ($\mu R \simeq 0.15$), to obtain ($0kl$) to ($4kl$). The reflection intensities were measured visually by means of a calibrated intensity scale. The Lorentz and polarization corrections were made. No correction for absorption was made. The data from the two crystal settings were put on the same relative scale by the method of Rollett and Sparks.[7] A total of 999 unique observed reflections were obtained. An additional 190 reflections were either unobserved or too weak to be measured with confidence. The relative intensities were converted to normalized structure factors, $|E_{hkl}|$, by the K-curve method of Karle and Hauptman.[8,9]

The orthorhombic unit cell dimensions are: at low temperature, $a = 6.952 \pm 0.002$ Å, $b = 17.527 \pm 0.005$ Å, $c = 8.016 \pm 0.001$ Å; at room temperature, $a = 7.181 \pm 0.002$ Å, $b = 17.873 \pm 0.005$ Å, $c = 8.053 \pm 0.001$ Å. All the unit cell dimensions were determined by the back-reflection Weissenberg technique. Other crystal data are: $d_c = 1.093$ g/cm³, $Z = 4$, $d_m = 1.130$ g/cm³, $V_{LT} = 994.86$ Å³, $V_{RT} = 1033.50$ Å³, $\mu = 6.11$/cm; systematic absences, $h00$ when h is odd, $0k0$ when k is odd, $00l$ when l is odd; space group, $P2_12_12_1$.

Structure Determination and Refinement.—The crystal structure was determined by application of the symbolic addition method for noncentrosymmetric crystals.[10-12] The structure was refined by block-diagonal least-squares methods (anisotropic temperature factors, hydrogen atoms held constant with isotropic temperature factors equal to those of the attached atom)

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(1) A portion of a thesis submitted by W. E. Scott in partial fulfillment of the requirements of The Institute of Paper Chemistry for the degree of Doctor of Philosophy from Lawrence University, Appleton, Wis., Jan 1969.

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(12) Five known phases, $\phi_{120} = -90°$, $\phi_{203} = 90°$, $\phi_{037} = 90°$, $\phi_{248} = 90°$, and $\phi_{043} = 0°$, along with one symbolic phase, $\phi_{016} = a$, were used to assign phases to 112 reflections from the original 135 $|E_{hkl}| \geq 1.5$ (σ-2 formula). The 12 largest peaks in an E map calculated from 181 phased $|E_{hkl}| \geq 1.3$ (tangent formula refined, $a = 180°$) were related in such a manner as to form a reasonable chemical structure ($R = 0.21$).

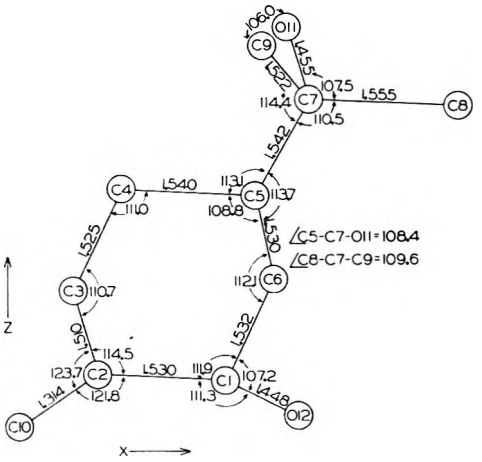

Figure 1.—The most significant atomic distances and bond angles in the molecule of *trans*-DHM given in the orthogonal projection on the plane (010).

to an R index of 0.083.[13] Weights were assigned during the final refinement cycles according to the equation

$$w = \left(1 + \frac{(|F_o| - b)^2}{a^2}\right)^{-1}$$

where the constants $a = 8.9$ and $b = 6.9$ were evaluated by the method suggested by Cruickshank.[19] Table I shows the final atomic parameters and their estimated standard deviations as determined by the least-squares refinement. The numbering system corresponds to that followed in Figure 1. The anisotropic temperature factors are normal for a structure determined near liquid nitrogen temperature.[20] Standard deviations in the bond lengths are 0.005 Å for carbon–oxygen bonds and 0.006 Å for carbon–carbon bonds. The standard deviations for the bond angles are 0.3° (Figure 1).

Results and Discussion

Figure 1 illustrates the general molecular features of the compound (abbreviated name, *trans*-DHM). The six-carbon ring takes on the ordinary chair conformation with an axial hydroxyl at C-1 and an equatorial 2-hydroxyisopropyl group at C-5.

The deviations from the mean plane calculated through the four carbon atoms associated with the ethylene bond, C-1, C-2, C-3, and C-10 are 0.003, −0.011, 0.003, and 0.004 Å, respectively. A similar analysis of ring carbons C-1, C-3, C-4, and C-6 revealed that the ring is slightly puckered, each atom being about 0.02 Å away from the mean plane.

The six-membered ring in *trans*-DHM is somewhat flatter than an ideal cyclohexane ring. The extent of flattening can be measured by its effect on the two dihedral angles formed by the chair conformation, as shown in Figure 2. This distortion from ideality has been discussed by Wohl.[22] Table II summarizes some dihedral angles associated with cyclohexane compounds. The contents of Table II indicate that the extent of ring

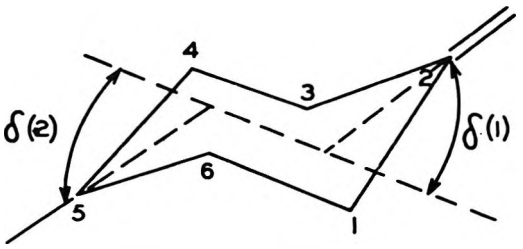

Figure 2.—Dihedral angles, $\delta(1)$ and $\delta(2)$, formed by the chair conformation of a six-membered ring.

TABLE I
ATOMIC PARAMETERS

Atom	Fractional coordinates X[a]	Y	Z
C-1	0.0597 (5)	0.1362 (4)	0.8786 (4)
C-2	0.3496 (5)	0.3889 (4)	0.1345 (4)
C-3	0.3098 (5)	0.4452 (5)	0.2728 (5)
C-4	0.3899 (5)	0.4162 (4)	0.4382 (5)
C-5	0.1073 (4)	0.0992 (4)	0.5744 (4)
C-6	0.1419 (5)	0.1600 (4)	0.7092 (5)
C-7	0.2005 (4)	0.1184 (4)	0.4050 (4)
C-8	0.4229 (5)	0.1240 (5)	0.4227 (5)
C-9	0.1236 (6)	0.1907 (5)	0.3234 (5)
C-10	0.2162 (5)	0.3613 (6)	0.0355 (5)
O-11	0.1591 (3)	0.0567 (3)	0.2892 (3)
O-12	0.1803 (4)	0.0752 (3)	0.9416 (3)
H-1 (C-1)[b]	0.060	0.180	0.945
H-1 (C-3)	0.338	0.486	0.216
H-2 (C-3)	0.195	0.460	0.280
H-1 (C-4)	0.338	0.370	0.500
H-2 (C-4)	0.365	0.455	0.500
H-1 (C-5)	0.160	0.055	0.620
H-1 (C-6)	0.080	0.200	0.670
H-2 (C-6)	0.270	0.165	0.715
H-1 (C-8)	0.318	0.120	0.405
H-2 (C-8)	0.475	0.075	0.485
H-3 (C-8)	0.500	0.138	0.318
H-1 (C-9)	0.000	0.190	0.313
H-2 (C-9)	0.195	0.210	0.233
H-3 (C-9)	0.150	0.230	0.388
H-1 (C-10)	0.235	0.325	0.970
H-2 (C-10)	0.085	0.365	0.030
H-1 (O-11)	0.205	0.015	0.370
H-1 (O-12)	0.110	0.068	0.050

[a] Estimated standard deviation times 10^3 Å in parentheses. [b] H-j (n-k) refers to the jth hydrogen atom bonded to the ith atom of kind n.

(13) The hydrogen atom positions were determined from a three-dimensional Fourier difference calculation after refinement to an R index of 0.11 (anisotropic temperature factors). The atomic scattering factors for carbon and oxygen were taken from Hanson, *et al.*,[14] and the hydrogen scattering factors were those of Stewart, *et al.*[15] Calculations were made on an IBM 1620 computer. Scaling programs (P. T. Beurskens[16]) and intensity correction and three-dimensional Fourier synthesis programs (R. Shiono, D. Hall, and S. C. Chu[17]) were provided by The Crystallography Laboratory, University of Pittsburgh. The refinement programs (F. R. Ahmed and G. Mair[18]) were provided by F. R. Ahmed. Programs for the application of the symbolic addition method were written locally by J. T. Ham and W. E. Scott.

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(19) D. W. J. Cruickshank, *et al.*, in "Computing Methods and the Phase Problem in X-ray Crystal Analysis," R. Pepinsky, J. M. Robertson, and J. C. Speakman, Ed., Pergamon Press, New York, N. Y., 1961, p 44.

(20) The tables and figures listed in this footnote will appear following these pages in the microfilm edition of this journal: tables containing anisotropic temperature factors, thermal ellipsoid volumes, observed and calculated structure factors, least-squares planes, bond lengths and bond angles, nearest neighbor distances, and interatomic distances and angles involved in hydrogen bonding; figures illustrating crystal packing and intermolecular hydrogen bonding.[21]

(21) Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth Street, N.W., Washington D. C. 20036, by referring to author, title of article, volume, and page number. Remit $3.00 for photocopy or $2.00 for microfiche.

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Table II
Dihedral Angles in Cyclohexane Compounds

Compd	Trigonal angle, deg	Other angles, deg	δ(1), deg	δ(2), deg	Ref
Cyclohexane[a]		109.5	60.0	60.2	22
Cyclohexane[b]		111.5	54.6	54.6	22
Methylenecyclohexane[c]	120.0	109.5	40.0[e]	59.5[e]	...[f]
Cyclohexanone[c]	116.0	109.5	51.2[e]	54.4[e]	...[g]
Bicyclohexylidene[d]	110.6	111.2	49.4	51.1	24
trans-DHM	114.5	110.9	45.5	52.6	

[a] Ideal model. [b] Electron diffraction. [c] Vector analysis calculations. [d] X-Ray diffraction. [e] Calculated from data given by authors. [f] E. Corey and R. Sneen, *J. Amer. Chem. Soc.*, **77**, 2505 (1955). [g] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *ibid.*, **83**, 4013 (1961).

flattening reflects two kinds of variations in the structures of methylenecyclohexane compounds: namely, an increase or decrease in the ring angle at the trigonal carbon, and an increase or decrease in the average bond angle in the ring. The dihedral angles found for *trans*-DHM indicate that these effects can be quite substantial.

The mean sp^3–sp^3 carbon–carbon bond distance in the ring of 1.533 Å agrees within 1 σ with that reported for cyclohexane[23] and within 1.5 σ with the average in bicyclohexylidene.[24] The difference between the mean sp^3–sp^2 carbon–carbon bond length (C-1–C-2, C-2–C-3) and the mean sp^3–sp^3 carbon–carbon bond length is significant at the 99% confidence level. Taken individually, however, bond C-1–C-2 is approximately equal to the mean sp^3–sp^3 bond length.

The two carbon–oxygen bond in *trans*-DHM are slightly longer than the value of 1.430 Å generally accepted for a carbon–oxygen single bond.[25]

The C-2–C-10 double bond (1.314 Å) is shorter than those reported in ethylene (1.334 Å)[26] and bicyclohexylidene (1.332 Å).[24]

The 2-hydroxyisopropyl group assumes an approximately staggered conformation relative to ring atoms C-4 and C-6, with C-9 anti to the hydrogen on C-5. There is considerable crowding, as is shown by the very short C-4–C-9 (3.13 Å) and C-6–C-8 (3.08 Å) distances. This arrangement probably allows O-11 to participate more effectively in hydrogen bonding and improves the molecular packing.

The longest dimension of the molecule is 6.562 Å (C-10–C-8). Comparison of distances C-1–C-3 (2.557 Å) and C-4–C-6 (2.501 Å) illustrates the effect of the large trigonal angle on the ring dimensions.

The average angle in the ring, excluding the trigonal angle, is 110.9°, with a range of 108.8–112.1°. This average compares favorably with the average angle of 111.1° reported for bicyclohexylidene (range, 110.4–111.9°),[24] and the 111.55 ± 0.15° determined for cyclohexane by electron diffraction.[23] The bond angles in the 2-hydroxyisopropyl group exhibit a range of 106.0–114.1°. These angles are probably influenced by the hydrogen bonding in which O-11 participates.

The molecules are held together in the crystal by a network of hydrogen bonds in which each hydroxyl participates in linkages with two other molecules. The individual molecules are bonded "heads-to-tails," forming polymerlike chains which extend through the unit cell approximately parallel to the *c* axis. A secondary chain pairing occurs through the association of two chains by lateral hydrogen bonds. Each unit cell contains one complete chain pair and shares two others with cells located on both sides along the *b* axis. The average distance between chain pairs is approximately 4.3 Å. The distances between each atom in the molecule and its nearest neighbor in another molecule appear to be normal. These distances all lie within a single chain pair. Figures and tables illustrating the molecular packing and hydrogen bonding can be obtained from the microfilm edition of this journal.[20]

As judged by their respective thermal ellipsoid volumes (range, 0.0018–0.0099 Å^3), the terminal methylene carbon C-10 exhibits the largest amount of thermal vibration. The two methyl carbons in the 2-hydroxyisopropyl group also show relatively large thermal motion. The smallest volumes are found in the ring, with C-4 and C-5 appearing to be the most restricted. In general, the results of the thermal analysis agreed with what would be expected.

Registry No.—*trans*-2,8-Dihydroxy-1(7)-*p*-menthene, 26963-80-4.

Acknowledgments.—Suggestions given by Drs. Donald C. Johnson and Dale G. Williams were appreciated. The authors thank Drs. Jerome and Isabella Karle for advice relative to the application of the symbolic addition method.

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Photoisomerization and Related Processes in 1,2-Diphenylcyclopropane[1]

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Received March 3, 1970

The kinetics of the photoisomerization of 1,2-diphenylcyclopropane (I) have been studied in cyclohexane at 25 and 65°. Geometrical isomerization predominates over branching into side products by a ratio of 4:1. Product analysis has revealed that *cis*- and *trans*-1,3-diphenylpropene (II), 1-phenylindan, and a polymer are side products produced by direct photolysis at 2537 Å. Other possible side products such as 1-phenylindene, 1,3-diphenylpropane, 1,2-diphenylpropene, and 1,2-diphenylpropane have not been observed. With *cis*-I at 1.56×10^{-3} *M* initial concentration, the steady-state *cis*–*trans*-I mole ratio approaches 5.0:1, and, with *trans*-I at 1.74×10^{-3} *M* initial concentration, the steady-state *cis*–*trans*-I mole ratio approaches 0.90:1. The steady-state mole ratio of geometrical isomers was found to be independent of incident light intensity. No true photostationary state is attained even with variation in initial concentration by a factor of three. Attainment of a true photostationary state for I is prevented by the branching into side products. The rate of production of 1-phenylindan from *cis*-I is greater than that from *trans*-I. The independence of *cis*–*trans*-II mole ratio on I isomer indicates a common intermediate for these structural isomers. Postulation of a trimethylene diradical accounts for the geometrical and structural isomerization of I. The primary process was found to be independent of temperature over the range of temperature studied. The primary quantum yields for all processes except polymer formation have been measured.

The 1,2-diphenylcyclopropane molecule behaves in some respects like an olefin and undergoes cis–trans isomerization. The Raman spectra[3] of the stereoisomers of this compound have indicated considerable conjugation between the three-membered cyclopropyl ring and the phenyl rings. The effect is much weaker for the cis isomer, owing to steric hindrance.[4,5] Upon irradiation of the molecule, absorption of energy most probably occurs by a $\pi-\pi^*$ transition.[6] Geometrical and structural isomerization has been induced in the molecule by a variety of methods: (1) thermal;[7-9] (2) photosensitization;[10-13] (3) direct photolysis;[14-16] and (4) radiolysis.[17]

Because of the current interest in cis–trans isomerization, this study was undertaken with the objective of determining kinetic and quantum yield information for the reaction processes resulting from the direct photolysis of *cis*- and *trans*-1,2-diphenylcyclopropane in solution and the formulation of a reasonable mechanism to account for the observed transformations.

Experimental Section

Materials.—The method of Beech, Turnbull, and Wilson,[18] employing the decomposition of 3,5-diphenyl-1-pyrazoline, was used to produce both *cis*- and *trans*-1,2-diphenylcyclopropane although other methods are known.[19-21] The cis-isomer fraction, bp 132–135° (4.5 mm) [lit.[22] bp 126.5–129° (3.8 mm)], and trans-isomer fraction, bp 150–152° (4.8 mm) [lit.[22] bp 144–145.3° (3.8 mm)], were retained. The samples were further purified by gas chromatography, using a $^3/_8$ in. o.d. × 10 ft 15% SE-30 column, operating at 170°. An F & M Model 5750 gas chromatograph equipped with flame ionization and thermoconductivity detectors was used in our work. The structures of the geometrical isomers were verified by their infrared spectra.[22-24]

The procedure described by Parham and Wright[25] was used to synthesize 1-phenylindene. The crude 1-phenylindene was transferred to a spining-band distillation column, and the middle fraction, bp 106–108° (0.38 mm) [lit.[25,26] bp 113–116° (0.40 mm)], was retained. The 1-phenylindene was further purified by gas chromatography. The collected fraction was a colorless oil which solidified to a white solid when stored at 0°.

A 1-phenylindan sample was prepared by the catalyzed hydrogen reduction of 1-phenylindene at room temperature, using 10% palladium–carbon catalyst. After reduction, the catalyst and cyclohexane solvent were easily removed, and the fraction, bp 99–100° (0.57 mm) [lit.[27] bp 103° (3 mm)], was collected. The sample, purified by gas chromatography, was 99.0% 1-phenylidan.[28]

The procedure incorporating a base-catalyzed condensation as described by Stoermer, Thier, and Laage[29] was employed for the synthesis of *trans*-1,3-diphenylpropene. The crude *trans*-1,3-diphenylpropene was purified by first chromatographing on an alumina column with *n*-hexane eluent followed by recrystallizing five times from *n*-hexane. The solvent was removed, and the *trans*-1,3-diphenylpropene was further purified by gas chromatography. The trans geometry was verified by the presence of the infrared absorption at 966 cm^{-1}.[30-32]

* To whom correspondence should be addressed.

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A photochemical pocedure similar to that described by Raunio and Bonner[33] was found to be the most convenient route for preparing adequate quantities of *cis*-1,3-diphenylpropene. Purified *trans*-1,3-diphenylpropene in cyclohexane was photolyzed at 2537 Å in a degassed quartz tube. After photolysis, the solvent was removed, and the *cis*-1,3-diphenylpropene was then separated from the reaction mixture by preparatory gas chromatography.

Although other synthetic routes to 1,3-diphenylpropane are known[34-37] the catalyzed hydrogen reduction of 1,2-diphenylcyclopropane[38,39] was a convenient route for our purposes. Following reduction at room temperature, the 10% palladium–carbon catalyst and cyclohexane solvent were removed. The 1,3-diphenylpropane was separated from the residual *cis*-1,2-diphenylcyclopropane by preparatory gas chromatography.

The 1,2-diphenylpropene was purchased from K & K Laboratories, under the name α-methylstilbene. This compound was stored in the dark in the solid form and was used without further purification.

The sample of several grams of bibenzyl was kindly furnished to us by Professor J. V. Swisher of our chemistry department. This bibenzyl sample was purified by recrystallizing three times from ethanol. The purified bibenzyl was stored in the solid form in the dark and was used as the internal standard for gas chromatographic analyses.

The cyclohexane used as the solvent in all photolyses was James Hinton spectrophotometric grade and was transparent to 2537 Å radiation. The cyclohexane was used as received without further purification.

Iodine was purified by sublimation before use in the radical scavenging experiments and was stored in a desiccator.

Two columns were used for analytical gas chromatography. The column used most was 0.25 in. o.d. × 10 ft 15% SE-30 on 60–80 mesh NAW Chromosorb P, and the more polar column was a 0.25 in. o.d. × 10 ft 20% Carbowax 20M on 60–80 mesh NAW Chromosorb P.

Optical Bench.—A standard single-rod optical bench was assembled in order to carry out our photolytic reactions in a carefully controlled manner. Aligned on the single-rod optical bench from left to right were the radiation source, a 2.75 in. diameter quartz lens, transmission filters, a thermostat, a 2 in. diameter focusing quatz lens at the exit collimator of the thermostat, and a detector. The temperature of the cell was controlled during photolysis to within 0.10° by circulating distilled water to the optical bench thermostat from a reservoir thermostat below the bench.

Light Source.—The light source for the photolytic reactions was a Hanovia spiral-quartz low-pressure mercury resonance lamp. The lamp was operated at 120 mA ac from a 5000-V transformer. The principle line emitted by this lamp was 2537 Å.

Transmission Filters.—Isolation of the 2537 Å line required a combination of transmission filters. The filtering system incorporated in series (a) a 10 cm path length × 5 cm o.d. quartz cell containing Cl_2 gas at 1 atm pressure, (b) a 10 cm path length × 5 cm o.d. quartz-window cell containing a solution of $NiSO_4$–$CoSO_4$,[40] and (c) a Corning CS 7-54 glass filter. The band width of the composite system was approximately 50 Å. Fresh $NiSO_4$–$CoSO_4$ filtering solution was added to the 10 cm path length cell for each 100 hr or less of exposure to the radiation source, depending on the sequence of experiments.

Radiation Detector and Recorder.—The detector used was an RCA 935 phototube. The dc signal from the phototube was fed through a Sencore R-C substitution unit into a Honeywell Electronik 17 strip chart recorder operated at 50 mV full-scale deflection. The recorder response to transmitted radiation at 2537 Å was calibrated by means of chemical actinometry.

Chemical Actinometry.—The potassium ferrioxalate system developed by Hatchard and Parker[41] was used for chemical actinometry in calibrating the recorder. Table I gives a summary of results for the calibration of the recorder response to 2537 Å radiation. These results are for 0.006 *M* $K_3Fe(C_2O_4)_3$ solution concentrations. The area of the cell windows exposed to the beam was 2.40 cm², and the recorder amplitude values in millivolts have been corrected for the cell absorptions.

TABLE I

SUMMARY OF CHEMICAL ACTINOMETRY CALIBRATION RESULTS

Time, min	Cell path length, mm	I_0^i, quanta, min^{-1}	Recorder amplitude, mV	I_0^i, quanta, mV^{-1} min^{-1}
90	1	5.456×10^{15}	20.60	2.649×10^{14}
40	2	5.087×10^{15}	18.80	2.706×10^{14}
45	2	4.429×10^{15}	16.70	2.652×10^{14}
70	2	5.742×10^{15}	22.00	2.610×10^{14}
			Av value =	2.654×10^{14}

Gas Chromatograph Calibration.—Bibenzyl, $PhCH_2CH_2Ph$, was chosen as the internal standard, and a calibration curve was produced by plotting the area ratio of component–bibenzyl *vs.* the mole ratio of component–bibenzyl for each component. The slope of the curve gives the factor for converting from area ratio to mole ratio.

Sample Preparation and Irradiation.—The cylindrical cells used for photolytic reactions were 22 mm o.d. × 1 mm and 2 mm path lengths with windows of "suprasil" quartz. Samples of 98.1% *trans*- and 94.4% *cis*-1,2-diphenylcyclopropane were used to make up starting solutions with cyclohexane solvent. The procedure was to begin with either cis or trans isomer and observe the growth of products with irradiation time. For each run an aliquot of starting solution was transferred to the cell. At the same time an aliquot of starting solution was taken and frozen down for later analysis to determine initial concentrations of solution components. The cell was then attached to a grease-free vacuum line and degassed five times by the freeze–pump–thaw procedure at a pressure of 5×10^{-6} Torr prior to sealing off under vacuum. The solutions were irradiated for varying times at 2537 Å on the optical bench with periodic mixing during photolysis.

Product Analysis.—In some of the early experiments light products were sought by reattaching the cell to the grease-free vacuum line after irradiation. The analysis section of the vacuum line was equipped with a LeRoy still, a McLeod gauge, and a Toeppler pump. After light-product analysis, a measured quantity of bibenzyl solution was added to the irradiated solution, and the heavy product concentrations were determined from the gas chromatograph area ratios, using the calibrated conversion factors. The final component concentrations were corrected for the values determined from the aliquot of initial solution.

Quantum Yield Calculations.—With prolonged irradiation heavy products accumulate in solution which also absorb part of the incident light. The quantity of light absorbed by the starting substrate alone can be calculated by a method described by Ishakawa and Noyes.[42] Corrections were also made for any decrease in incident light intensity during a run. The primary-quantum yields were calculated from the corrected product concentrations and the total quanta absorbed by the substrate for runs with less than 4% conversion of the initial substrate.

Results and Discussion

Photolysis of *cis*-1,2-Diphenylcyclopropane.—Samples of 1.74×10^{-3} *M* *cis*-1,2-diphenylcyclopropane in cyclohexane were photolyzed in a 2 mm path length cell with 2537 Å radiation. The growth of products during irradiation was followed from short exposure times, and the product yields shown at each interval in subsequent figures represent a separate irradiation with a fresh sample. Figure 1 shows the results for the photolytic reaction of *cis*-1,2-diphenylcyclopropane at room temperature. Because the incident light intensity varied significantly over the course of our work as a result of aging of the lamp, the exposure intervals were converted from hours to total quanta absorbed by the

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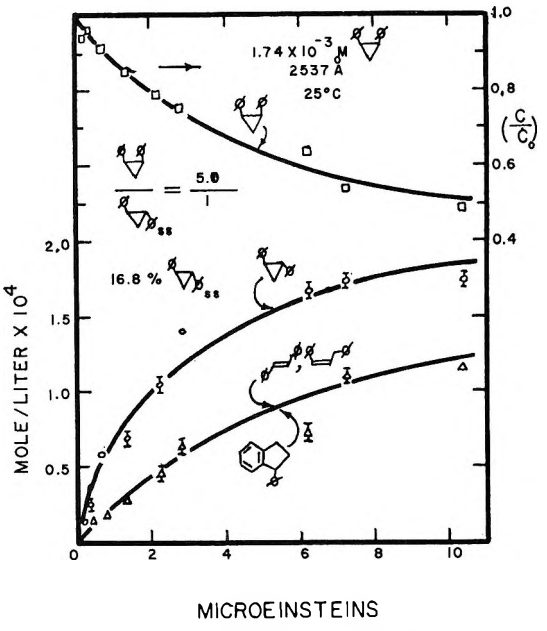


Figure 1.—Photolysis of 1.74×10^{-3} *M* *cis*-1,2-diphenylcyclopropane in cyclohexane at 25° with 2537 Å radiation.

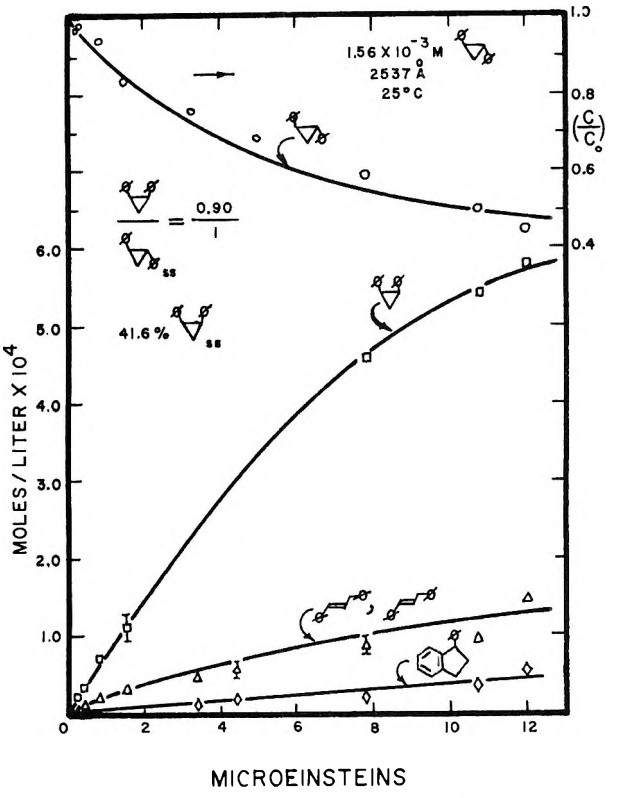


Figure 2.—Photolysis of 1.56×10^{-3} *M* *trans*-1,2-diphenylcyclopropane in cyclohexane at 25° with 2537 Å radiation.

photolyzed substrate. This procedure corrected product yields for the variation in incident light intensity.

The disappearance of *cis*-1,2-diphenylcyclopropane is displayed in Figure 1 in terms of the ratio of the concentration at the termination of an exposure interval to the initial concentration (C/C_0). Both *cis*- and *trans*-1,2-diphenylcyclopropane may be observed to asymptotically approach steady-state concentrations with continued irradiation. The steady-state cis–trans mole ratio is 5.0:1 for 1,2-diphenylcyclopropane, and at this level the solution contains 16.8% *trans*-1,2-diphenylcyclopropane (relative to the total soluble products present).

In agreement with Griffin, *et al.*,[14] *cis*- and *trans*-1,3-diphenylpropene and 1-phenylindan were observed as side products resulting from the direct photolysis of *cis*-1,2-diphenylcyclopropane. The yields of 1,3-diphenylpropenes and 1-phenylindan were found to be equal within experimental error. Under the conditions of our experiments, 1-phenylindene was not observed. Other products not observed were *cis*- and *trans*-1,2-diphenylpropene, 1,2-diphenylpropane, and 1,3-diphenylpropane. Griffin and coworkers[14] did not observe these same products when the 1,2-diphenylcyclopropanes were irradiated at 2537 Å in benzene; however, they did observe a trace amount of 1-phenylindene. This product may arise as a unique result of benzene sensitization of the reaction. With the columns and flame ionization detectors used, it was possible to detect components to a lower limit of 1×10^{-6} *M* concentration, corresponding to a lower limit of 10^{-4} for the quantum yields of products.

Analyses of solutions photolyzed for several hours were carried out in the grease-free vacuum system. By mass spectrometric analysis no light products such as H_2 or C_1–C_4 hydrocarbons were observed.

Authentic samples were used to identify observed products by retention times and infrared spectra, and a deliberate search was made for the unobserved heavy products. Since the retention time of 1-phenylindan and 1,3-diphenylpropane are the same on SE-30 columns, analyses of some photolyzed solutions were made on a more polar Carbowax 20M column in an effort to resolve the 1-phenylindan elution peak. The 1-phenylindan peak did not resolve on the Carbowax 20M column.

The mass balance deficiency increased with prolonged irradiation. After 65 hr of continuous photolysis, a mass deficiency of 14% was noted. This deficiency is attributed to the formation of a polymer. This polymer was not detected in our analyses since the retention time, if indeed the polymer would elute, would be significantly longer than our analysis times. As it is, the last product to elute from the SE-30 column, *trans*-1,3-diphenylpropene, has a retention time greater than 1 hr at the column temperatures used. Products with significantly longer retention times were searched for but not observed.

Photolysis of *trans*-1,2-Diphenylcyclopropane.—The reverse reaction, that of the photolysis of *trans*-1,2-diphenylcyclopropane, was carried out by the same procedure. Samples of 1.56×10^{-3} *M* *trans*-1,2-diphenylcyclopropane in cyclohexane were photolyzed in a 1 mm path length cell. Figure 2 presents the results for the photolytic reaction of *trans*-1,2-diphenylcyclopropane at room temperature. Both the trans substrate and the *cis*-1,2-diphenylcyclopropane again asymptotically approach steady-state levels, but these steady-state concentrations are not the same as those observed in the photolysis of *cis*-1,2-diphenylcyclopropane. At the steady state, the solution contains 41.6% *cis*-1,2-diphenylcyclopropane (of the total soluble products present), and the cis–trans mole ratio is 0.90:1 for the 1,2-diphenylcyclopropane isomers.

The data of Figure 2 indicate that equal yields of the 1,3-diphenylpropene isomers are again observed, but

the yield of 1-phenylindan is significantly lower. Comparing Figures 1 and 2, one observes a lower rate of production of 1-phenylindan from *trans*-1,2-diphenylcyclopropane than from the cis isomer. The 1-phenylindan appears to accumulate as irradiation progresses. The 1,2-diphenylpropenes, 1,2-diphenylpropane, 1,3-diphenylpropane, and 1-phenylindene were searched for again as possible products of photolysis but were not observed within the stated limits of detectability.

Increased mass deficiency with prolonged irradiation was again observed. This deficiency is attributed to the production of polymer. Visible quantities of polymer were actually observed when preparatory-scale quantities of substrate were irradiated at room temperature. This polymer was not characterized. Most probably the polymer formation is an irreversible reaction so that once the polymer is produced, it does not photolytically react to any appreciable extent. This continued removal of available substrate from the solution produces an increased mass depletion of soluble components with prolonged irradiation.

When the photoisomerization of 1,2-diphenylcyclopropane was promoted by sensitizers added to the solution, no side products were observed if the absorption was carefully restricted to that by the sensitizer.[12,13] Brown[17] also observed a different product distribution when the photoisomerization of 1,2-diphenylcyclopropane in benzene solutions was promoted by γ radiation. He did find the 1,3-diphenylpropenes as side products but did not detect 1-phenylindan. He also did not find 1,2-diphenylpropene, 1,2-diphenylpropane, or 1,3-diphenylpropane in agreement with our results. The photosensitized reactions and the reactions promoted by γ radiation may proceed by mechanisms different than those operative in direct photolysis.

Optical Density Variation during Photolysis.—Since highly absorbing products such as the 1,3-diphenylpropenes were accumulating in solution during irradiation, the question arose as to whether or not the photoreaction of the 1,2-diphenylcyclopropanes was slowing down or stopping as a result of the incident light being absorbed by the products to the exclusion of the initial substrate. If this were the case, it might account for the fact that the same steady-state levels were not being attained upon prolonged irradiation of the *cis*- and *trans*-1,2-diphenylcyclopropane isomers. A plot of the variation of optical density of solution components *vs.* microeinsteins of light absorbed by the substrate is shown in Figure 3 for the case of *trans*-1,2-diphenylcyclopropane photolysis.

In Figure 3 it may be seen that, although *cis*- and *trans*-1,3-diphenylpropene absorb in the range of 10–15% of the incident light upon prolonged irradiation of *trans*-1,2-diphenylcyclopropane, this quantity of light absorption by the products cannot account for the magnitude of leveling of the substrate concentration observed in Figure 1 and 2. The absorption by 1-phenylindan is insignificant. Figure 3 then is some evidence that the reaction is not stopping because light is prevented from reaching the substrate, so that other parameters were tested to determine what steady state the system tends to approach with continued irradiation of the initial isomer.

Concentration Dependence.—To test the concentration dependence of the 1,2-diphenylcyclopropane

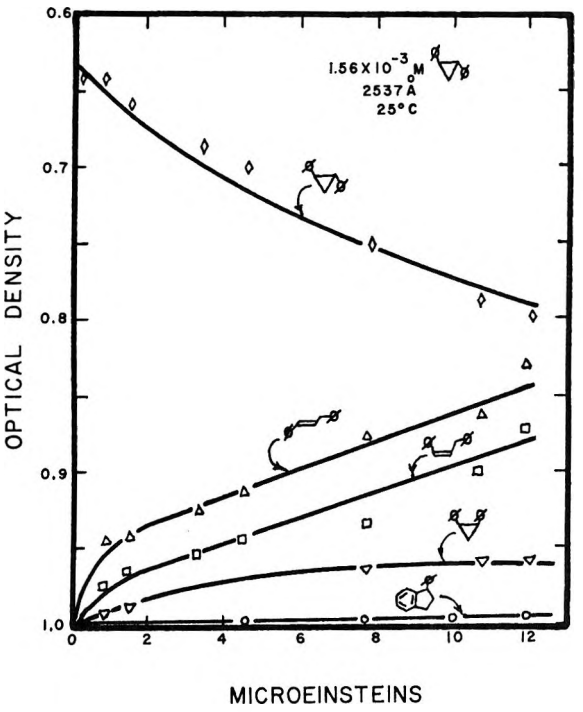


Figure 3.—Variation of the optical density of solution components during photolysis of *trans*-1,2-diphenylcyclopropane.

cis–trans mole ratio, the initial *trans*-1,2-diphenylcyclopropane concentration was decreased by a factor of three. For the same total exposure of the substrate, the cis–trans mole ratio was 0.19:1 for a 3.9×10^{-4} *M* *trans*-1,2-diphenylcyclopropane solution and 0.18:1 for 1.56×10^{-3} *M* solution. The invariance of the photoisomerization process with concentration change implies that no second-order processes are operative during photolysis.

Light Intensity Dependence.—No specific experiments were run in which the incident intensity was deliberately decreased with a neutral density filter, but over the course of the time during which the photolytic reactions of 1,2-diphenylcyclopropane were studied, the light intensity of the lamp decreased by a factor of three due to aging of the lamp. Over this range of intensity variation, no significant deviation from a smooth curve was observed in plots of the cis–trans mole ratio of 1,2-diphenylcyclopropane *vs.* irradiation time for the series of experiments conducted. No corrections for the variation in incident intensity were made in these plots as was done in Figures 1 and 2 so that from this it may be concluded that the steady-state cis–trans mole ratio for 1,2-diphenylcyclopropane is not light intensity dependent.

Mixtures of Isomers.—Attempts were made to answer two questions: (1) is the photoisomerization of an isomer sensitized by the presence of the other geometrical isomer, and (2) what factors determine the steady-state ratio of isomers?

A solution was made up in cyclohexane with an initial cis–trans mole ratio of 1.08:1. Aliquots of this solution were photolyzed for 3 hr and 57 hr to determine the mole ratios for short and long exposures. At 3 hr the cis–trans mole ratio had increased to 1.16:1 and, after 57 hr this ratio had grown to 1.33:1. The photolysis of mixtures of the 1,2-diphenylcyclopropane isomers did not show noticeably increased rates of photoisomer-

ization compared to photolysis of solutions of initially pure isomers. The conclusion reached was that the photoisomerization of 1,2-diphenylcyclopropane was not self-sensitized.

It is not likely that the side products can sensitize the photoisomerization since spectral studies indicate that λ_{max} (*cis*-1,3-diphenylpropene) equals 2430 Å and λ_{max} (*trans*-1,3-diphenylpropene) equals 2520 Å. These maxima correspond to singlet–singlet transitions for these molecules. They are all lower energy transitions than those of the isomers of 1,2-diphenylcyclopropane which have λ_{max} (*cis*-1,2-diphenylcyclopropane) equals 2260 Å and λ_{max} (*trans*-1,2-diphenylcyclopropane) equals 2300 Å. While the triplet states of the side products may be higher than those of the 1,2-diphenylcyclopropane isomers, no data are available at this time concerning the magnitude of splitting of the various levels, so that it is not possible to state conclusively that no significant triplet energy transfer from the side products to 1,2-diphenylcyclopropane takes place during photolysis. Our kinetic data, however, do not show an apparent rate change for photoisomerization of 1,2-diphenylcyclopropane as the side-product concentrations increase with continued irradiation.

Initially, the ratio of absorbances of cis–trans was $A_C/A_T = 0.0246$. After 3 hr $A_C/A_T = 0.0263$, and, after 57 hr, $A_C/A_T = 0.0299$, a change of over 20% from the initial value. The mole ratio of geometrical isomers for 1,2-diphenylcyclopropane appeared to be determined by the quantity of light absorbed by the isomers.

To test this, a nearly equiabsorbing mixture of 1,2-diphenylcyclopropane was made up in cyclohexane with an initial cis–trans mole ratio of 3.65:1. The ratio of the extinction coefficients for trans–cis is 4.42:1. An aliquot of the solution was photolyzed in a 1-mm path length cell of 144 hr. After this period, the cis–trans mole ratio was 3.37:1. When the limits of error of our method are taken into consideration, the change in the mole ratio can be considered insignificant for 144 hr of continuous irradiation. Griffin and coworkers[14] state that irradiation at 2537 Å of 0.1 *M cis*- or *trans*-1,2-diphenylcyclopropane solutions promoted photoisomerization in which the cis isomer was favored. They note that a cis–trans mole ratio of 1.54:1 was approached, and state that this value was determined by irradiating mixtures approaching this composition.[14] However, our results suggest that the quantity of light absorbed by each isomer tends to determine the steady-state ratio approached by the geometrical isomers with prolonged irradiation. Apparently, failure to reach the steady state can be accounted for by the degradative process of branching into side products which depletes the geometrical isomers with prolonged exposure.

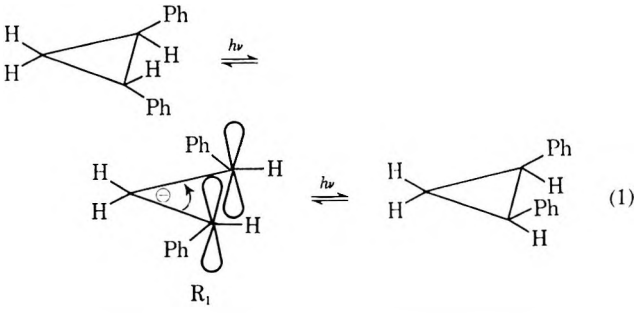
Primary Quantum Yields for 1,2-Diphenylcyclopropane Reactions.—The primary quantum yields for product formation were determined at less than 4% conversion of the initial substrates. Runs for 1 hr or less total irradiation time were used for determining the primary quantum yields by the procedure discussed previously. The results shown in Table II are the average of four runs and reflect the initial slopes of the product yield curves.

The products observed can be rationalized as arising from the cleavage of the 1,2 C–C bond on the cyclopropane ring of 1,2-diphenylcyclopropane followed by rearrangement. The primary step can be visualized as taking place by the production of a diradical intermediate of the type R_1 shown in reaction 1, but we have no

TABLE II
PRIMARY QUANTUM YIELDS FOR 1,2-DIPHENYLCYCLOPROPANE REACTIONS

cis-1,2-Diphenylcyclopropane photolysis		*trans*-1,2-Diphenylcyclopropane photolysis	
Product	Φ	Product	Φ
T[a]	0.084 ± 0.004	C[a]	0.089 ± 0.005
c-P[b]	0.022 ± 0.002	c-P[b]	0.023 ± 0.002
t-P[b]	0.022 ± 0.002	t-P[b]	0.023 ± 0.002
I[c]	0.022 ± 0.002	I[c]	3×10^{-3}

[a] C and T are *cis*- and *trans*-1,2-diphenylcyclopropane. [b] c-P and t-P are *cis*- and *trans*-1,3-diphenylpropene. [c] I is 1-phenylindan.



(1)

information from our kinetic data which will enable us to deduce with certainty which state is being populated by the intermediate diradical; however, it is probably a triplet state. The primary quantum yields indicate that geometrical isomerization is favored over branching by a ratio of 4:1.

The data of Table II indicate that the rates of production of either geometrical isomer from the common intermediate R_1 are equal. Since the trans isomer absorbs four times more energy than the cis isomer, and it is known from the quantum yields that the trans isomer is not produced four times faster from the intermediate than the cis isomer, the excess energy may be accounted for by considering the radiative processes operative. The radiative lifetime of an excited state bears an inverse relation to the transition probability of that state. As an approximation, the radiative lifetimes of absorbing compounds are found to be inversely proportional to their extinction coefficients,[43] so that one expects a shorter radiative lifetime for the trans isomer of 1,2-diphenylcyclopropane. Hence, one would expect an emission yield from the trans isomer four times greater than that from the cis isomer. At present no information is available on the radiationless processes operative in this system.

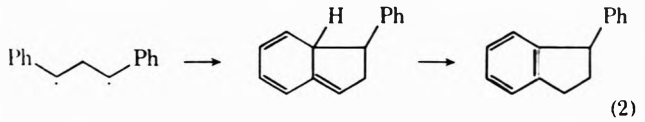
Equal yields of *cis*- and *trans*-1,3-diphenylpropene observed during the photolysis of both geometrical isomers of 1,2-diphenylcyclopropane implies a common intermediate for the 1,3-diphenylpropenes and also implies equal rates of formation of the 1,3-diphenylpropenes from this intermediate. Once this intermediate is formed, it appears to go cis or trans without preference. Although thermodynamically one would expect the trans isomer to dominate, this system is not at thermodynamic equilibrium and this result probably simply demonstrates kinetic control during photolysis.

(43) Reference 6, p 174.

From the quantum yield results, it is apparent that the production of observable products by direct photolysis is a highly inefficient process with less than 10% of the absorbed energy being utilized for geometrical isomerization. Hammond and Cole[11] also noted the inefficiency of this process. It is apparent that less than 15% of the absorbed energy is accounted for in terms of products. Of the remainder of the energy of the system, some is probably lost through radiative and radiationless processes. Since the yield of polymer was not determined quantitatively, it is not possible to estimate the quantity of energy consumed in producing polymer.

Cleavage of the 1,3 C–C bond of the cyclopropane ring of 1,2-diphenylcyclopropane would lead to *cis*- or *trans*-1,2-diphenylcyclopropene as products of photolysis. These products were not observed. If they are produced at all under our experimental conditions, their quantum yields are less than 10^{-4}. It may be that an unsymmetrical diradical intermediate produced by 1,3 bond cleavage has so much less resonance stabilization than the symmetric intermediate R_1 produced by 1,2 bond cleavage that its lifetime is considerably shortened and presents a highly unfavorable path for reaction.

The rate differences noted for the production of 1-phenylindan from *cis*- and *trans*-1,2-diphenylcyclopropane are also consistent with a diradical of the type R_1. From molecular models of the geometrical isomers of 1,2-diphenylcyclopropane one observes that, after removal of an H atom from the proper site on the benzene ring, there are four ways to cyclize to 1-phenylindan from *cis*-1,2-diphenylcyclopropane which require minimum rotation compared to only two easy routes from the trans isomer. Griffin[44] suggests that cyclization to 1-phenylindan may proceed as shown in reaction 2.

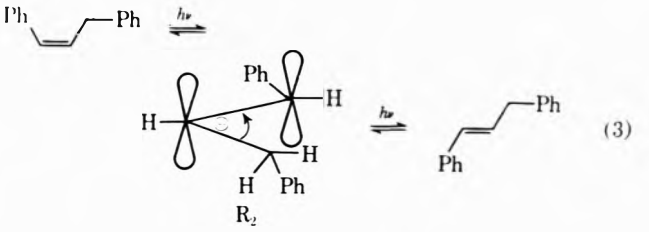


(2)

How much the solvent participates in the rearrangement process is unknown at the present time.

The photolytic reactions of 1.74×10^{-3} *M* *cis*-diphenylcyclopropane were run at 65° for irradiation time intervals up to 10 hr to compare the results with room temperature experiments. The trans isomer yields were 3.89×10^{-5} *M* and 7.06×10^{-5} *M* at 4.8 and 10.0 hr, respectively, and were plotted in the same manner as in Figure 2. Although the absolute yield of trans isomer was somewhat greater, the initial slopes of the curves for 25 and 65° were equal within experimental error. It is concluded that the primary process for geometrical isomerization does not appear to be temperature dependent over the range of temperatures studied. It can also be stated that since the yield of trans isomer was within experimental error of the expected value, the secondary processes appear to exhibit temperature invariance over the temperature range studied.

Photolysis of *cis*- and *trans*-1,3-Diphenylpropene.—We investigated the importance of back reactions from the 1,3-diphenylpropenes to 1,2-diphenylcyclopropane during photolysis. Aliquots of 10^{-4} *M* solutions of *cis*- and *trans*-1,3-diphenylpropene in cyclohexane were photolyzed under the same conditions as employed in the irradiation of 1,2-diphenylcyclopropane. Direct photolysis at 2537 Å did promote geometrical isomerization. The reaction can be most easily visualized as proceeding through a diradical intermediate R_2 shown in reaction 3.



(3)

Cyclization to 1,2-diphenylcyclopropane was also observed to accompany geometrical isomerization during the irradiation of 1,3-diphenylpropene in agreement with Griffin and coworkers,[14] but the cyclization yields were small under our experimental conditions. Equal yields of *cis*- and *trans*-1,2-diphenylcyclopropane were observed from either initial 1,3-diphenylpropene isomer and were produced with primary quantum yields of 5×10^{-3}. The production of 1,2-diphenylcyclopropane probably proceeds through a radical intermediate of type R_1, and the slow step in the formation of R_1 from R_2 may be hydrogen or phenyl migration.[45] The role of solvent participation in the radical rearrangement is at present unknown. No 1-phenylindan, 1-phenylindene, 1,2-diphenylpropenes, 1,2-diphenylpropane, or 1,3-diphenylpropane were observed within the limits of detectability of our method.

The rate of increase of mass deficiency was greater for the photolytic reactions of the 1,3-diphenylpropenes than that observed for the reactions of the 1,2-diphenylcyclopropanes. This increased rate of mass deficiency is attributed to the higher rate of polymer fromation from R_2 than from R_1. The back reaction from polymer is probably insignificant since the mass deficiency becomes quite pronounced with continued irradiation.

Photolysis of 1-Phenylindan.—Aliquots of 1.73×10^{-3} *M* 1-phenylindan in cyclohexane were irradiated at room temperature with 2537 Å radiation to determine the products of photolysis. After 16 hr of continuous irradiation, no detectable products were observed by gas chromatography. It appears that 1-phenylindan is highly unreactive under these conditions. This result is consistent with our observations on the photolytic reactions of 1,2-diphenylcyclopropane that 1-phenylindan accumulates during irradiation and also agrees with Brown's results.[17] From the remarks above it is evident that under the experimental conditions employed in our study the contribution of back reactions from the products to 1,2-diphenylcyclopropane during photolysis is negligible.

Radical Scavenging Attempts.—A solution 1.04×10^{-3} *M* in *cis*-1,2-diphenylcyclopropane plus 1.05×10^{-3} *M* in iodine in cyclohexane was made up for experiments designed to attempt the scavenging of radical intermediates during photolysis. Aliquots of this solution were irradiated in the manner described above for up to 6 hr to determine the effect of I_2 on product yields. Solution analyses by the usual gas chromatographic methods revealed no new peaks re-

(44) G. W. Griffin, private communication.

(45) G. W. Griffin, A. F. Marcantonio, and H. Kristinsson, *Tetrahedron Lett.*, 2951 (1965).

sulting from radical trapping by I_2. When correction was made for the quantity of light absorbed by the iodine, the product yields were shown to be within the experimental limits of those expected for irradiation of pure solutions of *cis*-1,2-diphenylcyclopropane of the same concentration for the same exposure.

During photolysis, it appears that, when the cyclopropane ring is opened to produce the diradical, the rotation rate of the p orbital about the C–C single bond is sufficiently greater than the rearrangement into side products that geometrical isomerization is favored. The average lifetime of this diradical intermediate must be at least longer than the rotation rate of the p orbitals about the C–C single bond but shorter than the reaction with I_2 since geometrical isomerization takes place but scavenging of the intermediate with I_2 is unsuccessful. Cookson, Nye, and Subrahmanyan[46,47] also attempted to intercept the trimethylene diradical. Griffin, *et al.*,[14] and Hammond and Cole[11] reported no success in trapping intermediates.

Photolyses of 1,2-diphenylcyclopropane samples not degassed prior to irradiation were performed. The scatter in the product yields was such as to render the results inconclusive, presumably since reproducibility of the O_2 content was a problem. The construction of the cells was such as to preclude the application of high pressures of O_2 over the solutions prior to sealoff.

Mechanism.—Our kinetic data indicate that the photoisomerization of 1,2-diphenylcyclopropane is not consistent with a mechanism involving a path through the 1,3-diphenylpropenes, *i.e.*

$$C \xrightarrow{h\nu} P \longrightarrow T$$

A chain reaction mechanism for the photoisomerization is also highly improbable when one considers the low quantum yields of products.

A mechanism is presented below which is consistent with our results. If one considers the arguments presented above and the difference in the rates of polymer formation from the 1,3-diphenylpropenes and the 1,2-diphenylcyclopropanes, the data can be correlated by postulating at least two diradical intermediates of types R_1 and R_2. C and T are *cis*- and *trans*-1,2-diphenylcyclopropane, c-P and t-P are *cis*- and *trans*-1,3-diphenylpropene, and I is 1-phenylindan.

$$C + h\nu \longrightarrow R_1 \quad (4)$$

$$R_1 \xrightarrow{k_5} T \quad (5)$$

$$R_1 \xrightarrow{k_6} C \quad (6)$$

$$T + h\nu \longrightarrow R_1 \quad (7)$$

$$R_1 \xrightarrow{k_8} I \quad (8)$$

$$R_1 \xrightarrow{k_9} R_2 \quad (9)$$

$$R_2 \xrightarrow{k_{10}} R_1 \quad (10)$$

$$R_2 \xrightarrow{k_{11}} \text{t-P} \quad (11)$$

$$R_2 \xrightarrow{k_{12}} \text{c-P} \quad (12)$$

$$\text{c-P} + h\nu \longrightarrow R_2 \quad (13)$$

$$\text{t-P} + h\nu \longrightarrow R_2 \quad (14)$$

$$R_2 \xrightarrow{k_{15}} \text{polymer} \quad (15)$$

The equal yields of the isomers of 1,3-diphenylpropene during photolysis of 1,2-diphenylcyclopropane implies that $k_{11} = k_{12}$. Similarly, the equal yields of the 1,2-diphenylcyclopropanes from 1,3-diphenylpropene irradiation suggests that $k_5 = k_6$. If $k_{10} < k_{11}, k_{15}$, this is consistent with the higher yields of geometrical isomerization and polymer formation over cyclization to 1,2-diphenylcyclopropane during 1,3-diphenylpropene photolysis. The slow step in the conversion of R_2 to R_1 may involve phenyl or hydrogen rearrangements. Since $k_8 < k_5$, this is consistent with the fact that no 1-phenylindan is observed as a cyclization product when the 1,3-diphenylpropenes are photolyzed.

Registry No.—*cis*-1,2-Diphenylcyclopropane, 1138-48-3; *trans*-1,2-diphenylcyclopropane, 1138-47-2; *cis*-1,3-diphenylpropene, 1138-83-6; *trans*-1,3-diphenylpropene, 3412-44-0; 1-phenylindan, 26461-03-0.

Acknowledgment.—One of us (E. W. V.) would like to thank the National Science Foundation for financial support under a traineeship held during the period 1966–1969.

(46) R. C. Cookson, M. J. Nye, and G. Subrahmanyan, *Proc. Chem. Soc., London*, 144 (1964).

(47) We thank Professor G. W. Griffin for calling our attention to ref 46.

Preparation and Mass Spectral Properties of Cystine and Lanthionine Derivatives. A Novel Synthesis of L-Lanthionine by Selective Desulfurization[1]

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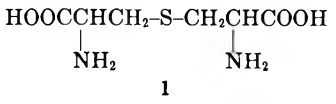
Received April 28, 1970

A useful conversion of certain cystine derivatives to the corresponding L-lanthionine compounds is described. *N,N'*-Dicarbobenzoxy-L-cystine diethyl ester (9) and *N,N'*-bis(trifluoroacetyl)-L-cystine dimethyl ester (7) were selectively desulfurized in high yield by tris(diethylamino)phosphine to the corresponding L-lanthionine derivatives. The trifluoroacetyl derivative of L-lanthionine was hydrolyzed to optically pure L-(+)-lanthionine (1). However, the peptide ethyl *N,N'*-dicarbobenzoxy-*O*-methyl-L-cystinylglycinate (11) under the same conditions rearranged to the symmetrical diethyl *N,N'*-dicarbobenzoxy-L-cystinyldiglycinate. The mass spectral fragmentation of cystine, lanthionine, and cysteamine derivatives is also discussed.

Because of the recognized importance of cystine in biological systems, this amino acid has received wide attention.[3] The sulfide analog, lanthionine (1), was first isolated as an artifact in wool hydrolysates[4,5] as a mixture of stereoisomers in 1941 and synthesized by du

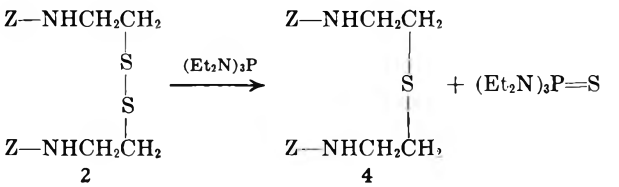


1

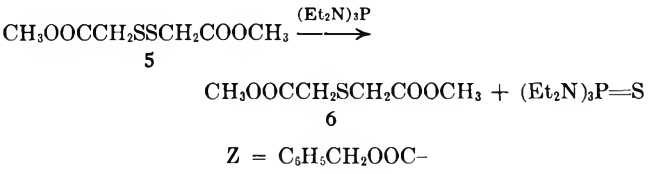
Vigneaud and Brown in the same year.[6] The first report of naturally occurring lanthionine was made in 1966 by Sloane and Untch[7] who isolated both L- and *meso*-lanthionine from the free amino acid pool of chick embryo. Subsequently, L-lanthionine has been found in the antibiotic, Nisin,[8] in the deprotonized haemolymph of various insects,[9] most notably the silkworm and Japanese Oak Moth, and in plant pollen.[10] The absence of the major sulfur-containing amino acids (cystine, cysteine, and methionine) in these sources is interesting. While several synthetic schemes for *meso*- and DL-lanthionine have been reported,[11] the only stereospecific synthesis of L-lanthionine involves the condensation of L-cysteine with methyl L-β-chloroalanate followed by strong alkaline hydrolysis. Low yields, coupled with problems of racemization,[12] render this approach unattractive for the synthesis of larger lanthionine peptides.

Results and Discussion

It appeared to us that selective removal of a sulfur atom from appropriate cystine derivatives would afford a convenient synthetic route to optically pure lanthionine and its derivatives. We have recently found[1,13] that, in simple disulfide systems (*e.g.*, dibenzyl or diamyl disulfide), aminophosphines can effect such a selective desulfurization. Since carboxylic acids are known to react with aminophosphines,[1,14] it was necessary to use cystine derivatives protected as the methyl or ethyl esters for this study. Preliminary work showed that the amide function would not interfere in the desulfurization as *N,N'*-dicarbobenzoxycysteamine (2) was desulfurized in 70% yield in refluxing benzene. Similarly, it was demonstrated that the ester function would not interfere since bis(carbomethoxymethyl) disulfide (5) was quantitatively desulfurized to the correspond-



2 4



5 6

Z = $C_6H_5CH_2OOC$–

ing sulfide 6 in less than 2 min at room temperature.

One cystine derivative chosen for study was *N,N'*-bis(trifluoroacetyl)-L-cystine dimethyl ester (7). The trifluoroacetyl (TFA) group was chosen as it can be removed under mild alkaline conditions (0.1 *N* NaOH). In addition, the enhanced volatility provided by the TFA group[15] would allow for a mass spectral study of the cystine and lanthionine derivatives. Disulfide 7 was prepared in 96% yield by the reaction of L-cystine methyl ester hydrochloride with trifluoroacetic anhydride in trifluoroacetic acid.

The desulfurization of disulfide 7 by aminophosphine 3 afforded the corresponding lanthionine derivative 8 in 96% yield, $[\alpha]^{25}D$ −21.6°. Structure proof of 8 obtains from its elemental analysis and mass spectrum (*vide infra*). Mild alkaline hydrolysis of 8 gave a 64% yield of L-(+)-lanthionine (1). The infrared spectrum of 1 was identical with that reported[7] for L-(+)-lanthionine and different from both meso and racemic lanthio-

* To whom correspondence should be addressed.

(1) Organic Sulfur Chemistry. Part IV. For part III, see D. N. Harpp and J. G. Gleason, *J. Org. Chem.*, **35**, 3259 (1970).

(2) Holder of an NRCC Studentship, 1968–1969.

(3) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Wiley, New York, N. Y., 1961, pp 1879–1924.

(4) M. J. Horn, D. B. Jones, and S. J. Ringel, *J. Biol. Chem.*, **138**, 141 (1941).

(5) W. R. Cuthbertson and H. Phillips, *Biochem. J.*, **39**, 7 (1945).

(6) G. B. Brown and V. du Vigneaud, *J. Biol. Chem.*, **140**, 767 (1941); V. du Vigneaud and G. B. Brown, *ibid.*, **138**, 151 (1941).

(7) N. H. Sloane and K. G. Untch, *Biochemistry*, **5**, 2658 (1966).

(8) (a) E. Gross and J. L. Morell, *FEBS Lett.*, 61 (1968); (b) E. Gross and J. L. Morell, *J. Amer. Chem. Soc.*, **92**, 2920 (1970).

(9) D. R. Rao, A. H. Ennor, and B. Thorpe, *Biochemistry*, **6**, 1208 (1967).

(10) V. Rossetti, *Ann. Chim. (Rome)*, **56**, 935 (1966); *Chem. Abstr.*, **66**, 397 (1967).

(11) Reference 3, p 2675.

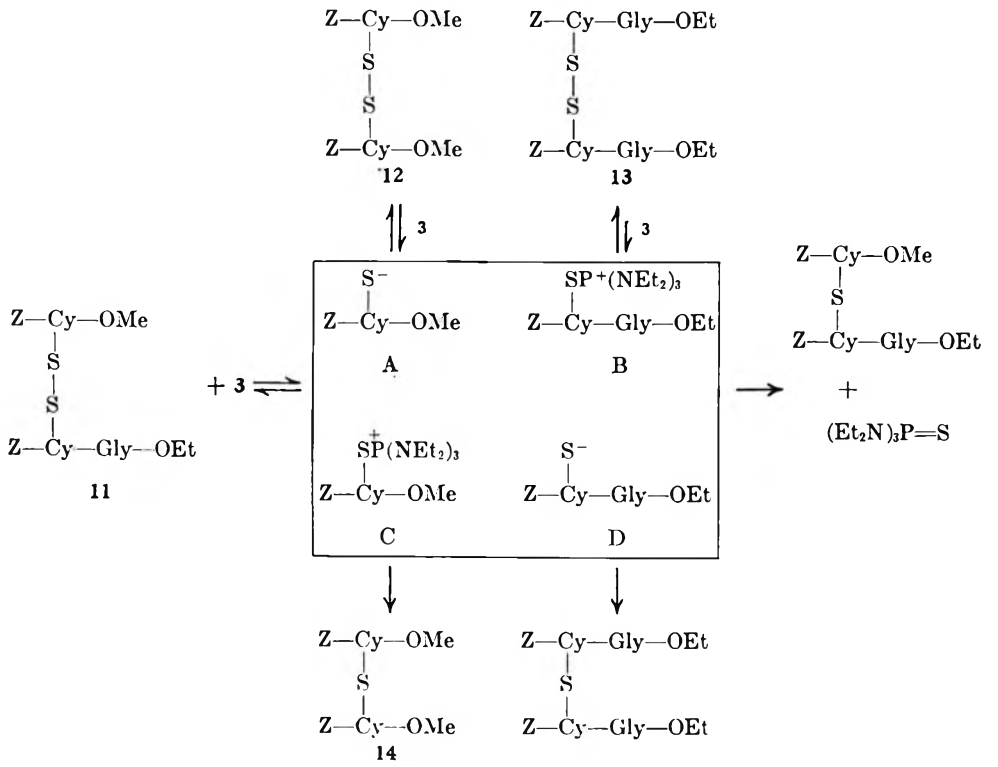
(12) Lanthionine undergoes complete racemization in 3–4 hr in 2.4 *N* NaOH solution; this reaction is much faster than previously reported.[7]

(13) D. N. Harpp, J. G. Gleason, and J. P. Snyder, *J. Amer. Chem. Soc.*, **90**, 4181 (1968).

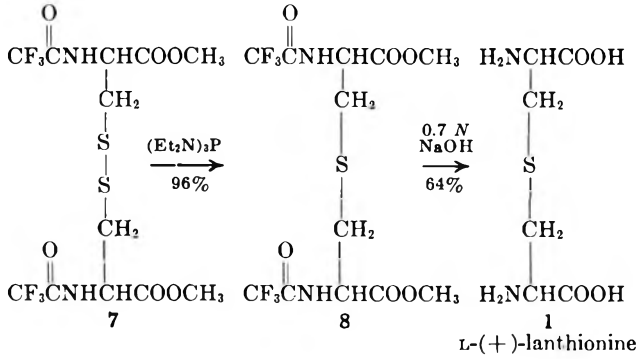
(14) R. Burgada, *Ann. Chim. (Rome)*, 347 (1963).

(15) F. Weygand, A. Prox, E. C. Jorgensen, R. Axen, and P. Kirchner, *Z. Naturforsch. B*, **18**, 93 (1963).

SCHEME I



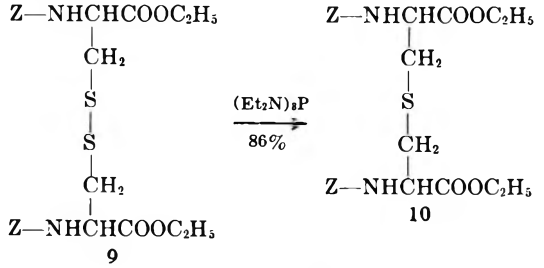
nine. The optical rotation of **1** in acid, $[\alpha]^{25}_{578}$ +4.0°, compares favorably with that previously reported[9]



L-(+)-lanthionine

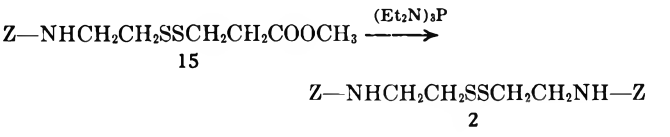
($[\alpha]^{25}_{578}$ +2.36°, +5.00°). Measurement of the optical rotation in base (2.4 *N* NaOH) gave a value of +9.4° (lit.[7] $[\alpha]_D$ +8.4°). On the basis of the above data, we conclude that this material is of high optical purity.

The versatility of the carbobenzoxy group makes lanthionine derivative **10** a useful starting material for peptide synthesis. This compound was prepared in 86% yield by desulfurization of *N,N'*-dicarbobenzoxy-L-cystine diethyl ester (**9**).



We felt it of considerable interest to examine the desulfurization of some unsymmetrical disulfides since most naturally occurring cystine peptides are of this type. An attempt was made to desulfurize the unsymmetrical peptide **11**; however, only the symmetrical disulfide **13** could be isolated. This observation would suggest that a phosphine-catalyzed equilibration[16] of disulfides **11**, **12**, and **13** (Scheme I) takes place. Presumably the extreme insolubility of **13** removes it from the reaction as rapidly as it is formed, while the formation of sulfide **14** proceeds *via* the remaining ion fragments A and C. As a result, the major products of the reaction are disulfide **13**, sulfide **14**, and phosphine sulfide.

A similar result was obtained for the unsymmetrical disulfide **15**. As in the case of peptide **11**, the symmetrical disulfide **2** was isolated in 88% yield. Since in this case no tris(diethylamino)phosphine sulfide was observed, equilibration of these disulfides must occur much faster than does desulfurization.



Mass Spectral Properties.—As might be expected, many of the spectral properties of the cystine and lanthionine derivatives are very similar. However, the fragmentation reactions which occur under electron impact in the mass spectrometer should be quite different.[17] To determine the effect of the sulfide and disulfide groups on the fragmentation of cystine and lanthionine derivatives, a detailed examination of the mass spectra of the TFA derivatives **7** and **8**, the carbo-

(16) The equilibration of disulfides **11**, **12**, and **13** may also occur *via* a mercaptide exchange reaction; see, for example, G. Dalman, J. McDermed, and G. Gorin, *J. Org. Chem.*, **29**, 1480 (1964).

(17) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, pp 276–296.

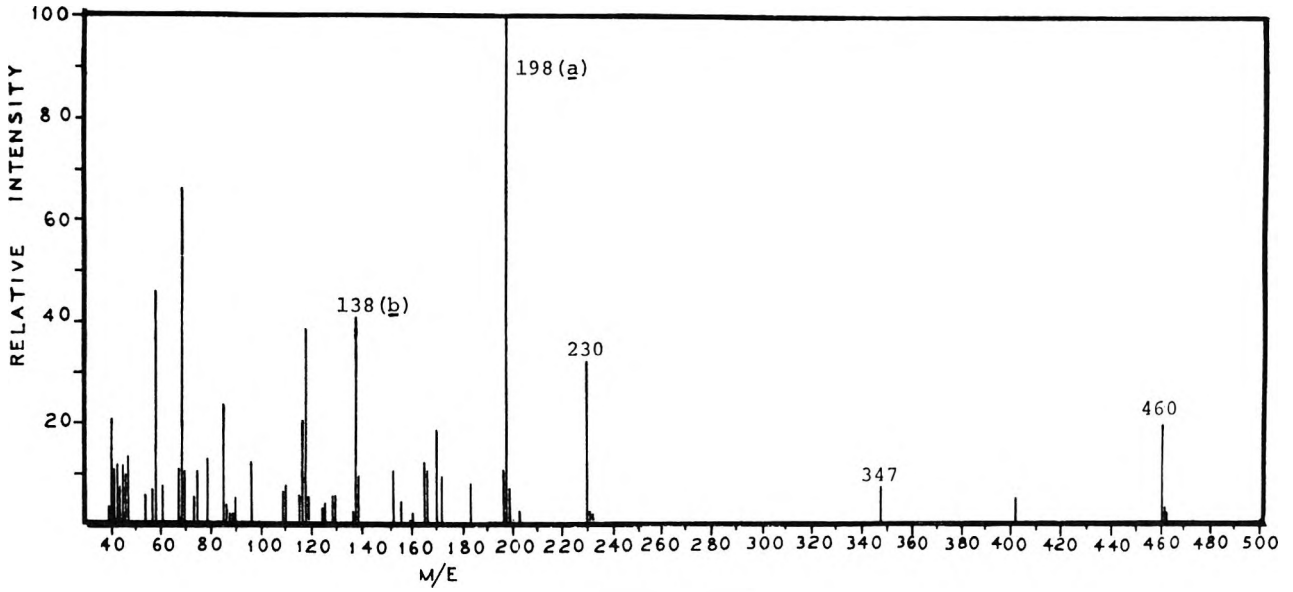


Figure 1.—*N,N'*-Bis(trifluoroacetyl)-L-cystine dimethyl ester (**7**).

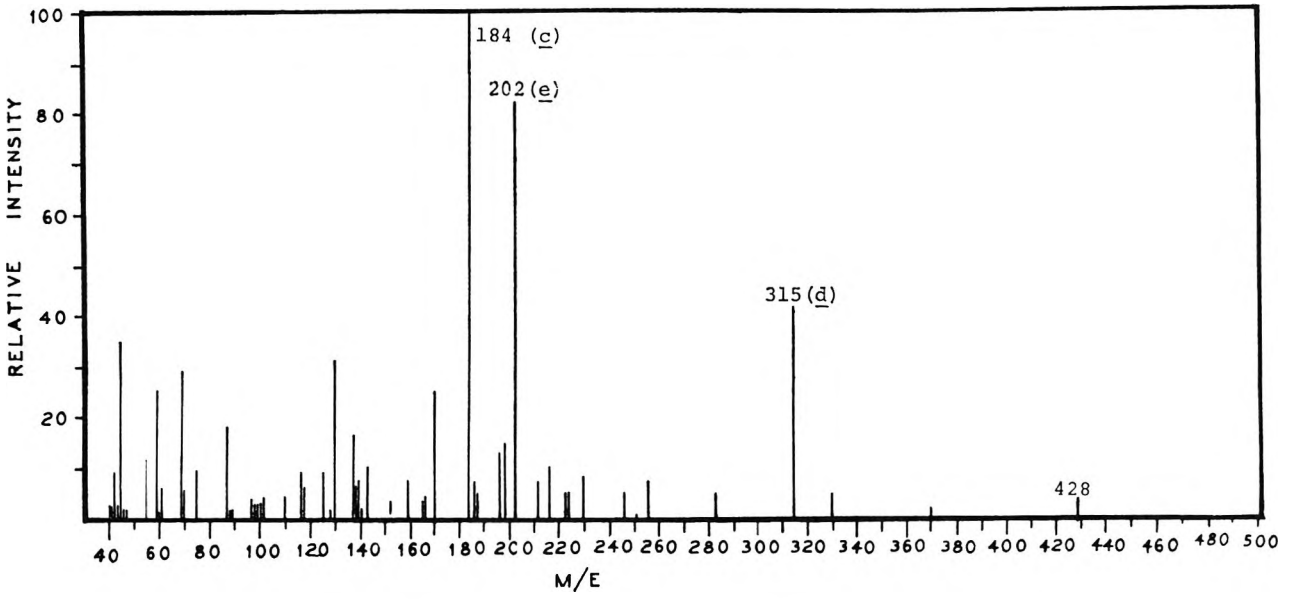


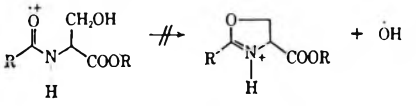
Figure 2.—*N,N'*-Bis(trifluoroacetyl)-L-lanthionine dimethyl ester (**8**).

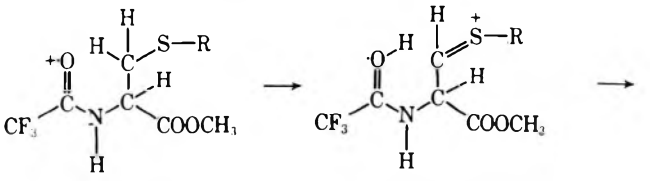
benzoxy derivatives **9** and **10**, and cysteamine derivatives **2**, **4**, and **15** was undertaken. The mass spectrum of the trifluoroacetylcystine dimethyl ester **7** (Figure 1) showed an intense molecular ion at *m/e* 460 (20%) with the base peak at *m/e* 198 arising from cleavage α to the disulfide (Scheme II). This ion a may be formulated as either an open chain ion a_1 or as an oxazoline ion a_2.[18]

The formation of ion a appears unique in that it is not observed in other acetyl and trifluoroacetyl amino acid esters.[19] The mass spectrum of *N,N'*-bis(trifluoroacetyl)-L-lanthionine dimethyl ester (**8**) (Figure 2) is radically different from the spectrum of the cystine derivative **7**. Here the major fragmentation (Scheme III) occurs β to the sulfide to form ion c, a process which is common to most acyl amino acid esters.[19a] Of more interest in the spectrum of **8** is the

(18) It would appear from preliminary deuterium-labeling studies that both ions a_1 and a_2 are formed since *N,N'*-dideuterio-**7** (from **7** by D_2O exchange) shows the loss of both methyl formate and methyl formate-d_1 in the fragmentation process 198 → 138.

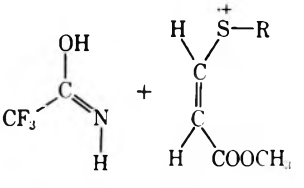
(19) (a) K. Heyns and H. F. Grützmacher, *Justus Liebigs Ann. Chem.*, **698**, 24 (1966). (b) This includes acetylserine ethyl ester where the loss of an OH radical would not be unexpected.





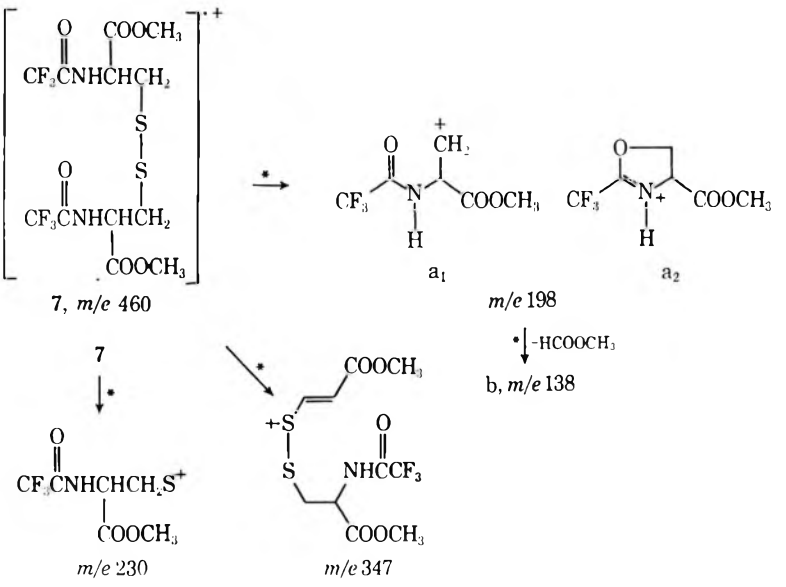
7, *m/e* 460
8, *m/e* 428

R = $SCH_2CH(NHCOCF_3)CO_2CH_3$
R = $CH_2CH(NHCOCF_3)CO_2CH_3$

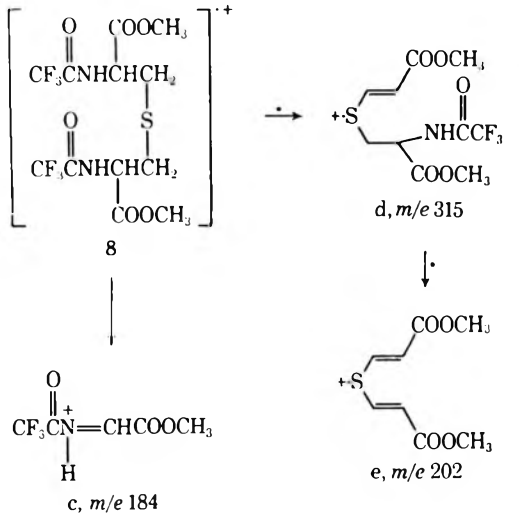


m/e 347
m/e 315

SCHEME II



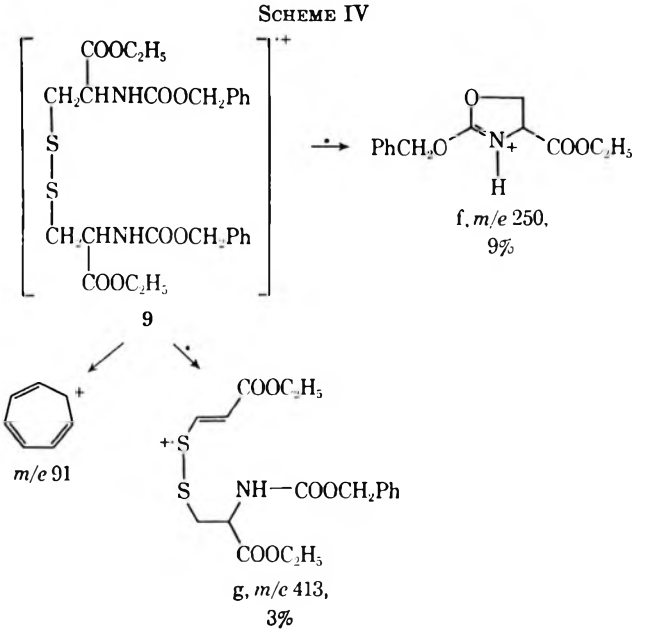
SCHEME III



loss of the elements of trifluoroacetamide to form ion d of *m/e* 315 which is 40% of the base peak. This ion subsequently loses another trifluoroacetamide molecule to form an intense ion e at *m/e* 202. The formation of d presumably results from hydrogen migration and cleavage of the C–N bond. This fragmentation is analogous to a McLafferty rearrangement;[20] however, unlike the McLafferty rearrangement, the charge is retained on the olefin fragment. It should be noted that no normal McLafferty rearrangement occurs as evidenced by the lack of an ion at *m/e* 113, $(CF_3CONH_2)\cdot^+$. This unusual fragmentation is observed only in special circumstances, as, for example, in the fragmentation of *N*-acetyl-β-phenylalanine esters to form styrene esters.[19a,20b]

While the formation of the oxazoline ion is the major pathway for the trifluoroacetyl disulfide **7** with this "reversed"[21] McLafferty rearrangement occurring to a small degree, exactly the opposite behavior is observed for the sulfide. This dichotomy of behavior must be due to an inherent difference between sulfide and disulfide groups. To further explore this mass spectral behavior, the spectra of several analogous *N*-carbobenzoxy derivatives were examined. The mass spectrum of *N*,*N*′-dicarbobenzoxy-L-cystine diethyl ester (**9**) (Figure 3) exhibited both oxazoline formation (ion f, *m/e* 250, 9%) and reversed[21] McLafferty rearrangement (ion g, *m/e* 413, 3%) (Scheme IV). As was the case for disulfide **7**, oxazoline formation predominates, here in a ratio of 3:1.

SCHEME IV



In contrast, relatively little oxazoline formation is observed in the mass spectrum (Figure 4) of the lanthionine derivative **10**; the reversed McLafferty rearrangement is the major fragmentation process (h, *m/e* 381, and i, *m/e* 230). This parallels the observations in the TFA derivatives.

The mass spectra of several structurally analogous cysteamine derivatives were studied to further explore this sulfide–disulfide dichotomy. The mass spectrum

(20) (a) Reference 17, p 155; (b) F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, New York, N. Y., 1966, pp 123–131. (c) While we have not yet been successful in verifying β-hydrogen transfer, there appears to be no other logical pathway.

(21) The term "reversed" is used here to emphasize that the charge resides on the olefin fragment in contrast to the normal McLafferty rearrangement.

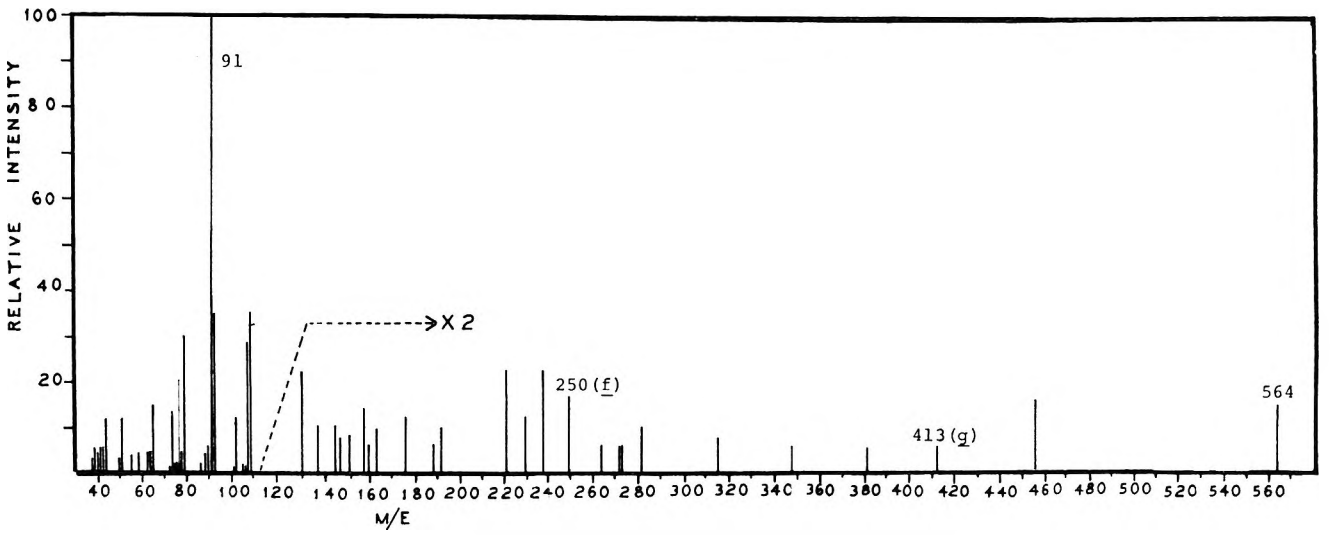


Figure 3.—*N*,*N*′-Dicarbobenzoxy-L-cystine diethyl ester (9).

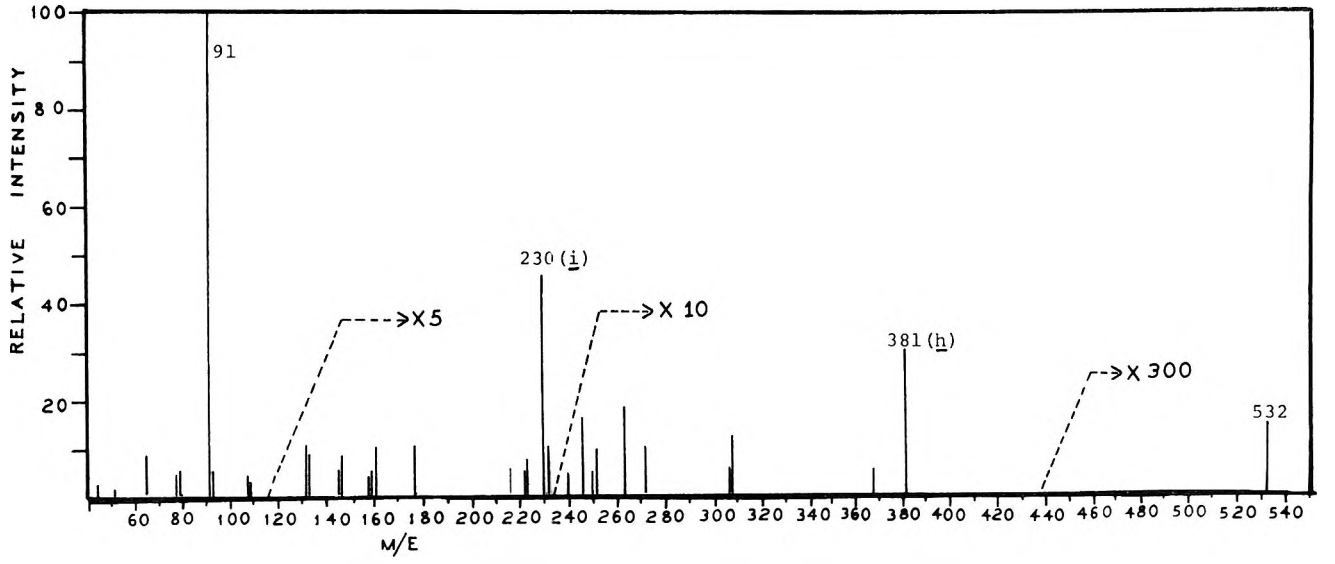
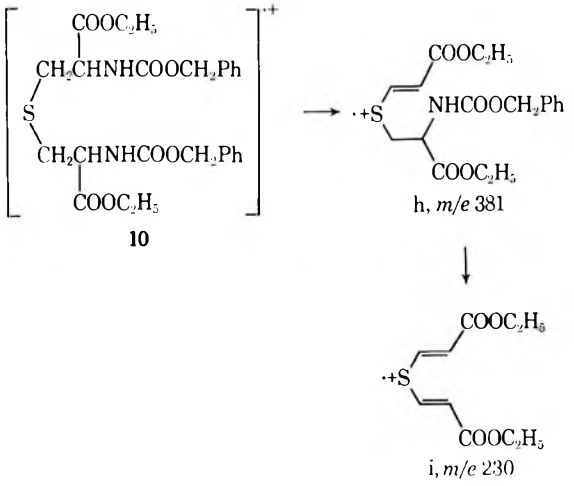


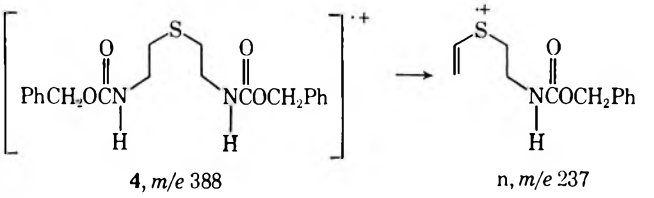
Figure 4.—*N*,*N*′-Dicarbobenzoxy-L-lanthionine diethyl ester (10).



of *N*,*N*′-dicarbobenzoxycysteamine (2) (Figure 5) had a strong ion at *m/e* 178 (8%) corresponding to the oxazoline ion (Scheme V) and a smaller ion at *m/e* 269 (1%) corresponding to a reversed McLafferty rearrangement.[21] The predominance of oxazoline formation again parallels the observation in the cystine series. Other ions observed in this spectrum and their origins are shown in Scheme V. Note that the oxazoline ion may arise from several pathways, although only path a (2 → j → k) and path b (2 → k) appear to be of major importance.

The mass spectrum of the unsymmetrical disulfide, *N*-carbobenzoxy-2-aminoethyl 2′-carbomethoxyethyl disulfide (15) (Figure 6), possessed a strong peak at *m/e* 178. This peak may be ascribed to *either* oxazoline ion l or ion m resulting from reversed McLafferty rearrangement. A high resolution spectrum of *m/e* 178 showed clearly the presence of two ions; the major ion at *m/e* 178.0879 (85%) was the oxazoline ion l (calcd for $C_{10}H_{12}NO_2$: 178.0868), while the minor ion (15%), *m/e* 178.0128 (calcd for $C_6H_{10}O_2S_2$: 178.0122), corresponded to the fragment m resulting from the reversed McLafferty rearrangement (Scheme VI).

In contrast to the behavior of 2 and 15, the sulfide derivative of 2, *N*,*N*′-dicarbobenzoxy-2,2′-diaminodiethyl sulfide (4) (Figure 7), showed very little oxazoline



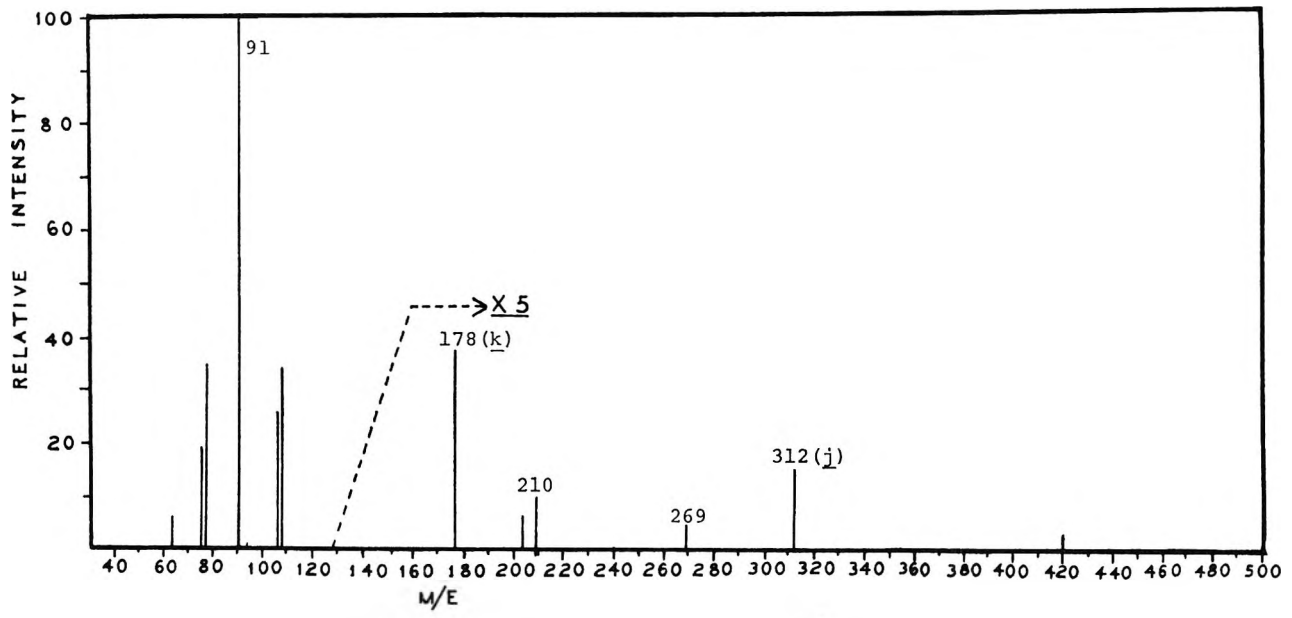
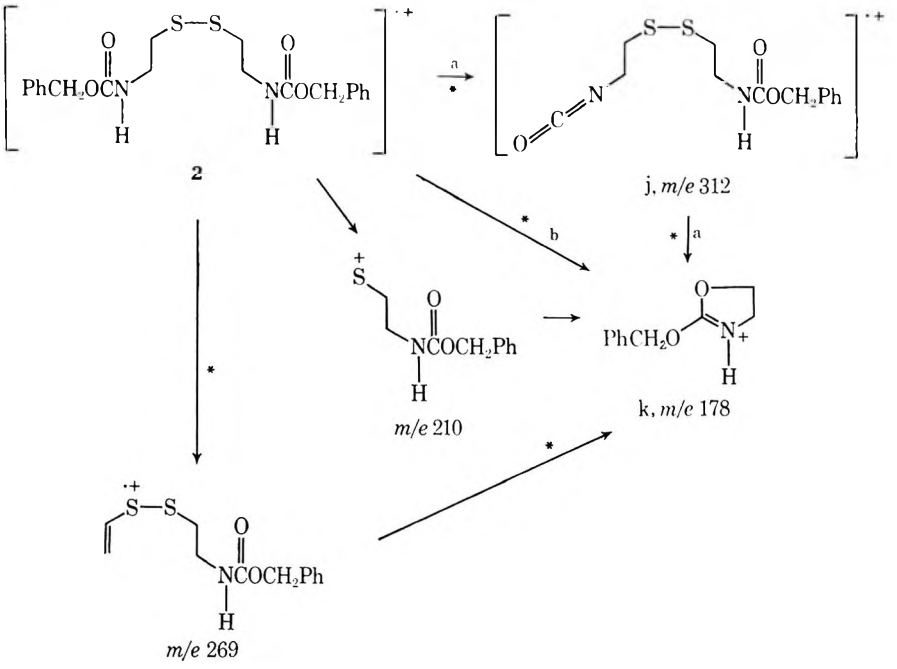
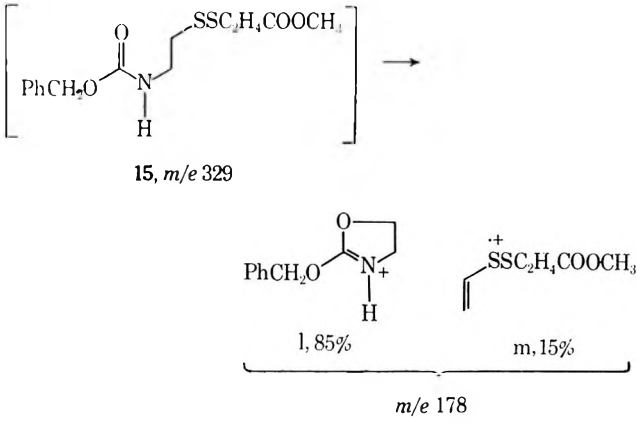


Figure 5.—*N*,*N*′-Dicarbobenzoxycysteamine (2).

SCHEME V



SCHEME VI



formation, but again showed only the formation of the vinyl sulfide ion n at *m/e* 237 (5%).

The major difference in the spectra of the sulfides as compared with the corresponding disulfides lies in the relative amounts of the oxazoline to reversed McLafferty processes (Table I). The ratio is high for the di-

TABLE I
ION ABUNDANCES

Compd	Parent ion, %	Oxazoline ion (X), %	Vinyl sulfide (disulfide) ion (Y), %	X/Y
		Disulfides		
7	19	100	9	11
9	7	9	3	3
2	0.4	8	2	4
15	3	4	0.7	6
		Sulfides		
8	4	15	42	0.35
10	0.005	0.5	3	0.2
4		0.5	5	0.1

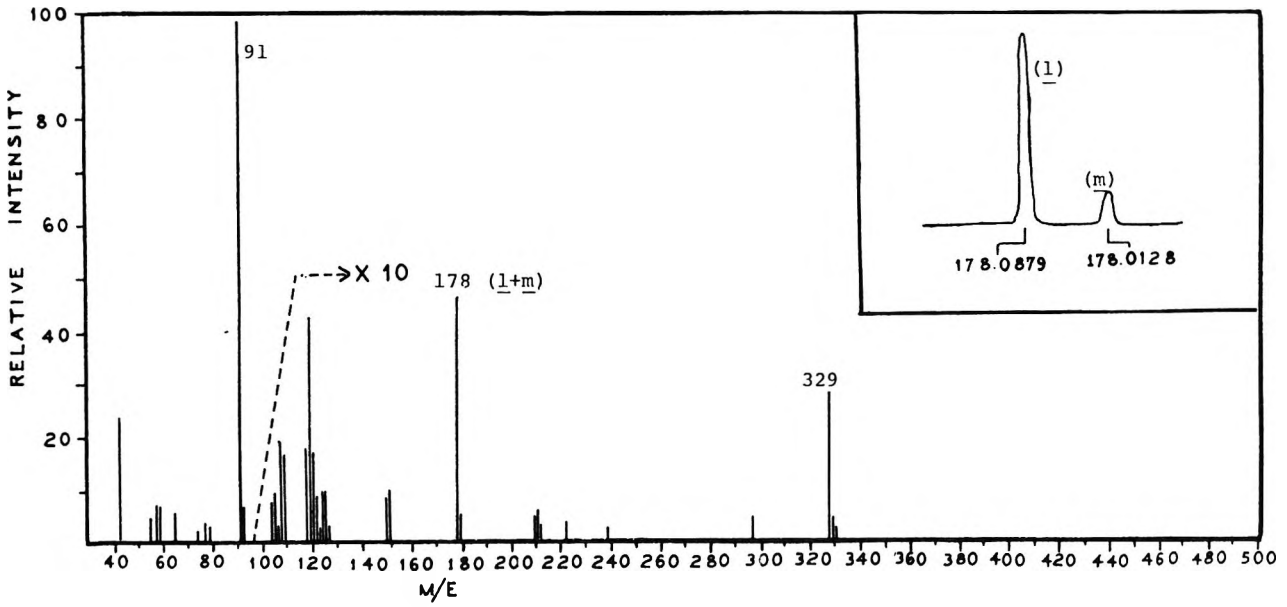
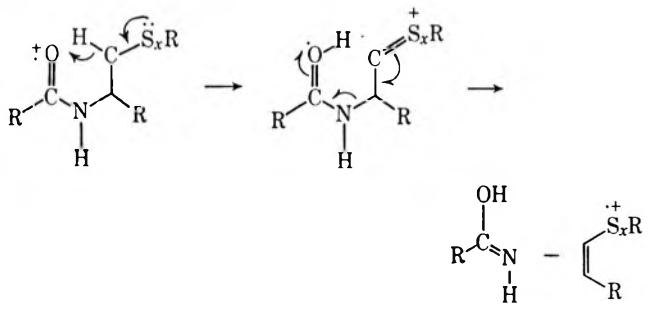


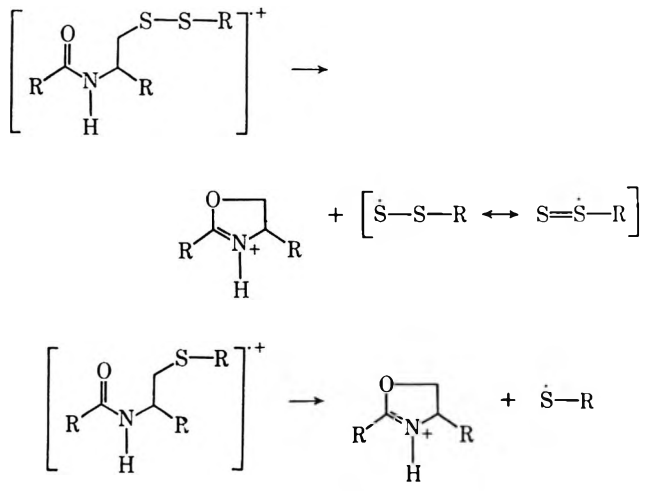
Figure 6.—*N*-Carbobenzoxy-2-aminoethyl 2′-carbomethoxyethyl disulfide (15).

sulfides and low for the sulfides. This difference between disulfides and sulfides could be the result of two additive effects. The electron-donor ability of sulfur would assist in the transfer of a hydrogen to the carbonyl oxygen during vinyl sulfide (disulfide) formation. Sulfides, better electron donors than disulfides,[22] would



$x = 1, 2$

be more likely to undergo this reversed McLafferty rearrangement. In contrast, the increased stability of the sulfthiyl radical (RSS·) over the thiyl radical (RS·) (which has been attributed to both inductive and resonance effects)[23] would result in the preferred formation of the oxazoline ion from disulfides rather than from sulfides.



Experimental Section

Melting points were determined on a Gallenkamp block and are corrected. Mass spectra were obtained on an AEI-MS-902 mass spectrometer at 70 eV using a direct-insertion probe. Nmr spectra were recorded on a Varian Associates A-60 spectrometer. Optical rotations were measured on a Carl Zeiss photoelectric precision polarimeter.

N,N′-**Dicarbobenzoxy-2,2′-diaminodiethyl Sulfide** (4).—To a suspension of 0.210 g (0.5 mmol) of *N,N′*-dicarbobenzoxycysteamine[24] (2) in 2 ml of dry benzene was added 0.20 g (0.8 mmol) of tris(diethylamino)phosphine. After the mixture was refluxed for 4 hr, the reaction was diluted with 25 ml of hexane. On standing, colorless crystals were obtained, 0.131 g (68%), mp 99–100°, which after crystallization from ethanol afforded an analytical sample: mp 99–100°; ir (KBr) 3150 (NH) and 1680 cm^{-1} (OCONH).

Anal. Calcd for $C_{20}H_{24}N_2O_4S$: C, 61.83; H, 6.22; N, 7.21; S, 8.25. Found: C, 61.81; H, 6.25; N, 7.04; S, 8.39.

Bis(carbomethoxymethyl) Sulfide (6).—To a solution of 4.20 g (17.5 mmol) of bis(carbomethoxymethyl) disulfide (5) in 10 ml of dry benzene was added slowly 6.0 g (24.3 mmol) of tris(diethylamino)phosphine. When the exothermic reaction was complete (about 2 min), the solvent was removed *in vacuo* and the residue distilled to afford 2.96 g (84%) of the sulfide 6: bp 82–84° (0.1 mm); nmr (CCl_4) τ 6.24 (singlet, 3 H), 6.62 (singlet, 2 H); ir (film) 1730 cm^{-1} (-COO-). Upon oxidation with hydrogen peroxide, the sulfide 6 yielded a crystalline sulfone, mp 111–112° (lit.[25] mp 114–116°).

N,N′-**Bis(trifluoroacetyl)-L-cystine Dimethyl Ester** (7).—A suspension of 4.50 g of cystine dimethyl ester hydrochloride in 15 ml of trifluoroacetic acid was cooled to −5°; 10 ml of trifluoroacetic anhydride was added dropwise. The resulting solution was stirred for 1 hr at −5° and then 1 hr at room temperature. The reaction mixture was poured over 200 ml of ice–H_2O; the mixture was stirred for 10 min and filtered; the crystalline product was washed well with water and then dried *in vacuo* to yield 6.2 g (95%) of white crystals: mp 152–154°; $[\alpha]^{25}D$ −183° (c 2.5, MeOH) (lit.[15] mp 152–153°; $[\alpha]^{25}D$ −194°).

N,N′-**Bis(trifluoroacetyl)-L-lanthionine Dimethyl Ester** (8).—To a suspension of 2.30 g (5.0 mmol) of disulfide in 25 ml of dry benzene was added slowly 1.40 g (5.5 mmol) of tris(diethylamino)phosphine. The resulting mixture was stirred under N_2 for 10 min. The suspended amide slowly dissolved and then reprecipitated as a gel. After addition of 50 ml of hexane, the re-

(22) M. Good, A. Major, J. Nog-Chaudhuri, and S. McGlynn, *J. Amer. Chem. Soc.*, **83**, 4329 (1961).

(23) E. Muller and J. B. Hyne, *ibid.*, **91**, 1907 (1969).

(24) We acknowledge the generous gift of this compound from Professor Richard G. Hiskey.

(25) H. J. Backer and W. Stevens, *Recl. Trav. Chim. Pays-Bas*, **59**, 444 (1940).

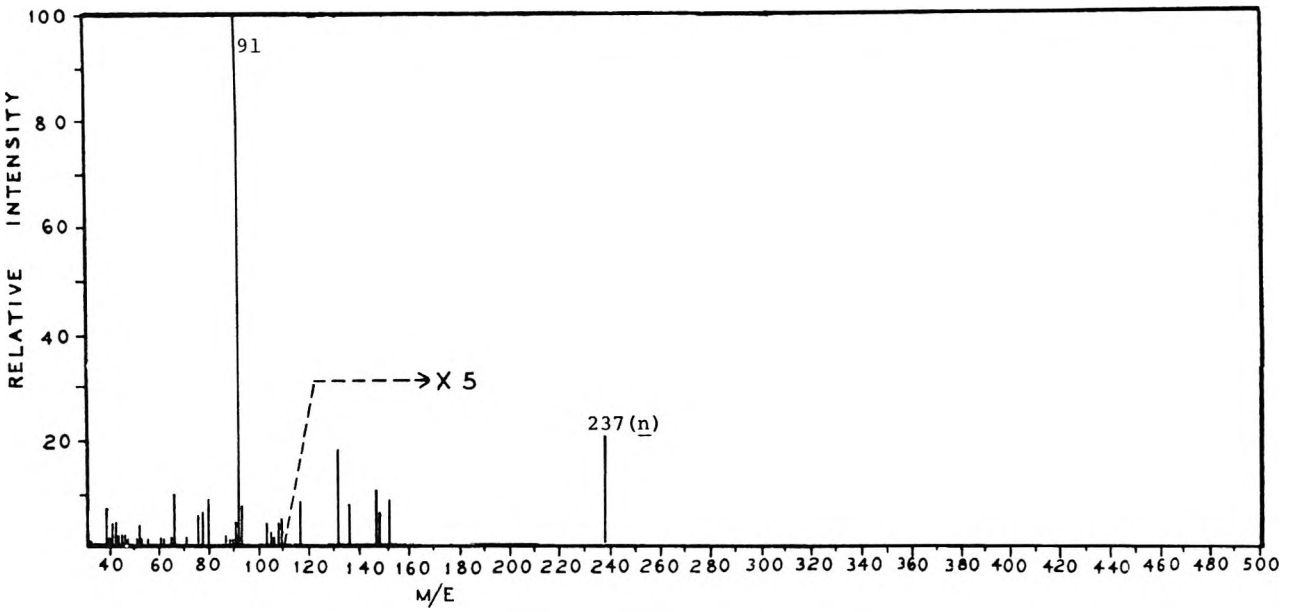


Figure 7.—*N,N'*-Dicarbobenzoxy-2,2'-diaminodiethyl sulfide (**4**).

sulting suspension was filtered and the white crystals were washed well with hexane to yield 2.07 g (96%) of white crystals, mp 103–109°.

After three recrystallizations from aqueous methanol, an analytical sample was obtained: mp 117–118°; $[\alpha]^{25}D$ −32.4° (*c* 0.4 MeOH); ir (KBr) 3300 (NH), 1760 (–COO–), and 1705 cm^{-1} (CONH).

Anal. Calcd for $C_{12}H_{14}N_2O_6SF_6$: C, 33.57; H, 3.30; N, 6.54; S, 7.49; F, 26.63. Found: C, 33.92; H, 2.91; N, 6.59; S, 7.61; F, 27.05.

L-(+)-Lanthionine (1).—A solution of 1.290 g (3.0 mmol) of the bis(trifluoroacetyl)lanthionine dimethyl ester **8** in 15 ml of dioxane was cooled to 0° in an ice bath; 27 ml of 1.0 *N* NaOH was added slowly. After 0.5 hr at 5°, the mixture was acidified with 12 ml of 2 *N* HCl. After adjusting the pH to 6.0, the solvent was removed under vacuum. To the residue was added 15 ml of H_2O and the crystalline L-(+)-lanthionine was collected by filtration and dried *in vacuo*, yield 0.398 g (64%) of white crystals: mp 295–296° dec; $[\alpha]^{25}D$ +9.4° (*c* 1.4, 2.4 *N* NaOH) (lit.[7] mp 295° dec, $[\alpha]^{25}D$ +8.4°); $[\alpha]^{25}_{578}$ +4.0° (*c* 1.0, 1 *N* HCl) (lit.[9] $[\alpha]^{25}_{578}$ +2.36°, +5.00°). The infrared spectrum of this material was identical with that reported[7] for L-(+)-lanthionine.

***N,N'*-Dicarbobenzoxy-L-lanthionine Diethyl Ester (10).**—To a suspension of 2.261 g (4.0 mmol) of *N,N'*-dicarbobenzoxy-L-cystine diethyl ester[24] (**9**) in 10 ml of dry benzene was added slowly 1.20 g (4.8 mmol) of tris(diethylamino)phosphine. An exothermic reaction occurred and the peptide dissolved. After the mixture was stirred for 1 hr, the solvent was removed under vacuum and the residue chromatographed over silica gel. The phosphine sulfide (1.09 g, 99%) was eluted with 9:1 hexane–ethyl acetate, followed by a small amount of impurities (0.05 g). Elution with 1:1 hexane–ethyl acetate afforded a colorless oil which on standing crystallized to give 1.83 g (86%) of white crystals, mp 63–67°, which after three recrystallizations from cyclohexane afforded an analytical sample: mp 67–68°; $[\alpha]^{25}D$ −15.9° (*c* 1.1, MeOH); ir (KBr) 3320 (NH), 1750 (–COO–), and 1690 cm^{-1} (–OCONH). The infrared spectrum of the analytical sample was identical with that of the crude (mp 63–67°) crystals obtained from the column.

Anal. Calcd for $C_{26}H_{32}N_2O_8S$: C, 58.62; H, 6.06; N, 5.26; S, 6.02. Found: C, 58.68; H, 6.20; N, 5.37; S, 6.22.

Reaction of Ethyl *N,N'*-Dicarbobenzoxy-*O*-methyl-L-cystinylglycinate (11) with Tris(diethylamino)phosphine.—A suspension of 131 mg (0.22 mmol) of **11**[24] and 100 mg (0.4 mmol) of phosphine **3** in 100 ml of anhydrous ether was stirred for 2 hr during which time the texture of the suspension changed. Filtration afforded a white crystalline material, 60 mg (82% based on complete conversion of **11** to **13**), mp 165–170°, which was identical (melting point, ir, and nmr) with that of the authentic disulfide **13**. The tlc (chloroform) of the filtrate of **13** showed the presence of tris(diethylamino)phosphine sulfide and sulfide **14**, both identified by comparison with authentic samples.

***N*-Carbobenzoxy-2-aminoethyl 2'-Carbomethoxyethyl Disulfide (15).**—A solution of 0.50 g (1.57 mmol) of 3-[2-(*N*-carbobenzoxy)aminoethyl]dithiopropanoic acid and 1.0 ml of phosphorus trichloride in 10 ml of chloroform was stirred at room temperature for 1 hr. The excess phosphorus trichloride and chloroform were removed under vacuum and the residue diluted with 10 ml of methanol. After the mixture was stirred for 10 min, the solvent was removed under vacuum and the residue chromatographed over silica gel. Elution with chloroform afforded an oil which resisted all attempts at crystallization. Removal of all traces of solvent *in vacuo* afforded a colorless oil, 0.405 g (70%), which was homogeneous on tlc (silica gel, $CHCl_3$): ir (film) 3180 (NH) and 1720 cm^{-1} (broad, –OCO– and OCONH); nmr ($CDCl_3$) τ 2.58 (singlet, 5 H, aromatic), 4.6 (broad, 1 H, NH), 4.80 (singlet, 2 H, benzylic), 6.21 (singlet, 3 H, $-OCH_3$), 6.40 (quartet, 2 H, $-CH_2N$), 7.1 (multiplet, 6 H); mass spectrum, parent ion at *m/e* 329.0757 (calcd for $C_{14}H_{19}NO_4S_2$: 329.0755).

Anal. Calcd for $C_{14}H_{19}NO_4S_2$: C, 51.05; H, 5.81; N, 4.25; S, 19.43. Found: C, 50.81; H, 5.59; N, 4.36; S, 19.22.

Reaction of Disulfide 15 with Tris(diethylamino)phosphine.—To a solution of 0.33 g (1.0 mmol) of **15** in 3 ml of dry benzene was added 0.30 g (1.2 mmol) of tris(diethylamino)phosphine. A white precipitate which formed immediately on addition of the phosphine was obtained by filtration as colorless crystals, 0.184 g (88% based on complete conversion of **15** to **2**): mp 124–124.5°; mmp 124–125°, identical (ir, nmr) with that of the authentic disulfide **2**.

Registry No.—**1**, 922-55-4; **2**, 26542-61-0; **4**, 26630-73-9; **6**, 16002-29-2; **7**, 26527-24-2; **8**, 26527-25-3; **9**, 26527-26-4; **10**, 26527-27-5; **13**, 2790-85-4; **15**, 26599-16-6.

Nor Steroids. IX. Synthesis of A-Norandrostanes *via* the Dieckmann Cyclization[1,2]

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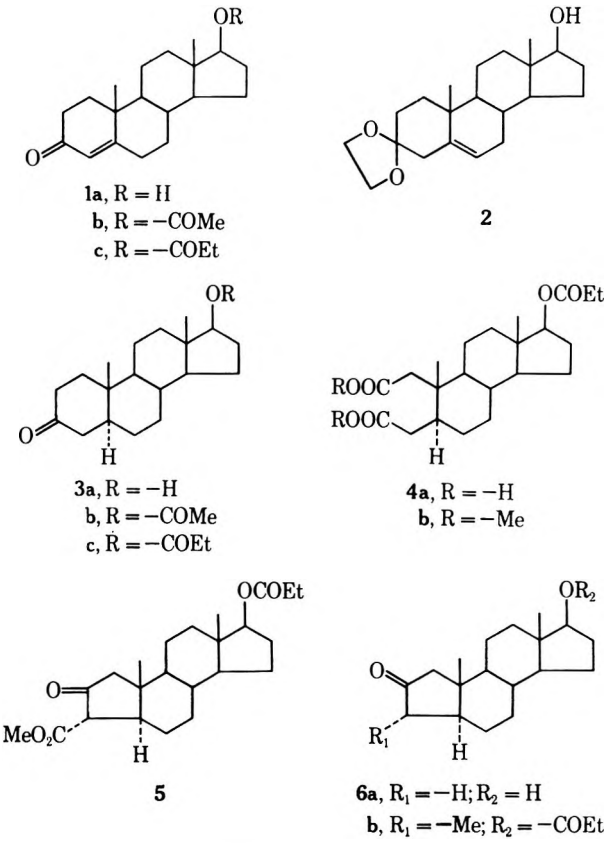
Received June 24, 1970

The Dieckmann cyclization of dimethyl 2,3-*seco*-5α-androstan-17β-ol-2,3-dioate 17-propionate (**4b**) to 3α-carbomethoxy-*A*-nor-5α-androstan-17β-ol-2-one 17-propionate (**5**), followed by methylation at C-3 and subsequent hydrolysis and decarboxylation to give 3α-methyl-*A*-nor-5α-androstan-17β-ol-2-one 17-propionate (**6b**), is described. Improved procedures for the reduction of testosterone esters to the 5α-3-keto compound and oxidation of this to the 2,3-*seco* acid are also reported.

Of the various methods available for the preparation of A-nor steroids, Fuchs and Loewenthal[4] reported that the Dieckmann cyclization of the 2,3-seco dimethyl ester of cholestanedioic acid proceeded in good yield to the A-nor β-keto ester.[5] If the β-keto ester could be alkylated at the active methylene group in good yield, hydrolysis and decarboxylation of the product would provide a good route to A ring alkylated A-nor ketones, which are often difficult to prepare from the A-nor ketones.[6] This paper reports the successful application of this method to the synthesis of 3α-methyl-*A*-nor-5α-androstan-17β-ol-2-one 17-propionate (**6b**).

For the cyclization step, the dimethyl ester of a 2,3-*seco*-5α-androstan-17β-ol-2,3-dioic acid derivative was required, and was obtained by oxidation and subsequent esterification of a 5α-androstan-17β-ol-3-one derivative. The most readily available starting material for this sequence was testosterone (**1**, R = Me or Et) in the form of the 17-acetate or -propionate. However, catalytic hydrogenation of these compounds with palladium–charcoal gave mixtures of the 5α- and 5β-androstanes, a result also obtained by Shoppee and Krueger.[7] Reduction with palladium on calcium carbonate[8] also gave substantial amounts of the 5β isomer. Reduction of 3,3-ethylenedioxyandrost-5-en-17β-ol (**2**) with a palladium–charcoal catalyst gave a 44% yield of the α isomer by simple crystallization.[9] Reduction with lithium–ammonia[10] proved to be a superior method for obtaining the desired α isomer, **3**, in yields of 81–88%, from testosterone acetate or propionate. Some 3β-hydroxy compound was also formed, but was not separated, since it was reoxidized to the ketone in the subsequent step.

The oxidation of 5α-androstan-17β-ol-3-one 17-hexahydrobenzoate with chromium trioxide in acetic acid at 55–65° was reported by Rull and Ourisson[11] to proceed in about 75% yield. These conditions gave low yields (~25%) when applied to the 17-acetate or -propionate, but when the temperature was raised to 70–80°, yields of 75% of the seco acid 17-propionate **4a** were obtained. The seco acid was then esterified with diazomethane to give the dimethyl ester **4b** in 90% yield.



The Dieckmann cyclization was first carried out using potassium *tert*-butoxide in benzene and gave 3α-carbomethoxy-*A*-nor-5α-androstan-17β-ol-2-one 17-propionate (**5**) in only 20% yield. However, when the cyclization was carried out in (5:1) benzene–dimethyl sulfoxide[12] the yield of β-keto ester was increased to 62%. That the β-keto ester was the 2-one and not the 3-one was shown by hydrolysis to the β-keto acid and decarboxylation to give the known *A*-nor-5α-androstan-17β-ol-2-one (**6a**)[5a,13] in 95% yield. The 3α configuration was assigned to the carbomethoxy group in **5** on the basis of the C-19 methyl resonance at δ 1.17 in the nmr spectrum. This corresponds to a value of δ 1.23 for the C-19 methyl resonance in the A-nor ketone **6a**. If the

* To whom correspondence should be addressed.

(1) For the previous paper in the series, see H. R. Nace and E. M. Holt, *J. Org. Chem.*, **34**, 2692 (1969).

(2) Supported in part by the USPHS under Grant AM 05249-02.

(3) Abstracted from the Ph.D. Thesis of J. L. P., Brown University, 1967; University Fellow, 1962–1963.

(4) B. Fuchs and H. J. E. Loewenthal, *Tetrahedron*, **11**, 199 (1960).

(5) Two more examples have been reported since completion of this work. See (a) S. Hara, *J. Pharm. Soc. Jap.*, **88**, 1227 (1968); (b) K. Oka and S. Hara, *Chem. Commun.*, 368 (1969).

(6) D. H. Nelander, Ph.D. Thesis, Brown University, 1963.

(7) C. W. Shoppee and G. Krueger, *J. Chem. Soc.*, 3641 (1961); see also A. Butenandt, K. Tscherning, and G. Hanisch, *Ber.*, **68**, 2097 (1935).

(8) R. Mozingo, *Org. Syn.*, **26**, 77 (1946).

(9) After completion of this work a similar reduction was reported by J. Pospisek, Z. Vesely, and J. Trojanek, *Collect. Czech. Chem. Commun.*, **34**, 3632 (1969).

(10) E. E. van Tamelen and W. C. Proost, Jr., *J. Amer. Chem. Soc.*, **76**, 3632 (1954); F. L. Weisenborn and H. E. Applegate, *ibid.*, **81**, 1960 (1959).

(11) T. Rull and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1573 (1958).

(12) H. E. Zaugg, B. W. Horrom, and S. Borgwardt, *J. Amer. Chem. Soc.*, **82**, 2895 (1960).

(13) R. E. Marker, O. Kamm, D. M. Jones, and L. W. Mixon, *ibid.*, **59**, 1363 (1937).

carbomethoxy group were β, it would be expected to exert a much larger deshielding effect on the C-19 methyl, resulting in a larger downfield shift. This assignment is opposite to that of Fuchs and Loewenthal[4] for the analogous product in the cholestane series. Their assignment was based on a series of chemical transformations and assumptions of reactivity based on stereochemical considerations. However, unpublished results obtained in this laboratory,[14] based mainly on nmr studies, indicate that the carbomethoxy group in their compound is also α, and their assignment is incorrect. Stereochemical considerations also suggest that the α configuration is more stable, avoiding 1,3-diaxial interactions with the 19-methyl group.

The β-keto ester was alkylated by treatment with sodium hydride and methyl iodide and the alkylated product (not isolated) was hydrolyzed and decarboxylated to give 3α-methyl-*A*-nor-5α-androstan-17β-ol-2-one 17-propionate (**6b**) in 55% yield. The α assignment of the methyl group is tentative and is based on the fact that the α configuration is sterically favored over the β configuration and is accessible through the enolic intermediate formed in the decarboxylation step.

Experimental Section[15]

Catalytic Reduction of the Dioxolate Derivative 2.—Testosterone (2.0 g, 0.694 mmol), 2-methyl-2-ethyl-1,3-dioxolane (20.8 g, 0.18 mol), and *p*-toluenesulfonic acid (60 mg) were heated at reflux temperature, and methyl ethyl ketone was removed by means of a Dean–Stark trap. After 5 hr, 16 ml of distillate had been collected and no further production occurred. The reaction mixture was taken up in benzene and washed with 5% $NaHCO_3$ and water. The solution was dried (Na_2SO_4), the solvent was removed, and recrystallization gave 1.35 g (58%) of 3,3-ethylenedioxyandrost-5-en-17β-ol (**2**), mp 180–184° (lit.[16] 183–184°). There was no carbonyl absorption in the infrared spectrum.

The product, 498 mg, dissolved in 150 ml of ethanol and was hydrogenated using 5% Pd–C catalyst at ambient conditions. Hydrogen (1 equiv) was absorbed, and no further uptake occurred. After removal of the catalyst and the solvent, the crude product was hydrolyzed by boiling under reflux with 50 ml of acetone for 12 hr. Addition of 500 ml of water precipitated the product, which was recrystallized from heptane–ethyl acetate to give 5α-androstan-17β-ol-3-one (**3a**): 245 mg (44%); mp 176.5–179°; $[\alpha]_D$ +34° (*c* 1.0, EtOH); ir (KBr) 1710 cm^{-1}; R_f^{BE} 0.37 (silica) (lit.[17] mp 181°, $[\alpha]_D$ +32°).

Reduction of Testosterone Acetate to 5α-Androstan-17β-ol-3-one 17-Acetate (3b).—To a solution of 10.0 g (29.6 mmol) of testosterone acetate (**1b**) in 250 ml of anhydrous ether was added 500 ml of liquid ammonia, and then 2.1 g (0.303 g-atom) of lithium was added in small pieces. After the addition was complete, ammonium chloride was added slowly until the solution was white and pasty. Water (150 ml) was added slowly until the inorganic salts had dissolved and the solution was allowed to stand overnight while the ammonia evaporated. The residue was extracted with ether and with methylene chloride, and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The oily residue was crystallized from ethyl acetate–heptane and gave 8.50 g (86%) of 5α-androstan-17β-ol-3-one 17-acetate (**3b**), mp 154–156° (lit.[18] mp 158.5–159.5°).

Reduction of Testosterone Propionate—To a solution of 800 mg (0.116 g-atom) of lithium in 750 ml of liquid ammonia was added over a period of 20 min a solution of 6.98 g (21.1 mmol) of testosterone propionate (**1c**) in 60 ml of dioxane and 50 ml of ether. A small amount of lithium was added to restore the deep blue color of the solution and then after 20 min it was worked up as above to give 6.16 g (84%) of 5α-androstan-17β-ol-3-one 17-propionate (**3c**), mp 119.5–120.5° (lit.[18] mp 121–121.7°).

2,3-*seco*-5α-Androstan-17β-ol-2,3-dioic Acid 17-Propionate (4a).—To a solution of 571 mg (1.65 mmol) of **3c** in 30 ml of glacial acetic acid at 65° was added dropwise with stirring, a suspension of 579 mg (5.79 mmol) of chromium trioxide in 40 ml of glacial acetic acid, and the temperature was kept at 65–70° during the addition. After the addition the temperature was kept at 75–80° for 8 hr, then the solution was cooled to 55° and 100 ml of water was added. The resulting mixture was then heated on a steam bath under an air stream with periodic addition of water until the odor of acetic acid was no longer distinguishable and then extracted (fifteen 100-ml portions) with ether, and the ether extracts were combined, reduced in volume, and extracted with three 10-ml portions of 5% Na_2CO_3 solution. The basic extract was acidified with hydrochloric acid and extracted exhaustively with ether. The ether extract was dried (Na_2SO_4) and the ether was evaporated. The residue was recrystallized from ethanol to give 490 mg (75%) of the seco acid **4a**: mp 223–225°; $[\alpha]_D$ +30° (*c* 1.0, $CHCl_3$); ir (KBr) 5.76, 5.80 μ; R_f^{BE} 0.05.

Anal. Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 66.90; H, 8.90.

Dimethyl 2,3-*seco*-5α-Androstan-17β-ol-2,3-dioate 17-Propionate (4b).—A solution of diazomethane in 60 ml of ether, prepared from 3.0 g of *N*-nitroso-*N*-methylurea,[19] was dried over solid KOH for 1 hr at 0° and then added to an ice-cold solution of 520 mg (1.32 mmol) of the seco acid **4a** in 250 ml of ether. The solution was cooled in an ice bath for 2 hr and allowed to come to room temperature, the solvent and excess diazomethane were removed under reduced pressure, and the residue was recrystallized from ethanol to give 500 mg (90%) of the dimethyl ester **4b**: mp 72.5–74°; ir (KBr) 5.77 μ; [α] +43.0° (589), +30.7° (578), +28.5° (436), +83.8° (365 mμ) (*c* 0.10, EtOH); nmr δ 0.89 (C-18 CH_3), 1.12 (C-19 CH_3), 3.70 (center of quadruplet, $-CH_2-$ of side chain), and 3.70 (s, 6, ester CH_3); tlc R_f^{BE} 0.64. A trace of seco acid was observed at R_f 0.04. The ester was not further purified but was used directly in the following transformation.

3α-Carbomethoxy-*A*-nor-5α-androstan-17β-ol-2-one 17-Propionate (5). A. By Cyclization in Benzene.—In a drybox operation, 240 mg (2.14 mmol) of potassium *tert*-butoxide was added to a solution of 500 mg (1.18 mmol) of the seco ester **4b** in 40 ml of anhydrous benzene (further dried over $MgSO_4$) and the resulting mixture was boiled under reflux ($CaCl_2$ tube) for 14 hr. The mixture was then cooled, 25 ml of dilute HCl was added, the aqueous layer was removed, and the benzene layer was washed with water, dilute $KHCO_3$ solution, and water, and dried (Na_2SO_4), and the solvent removed to give an oily residue which could not be crystallized. Tlc (alumina) analysis with benzene indicated the presence of two major components, starting material, R_f 0.85 (yellow spot with 2,4-DNP), and the desired product, R_f 0.15 (orange spot with 2,4-DNP). Column chromatography on silica and elution with benzene gave starting material: mp and mmp (with an authentic sample) 72–73°; R_f 0.85 (silica); ir spectra superimposable. Elution with ether–methanol gave the product **5**: 90 mg (20%); R_f 0.18 (benzene); ir ($CHCl_3$) 5.74, 5.80, 6.10 μ; mp 113.5–115°, after recrystallization from methanol; [α] +89.0° (589), +48.2° (578), +51.3° (546), +85.5° (436 mμ) (*c* 0.10, EtOH); purple color with ferric chloride; nmr δ 0.96 (C-18 CH_3), 1.07 (t, side chain CH_3), 1.17 (C-19 CH_3), 3.70 (q, side chain $-CH_2-$, and s, ester CH_3).

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.48; H, 8.65.

B. By Cyclization in Benzene–Dimethyl Sulfoxide.—To a solution of 600 mg (1.42 mmol) of the seco diester in 95 ml of anhydrous benzene and 20 ml of freshly distilled dimethyl sulfoxide

(14) A. H. Smith, Ph.D. Thesis, Brown University, 1968.

(15) Melting points were determined with a Hershberg apparatus and Anshutz thermometers and are corrected. Microanalyses by Dr. S. M. Nagy and associates, Microchemical Laboratory, Massachusetts Institute of Technology. Ir spectra were determined with a Perkin-Elmer Infracord or Model 237 spectrometer. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter. Nmr spectra were determined with a Varian HR-60 spectrometer in deuteriochloroform solution using TMS as an internal standard. Column chromatography was done with Baker chromatographic grade silica gel or Merck chromatographic grade alumina. Tlc was carried out with silica gel or alumina and the plates were developed with a solution of 2,4-dinitrophenylhydrazine in phosphoric acid and ethanol.

(16) "Elsevier's Encyclopedia of Organic Chemistry," Vol. 14, E. Radt, Ed., Elsevier, New York, N. Y., 1940, p 141.

(17) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 519.

(18) Reference 16, p 2597s.

(19) A. H. Blatt, *Org. Syn.*, **2**, 165 (1943).

was added 282 mg (2.52 mmol) of potassium *tert*-butoxide in a drybox operation, and the resulting mixture was boiled under reflux with a Dean–Stark trap for 16 hr, during which time 20 ml of solvent was removed from the trap. Then the reaction mixture was cooled and extracted with 100 ml of dilute HCl and this extract was extracted extensively with ether ("acid extract"). The reaction mixture was next extracted with 10% $KHCO_3$ solution, and this extract was neutralized with hydrochloric acid and extracted extensively with ether ("basic extract"). The mother liquor (now DMSO-free) and the two extracts were dried separately (Na_2SO_4); the solvent was removed under reduced pressure.

The mother liquor gave, after recrystallization from methanol, 30.6 mg of starting material, mmp 72–76°, infrared spectra and R_f identical.

The basic extract yielded, after recrystallization from methanol, 278 mg of β-keto ester **5**: mp 98–101°; $[\alpha]_D$ +80.5° (*c* 0.1, EtOH); ir (KBr) 5.73, 5.77, 6.05 μ; R_f^{BE} 0.05 (silica). The acid fraction yielded in the same manner 65 mg of β-keto ester (total yield, 62%).

***A*-Nor-5α-androstan-17β-ol-2-one (6a).**—To a solution of 30 mg (0.077 mmol) of the β-keto ester **5** in 50 ml of a saturated solution of Na_2CO_3 in methanol was added 10 ml of water and the solution was stirred for 15 hr, then acidified with dilute HCl, and extracted with three 100-ml portions of ether. The extract was dried (Na_2SO_4) and the solvent was removed to give an oily residue. Tlc on silica with (1:1) ether–benzene gave R_f 0.87 (product) and 0.12 (starting material). Column chromatography on silica and elution with (1:1) benzene–ether gave 20 mg (95%) of *A*-nor-5α-androstan-17β-ol-2-one (**6a**): mp 195–197° (lit.[13] mp 197°); ir (KBr) 5.78, 5.83 μ; nmr δ 0.96 (18-CH_3) and 1.23 (19-CH_3).

3α-Methyl-*A*-nor-5α-androstan-17β-ol-2-one 17-Propionate (6b).—To a solution of 62 mg (0.159 mmol) of the β-keto ester **5** in the minimum amount of anhydrous benzene was added 5.0 mg (0.20 mmol) (Nujol dispersion) of sodium hydride and the mixture was stirred 2 hr at room temperature until hydrogen evolution ceased. Then 312 mg (2.2 mmol) of methyl iodide was added and the solution was stirred at room temperature for 9 hr and at 40° for 5 hr. Then 1 ml of methanol was added slowly followed by 5 mg of *p*-toluenesulfonic acid in 10 ml of acetic acid and 5 ml of water, and the resulting mixture was stirred at 60° for 9 hr. After cooling, the aqueous layer was removed and extracted with ether, and the extract was added to the organic layer. This solution was then evaporated under reduced pressure, the residue was taken up in ether, and this solution was washed with saturated Na_2CO_3 solution and with water, and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was recrystallized from methanol and gave 30.5 mg (55%) in two crops: mp 169.5–171°; ir (KBr) 5.78 and 5.82 μ; $[\alpha]_D$ +38.8° (*c* 0.01, EtOH); nmr δ 0.76 (C-3 CH_3), 0.87 (C-18 CH_3), and 1.13 (C-19 CH_3); R_f 0.76 (ether–methanol).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 75.88; H, 9.64.

Registry No.—**3a**, 521-18-6; **4a**, 26686-22-6; **4b**, 26686-23-7; **5**, 26731-53-3; **6a**, 1032-10-6; **6b**, 26686-25-9.

Steroidal Adducts. III.[1,2] Novel Dehydrogenations of Steroids *via* Ene Adducts with Tetracyanoethylene

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Received June 10, 1970

Tetracyanoethylene reacts with the steroidal ring-B dienes, ergosteryl acetate and 9(11)-dehydroergosteryl acetate, to give principally products of ene reactions. A by-product of both reactions is assigned the cycloadduct structure **7**, chiefly from spectral data, including nmr solvent shifts, and is shown to arise from dehydrogenation reactions involving ene adducts. Other reactions between tetracyanoethylene and unsaturated steroids are also discussed.

Tetracyanoethylene reacts rapidly with most cisoid 1,3-dienes to give Diels–Alder adducts.[5] With dienes which cannot assume a cisoid configuration, cyclobutane derivatives are formed[6,7] by 2 + 2 addition to one of the double bonds. In a preliminary communication,[2] we reported the first instances of Alder ene reactions[8–10] between tetracyanoethylene and dienes, and recently some complementary results have been described by others.[11] We now amplify the preliminary report and describe some further reactions of tetracyanoethylene with unsaturated steroids.

Tetracyanoethylene reacts rapidly with ergosteryl acetate **1** in benzene solution to give, after an initial olive-green coloration due to a charge-transfer complex,[12] a 1:1 adduct, mp 135°, in 65% yield, as previously reported.[2] The ene adduct structure **2** was assigned to this compound, chiefly on the basis of uv and nmr data,[13–16] and by analogy with the structures of the three adducts (**3**–**5**) formed between ergosteryl acetate and acrylonitrile.[13]

The reactions of the adduct **2** are dominated by the lability of the tetracyanoethyl group. The compound is fairly stable in dry, nonprotic, neutral solvents, but loses hydrogen cyanide very readily in moist air, or with basic or protic solvents, apparently giving polymeric products. When **2** was warmed with excess dry ammonia in chloroform, a compound was obtained, which analyzed correctly for the loss of hydrogen

(1) For part II, see M. E. Birckelbaw, P. W. Le Quesne, and C. K. Wocholski, *J. Org. Chem.*, **35**, 558 (1970).

(2) Preliminary communication: A. M. Lautzenheiser and P. W. Le Quesne, *Tetrahedron Lett.*, **3**, 207 (1969).

(3) Kent State University.

(4) To whom correspondence should be addressed: University of Michigan.

(5) W. J. Middleton, R. E. Heckert, E. L. Little, and C. G. Krespan, *J. Amer. Chem. Soc.*, **80**, 2783 (1958).

(6) A. T. Blomquist and Y. C. Meinwald, *ibid.*, **79**, 5316 (1957).

(7) J. K. Williams, *ibid.*, **81**, 4013 (1959).

(8) K. Alder, F. Pascher, and A. Schmits, *Ber.*, **76B**, 27 (1943).

(9) C. Agami, M. Andrac-Taussig, C. Justin, and C. Prévost, *Bull. Soc. Chim. Fr.*, 1195 (1966).

(10) H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969).

(11) K. D. Bingham, G. D. Meakins, and J. Wicha, *J. Chem. Soc. C*, 671 (1969).

(12) *Cf.* C. A. Stewart, Jr., *J. Org. Chem.*, **28**, 3320 (1963).

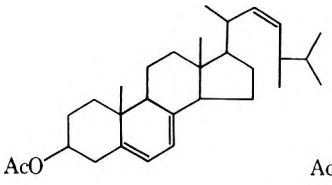
(13) D. N. Jones, P. F. Greenhalgh, and I. Thomas, *Tetrahedron*, **24**, 5215 (1968).

(14) A. van der Gen, J. Lakeman, U. K. Pandit, and H. O. Huisman, *ibid.*, **21**, 3641 (1965).

(15) N. S. Bhacca and D. H. Williams, "Applications of N.M.R. Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 19 ff.

(16) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

cyanide from 2. The chemistry of this reaction is under study and will be reported later.



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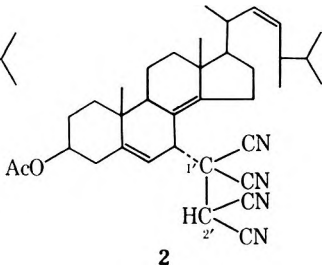

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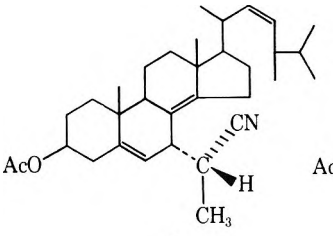

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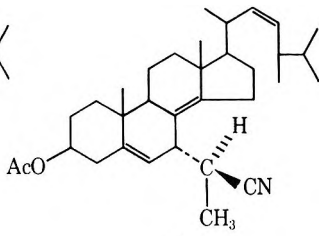

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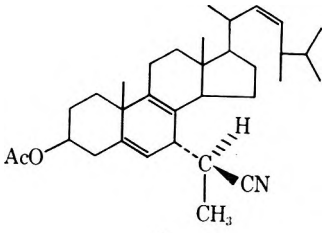
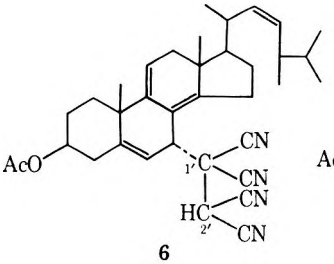
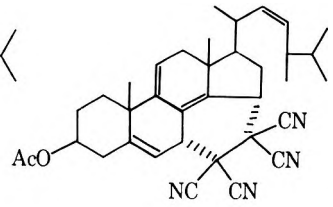


5

In an analogous reaction to that leading to 2, 9(11)-dehydroergosteryl acetate with tetracyanoethylene gives the ene adduct 6, mp 125°, in 29% yield, as reported previously.[2]



6



7

The mother liquors from the reaction of tetracyanoethylene with ergosteryl acetate 1 gave no $\Delta^{8(9)}$ compound analogous to 5, which might have arisen from an ene reaction involving the 9α proton of the steroid. There were obtained, however, a new compound, mp 212°, in 1.5% yield, and small quantities of tetracyanoethane. The compound of mp 212° was also obtained, in up to 25% yield, from the mother liquors of the reaction between tetracyanoethylene and 9(11)-dehydroergosteryl acetate after removal of the ene adduct 6. When this reaction was carried out in nitromethane–chloroform solution, no adduct 6 was obtained, but the yield of the compound of mp 212° was increased to 39%. The structure 7 is assigned to this compound from spectroscopic data and the reactions described below. Microanalyses did not conclusively distinguish between the formulas $C_{36}H_{44}N_4O_2$ (mol wt 564) and $C_{36}H_{42}N_4O_2$ (mol wt 562), but the latter was established by mass spectroscopy.

Although 7 slowly decomposes under polar, acidic, or basic conditions, it is much less labile than the ene adducts 2 and 6. This fact, and the absence from the nmr spectrum of any signals due to isolated $-CH(CN)_2$ protons, eliminated ene adduct structures from consideration and showed that 7 is a cycloaddition product. The nmr spectrum of 7 shows signals from four vinyl protons. A 2 H multiplet at τ 4.85 was assigned to the side-chain unsaturation, in good accord with the nmr spectra of other ergosterol derivatives. The two remaining vinyl protons appear at τ 4.36 as a one-proton singlet and a one-proton doublet superimposed to give a broadened single peak A Dreiding model of structure 7 shows that the C-6 and C-7β protons have a dihedral angle of almost 90°, and that the C-11 proton has a dihedral angle of almost 90° with the C-12α proton, and one of *ca.* 30° with the C-12β proton. Thus the shape of the τ 4.36 signal is reasonable for the C-6 and C-11 protons, if virtually coincident chemical shifts for these protons are assumed. Upfield from the vinyl proton signals are three groups of signals for the seven methine protons of 7. A broad one-proton signal at τ 5.30 was assigned to the C-3α proton, a broad two-proton peak at τ 6.68 to the C-7β and C-15β protons, and a broad four-proton group of superimposed signals at τ 7.34–7.55 to the C-17, C-20, C-24, and C-25 protons. The appearance of this latter signal is consistent with the observed splitting (5–6 Hz) of the side-chain methyl signals between τ 8.92 and 9.18. Signals from 13 protons appear between τ 7.9 and 8.9. Structure 7 contains eight allylic and six nonallylic ring methylene protons. The lower field group of these, near the acetate methyl signal at τ 7.95, integrated for *ca.* seven protons, and the higher field group, between the acetate and side-chain methyls, for *ca.* six protons, consonant with structure 7. The C-19 and C-18 methyl signals appear at τ 8.78 and 8.98. The values calculated[16] for structure 7 without the tetracyanoethano bridge are τ 8.94 and 9.19, respectively, which implies that the bridging group exerts a similar considerable deshielding effect on each angular methyl group. This also is consistent with structure 7.

All the signals except those for the vinyl protons and the C-3α proton are shifted upfield when the nmr spectrum is taken in benzene solution. The greatest shielding effect was observed for the C-7β and C-15β protons. This is in accord with their closeness to the nitrile functions, which are expected to be strongly solvated by benzene.[17] The shifts are listed in Table I. In a similar

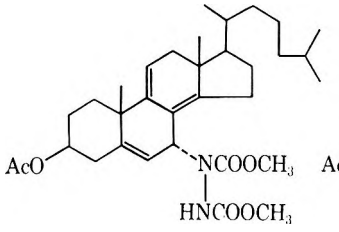
TABLE I
NMR SOLVENT SHIFTS FOR ADDUCT 7

Proton attached to	τC_6H_6	$\tau CDCl_3$	$\tau C_6H_6-CDCl_3$
C-6,11	4.15	4.36	−0.21
C-22,23	4.78	4.68	+0.10
C-3α	5.30	5.30	0.00
C-7β, C-15β	7.35	6.68	+0.67
C-17, C-20	7.70	7.34	+0.36
C-24, C-25	7.84	7.48	+0.32
	7.38	7.55	+0.33
CH_3COO-	8.22	7.95	+0.27
Ring $-CH_2$'s	7.9–8.9	7.7–8.7	+0.20
C-19	9.14	8.78	+0.36
C-18	9.32	8.98	+0.34

(17) Reference 15, pp 161 ff; compare also R. C. Fort, Jr., and T. R. Lindstrom, *Tetrahedron*, **23**, 3227 (1966).

way, the spectrum of adduct **2** in benzene solution shows large upfield shifts for protons adjacent to the nitrile groups; the C-2′ proton is shifted upfield by 1.57 ppm from chloroform to benzene solution, and the C-6 proton is shifted upfield by 0.50 ppm.

The uv spectrum of **7** shows a solvent-invariant maximum at 284 nm (ϵ 8550), which verified the presence of a homoannular diene. Although **7** is calculated from the Woodward–Fieser rules[18] to have λ_{max} 293 nm, the ene adduct **6**, which contains the same array of double bonds as **7**, has λ_{max} 280 nm (ϵ 6550),[2] and the analogous adduct **8** has λ_{max} 283 nm (ϵ 4200).[19]



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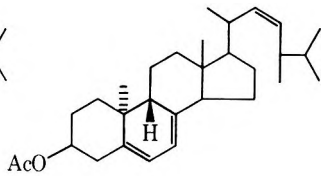
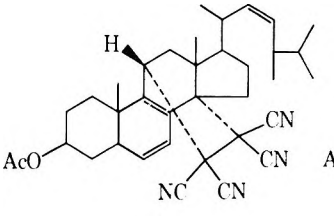


9

The widely invoked "rule of rear attack" suggests that the bulky tetracyanoethylene would approach the steroid nucleus from the α face in most reactions; this has been established for the ene reactions of ring B dienes already described,[2] and is implicit in structure **7**. Some support for this suggested stereochemistry is given by the observations that **7** was unreactive to maleic anhydride or to further treatment with tetracyanoethylene. Models show that ring C is shielded to the approach of dienophiles, by the angular methyl groups on the β face, and by the tetracyanoethano bridge on the α face, of the molecule. The unreactivity of lumisteryl acetate **9** toward tetracyanoethylene[11] is similarly explained. Also, in the present work, compounds **10** and **11**[20] [prepared by reaction of tetracyanoethylene and maleic anhydride, respectively, with 3β-acetoxyergosta-6,8(14),9(11), 22-tetraene[20]] were unreactive to dienophiles.



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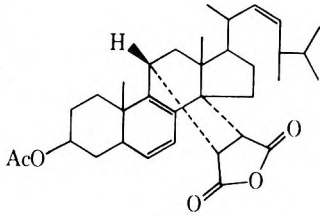
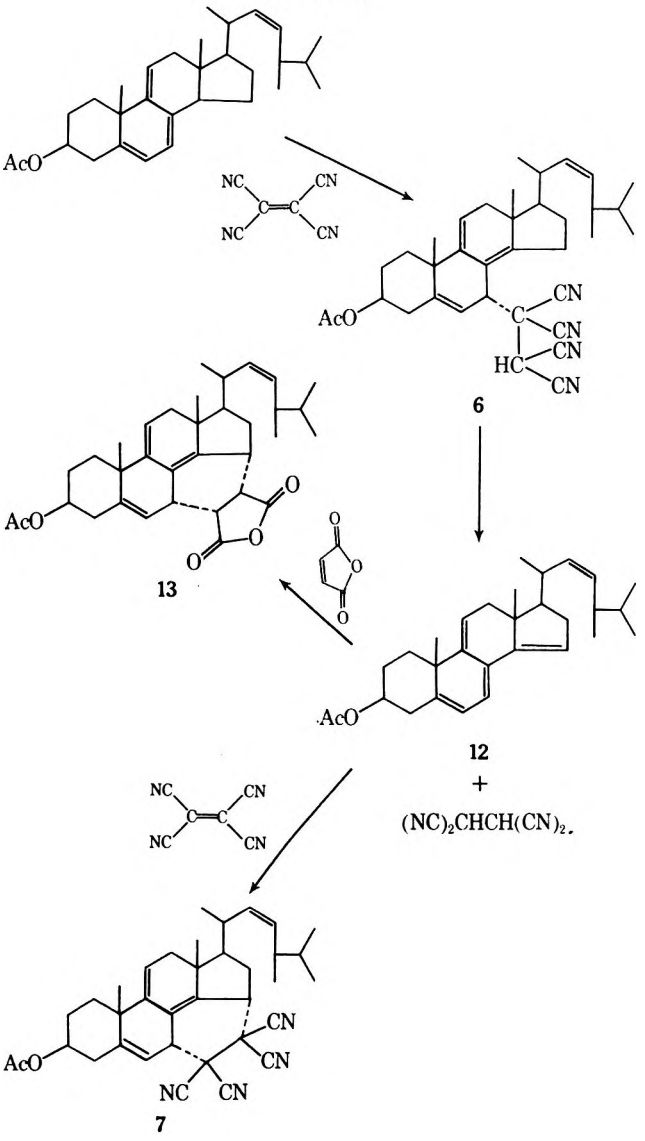


11

A suggested sequence of reactions leading to **7** from 9(11)-dehydroergosteryl acetate is outlined in Scheme I.

Elimination of tetracyanoethane from the ene adduct **6** in this scheme gives the reactive pentaene **12**, which with further tetracyanoethylene gives **7**. The pentaene **12** was not isolated in our work but was trapped by reaction of the ene adduct **6** with maleic anhydride in chloroform–nitromethane to give an adduct, mp 207°, $C_{34}H_{44}O_5$, whose spectral characteristics are fully in accord with structure **13**.

SCHEME I



This is to our knowledge the first report of elimination of tetracyanoethane from an isolated tetracyanoethylene ene adduct. This reaction formally resembles the pyrolysis of the adduct **14**, to 1,2-dicarboethoxyhydrazine and cholestatriene derivatives.[21] Tetracyanoethylene has, however, been known to aromatize 1,4-dihydrobenzenes.[22] The formation of small amounts of **7** from ergosteryl acetate and tetracyanoethylene could be explained in three different ways. First, the ergosteryl acetate may have been contaminated by small quantities of the 9(11)-dehydro compound; secondly, dehydrogenation could have occurred by radical abstraction of the 9α and 11α hydrogens by tetracyanoethylene; or thirdly, a $\Delta^{8(9)}$ ene adduct with tetracyanoethylene analogous to **5** may have been formed, which then gave tetracyanoethane and 9,(11)-dehydroergosteryl acetate in a manner analogous to the reactions shown in Scheme I (*cf.* dehydrogenation of steroids by mercuric acetate[23]). Spectral examination of the ergosteryl ace-

(18) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 17.

(19) A. van der Gen, W. A. Zunnebeld, U. K. Pandit, and H. O. Huisman, *Tetrahedron*, **21**, 3651 (1965).

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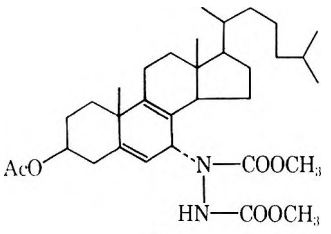
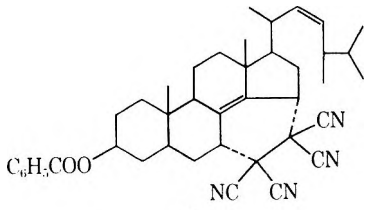
tate used indicated that it was uncontaminated by the 9(11)-dehydro compound, which suggests that either of the two latter possibilities is feasible. We have observed no $\Delta^{8(9)}$-ene adduct to be formed in the reaction between ergosteryl acetate and tetracyanoethylene, but as yet cannot distinguish between the latter two possibilities.

The rapid reaction between the $\Delta^{7(14)}$-diene ergosteryl-B_3 benzoate (3β-benzoyloxyergosta-7,14,22-triene) and tetracyanoethylene has already been reported;[2] the sole product was the Diels–Alder adduct **15**.



14



15

The mass spectra of these adducts, which will be discussed in detail in a later publication, are of considerable interest. The Diels–Alder adducts on electron impact in general undergo retro-Diels–Alder reactions, and the subsequent fragmentations of the diene portions are usually strikingly similar to those of the dienes themselves. The ene adducts undergo retro-ene reactions, in which the fragmentations after the loss of tetracyanoethylene are again similar to those of the parent steroids. The mass spectral retro-ene reaction may be regarded as an analog of the well-known McLafferty rearrangement.[24]

Tetracyanoethylene did not react with 3β-benzoyloxyergosta-7,22-diene or with the transoid diene 3β-benzoyloxyergosta-7,9(11)22-triene, under the conditions used in the ene reactions described above. Further investigations of the mechanisms of the reactions described in this paper, and of reactions of tetracyanoethylene with other unsaturated steroids, are in progress.

Experimental Section

Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Melting points were determined on a Thomas–Hoover capillary apparatus and are uncorrected. Optical rotations were measured in a 0.1-dm cell with a Bendix–Ericsson automatic polarimeter, and nmr spectra with Varian A-60 or HA-100 spectrometers in deuteriochloroform solution unless otherwise specified, using tetramethylsilane as internal reference. Infrared spectra were taken with a Perkin-Elmer 237 spectrophotometer, ultraviolet spectra with a Perkin-Elmer 202 spectrophotometer, and mass spectra with an AEI MS-12 spectrometer.

Reaction of Ergosteryl Acetate 1 with Tetracyanoethylene in Benzene.—Ergosteryl acetate **1** (11.7 g, 0.027 mol) was dissolved in sodium-dried benzene (75 ml) with gentle warming, and tetracyanoethylene (white crystals, 3.45 g, 0.027 mol, Aldrich Chemical Co.) was added gradually to the cooled solution. The olive-green coloration initially observed rapidly changed to light amber. Dry heptane (75 ml) was then added, and the mixture concentrated to 50 ml under reduced pressure at 25°. The large pink crystals gradually deposited (*ca.* 9.6 g, 65%) had mp 112–118° but were the substantially pure (by ir) ene adduct. Repeated crystallizations of this material from benzene–heptane gave an analytical sample of 3β-acetoxy-7α-(1′,1′,2′,2′-tetracyanoethyl)ergosta-5,8(14),22-triene (**2**) as rosettes of needles: mp 135° dec; $[\alpha]^{23}D$ −170° (*c* 1.0, $CHCl_3$); uv $\lambda_{max}^{cyclohexane}$ 213 nm (ε 8080); nmr τ 4.80–4.92 (3 H, m, C-6, 22, 23 H's), 5.43 (1 H, H-2′), ~5.45 (1 H, m, C-3α H), 6.42 (1 H, d, J = 4 Hz, C-7 H), 7.98 (3 H, s, C-3 CH_3COO–), 9.05 (6 H, s, C-18 and C-19 CH_3's). *Anal.* Calcd for $C_{36}H_{46}N_4O_2$: C, 76.29; H, 8.18; N, 9.89. Found: C, 76.19, 76.28; H, 8.08, 8.21; N, 9.89, 9.86.

A minor by-product from the recrystallization of this compound was tetracyanoethane (91.4 mg, 2.6%), mp 187–188°, of identical infrared spectrum with an authentic sample kindly provided by Dr. D. T. Longone.

The mother liquors after the removal of the adduct **2** yielded **7** (0.13 g), mp 196°, of virtually identical ir spectrum with that obtained from 9(11)-dehydroergosteryl acetate (below). Repeated crystallization from toluene–heptane gave an analytical sample of 3β-acetoxy-7α,15α-tetracyanoethanoergosta-6,8(14),-9(11),22-tetraene (**7**) as fine needles: mp 212° dec; $[\alpha]^{25}D$ −236° (*c* 1.0, $CHCl_3$); uv $\lambda_{max}^{cyclohexane}$ 284 nm (ε 8500); nmr cited in full in text. *Anal.* Calcd for $C_{36}H_{42}N_4O_2$: C, 76.83; H, 7.52; N, 9.96. Calcd for $C_{36}H_{44}N_4O_2$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.76; H, 7.69; N, 10.02.

Reaction of Tetracyanoethylene with 9(11)-Dehydroergosteryl Acetate. A. In Benzene.—A solution of tetracyanoethylene (386 mg, 0.003 mol) in dry benzene (25 ml) was added dropwise to a stirred solution of 9(11)-dehydroergosteryl acetate[25] (1.315 g, 0.003 mol) in dry benzene (10 ml) at 5° under nitrogen. The initially green solution turned yellow, and after 4 hr the solution was concentrated under reduced pressure and crystallization induced by addition of heptane and setting aside at 5°. Crude yields of products ranged from 50 to 75%; the first compound obtained in the fractional crystallization was the ene adduct **6**, 3β-acetoxy-7α-(1′,1′,2′,2′-tetracyanoethyl)ergosta-5,8(14),9(11),-22-tetraene, an analytical sample of which crystallized as needles from benzene–heptane: mp 125–126°; $[\alpha]^{25}D$ −99° (*c* 1.0, $CHCl_3$); uv $\lambda_{max}^{cyclohexane}$ 280 nm (ε 6550); nmr τ 4.39 (1 H, m, C-11 H), 4.68 (1 H, d, J = 2.5 Hz, C-6 H), 4.87 (2 H, m, C-22, 23 H's), 5.41 (1 H, *m*, C-3α H), 5.33 (1 H, s, C-2′ H), 6.33 (1 H, d, J = 2.5 Hz, C-7 H), 7.99 (3 H, s, CH_3COO–), 8.73 (3 H, s, C-18 CH_3), 9.17 (3 H, s, C-19 CH_3). *Anal.* Calcd for $C_{36}H_{44}N_4O_2$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.46; H, 7.91; N, 10.01. This compound was obtained pure in 29% yield. The mother liquors after removal of the adduct **6** yielded adduct **7** in variable (4–25%) yield. Relatively greater yields of **7** were obtained from reactions which appeared to contain traces of water and which gave a lower yield of the ene adduct **6**. The adduct **7** obtained from these reactions was identical in all respects with that obtained from the reaction of tetracyanoethylene with ergosteryl acetate (see above).

B. In Nitromethane–Chloroform.—A solution of 9(11)-dehydroergosteryl acetate (4.85 g, 0.011 mol) in dry chloroform (30 ml) was diluted with dry nitromethane (90 ml) and stirred in an ice bath. A suspension of tetracyanoethylene (1.42 g, 0.011 mol) in chloroform (50 ml) was added dropwise, and the residue rinsed through the dropping funnel with further nitromethane (10 ml). The green color initially observed changed to amber within 25 min, and after 1 hr the solvent was removed under reduced pressure at 20° and replaced by anhydrous ether. Adduct **7** crystallized in several crops of needles, mp 211–212° (total 2.48 g, 39%), identical with that obtained previously. The last two of five crops were obtained after addition of 30–60° light petroleum and standing at 5°. Concentration of the mother liquors, further standing at 5°, and final addition of a little methanol gradually returned the crystalline starting steroid (1.11 g, 23%). None of the ene adduct **6** was obtained.

Synthesis of Adduct 7 from Adduct 6 and Tetracyanoethylene.—Adduct **6** (924 mg, 1.64 mmol) and tetracyanoethylene (219 mg, 1.71 mmol) were stirred in solution in chloroform–nitromethane at 0° for 0.5 hr and at 20° for 1 hr. Removal of solvent under reduced pressure and addition of chloroform precipitated

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tetracyanoethane (63 mg, 29%), identified by ir comparison with authentic material. Replacement of the chloroform by ether–heptane gave crystalline adduct **7**, mp 210–211° (518 mg, 56%), identical with material obtained above.

Reaction of Adduct 6 with Maleic Anhydride in Nitromethane–Chloroform.—The adduct (718 mg) and maleic anhydride (155 mg, 20% excess) were dissolved in chloroform (5 ml) and nitromethane (5 ml) and kept at 55° for 3 hr and then at 0° overnight. Solvents were removed under reduced pressure, and chloroform was added to precipitate tetracyanoethane (106 mg, 64%), identified by ir comparison with authentic material. The chloroform was replaced by methanol, which caused crystallization of slightly impure 3β-acetoxy-7α,15α-ethanoergosta-5,8(14),9(11),-22-tetraene-1′,2′-dicarboxylic acid anhydride (**13**), mp 194–200° (orange melt) (465 mg, 69%). Recrystallization from chloroform–methanol or benzene–heptane gave an analytical sample as feathery needles of the same melting point in air, but mp (evacuated tube) 207–208° (colorless melt); $[\alpha]^{23}D$ −70° (c 1.0, $CHCl_3$); uv $\lambda_{max}^{CHCl_3}$ 280 nm (ε 4360); ir ($CHCl_3$) 1840, 1780 (anhydride C=O), 1725 (acetate −C=O) cm^{-1}; nmr τ 4.49 (1 H, m, C-11 H), 4.68 (1 H, m, C-6 H), 4.82 (2 H, m, C-22, 23 H), 5.42 (1 H, m, C-3α H), 6.68 (2 H, m, C-7β,15β H), ~7.2 (2 H, m, C-1′,2′ H), 8.05 (3 H, s, CH_3COO–), 8.89 (3 H, s, C-19 CH_3), 9.18 (3 H, s, C-18 CH_3). *Anal.* Calcd for $C_{34}H_{44}O_5$: C, 76.66; H, 8.33. Found: C, 76.74; H, 8.39.

Reaction of Tetracyanoethylene with Ergosteryl-B_3 Benzoate (3β-Benzoyloxyergosta-7,14,22-triene).—To a stirred solution of tetracyanoethylene (100 mg) in dry benzene (3 ml), ergosteryl-B_3 benzoate[26] was added in small portions. Each addition caused an immediate lightening of the yellow color of the solution, which became colorless after the addition of 497 mg of the steroid. The solution was then heated to boiling, diluted with dry heptane (5 ml), and let cool. The crystalline product (422 mg, mp 211–212°, 86%) was recrystallized once for analysis to give fine needles of **15**, 3β-benzoyloxy-7α,15α-tetracyanoethanoergosta-8(14),22-diene: mp 212°; $[\alpha]^{25}D$ −93° (c 1.0, $CHCl_3$); uv $\lambda_{max}^{cyclohexane}$ 229 nm (ε 16,800, benzoate); nmr τ 2.3 (5 H, m, C_6H_5-COO), 4.75 (2 H, m, C-22,23 H), ~5.2 (1 H, m, C-3α H), 9.00 (3 H, s, C-18 CH_3), 9.17 (3 H, s, C-19 CH_3). *Anal.* Calcd for $C_{41}H_{48}N_4O_2$: C, 78.31; H, 7.69; N, 8.91. Found: C, 78.37; H, 7.54; N, 8.88.

Diels–Alder Adducts of 3β-Acetoxyergosta-6,8(14),9(11)-22-tetraene. 1. With Tetracyanoethylene.—A solution of 3β-acetoxyergosta-6,8(14),9(11)-22-tetraene[20] (323 mg, 0.74 mmol) and tetracyanoethylene (112 mg, 0.88 mmol) in benzene was held at 20° for 12 hr. Solvent was removed under reduced pressure; the residue was triturated with chloroform and unreacted tetracyanoethylene filtered off. The chloroform-soluble fraction was recrystallized from benzene–heptane to give the adduct, mp 207–208° (290 mg, 69%). One recrystallization from ethyl acetate gave an analytical sample of the adduct **10**, 3β-acetoxy-11α,14α-tetracyanoethanoergosta-6,8(9),22-triene, as needles: mp 210–211°; $[\alpha]^{23}D$ −82° (c 1.0, $CHCl_3$); uv $\lambda_{max}^{Et_2O}$ 280 nm (ε 5300); nmr τ 3.97, 4.30 (2 H, AB quartet, J_{AB} = 9 Hz, C-6, 7 H), 4.74 (2 H, m, C-22,23 H), 5.25 (1 H, m, C-3α H), 7.98 (3 H, s, CH_3COO–), 9.03 (3 H, s, C-19 CH_3), 9.20 (3 H, s, C-18 CH_3). *Anal.* Calcd for $C_{36}H_{44}N_4O_2$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.48; H, 7.88; N, 9.88.

2. **With Maleic Anhydride.**—The adduct **11**, 3β-acetoxy-11α,-14α-ethanoergosta-6,8(9)22-triene-1′,2′-dicarboxylic acid anhydride, had the physical constants described in ref 20. In addition, nmr τ 4.13, 4.60 (2 H, AB_q, J_{AB} = 9 Hz, C-6, 7 H), 4.75 (2 H, m, C-22, 23 H), 5.25 (1 H, m, C-3α H), 8.02 (3 H, s, CH_3COO–), 9.14 (3 H, s, C-19 CH_3), 9.33 (3 H, s, C-18 CH_3).

Both of these adducts were inert to tetracyanoethylene or maleic anhydride in refluxing benzene or refluxing 1,2-dichloroethane, pure starting materials being recovered in good yields from attempted reactions.

Attempted Reactions of Tetracyanoethylene with 3β-Benzoyloxyergost-7-ene and 3β-Benzoyloxyergosta-7,9(11)-diene.—Tetracyanoethylene (9 mg, 0.070 mmol) was dissolved in a solution of 3β-benzoyloxyergost-7-ene[27] [38 mg, 0.075 mmol in benzene (5 ml)] and the solution heated under reflux for 1 hr and then held at 20° for 12 hr. Solvent was removed under reduced pressure, chloroform added, and tetracyanoethylene filtered off. The chloroform soluble fraction crystallized on addition of heptane and was identified as the starting steroid (13 mg, 33%), identified by melting point (179°) and ir. No other steroidal derivatives were detected.

Similar experiments were performed with 3β-benzoyloxyergosta-7,9(11)-diene[28] as steroidal substrate, and with refluxing benzene or chloroform–nitromethane at 0° as solvents. Reactions were monitored by ir and nmr. No reaction products could be detected. Pure starting materials were recovered.

Registry No.—Tetracyanoethylene, 670-54-2; **2**, 21549-35-9; **6**, 21549-36-0; **7**, 26885-77-8; **10**, 26929-70-4; **11**, 26885-78-9; **13**, 26885-79-0; **15**, 21549-37-1.

Acknowledgments.—We gratefully acknowledge valuable discussions with Professors Ernest Wenkert, Daniel T. Longone, and Mark M. Green, and the assistance of Miss Mary Birckelbaw and Mr. Jack Eyman with some spectral data. We thank the American Cancer Society for partial support of this work through institutional research grants to The University of Michigan, and the National Science Foundation for funds to purchase the mass spectrometer at Kent State University.

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On the Mechanism and Chirality of Enol and Ketophosphonium Salt Formation from the Reactions of α-Halo Ketones or α,α-Dihalo Ketones with Tertiary Phosphines[1]

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Received June 8, 1970

α-Bromacetophenones, which are further substituted at the α position by bromine or phenyl, react with triphenylphosphine to give isolable enol phosphonium halides. *dl*-Methylpropylphenylphosphine (MPPP) reacts with unhindered α-haloacetophenones to give ketophosphonium salts and with several α,α-dihaloacetophenones or hindered α-haloacetophenones to give enol phosphonium salts. In several cases wherein an α-bromo or α-chloro ketone gives an enol phosphonium salt, the corresponding α-mesyloxy ketone gives the ketophosphonium salt. The reactions of optically active MPPP with α-halopropiophenones, α-chlorobenzyl phenyl ketone, or the corresponding α-mesyloxy ketones, give ketophosphonium salts with *retention* of configuration at phosphorus. The proof of stereochemistry includes base hydrolysis of several of the phosphonium salts to methylpropylphenylphosphine oxide (known to generally occur with inversion at phosphorus) and the Wittig reaction of a derived keto ylide (known to occur with retention at phosphorus). The reaction of α,α-dibromo-α-phenylacetophenone with MPPP to form an enol phosphonium salt occurs with *inversion* of configuration at phosphorus. This is proven by the conversion of the enol phosphonium salt to several products of known chirality in the MPPP series. The basic hydrolysis of enol phosphonium salts is shown to occur by reaction at phosphorus by the use of oxygen-18-labeled sodium hydroxide. The data indicate that ketophosphonium halides are formed by SN2-type displacement of halide ion by a tertiary phosphine. It suggests that enol phosphonium halides are formed *via* enolate halophosphonium intermediates which occur by attack of the phosphine on halogen.

Our previous papers in this series have described the following reactions of triphenylphosphine (TPP) with α-halo ketones. α-Haloacetophenones,[3] α-halopropiophenones,[4] and α-halobenzyl phenyl ketones[5] react with TPP to give α-ketophosphonium salts. α-Bromocyclohexanone gives α- and β-ketophosphonium salts,[4] and α-halo- or α-mesyloxyisobutyrophenone give only β-ketophosphonium salts.[6] The β-ketophosphonium salts occur *via* elimination to the α,β-unsaturated ketone followed by Michael addition of TPP to the β position of the protonated enone.[6] The mechanism of α-ketophosphonium salt formation will be discussed later in this paper.

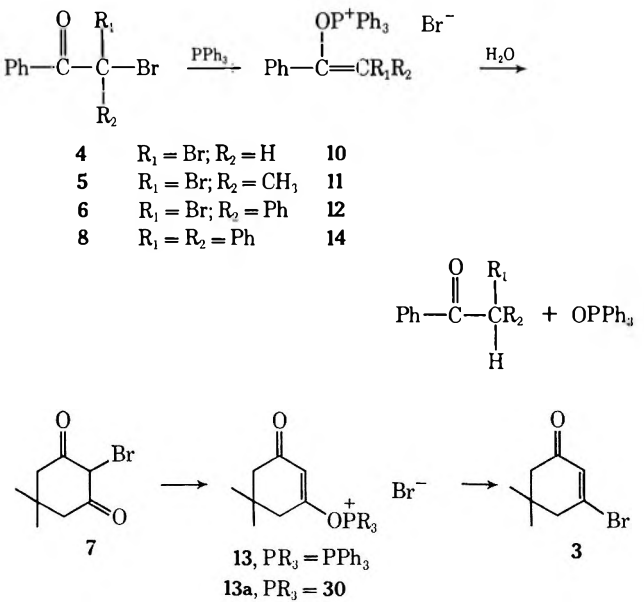
There has also been data on the structural features required for enol phosphonium salt formation. These species have been isolated from the reactions of TPP with α-chloro-α,α-diphenylacetophenone,[7] several α,α-dihalo ketones,[8] and, more recently, from α-bromobenzyl phenyl ketone (**1**) and α-chlorobenzyl phenyl ketone (**2**).[5] They have also been implicated in the reactions of TPP with polyhalo ketones, 2-halo-1,3-diketones,[4,9,10] and in some other cases.[4,10,11]

We now report the isolation of a number of new enol phosphonium salts derived from TPP or from methyl-*n*-propylphenylphosphine (MPPP) and some observations relevant to the pathways involved in their formation. The chirality of the conversions of optically active MPPP to α-keto- or enol phosphonium salts, which allow more rigorous mechanistic conclusions, is also discussed.

Results and Discussion

Enol Triphenylphosphonium Salts.—The reactions of TPP with various α-haloacetophenones and with several other species are presented in Scheme I. It is

SCHEME I



concluded that the presence of a second α-halogen or an α-phenyl group is sufficient to cause enol phosphonium salt formation. 2-Bromodimedone (**7**) reacts rapidly to give 5,5-dimethyl-3-bromocyclohexenone (**3**), presumably *via* **13**.[4]

The acyclic enol phosphonium halides are isolable solids which can be stored for some time under anhydrous conditions. They are readily hydrolyzed by water or aqueous base in solution, however, to give the corresponding ketone and triphenylphosphine oxide (TPPO). We have now shown that the base hydrolysis of enol phosphonium salts proceeds by attack of hy-

(1) This investigation was supported by National Science Foundation Grants No. 5978 and 8676. This is part XI of the series, Organophosphorus Chemistry.

(2) To whom correspondence should be addressed.

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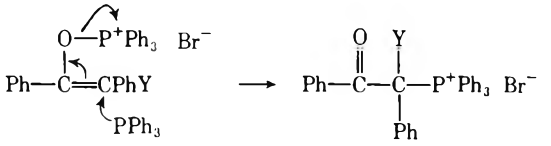
droxide ion at phosphorus (see below). Treatment of **12** with TPP (1 equiv) at reflux in xylene gave only TPPO, probably formed upon hydrolysis of **12** during work-up. Thus the rearrangement of an enol phosphonium salt to a ketophosphonium salt does not occur in this system. We have previously demonstrated the recovery of the enol phosphonium salt from α-chlorobenzyl phenyl ketone under similar conditions.[5] The rearrangement of an enol to a ketophosphonium salt could have occurred as shown (Scheme II).

SCHEME II



Y = Br, Cl, Ph, H

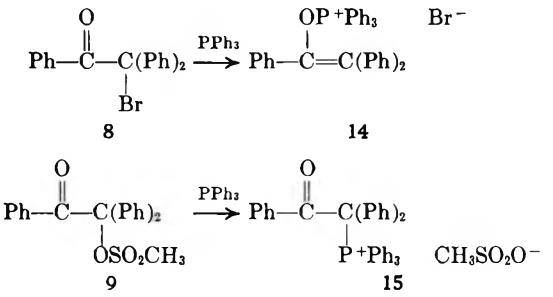
Proton nmr spectral data for **10**–**14** are given in the Experimental Section. Although previous workers[7,8,10] have reported ^{31}P nmr data for several enol phosphonium salts, we were not able to get satisfactory spectra for our compounds.[12]

The geometric isomerism of the enol phosphonium salts formed remains an unsolved problem which is currently under investigation.

The reaction of dibromo ketones, such as **4**, to give the enol phosphonium bromide, followed by hydrolysis to α-bromoacetophenone, constitutes a mild method for the conversion of α,α-dibromo ketones to α-monobromo ketones. Several examples are given in the Experimental Section.

The Reactions of α-Mesyloxy Ketones with Phosphines.—In contrast to **8**, which gives the enol phosphonium salt **14**, the α-mesyloxy ketone **9** reacts with TPP to give the α-ketophosphonium mesylate **15** (Scheme III). The keto- and enol phosphonium salts **14**

SCHEME III

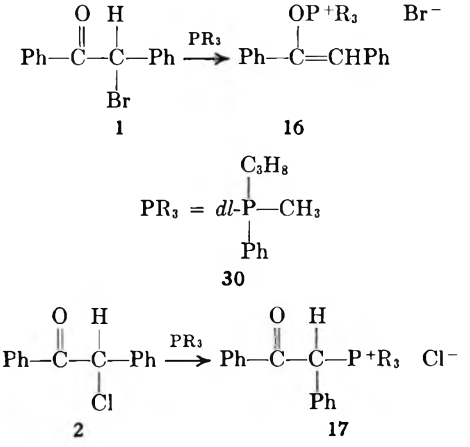


and **15** were shown to be stable to further reaction with TPP (see Experimental Section); *i.e.*, they do not interconvert.

This tendency of an α-mesyloxy ketone to give the α-ketophosphonium salt, even when the corresponding α-bromo or α-chloro ketone gives an enol phosphonium salt, has been previously noted and discussed by us in the benzyl phenyl ketone series.[5] It appears to be generally true that primary and secondary α-mesyloxy ketones react with TPP to form ketophosphonium mesylates. These reaction systems avoid the complications found with some α-halo ketones: dehalogenation and enol phosphonium salt formation. Tertiary α-mesyloxy ketones give either α-ketophosphonium salts, as does **9**, or β-ketophosphonium salts, as does the isobutyrophenone system. Further examples of the reactions of α-mesyloxy ketones (for general syntheses, see ref 24) with TPP and with *dl*-methyl-*n*-propylphenylphosphine (MPPP) are given in Table I.

The Reactions of *dl*-MPPP with α-Halo Ketones.—The recent and elegant work of Mislow and Horner has provided a simplified route to optically active phosphines such as MPPP **30**.[13] Since we wished to utilize **30** in determining the chirality of the formation of enol and ketophosphonium salts, we initially investigated its reactions with various α-halo ketones and related species. The data thus obtained are summarized in Tables I and II. We conclude that **30** behaves reasonably similarly to TPP so that stereochemical and mechanistic results obtained with the former phosphine will probably be valid for the latter. The major difference noted is the tendency for **30** to form enol phosphonium salts in some cases where TPP does not. Thus α-bromoisobutyrophenone forms an enol phosphonium salt with **30** while it undergoes dehydrobromination with TPP as already mentioned. The reactions of α-bromobenzyl phenyl ketone **1** and α-chlorobenzyl phenyl ketone **2** with TPP have been previously shown by us to give mixtures in which enol phosphonium salts predominate at 25° in nonpolar solvents and ketophosphonium salts predominate at higher temperatures and in polar solvents.[5] The reactions with **30** are much cleaner since **1** gives only the enol phosphonium bromide **16** while **2** gives only the ketophosphonium chloride **17** (Scheme IV).

SCHEME IV



Finally, the reactions of 2,4,6-trimethyl-α-bromoacetophenone **18** and 2,4,6-trimethyl-α-mesyloxyacetophenone **19** are of interest. While the α-bromo compound leads rapidly to the enol phosphonium bromide **20**, the α-mesyloxy ketone **19** reacts much more slowly to give the ketophosphonium mesylate **21** (Scheme V). These results are in contrast to the reaction of **18** with TPP which is rather complex.[14]

(12) Attempted ^{31}P nmr spectra at 23.8 MHz were done by Mr. Hara of Jeolco on a C-60 H nmr spectrometer at Upsala College.

(13) (a) O. Korpiun, R. A. Lewis, J. Chickos, and K. Mislow, *J. Amer. Chem. Soc.*, **90**, 4842 (1968); (b) J. P. Casey, R. A. Lewis, and K. Mislow, *ibid.*, **91**, 2789 (1969); (c) L. Horner and W. D. Balzer, *Tetrahedron Lett.*, 1157 (1965).

(14) R. F. Hudson and G. Salvadori, *Helv. Chim. Acta*, **49**, 96 (1966).

TABLE I
CONVERSION OF α-MESYLOXY KETONES TO KETOPHOSPHONIUM SALTS

α-Mesyloxy ketone	Reaction conditions	Yield, %	Registry no.[a]	Properties of ketophosphonium salts: Mp, °C	Ir (CH_2Cl_2), μ	Nmr ($CDCl_3$), τ
α-Mesyloxyacetophenone	TPP, glyme, reflux, 3 days	82	26709-81-9	147–148.5	5.95 (C=O), 8.20–8.50 ($CH_3SO_2O^-$)	7.40 (s, 3, OSO_2CH_3), 4.0 (d, 2, J_{PH} = 13 Hz), 1.60–2.50 (m,, 20, phenyl H)
α-Mesyloxypropiophenone	As above	80	26709-82-0	149–151.5	5.95 (C=O), 8.1–8.5 ($CH_3SO_2O^-$)	8.1 (q, 3, CH_3, J_{PH} = 19 Hz, J_{HH} = 5.0 Hz), 7.20 (s, 3, OSO_2CH_3), 1.70–2.90 (m, 21, phenyl, methine H)
α-Mesyloxycyclohexanone	TPP, glyme, reflux, 20 days	72	14724-77-7	212.5–214	*b*	*b*
α-Mesyloxycyclododecanone	As above	87[d]	26709-84-2	Oil[c]	5.85, 8.1–8.7	
α-Mesyloxyacetophenone	MPPP	100[e]				
2,4,6-Trimethylacetophenone	MPPP, $CDCl_3$, 45°, 7 days	100[e]	26709-85-3	163–165	5.9, 7.9–8.6	7.95 (s, 3, *p*-CH_3), 7.8 (s, 6, *o*-CH_3), 7.4–9.3 (m, 7, propyl H), 7.55 (d, 3, PCH_3, J_{PH} = 13.5 Hz), 7.45 (s, 3, OSO_2CH_3), 5.1 (d, 1, J_{PH} = 13.5 Hz), 1.7–3.3 (m, 7, aryl H)
α-Mesyloxybenzyl phenyl ketone	MPPP, CH_3NO_2, reflux, 4 hr	76	26697-52-9	130–135	5.9, 8.2–8.4	8.9 (t, 3), 7.6 (d, PCH_3, J_{PH} = 14 Hz), 7.5 (d, J_{PH} = 14 Hz), 7.2 (s, 3), 6.7–8.6 (m, 4), 1.7–2.8 (m, 16, phenyl, methine H)

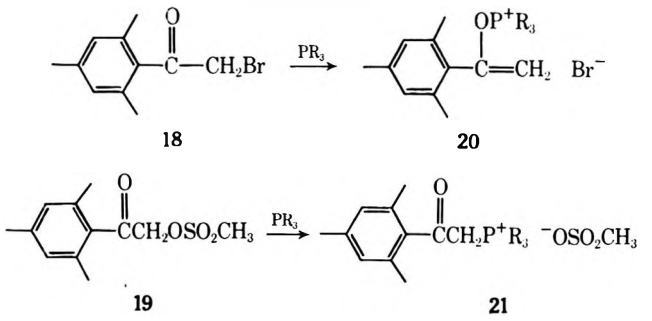
[a] The salt. [b] Previously reported.[24] [c] Purified as keto ylide. [d] Crude. [e] Nmr tube experiment.

TABLE II
REACTIONS OF METHYL-*n*-PROPYLPHENYLPHOSPHINE WITH α-HALO KETONES

α-Halo ketone	Reaction time[a]	Yields, %: Enol phos	Yields, %: Ketophos	Registry no.	Spectral data: Ir (CH_2Cl_2), μ	Spectral data: Nmr ($CDCl_3$),[b] τ
α-Bromoacetophenone	5 min	0	100[d]	26709-86-4[j]		1.6–2.9 (m, 10), 4.25 (d, 2, J_{PH} = 14 Hz)
α-Bromopropiophenone	30 min, glyme	0	94[e]	26697-53-0[j]	5.98 (C=O), 8.25, 11.0	1.3–2.7 (m, 10), 3.0–3.8 (m, 1), 8.0–8.5 (m, 3, CCH_3)
α-Chloropropiophenone	24 hr[c]	0	100[d]	26709-87-5[j]	5.95, 8.3, 11.1	
	48 hr, glyme	0	65–76[e]			
α-Bromoisobutyrophenone	6 days	100[d,f]		26709-88-6[k]	3.2–3.7, 6.9, 8.6–9.4, 9.5–10.1, 10.6–11.6	1.6–2.7 (m, 10), 8.05 (d, 3, vinyl CH_3, J_{PH} = 2.1 Hz), 8.29 (d, 3, vinyl CH_3, J_{PH} = 3.0 Hz)
α-Chloroisobutyrophenone	30 days	0[d]	0[d]			
α-Bromobenzyl phenyl ketone	5 min	100[d]	0[d]	26709-89-7[k]	3.2–3.6, 7.0, 9.0, 9.9–10.4	1.7–2.8 (m, 15), 3.25 (d, 1, vinyl H, J_{PH} = 2.8 Hz)
α-Chlorobenzyl phenyl ketone	30 min	0	100[d] 77[e]	26709-90-0[j]	6.0 (C=O), 6.3, 6.95, 7.4–7.9, 8.0–8.5, 9.0, 9.9, 10.0, 14.5	1.25–3.0 (m, 16, phenyl, methine H), 7.35 (d, PCH_3, J_{PH} = 14 Hz), 7.60 (d, PCH_3, J_{PH} = 14 Hz)
2,4,6-Trimethyl-α-bromoacetophenone	10 min	100[d,g]	0	26709-91-1[k]		1.7–3.2 (m, 7), 4.2 (s, 1, vinyl H), 5.2 (s, 1, vinyl H), 7.7 (s, 3, *p*-CH_3), 7.85 (s, 6, *o*-CH_3)
α,α-Dibromoacetophenone	5 min	100[h]	0	26709-92-2[k]	3.2–3.7, 7.0, 9.0–9.7, 9.8–10.3	1.6–2.7 (m, 10), 3.3 (d, 1, vinyl H, J_{PH} = 1.9 Hz)
α,α-Dibromopropiophenone	5 min	100	0	26709-93-3[k]	3.2–3.7, 7.0, 9.8–10.3	1.7–2.7 (m, 10), 7.47 (d, vinyl CH_3, J_{PH} = 2 Hz), 7.72 (d, vinyl H, J_{PH} = 3.2 Hz); ratio of 1:2 (vinyl isomers)
α,α-Dibromobenzyl phenyl ketone	5 min	100[d] 87[e,i]	0	26709-94-4[k]	3.2–3.5, 8.2, 8.9, 9.2–9.6, 10.3–10.6	1.65–3.1 (m, 15), 7.25 (d, PCH_3, J_{PH} = 14 Hz), 7.7 (d, PCH_3, J_{PH} = 14 Hz)

[a] All reactions at 25° in $CDCl_3$ under nitrogen unless otherwise indicated. [b] All compounds also gave τ *ca.* 7.1 (d, 3, PCH_3, J_{PH} = 14 Hz), 6.5–9.2 (m, 7, propyl H), except as noted. [c] In nitromethane. [d] Estimated yield from nmr spectrum. [e] Isolated yield. [f] Characterized by hydrolysis with D_2O to give methyl-*n*-propylphenylphosphine oxide (100%) and α-deuterioisobutyrophenone (100%). [g] Characterized by hydrolysis with H_2O (5 min) to **35** (100%) and 2,4,6-trimethylacetophenone (100%). [h] Characterized by hydrolysis to α-bromoacetophenone and **35** (100% each). [i] Characterized by hydrolysis to α-bromobenzyl phenyl ketone (98%) and **35** (96%). [j] Keto. [k] Enol.

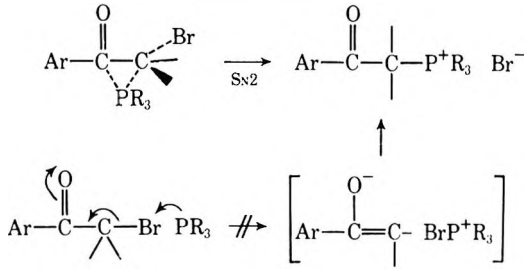
SCHEME V



In contrast to the result for TPP, α-bromodimedone **7** reacts with **30** to rapidly give the enol phosphonium bromide **13a**, which is then slowly converted to the bromo-enone **3** (see Scheme I). This may reflect the fact that methyl-*n*-propylphenylphosphine oxide is a poorer leaving group than is triphenylphosphine oxide.

We have recently argued that different mechanistic pathways are involved for the formation of keto- and enol phosphonium salts.[5] Our previous arguments are enforced by the data presented in Tables I and II. The accumulated data strongly suggest that α-ketophosphonium salts are formed by an SN2 type of displacement of halide or mesylate ion by the tricovalent phosphine. We have shown that kinetic studies of the formation of α-ketophosphonium bromides from aryl-substituted α-bromoacetophenones[3b] and α-bromopropiophenones[15] give Hammett ρ values of +0.44 and +0.67, respectively. These values are compatible with simple displacement of halide ion in these systems as found for solvolysis of α-bromoacetophenones by pyridine[15,16a] or ethanol.[16b] They are in contrast to ρ 2.6 found for attack on halogen of α,α-dihaloamides by TPP.[16c] Such data are not compelling, however, since we cannot be sure that our previously postulated mechanism involving attack on halogen (Scheme VI) would

SCHEME VI



give a ρ value that is quite different. We had argued that such a scheme should lead to a larger positive ρ value. Recent work, however, on the base-catalyzed bromination of aryl-substituted acetophenones, wherein formation of the respective enolates is rate determining, has given a ρ value of only +0.75 at 30°.[17a] We therefore felt that further evidence was needed and we have proven the SN2 pathway by the use of optically active **30** (see below.)

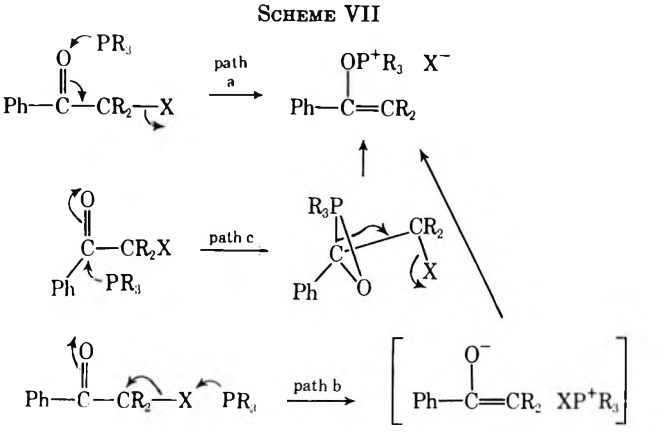
(15) H. Parnes, Ph.D. Thesis, Yeshiva University, 1970.

(16) (a) R. G. Pearson, S. H. Langer, F. V. Williams, and W. J. McGuire, *J. Amer. Chem. Soc.*, **74**, 5130 (1952); (b) D. J. Pasto, K. Garves, and M. P. Serve, *J. Org. Chem.*, **32**, 774 (1967); (c) A. J. Speziale and L. J. Taylor, *ibid.*, **31**, 2450 (1966).

(17) (a) D. N. Nanda, P. L. Nayak, and M. K. Rout, *Indian J. Chem.*, **7**, 469 (1969); (b) S. Trippett, *J. Chem. Soc.*, 2337 (1962).

The suggested mechanisms for the formation of enol phosphonium salts include: (path a) direct attack on carbonyl oxygen by the phosphine,[10a,17b] (path b) attack on halogen by phosphine to give an enolate halophosphonium ion pair which then interacts to give O-phosphorylation,[5,7,8,10b] and (path c) addition of the phosphine to carbonyl carbon (or across the carbonyl) to give an intermediate which rearranges to the O-phosphonium salt (Scheme VII). Other possibilities are eliminated

SCHEME VII



by our observations that keto- and enol phosphonium halides are not interconvertible.

We believe that path c is eliminated by our observations. Thus the fact that **18**, known to have a hindered carbonyl,[16a] reacts rapidly with MPPP to give **20** cannot be explained by path c. Also, if path c were operative, α-bromocyclohexanone **22** and α-chlorocyclohexanone **23** should readily react to give enol phosphonium salts. This would be expected since addition to cyclohexyl carbonyl is most facile.[18] This expectation is borne out in the reactions of **22** and **23** with triethyl phosphite (TEP) to give enol phosphates readily at about the same reaction rate.[19] These reactions are best explained by rate-determining carbonyl addition.[19,20] The reactions of **22** and **23** with TPP occur slowly, however, in anhydrous media to give mixtures of α- and β-ketophosphonium salts.[4,21] Finally the fact that highly substituted halo ketones, such as **3**, **6**, or **8**, react rapidly with either TPP or MPPP to give enol phosphonium salts does not seem to be compatible with path c. We suggest that direct addition of a "soft" phosphine to the "hard" oxygen of carbonyl (path a),[22] is not a likely process. Path a would require that the postulated SN2′-type of reaction should be much better for **18** than for **19**, for example, while **19** prefers to react more slowly by an SN2 process. It is not obvious why this should be so.

Path b, in our opinion, best explains all of the observations involving enol phosphonium salt formation. Attack on "soft" halogen by a "soft" phosphine should be enhanced by further substitution at the α carbon by bulky and electron-withdrawing groups such as phenyl or bromine. Such substitution has the effect of (a)

(18) H. C. Brown and K. Ichikawa, *Tetrahedron Lett.*, 221 (1957).

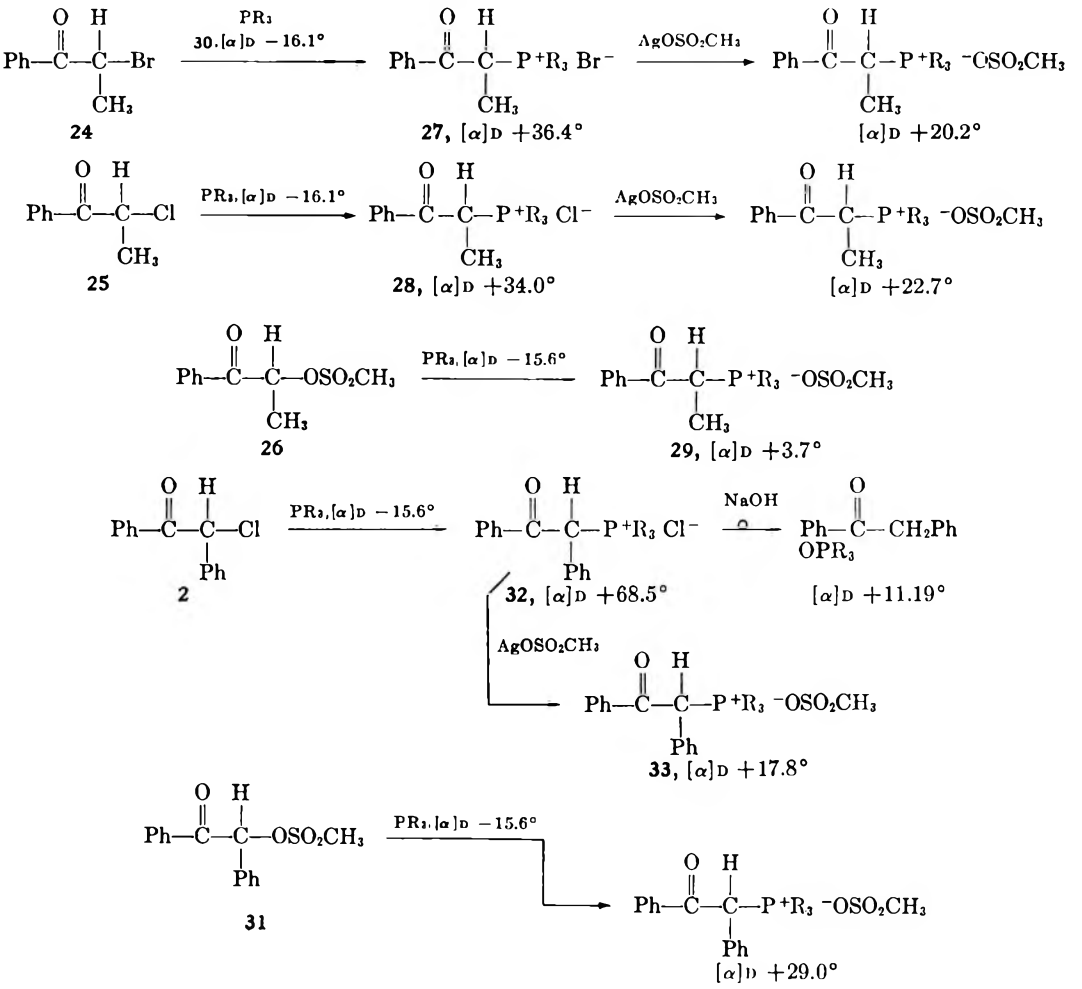
(19) I. J. Borowitz, M. Anschel, and S. Firstenberg, *J. Org. Chem.*, **32**, 1723 (1967).

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

(21) P. A. Chopard and R. F. Hudson, *J. Chem. Soc. B*, 1089 (1966).

(22) (a) R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967); (b) B. Saville, *Angew. Chem., Int. Ed. Engl.*, **6**, 928 (1967).

SCHEME VIII



retarding the normal SN2 displacement of halide ion because of steric reasons, and (b) stabilizing the real or incipient enolate ion which results from removal of positive halogen by the phosphine. Indeed we have found that the acid-catalyzed debromination of α-bromobenzyl phenyl ketone **1** with TPP is much more rapid than the corresponding debromination of α-bromoacetophenone.[23] These debromination reactions involve attack on bromine by TPP.[15,23]

The tendency for MPPP to form enol phosphonium salts more readily than does TPP may indicate that the "halophilicity" (reactivity of a nucleophile toward halogen) of a given phosphine is enhanced by electron-donating groups as much or more than its "carbophilicity" or reactivity toward carbon. Studies on the relative halophilicities of various tricovalent phosphines and other "soft" nucleophiles are in progress.

Finally, path b would be expected to be operative for bromine > chlorine ≫ mesyloxy groups which is the observed order of ease of enol phosphonium salt formation. This relative reaction order is also found for the conversion of α-halo ketones and α-mesyloxy ketones to ketones by diphenylphosphine. These reactions have been postulated to involve attack on halogen or mesyloxy oxygen by the phosphorus.[24]

In order to further probe the mechanisms of keto- and enol phosphonium salt formation, we determined the chirality of their formation with optically active MPPP **30**.

The Chirality of Ketophosphonium Salt Formation.— The reactions of α-substituted propiophenones and benzyl phenyl ketones with (−)-(*R*)-**30** are given in Scheme VIII and the Experimental Section. All of the reactions led to optically active phosphonium salts with the same (+) sign of rotation. Although the chirality of the phosphonium salts was not directly determinable, we argued that all of these reactions must be occurring with retention of configuration at phosphorus since this would be the result of SN2 displacement of the leaving group by the phosphine and since the SN2 pathway is the only tenable one for the α-mesyloxy ketones at least.

This assignment of retention at phosphorus, and confirmation of the SN2 pathway for the formation of all of the keto phosphonium salts, was verified as shown in Scheme IX. Hydrolysis of the (−)-phosphonium bromide **27** from (+)-(*S*)-**30** with aqueous base gave (−)-methyl-*n*-propylphenylphosphine oxide **35**, an overall *inversion* of configuration from **30** to **35**.[25] Since base hydrolysis of most phosphonium salts is known to occur with *inversion* of configuration at phosphorus,[26] our result indicates that the conversion of **30** to the phosphonium salt **27** must occur with retention at phosphorus.

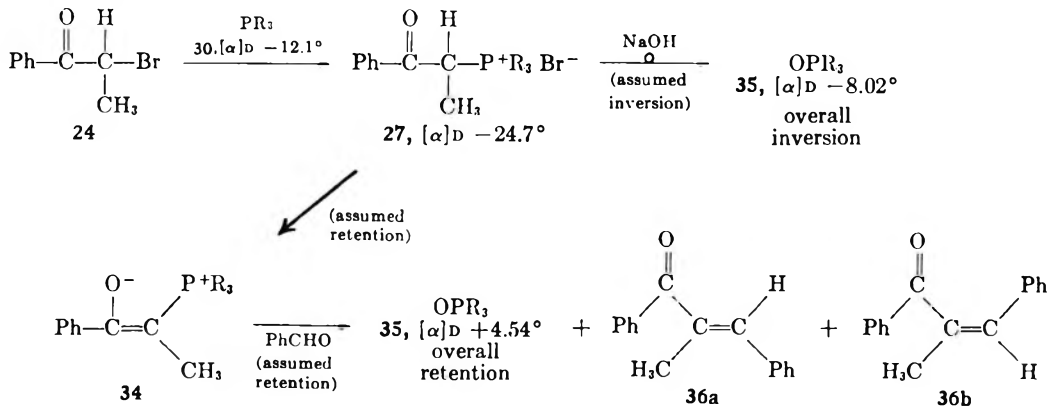
(23) Performed by Dr. E. Lord, Yeshiva University.

(24) I. J. Borowitz, K. Kirby, P. E. Rusek, and E. Lord, *J. Org. Chem.*, **34**, 2687 (1969).

(25) The conversion of (−)-**30** to (−)-**35** involves retention of configuration at phosphorus: L. Horner, *Pure Appl. Chem.*, **9**, 225 (1964).

(26) W. E. McEwen, *et al.*, *J. Amer. Chem. Soc.*, **81**, 3806 (1959). See ref 41 for more recent confirmatory evidence.

SCHEME IX



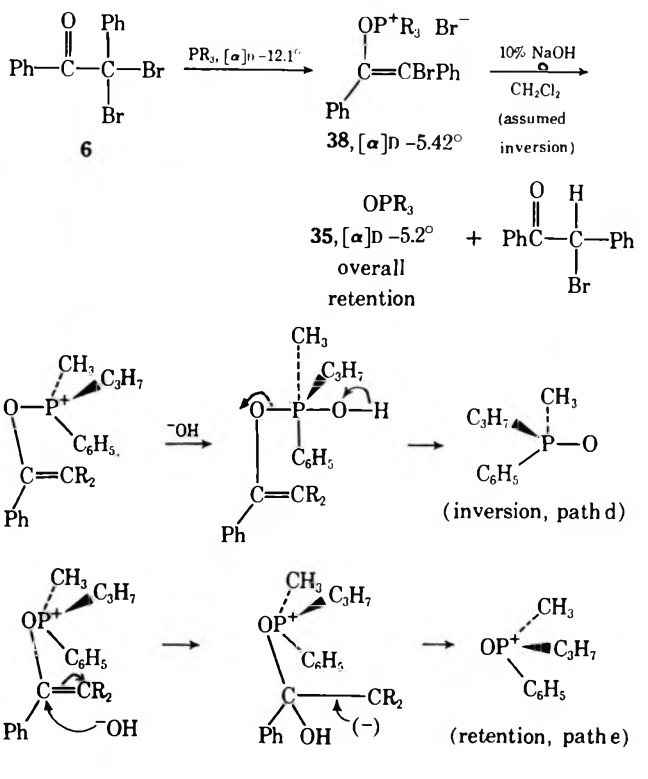
Finally, the keto ylide **34**, derived from **27**, gave a Wittig reaction with benzaldehyde to give the methylchalcone **36a**–**36b** in 93.5:6.5 ratio (see Experimental Section) and (+)-**35**, an overall *retention* of configuration from **30** to **35**. Since both conversion of a phosphonium salt to the corresponding ylide and the Wittig reaction of ylides are known to occur with *retention* of configuration at phosphorus,[27a] again the conversion of **30** to **27** must occur with *retention* at phosphorus. In a similar hydrolysis the phosphonium chloride **32** from **2** was shown to form with retention on phosphorus (Scheme VIII).

Some racemization is evident in some of these reactions. Whether this racemization involves pseudorotation of pentacovalent phosphorus intermediates or is otherwise mechanistically significant is not clear from our available data.[27b]

The Chirality of Enol Phosphonium Salt Formation.— It was anticipated that differentiation between paths a and b (Scheme VII) for enol phosphonium salt formation should be possible *via* the use of optically active **30**. Thus direct attack on carbonyl oxygen (path a) should give enol phosphonium salts with *retention* of configuration on phosphorus. Path b should involve *inversion* at phosphorus, perhaps accompanied by some racemization depending upon the extent of involvement of pentacovalent intermediates and resultant pseudorotation. This approach has been previously utilized.[28]

The reaction of (−)-**30** with **6** to give (−)-enol phosphonium salt **38** is shown in Scheme X. Since the chirality of **38** could not be determined directly, several reactions of **38** involving predictable chiral changes were undertaken to convert it to **35**. Base hydrolysis of **38** gave (−)-**35**, an overall *retention* of configuration from (−)-**30**. The cause of the partial loss of optical activity noted is not clear. The maximum value should be **35**, $[\alpha]D$ −12.4°, from **30**, $[\alpha]D$ −12.1°.[13b] Since the hydrolysis of **38** probably occurs by inversion at phosphorus (path d, Scheme X), the observed overall retention from **30** to **35** requires that **30** is converted to **38** with *inversion* of configuration. The base hydrolysis of enol phosphonium salts could conceivably occur by Michael addition to carbon of **38**, as in path e,[29] resulting in retention of configuration. We proved that path d, and not path e, is involved in the base hydrolysis of enol phosphonium salts as follows. The reaction of *dl*-**38** with $NaO^{14}H$, prepared from H_2O^{18} containing 10 atom % excess oxygen-18, gave *dl*-**35** which contained all of the excess oxygen-18 as determined by mass spectrometry. A similar result was obtained in the base hydrolysis of the enol triphenylphosphonium salt **14**.

SCHEME X



The mass spectral results for **35** are based on a comparison of the relative intensity of the peaks at 139,

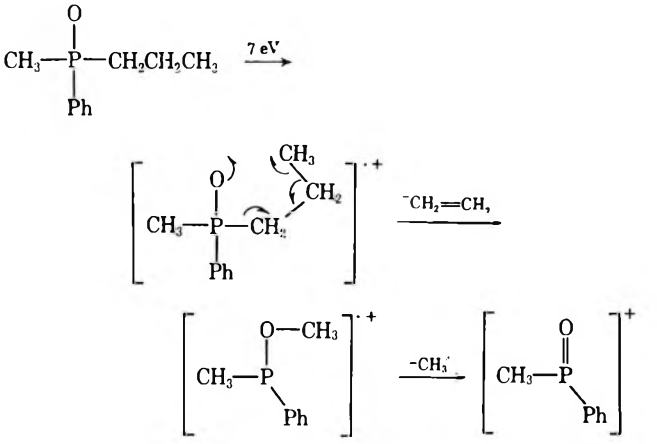
(27) (a) L. Horner and H. Winkler, *Tetrahedron Lett.*, 3265 (1964); (b) the reaction of **26** with **30** is slow, therefore giving racemization of **30** during the reaction.

(28) (a) M. J. Gallagher and I. D. Jenkins in "Topics in Sterochemistry," Vol. 3, N. L. Allinger and E. L. Eliel, Ed., Wiley, New York, N. Y., 1968. (b) For the reactions of chloral with (−)-**30**, see D. B. Denney and N. E. Gershman, *Tetrahedron Lett.*, 3899 (1965). See also D. B. Denney and N. G. Adin, *ibid.*, 2569 (1966).

(29) Such enol phosphonium salts do give Michael additions of halide ion upon pyrolysis.[7,8]

154, and 182 for O^{16}-**35** with those of the O^{18}-enriched **35** as well as the corresponding peaks at M + 2 (see Experimental Section). These peaks presumably arise as shown in Scheme XI.

SCHEME XI



The introduction of oxygen-18 into the phosphine oxide **35** derived from **38** supports the assumption of inversion of configuration in the hydrolysis. Thus enol phosphonium salts are formed with inversion of configuration at phosphorus, a fact which eliminates direct attack on carbonyl oxygen by phosphorus but which can be explained by path b (Scheme VII) involving attack at halogen by phosphorus.

Attempts to displace the phosphine moiety from (−)-**38** and thus regenerate **30** with tributylphosphine or tris(dimethylamino)phosphine were unsuccessful.

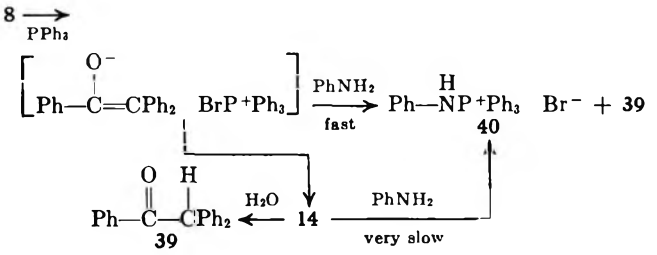
The reaction of (−)-**30** with bromodimedone gave *dl*-**35**. Since racemization could have occurred for a variety of reasons no mechanistic conclusions can yet be made for this case.[30]

Further Data on Enol Phosphonium Salt Formation.—As additional evidence that the formation of enol phosphonium salts may involve displacement on halogen by a tertiary phosphine, we have trapped the initial product, bromotriphenylphosphonium ion, resulting from such attack, as follows. The reaction of **8** with TPP and aniline (1 equiv) in acetonitrile rapidly gives the debrominated ketone **39** and anilinotriphenylphosphonium bromide **40** (88%). We have formed **40** from the reaction of bromotriphenylphosphonium bromide and aniline. The enol phosphonium bromide **14**, upon treatment with aniline in acetonitrile for a longer time period, gives only 4% yield of **40** (Scheme XII). Thus, at least in the presence of aniline, TPP removes positive bromine from **8**.[31] Our results confirm the previous work in this area by Speziale,[8,10b] Hoffmann,[9] Denney,[11,28] and our group.[3-6,24]

Experimental Section[32]

All of the solvents used were dried by distillation from phosphorus pentoxide, calcium hydride, or lithium aluminum hydride.

SCHEME XII



Reactions were conducted under an atmosphere of prepurified nitrogen. Organic solutions were dried over magnesium sulfate. α,α-Dibromoacetophenone, α-bromobenzyl phenyl ketone, α-chlorobenzyl phenyl ketone, 2,4,6-trimethyl-α-mesyloxyacetophenone, α-chloropropiophenone, and α-bromopropiophenone were prepared as previously described[4,19] or purchased. Most reactions with triphenylphosphine (TPP) were run to completion as shown by the absence of a mercuric chloride adduct.[4]

α,α-Dibromopropiophenone was prepared in 89% yield from the bromination of propiophenone, bp 179–181° (60 mm) [lit.[33] bp 180° (64 mm)]. α,α-Dibromobenzyl phenyl ketone was synthesized from benzyl phenyl ketone in 70% yield, mp 110–112° (lit.[34] mp 110–112°). α-Bromo-α,α-diphenylacetophenone was synthesized from the bromination of diphenylacetophenone in benzene at reflux for 5 hr, mp 85–95° (88% yield); recrystallized from heptane, mp 95.5–97.5° (lit.[35] mp 97–98°). Diphenylacetophenone was synthesized from the reaction of α-chlorobenzyl phenyl ketone with benzene and aluminum chloride in 87% yield, yellow needles from 95% ethanol, mp 135–137.5° (lit.[36] mp 135–137°).

Formation of Enol Triphenylphosphonium Bromide from α-Bromo-α,α-diphenylacetophenone.—A mixture of α-bromo-α,α-diphenylacetophenone (3.51 g, 0.010 mol) and TPP (2.62 g, 0.01 mol) at 25° in glyme (50 ml) for 22 hr ($HgCl_2$ test then negative) gave the enol triphenylphosphonium bromide **14**: 5.35 g, 0.0087 mol, 87%; mp 165–167°; ir ($CHCl_3$) 3.40 (s), 6.30 (m), 6.90 (s), 8.10 (m), 8.53 (m), 8.90 (s) 9.10, 9.35, 10.0, 10.31, and 11.15 μ (m), similar to literature values for corresponding chloride.[7,8]

Anal. Calcd for $C_{38}H_{30}BrOP$: C, 74.39; H, 4.93; Br, 13.02; P, 5.05. Found: C, 74.10; H, 5.05; Br, 12.92; P, 5.04.

Treatment of **14** with H_2O–CH_3OH (1:3) rapidly gave α,α-diphenylacetophenone (identical by tlc using 5% EtOAc–C_6H_6 with a genuine sample). Treatment of **14** (1.29 g, 0.0021 mol) with TPP (1.10 g, 0.0042 mol) in acetonitrile (10 ml) at reflux for 18 hr led to recovery of **14** (1.05 g, 0.0017 mol, 82%), mmp 169–172° with a genuine sample of **14** (mp 171–173°).

Reaction of α,α-Dibromoacetophenone with Triphenylphosphine.—A mixture of α,α-dibromoacetophenone (10.0 g, 0.0360 mol) and TPP (9.45 g, 0.0360 mol) was stirred at 25° in glyme (45 ml) for 10 days. The mixture was then slurried in additional glyme (20 ml) and the solid was quickly filtered off on a sintered glass funnel dried at 200°. After quickly transferring the solid to a predried flask, the remainder of the glyme was removed with a vacuum pump. Purification of the solid by repeated slurrying in dry glyme, followed by filtration and drying, gave a white solid, 1-phenyl-1-triphenyloxyphosphonium-2-bromoethylene bromide (**10**): 14.2 g, 0.0261 mol, 72.5%; ir (CH_2Cl_2) 3.6, 3.8,

(30) Thus hydrogen bromide could have racemized optically active **35** had it formed. See ref 28 and D. B. Denney, A. K. Tsolis, and K. Mislow, *J. Amer. Chem. Soc.*, **86**, 4486 (1964).

(31) We realize that the presence of aniline could change another mechanism to one involving attack on bromine. Alcohols do this, in some halo ketone cases, presumably *via* hydrogen bonding to carbonyl oxygen.[23] In the aniline reactions, the active agent could be aniline hydrobromide. Further work on this point is in progress.

(32) Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded on Beckman IR-8 and Perkin-Elmer 257 infrared spectrophotometers. Gas chromatograms were recorded on Varian Aerograph A-700 and Hy-Fi III gas chromatographs. Nmr spectra were recorded on a Varian A-60A spectrometer with TMS as an internal standard. Melting points were taken on Mel-Temp and Thomas–Hoover "Uni-Melt" apparatus. They as well as boiling points are uncorrected. Optical rotations were taken on a Bendix-NPL automatic polarimeter. Thin layer chromatography plates were prepared with Brinkmann silica gel HF_{254} and were developed in various solutions as indicated. Mass spectra were done on Hitachi RMU-6 mass spectrometers at Einstein Medical School, N. Y., and Columbia University.

(33) R. Levine and J. R. Stephens, *J. Amer. Chem. Soc.*, **72**, 1642 (1950).

(34) H. Limpricht and H. Schwanert, *Justus Liebigs Ann. Chem.*, **155**, 59 (1850).

(35) C. C. Stevens and J. J. DeYoung, *J. Amer. Chem. Soc.*, **76**, 718 (1954); R. Anschutz and P. Forster, *Justus Liebigs Ann. Chem.*, **368**, 89 (1909).

(36) H. Rinderknecht, *J. Amer. Chem. Soc.*, **73**, 5770 (1951).

6.35, 7.0, 9.7, 9.9, and 10.1 μ; nmr ($CDCl_3$) τ 2.0–2.9 (m, 20, aryl H) and 3.5 (d, 1, vinyl H, $J_{^{31}PH}$ = 1.8 Hz).

Reaction of α,α-Dibromobenzyl Phenyl Ketone with Triphenylphosphine.—Similar reaction of TPP (15.0 g, 0.0575 mol), α,α-dibromobenzyl phenyl ketone (20.4 g, 0.0575 mol) in dry glyme (125 ml) for 24 hr gave 1-phenyl-1-triphenyloxyphosphonium-2-phenyl-2-bromoethylene bromide (**12**): 30.0 g, 0.0487 mol, 84%; ir (CH_2Cl_2) 3.6, 3.8, 6.3, 9.0, 9.6, 9.9, and 10.1 μ; nmr ($CDCl_3$) τ 2.0–3.0 (m, 25, aryl H).

Anal. Calcd for $C_{32}H_{25}OPBr_2$: C, 62.30; H, 4.05. Found: C, 62.59; H, 4.26.

Treatment of **12** with TPP (1 equiv) in xylene at reflux for 17 hr gave recovered **12** which was hydrolyzed to triphenylphosphine oxide and α-bromobenzyl phenyl ketone and no other products.

***In Situ* Formation of α-Mesyloxy-α,α-diphenylacetophenone and Reaction with Triphenylphosphine.**—α-Bromo-α,α-diphenylacetophenone (3.51 g, 0.010 mol) and silver mesylate (2.03 g, 0.010 mol) at 25° for 1 hr in benzene (35 ml) gave crude **9**. Silver bromide was removed by filtration, triphenylphosphine (2.62 g, 0.010 mol) was added to the residual solution, and the mixture was stirred overnight at 25° to give a precipitate which was filtered and dried to give crude α,α-diphenylphenacyltriphenylphosphonium mesylate (**15**, 4.21 g, 0.0067 mol, 67%). Crude **15** was recrystallized twice from ethyl acetate–methanol and once from diethyl ether–methylene chloride to give **15**, mp 184–186°; ir and nmr spectra of the crude salt and analytical sample were very similar: ir ($CHCl_3$) 3.30 (m), 3.37 (m), 5.99 (s), 6.25 (m), 6.73 (m), 6.95 (m), 8.32 (s), 9.00 (m), 9.12 (m), 9.61 (s), and 10.01 μ (m); nmr ($CDCl_3$) τ 7.30 (s, 3, methyl H) and 2.60 (m, 30, aromatic H).

Anal. Calcd for $C_{39}H_{33}O_4PS$: C, 74.52; H, 5.25; P, 4.94. Found: C, 74.61; H, 5.10; P, 4.83.

Several attempts to isolate α-mesyloxy-α,α-diphenylacetophenone resulted in unstable tars and oils in addition to yields from 80 to 100% of silver bromide.

The Stability of α,α-Diphenylphenacyltriphenylphosphonium Mesylate (15).—A mixture of **15** (0.520 g, 0.0083 mol) and triphenylphosphine (0.218 g, 0.0083 mol) was heated at reflux overnight in acetonitrile (10 ml), solvent was removed *in vacuo*, and benzene was added to the residual oil which solidified upon scratching to give **15** (0.390 g, 0.0062 mol, 75% recovery), tlc (50% CH_3OH–C_6H_6) one spot with same R_f value as for genuine **15**.

Reactions of α-Mesyloxy Ketones with Triphenylphosphine and with *dl*-Methyl-*n*-propylphenylphosphine.—The synthesis of α-mesyloxy ketones has been described.[24] In a general procedure, TPP and the appropriate α-mesyloxy ketone were heated at reflux in dry glyme for several days. The corresponding ketophosphonium mesylates were usually isolated by filtration after the reaction mixture was cooled. Spectral and other data are given in Table I.

α-Triphenylphosphoniumcyclododecanone mesylate (41), thus synthesized, was difficult to isolate. Crude **41** (1.8 g, 0.0034 mol) in $CHCl_3$ (100 ml) was stirred with 1 *N* NaOH (50 ml, 0.050 mol) for 1 hr. Removal of the $CHCl_3$ layer, drying, and evaporation *in vacuo* gave an oil which was crystallized from petroleum ether to give the keto ylide **42** (0.69 g, 0.0016 mol, 42%): mp 190–192°; ir (CH_2Cl_2) 6.75 μ (C=O); nmr ($CDCl_3$) τ 2.0–2.9 (m, 15, aryl H) and 7.8–8.7 (m, 20 alicyclic H).

Anal. Calcd for $C_{30}H_{35}OP$: C, 81.41; H, 7.97. Found: C, 81.68; H, 7.85.

2,4,6-Trimethylphenacyl methyl-*n*-propylphenylphosphonium mesylate (21) was isolated from $CDCl_3$.

Anal. Calcd for $C_{22}H_{31}O_4PS$: C, 62.53; H, 7.39. Found: C, 62.22; H, 7.33.

The Reaction of α-Halo Ketones with *dl*-Methyl-*n*-propylphenylphosphine.—In a general procedure, the α-halo ketone and *dl*-MPPP **30** (0.001–0.006 mol each) were mixed with $CDCl_3$ (1 ml) in a 5-mm nmr tube. The nmr spectrum of the resulting mixture was recorded after *ca.* 5 min (for α-bromo ketones) to *ca.* 24 hr (for α-chloro ketones). In some cases larger scale reactions were run. The reaction conditions and spectral data are given in Table II. Similar conditions were used for reactions with TPP.

α-Methylphenacyl methyl-*n*-propylphenylphosphonium bromide (from α-bromopropiophenone and **30**) was recrystallized from Et_2O–CH_2Cl_2, mp 164–165°.

Anal. Calcd for $C_{19}H_{24}BrOP$: C, 60.17; H, 6.38; Br, 21.07; P, 8.19. Found: C, 60.40; H, 6.52; Br, 21.22; P, 8.19.

α-Methylphenacyl methyl-*n*-propylphenylphosphonium chloride (from α-chloropropiophenone and **30**) was crystallized from glyme, mp 137–139.5°.

Anal. Calcd for $C_{19}H_{24}OPCl$: C, 68.36; H, 6.94. Found: C, 68.16; H, 7.11.

α-Phenylphenacyl methyl-*n*-propylphenylphosphonium chloride (from α-chlorobenzyl phenyl ketone and **30**) was crystallized from glyme.

Anal. Calcd for $C_{24}H_{26}OPCl$: C, 72.63; H, 6.60. Found: C, 72.33; H, 6.48.

Enol phosphonium bromide 38 (from **30** and **6**) gave the following analysis.

Anal. Calcd for $C_{24}H_{25}Br_2OP$: C, 55.41; H, 4.84; ionic Br, 15.36. Found: C, 54.38; H, 4.89; ionic Br, 15.01. The analysis could not be improved.

Reaction of 2-Bromodimedone (7) with Methylphenyl-*n*-propylphosphine.—Methylphenyl-*n*-propylphosphine (0.302 g, 0.00182 mol) in $CDCl_3$ (1 ml) was added to an nmr tube containing **7** (0.398 g, 0.00182 mol). After 5 min, the reaction gave enol phosphonium salt (100% by nmr): nmr ($CDCl_3$) τ 1.65–2.3 (m, 5, phenyl H), 4.32 (m, 1, vinyl H), 6.75 (d, 3, PCH_3, $J_{^{31}PCH_3}$ = 14 Hz), 7.2 (s, 2, C_4H), 7.7 (s, 2, C_6H), 8.95 (s, 6, methyl H), and 6.2–9.2 (m, 7, propyl H). After 10 days 5,5-dimethyl-3-bromocyclohex-2-enone (**3**) (100% by nmr) [nmr ($CDCl_3$) τ 3.72 (t, 1, vinyl, *J* = 1 Hz)[4]] and methylphenyl-*n*-propylphosphine oxide (100% by nmr) were present. The decrease of τ 4.32 (vinyl H of **13a**) and increase of τ 3.72 (vinyl H of **3**) could be followed with time. Similar reaction of **7** with TPP immediately gave **3** (nmr) and no evidence of **13**.

Methyldiphenylphosphine was synthesized from chlorodiphenylphosphine and methylmagnesium bromide in 63% yield: bp 136–143° (0.25 mm) (lit.[37] bp 248°); nmr ($CDCl_3$) τ 2.71 (m, 10, phenyl H) and 8.42 (d, 3, CH_3, $J_{^{31}PH}$ = 3.5 Hz).

Treatment of methyldiphenylphosphine with *n*-propyl iodide in benzene at reflux for 3 days gave **methyl-*n*-propyldiphenylphosphonium bromide (43)** in 62–89% yield, mp 210–213.5°.

Methyl-*n*-propylphenylphosphine Oxide (*dl*-35).—A mixture of silver oxide (0.275 mol) and **43** (64 g, 0.20 mol) in distilled water (1500 ml) was heated on a steam bath for 1 hr with stirring and was cooled. After filtration of solids, the filtrate was extracted with $CHCl_3$ (five 100-ml portions). The organic solution was dried, evaporated *in vacuo*, and distilled to give *dl*-**35** (25.0 g, 0.137 mol, 69%): bp 110° (0.025 mm) [lit.[38] bp 180° (13 mm)]; nmr ($CDCl_3$) τ 2.0–2.4, 2.45–2.65 (m, 5, aryl H), 8.4 (d, 2, PCH_3, $J_{^{31}PH}$ = 13.5 Hz), 7.85–8.85 (m, 4), and 9.05 (t, 3, CCH_3).

Methylphenyl-*n*-propylphosphine.—Trichlorosilane (26.8 g, 0.20 mol) was added dropwise to a well-stirred solution of phenylmethylpropylphosphine oxide (25.0 g, 0.137 mol) and triethylamine (20.24 g, 0.200 mol) in dry benzene (200 ml, distilled from $LiAlH_4$). After stirring for 24 hr, sodium hydroxide (30%) was slowly added until solution occurred. The benzene layer was separated, dried, and evaporated *in vacuo*, to leave an oil which was distilled to give methylphenyl-*n*-propylphosphine (13.0 g, 0.08 mol, 58%): bp 97–98° (0.5 mm); nmr ($CDCl_3$) τ 2.3–3.0 (m, 5, phenyl H), 8.45 (d, 3, methyl, $J_{^{31}PH}$ = 3.0 Hz), and 8.2–9.3 (m, 7, propyl H).

Optically active methyl-*n*-propylphenylphosphine oxide (35) was synthesized by known procedures[13a] to give (+)-**35**: bp 108–110° (0.05 mm); $[\alpha]^{20}D$ +17.2° (*c* 0.535, CH_3OH); nmr ($CDCl_3$) τ 2.0–2.9 (m, 5, phenyl H), 8.39 (d, 3, methyl H, $J_{^{31}PH}$ = 13.5 Hz), 9.1 (t, 3, CH_2CH_3), and 7.8–9.1 (m, 4, methylene H).

(−)-Methylphenyl-*n*-propylphosphine.[13c]—To a cooled mixture of (+)-**35** [8.1 g, 0.0445 mol, $[\alpha]^{20}D$ +17.2° (*c* 0.535, methanol)] and triethylamine (222 g, 2.18 mol) in C_6H_6 (500 ml), trichlorosilane (162 g, 1.2 mol) was added dropwise. After a reflux period of 1 hr, 30% aqueous sodium hydroxide was added dropwise until complete solution occurred. The aqueous layer was extracted with chloroform (four 400-ml portions) and dried, and the solvent was removed *in vacuo*, to leave an oil which was distilled to give methylphenyl-*n*-propylphosphine (5.2 g, 0.032 mol, 71%): $[\alpha]^{20}D$ −16.1° (*c* 0.790, methanol); bp 47–48° (0.5 mm); nmr ($CDCl_3$) τ 2.0–2.8 (m, 5, phenyl H), 8.8 (d, 3, methyl H, $J_{^{31}PCH_3}$ = 3.5 Hz), and 8.2–9.2 (m, 7, propyl H).

Reaction of (−)-Methylphenyl-*n*-propylphosphine with α-Chloropropiophenone.—α-Chloropropiophenone (0.76 g, 0.0045

(37) A. Michaelis and E. Kohler, *Chem. Ber.*, **10**, 807 (1877).

(38) J. Meisenheimer and R. Lichtenstadt, *Justus Liebigs Ann. Chem.*, **449**, 213 (1926).

mol) and (−)-methylphenyl-*n*-propylphosphine [0.75 g, 0.0045 mol, $[\alpha]^{20}D$ −16.1° (*c* 0.790, CH_3OH)] were stirred in dry glyme (5 ml, distilled from $LiAlH_4$) for 24 hr. A white solid was filtered off and dried *in vacuo* to give α-methylphenacylmethylphenyl-*n*-propylphosphonium chloride (**28**): 1.25 g, 0.0035 mol, 84%; mp 136–139°; ir (CH_2Cl_2) 3.2–3.7, 5.95 (C=O), 8.3, and 11.1 μ; nmr ($CDCl_3$) τ 1.3–2.9 (m, 10, phenyl H), 2.95–3.4 (m, 1, methine H), 8.29 (d, $J_{^{31}PH}$ = 7.5 Hz), 8.60 (d, $J_{^{31}PH}$ = 7.5 Hz), 7.45 (d, 3, PCH_3, $J_{^{31}PCH_3}$ = 14 Hz), 6.6–7.3, 8.0–8.7 (m, 4), and 8.95 (m, 3, propyl CH_3); $[\alpha]^{20}D$ +34° (*c* 0.682, CH_2Cl_2).

Anal. Calcd for $C_{19}H_{24}OPCl$: C, 68.36; H, 6.94. Found: C, 68.37; H, 6.95.

Reaction of (+)-28 with Silver Mesylate.—α-Methylphenacyl methylphenyl-*n*-propylphosphonium chloride [0.50 g, 0.0015 mol, $[\alpha]^{20}D$ +34° (*c* 0.682, CH_2Cl_2)] in acetonitrile (25 ml) was added to a solution of silver mesylate (0.30 g, 0.00148 mol) in acetonitrile (5 ml). The silver chloride was filtered off and the solvent removed *in vacuo* to give an oil **29** (0.535 g, 0.00135 mol, 91%). Since all attempts to crystallize the oil failed, the purity of the product was checked by thin layer chromatography (5% ethyl acetate–benzene on silica gel plates). For the oil **29**: ir (CH_2Cl_2) 6.01 (C=O) and 8.20–8.50 μ (mesylate); $[\alpha]^{20}D$ +22.7° (*c* 0.227, CH_2Cl_2); no halogen (negative $AgNO_3$ test).

Reaction of α-Bromopropiophenone with Optically Active Methylphenyl-*n*-propylphosphine.—To α-bromopropiophenone (0.963 g, 0.0045 mol) in dry glyme (5 ml) was added (−)-**30** [0.75 g, 0.0045 mol, $[\alpha]^{20}D$ −16.1° (as above)] with stirring. After 24 hr, the white solid was filtered off (five crops) to give α-methylphenacyl methylphenyl-*n*-propylphosphonium bromide (**27**): 0.75 g, 0.00197 mol, 44%; mp 160–163°; $[\alpha]^{20}D$ +36.4° (*c* 0.532, CH_2Cl_2): ir (CH_2Cl_2) 5.95 (C=O), 8.21, and 10.9 μ; nmr ($CDCl_3$) τ 1.0–2.5 (m, 10, phenyl H), 3.1–3.5 (m, 1, methine H), 7.39 (d, 3, PCH_3, $J_{^{31}PCH_3}$ = 14 Hz), 8.20 (q, CCH_3, J_{HH} = 8, $J_{^{31}PH}$ = 3 Hz), 8.52 (q, CCH_3, J_{HH} = 7.5, $J_{^{31}PH}$ = 3 Hz), 6.5–7.5 and 8.1–8.6 (m, 4, methylene H), and 8.9 (m, 3, methyl H).

Reaction of (+)-27 with Silver Mesylate.—To (+)-**27** (0.60 g, 0.0015 mol) in acetonitrile (50 ml) was added silver mesylate (0.50 g, 0.0024 mol) as above, to give an oil: pure by tlc (5% ethyl acetate–benzene on silica gel plates); ir (CH_2Cl_2) 6.0 (C=O) and 8.35 μ (mesylate); $[\alpha]^{20}D$ +20.2° (*c* 0.480, CH_2Cl_2); no halogen (negative $AgNO_3$ test).

Reaction of α-Chlorobenzyl Phenyl Ketone (2) with Optically Active Methylphenyl-*n*-propylphosphine.—To **2** (1.04 g, 0.0045 mol) in dry glyme (5 ml) was added (−)-**30** (0.75 g, 0.0045 mol). After the mixture was stirred for 24 hr, a white solid was filtered off in several crops to give α-phenylphenacyl methylphenyl-*n*-propylphosphonium chloride (**32**): 0.94 g, 0.00324 mol, 72%; ir (CH_2Cl_2) 3.2–3.7, 6.0, 6.3, 6.95, 7.4–7.9, 8.0–8.5, 9.0, 9.9, 10.0, and 14.5 μ; nmr ($CDCl_3$) τ 1.25–3.0 (m, 15, phenyl and methine H), 7.35 (d, 1.5, CH_3, $J_{^{31}PCH_3}$ = 14 Hz), 7.60 (d, 1.5, PCH_3, $J_{^{31}PCH_3}$ = 14 Hz), 6.6–8.8 (m, 4), and 9.05 (m, 3, CCH_3); $[\alpha]^{20}D$ +68.5° (*c* 0.475, CH_2Cl_2).

Reaction of (+)-32 with Silver Mesylate.—A mixture of (+)-**32** (0.50 g, 0.00126 mol) and silver mesylate (0.75 g, 0.0037 mol) was stirred overnight in acetonitrile (100 ml) and treated as above, to give α-phenylphenacyl methylphenyl-*n*-propylphosphonium mesylate (**33**, 0.506 g, 0.00111 mol, 88%), $[\alpha]^{20}D$ +17.8° (*c* 0.797, CH_2Cl_2). The oil was pure by tlc (5% ethyl acetate–benzene on silica gel plates): ir (CH_2Cl_2) 5.9 (C=O) and 8.2–8.4 μ (mesylate); no halogen (negative $AgNO_3$ test).

Reaction of α-Mesyloxybenzyl Phenyl Ketone (31) with (−)-30.—A mixture of **31** (1.76 g, 0.00604 mol) and (−)-**30** [1.0 g, 0.00604 mol, $[\alpha]^{20}D$ −15.6° (CH_3OH)] was heated at reflux for 2 hr in dry glyme (10 ml). After the mixture was cooled at 5–10° for 3 days, a white solid was filtered off to give α-phenylphenacyl methylphenyl-*n*-propylphosphonium mesylate (2.26 g, 0.00495 mol, 82%): mp 137–141°; ir (CH_2Cl_2) 5.9 (C=O) and 8.2–8.4 μ (mesylate); nmr ($CDCl_3$) τ 1.7–2.8 (m, 16, phenyl, methine H), 7.2 (s, 3, mesylate H), 7.45 (d, 1.5, methyl, $J_{^{31}PCH_3}$ = 14 Hz), 7.65 (d, 1.5, methyl, $J_{^{31}PCH_3}$ = 14 Hz), 8.7–9.1 (t, 3, methyl H), and 6.7–8.6 (m, 4, methylene H); $[\alpha]^{20}D$ +29° (*c* 0.525, CH_2Cl_2).

Anal. Calcd for $C_{33}H_{35}OSP$: C, 65.77; H, 6.40. Found: C, 65.64; H, 6.46.

Reaction of α-Mesyloxypropiophenone with (−)-30.—α-Mesyloxypropiophenone (1.37 g, 0.00604 mol) and (−)-**30** (1.0 g, 0.00604 mol, $[\alpha]^{20}D$ −15.6°) were heated at reflux for 2 hr in dry glyme (10 ml). Isolation as above gave α-methylphenacyl methylphenyl-*n*-propylphosphonium mesylate (**29**): 0.285 g, 0.000725 mol, 12%; mp 140–141.5°; $[\alpha]^{20}D$ +3.7° (*c* 0.817, CH_2Cl_2); ir (CH_2Cl_2) 6.0 (C=O) and 8.20–8.50 μ (OSO_2CH_3); nmr ($CDCl_3$) τ 1.7–2.7 (m, 10, phenyl H), 3.90–4.3 (m, 1, methine H), 7.3 (s, 3, mesylate), 7.55 (d, 3, methyl, $J_{^{31}PCH_3}$ = 14 Hz), 8.4 (q, 3, methyl, J_{HH} = 8 Hz, $J_{^{31}PCH_3}$ = 18 Hz), 6.8–8.7 (m, 4, methylene H), and 8.8–9.3 (m, 3, methyl H).

Anal. Calcd for $C_{20}H_{27}O_4SP$: C, 60.89; H, 6.89. Found: C, 60.79; H, 6.97.

Base Hydrolysis of Optically Active Ketophosphonium Salts.—α-Bromopropiophenone reacted with (+)-**30**, $[\alpha]^{20}D$ +12.0°, to give the ketophosphonium bromide (**27**, 62%, $[\alpha]^{20}D$ −24.7°).

Anal. Calcd for $C_{19}H_{24}OBrP$: C, 60.17; H, 6.38. Found: C, 59.98; H, 6.48.

The bromide (−)-**27** (0.186 g, 0.00049 mol) was hydrolyzed with 10% aqueous NaOH (4 ml, 0.01 mol) at reflux for 24 hr to give, after Et_2O extraction, drying, and evaporation, a yellow oil (0.134 g) which contained propiophenone (0.0543 g, 82%) and (−)-**35** (0.079 g, 89%) crude, $[\alpha]^{20}D$ −8.74° by nmr analysis. The oil was chromatographed on basic alumina (Merck, Brockman grade I, 25 g) to give propiophenone (0.021 g, 32%, ether elution) and (−)-**35** [0.079 g, 89%, CH_3OH elution, $[\alpha]^{20}D$ −8.02° (*c* 0.53, CH_3OH) after sublimation at bath temperature of 60° and collector temperature of −78°]; nmr spectra were identical with genuine samples. The ketophosphonium chloride (+)-**32**, from α-chlorobenzyl phenyl ketone and (−)-**30** ($[\alpha]^{20}D$ −16.1°, 0.0728 g, 0.000202 mol) was similarly hydrolyzed to give benzyl phenyl ketone **44** (0.0289 g, 73%, mp 53–55°), and (+)-**35** [0.0362 g, 99%, $[\alpha]^{20}D$ +11.19° (*c* 0.19, CH_3OH)]. Both products were identical with genuine samples (by nmr, mmp 53–55° for ketone with genuine **44** of mp 53–56°). Base hydrolysis of *dl*-**32** had previously given **44** (57%) and *dl*-**35** (79%).

Conversion of (−)-27 to Keto Ylide 34 and Reaction of 34 with Benzaldehyde.—Treatment of (−)-**27** (0.188 g, 0.000497 mol) with 10% aqueous NaOH (5 ml, 0.013 mol) in tetrahydrofuran (10 ml) for 10 min, extraction with Et_2O (four 5-ml portions), drying, and evaporation of the organic layer gave crude keto ylide **34** (0.160 g) as a syrupy white solid. Benzaldehyde (0.0673 g, 0.000634 mol) in tetrahydrofuran (30 ml) was added, and the mixture was heated at reflux for 24 hr and then cooled. Evaporation *in vacuo* gave a yellow oil (0.252 g) which was chromatographed on Merck basic alumina (25 g) to give the chalcone **36** [0.0914 g, 0.000411 mol, 83%, petroleum ether and ether elution; uv max (95% EtOH) 228 nm (log ε 3.96), 251, (4.02), and 289 (4.09) (lit.[39] uv max for *trans*-**36** (95% EtOH), 225 nm (log ε 4.02), 260 (4.05), and 290 (4.24); nmr spectrum ($CDCl_3$) identical with genuine sample] and (+)-**35** [0.0879 g, 0.00055 mol, 97% (CH_3OH elution); $[\alpha]^{21}D$ +4.54° (*c* 1.36, CH_3OH)].

The Wittig Reaction of α-Methylphenacyltriphenylphosphorane 45 with Benzaldehyde.—Reaction of ylide **45** (2.214 g, 0.00561 mol) with benzaldehyde (0.613 g, 0.00577 mol) in tetrahydrofuran (70 ml) for 24 hr at reflux gave a crude mixture (2.62 g) which was chromatographed on Fisher alumina (A-540, 25 g) to give the chalcones **36a** and **36b** [petroleum ether elution, 0.988 g, 0.0044 mol, 79%; uv max (95% EtOH) 223.5, 260, and 290 nm; mass spectrum (70 eV) *m/e* (rel intensity) 222 (62, $M^{\cdot+}$), 221 (42), 179 (7), 178 (4), 145 (10), 144 (7), 131 (8), 117 (20), 115 (36), 105 (100), 91 (17), and 77 (98); nmr ($CDCl_3$) τ 2.1–3.0 (m, 11, phenyl and vinyl H), 7.75 (d, 2.8, CH_3 of **36a**, *J* = 1.7 Hz), and 7.87 (d, 0.2, CH_3 of **36b**, *J* = 1.4 Hz)] and triphenylphosphine oxide [Et_2O, CH_3OH elution, 1.44 g, 92%; mp 152–155°, mmp 153–156° with genuine sample (mp 155–156°); ir and nmr spectra identical with genuine sample].

The assignment of the trans configuration **36a** to the major isomer is based on previous uv evidence for the trans nature of **36** as formed by aldol condensation,[39] and on the fact that Wittig reactions of stabilized ylides give predominantly the trans olefinic product.[40]

Reaction of α-Bromodimedone with (−)-30.—α-Bromodimedone (5.7 g, 0.026 mol) and (−)-**30** [4.32 g, 0.026 mol, $[\alpha]^{20}D$ −11.6° (methanol)] were mixed in $CDCl_3$ (15 ml) at −78°. After the mixture was stirred for 5 days, the solvent was removed *in vacuo*. Distillation of the residual oil gave 5,5-dimethyl-3-bromocyclohexenone [4.2 g, 0.0205 mol, 79%, bp 60° (0.025 mm)] and methylphenyl-*n*-propylphosphine oxide [3.22 g, 0.0176 mol, 68%, bp 110° (0.025 mm), $[\alpha]^{20}D$ 0.0° (*c* 0.471, C_2H_5OH)].

(39) W. B. Black and R. E. Lutz, *J. Amer. Chem. Soc.*, **77**, 5134 (1955).

(40) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 253.

Reaction of α,α-Dibromobenzyl Phenyl Ketone with (−)-30.—To a solution containing **6** (6.39 g, 0.01806 mol) in dry glyme (50 ml) was quickly added (−)-**30** (3.0 g, 0.01806 mol, $[\alpha]^{20}D$ −12.1° (*c* 4.92, CH_3OH). The mixture was stirred overnight at 0° to give **38** (9.1 g, 0.0178 mol, 98%): $[\alpha]^{20}D$ −5.42° (*c* 1.45, CH_2Cl_2); ir (CH_2Cl_2) 3.2–3.5, 8.2, 8.9, 9.2–9.6, and 10.3–10.6 μ; nmr ($CDCl_3$) τ 1.65–3.1 (m, 15, phenyl H), 7.25 (d, PCH_3, $J_{^{31}PCH_3}$ = 14 Hz), 7.7 (d, PCH_3, $J_{^{31}PCH_3}$ = 14 Hz), and 6.8–9.2 (m, 7, propyl H). A repetition using **30**, $[\alpha]^{20}D$ −11.6°, gave **38** (63%), $[\alpha]^{20}D$ −5.10° (*c* 1.45, CH_2Cl_2).

Reaction of Optically Active 38 with Sodium Hydroxide.—To **38** [7.0 g, 0.0134 mol, $[\alpha]^{20}D$ −5.42° (c 1.45, CH_2Cl_2)] in methylene chloride (100 ml) was added sodium hydroxide (100 ml, 10%). The solution was stirred for 2 hr, each layer separated, and the water portion extracted with methylene chloride (500 ml). After drying, the solvent was removed *in vacuo* and the residual oil distilled to give methylphenyl-*n*-propylphosphine oxide (**35**): 1.2 g, 0.007 mol, 49%; $[\alpha]^{20}D$ −5.2° (*c* 12.5, CH_3OH); nmr ($CDCl_3$) τ 1.7–2.6 (m, 5, phenyl H), 8.4 (d, 3, methyl H, $J_{^{31}PH}$ = 13.5 Hz), and 8.0–9.2 (m, 7, propyl H). A repetition using **38**, $[\alpha]^{20}D$ −5.1°, gave **35** (43%), $[\alpha]^{20}D$ −4.6° (*c* 12.5, CH_3OH).

The Hydrolysis of Enol Phosphonium Salts with Sodium Hydroxide Enriched with O^{18}.—A solution of *dl*-**38** (0.280 g, 0.000538 mol, from **6** and *dl*-**30**) in CH_2Cl_2 (5 ml) was added to 10% aqueous $NaO^{18}H$ [from sodium (0.27 g, 0.019 g-atom) and 10% O^{18}-enriched "low deuterium" water (5.00 g)] and then stirred for 2 hr. Removal of the organic layer, extraction of the water layer with CH_2Cl_2 (two 1-ml portions), combination of the organic layers, drying, and evaporation *in vacuo* at 25° gave a yellow oil (0.23 g) which was chromatographed on Merck basic alumina (25 g) to give **1** (90%) and O^{18}-enriched **35** (0.0838 g, 0.00046 mol, 86%, CH_3OH elution): mass spectrum (7 eV) *m/e* (rel intensity) 182 (100, $M\cdot^+$), 183 (18.21), 184 (14.03), 154 ($M\cdot^+ - C_2H_4$, 83.6), 155 (7.9), 156 (10.9), 139 (81.4, $M\cdot^+ - C_3H_7$), 140 (6.8), and 141 (11.3). Oxygen-16 **35** has a mass spectrum (7 eV) *m/e* (rel intensity) 182 (100), 183 (11.36), 184 (1.24), 154 (34.7), 155 (3.6), 156 (0.1), 139 (14.4), 140 (0.2), and 141 (0.1). On the basis of these data, scale expanded data at these peaks, and corrections for natural abundance of isotopes, the O^{18}-enriched **35** was estimated to have 10.9–11.5% O^{18} enrichment; *i.e.*, all of the original 10% enrichment was retained.[41,42]

In a similar manner, **14** was hydrolyzed with $NaO^{18}H$ to give **39** (81%) and triphenylphosphine oxide (94%): mass spectrum (10 eV) *m/e* (rel intensity) 278 (100, M), 279 (27.61), and 280 (15.26). Oxygen-16 triphenylphosphine oxide had 278 (100, M), 279 (19.24), and 280 (2.79). The enriched triphenylphosphine oxide from **14** was calculated to have 10.7% O^{18} enrichment; *i.e.*, again all of the excess O^{18} was retained.[42]

Reactions of 38 Attempted with Tributylphosphine or Trisdimethylaminophosphine.—To an nmr tube containing α,α-dibromobenzyl phenyl ketone (0.240 g, 0.000679 mol) in $CDCl_3$ (1 ml) was added **30** (0.113 g, 0.000678 mol). The nmr spectrum indicated complete formation of the enol phosphonium salt **38**. To the mixture was added tributylphosphine (0.137 g, 0.000679 mol). After 1 hr, nmr indicated a complete absence of reaction. A similar attempted reaction with trisdimethylaminophosphine also failed.

Reaction of Optically Active Methylphenyl-*n*-propylphosphine with α-Bromopropiophenone and Water.—Methylphenyl-*n*-propylphosphine [3.7 g, 0.0222 mol, $[\alpha]^{24}D$ −13.7° (CH_3OH)] was added to a mixture of α-bromopropiophenone (4.75 g, 0.0222 mol), water (9 ml), and dioxane (21 ml). After 10 min the solvent was removed *in vacuo* to give an oil which was dissolved in methylene chloride and dried, and the solvent removed *in vacuo*. Distillation of the residual oil gave methylphenyl-*n*-propylphosphine oxide (3.6 g, 0.0197 mol, 89%): $[\alpha]^{20}D$ 0.0° (CH_3OH); bp 110° (0.025 mm); nmr ($CDCl_3$) as above.

Treatment of the Enol Phosphonium Bromide 14 with Aniline.—A mixture of **14** (5.33 g, 0.0083 mol) and aniline (0.93 g, 0.01 mol) was stirred under nitrogen in acetonitrile (100 ml) at 25° for 40 min, methanol (10 ml) was added, the solvent evaporated, and the residue extracted with benzene to give as an insoluble fraction, anilinotriphenylphosphonium bromide **40** [CH_2Cl_2 soluble, 0.16 g, 0.00037 mol, 4%; mp 200–201°; ir and nmr identical with genuine sample] and aniline hydrobromide (CH_2Cl_2 insoluble, 0.23 g, 0.0013 mol, 16%).

The benzene soluble fraction contained methyltriphenylphosphonium bromide (0.12 g, 0.0003 mol, 4%), triphenylphosphine oxide, aniline, diphenylacetophenone (by tlc), and traces of other products.

Reaction of α-Bromo-α,α-diphenylacetophenone with TPP and Aniline.—Under similar reaction conditions as above, the bromo ketone **8** (3.5 g, 0.01 mol), TPP (2.62 g, 0.010 mol), and aniline (0.93 g, 0.01 mol) were stirred for 20 min, methanol was added, and the procedure outlined above was used to give **40** (3.84 g, 0.0088 mol, 88%), aniline hydrobromide (0.114 g, 0.0007 mol, 7%), diphenylacetophenone, triphenylphosphine oxide (by tlc), trace amounts of other products, and no aniline.

Anilinotriphenylphosphonium Bromide 40.—Bromine (3.20 g, 0.020 mol), in benzene (20 ml) was added dropwise to a mixture of triphenylphosphine (5.24 g, 0.020 mol) and aniline (6.00 g, 0.065 mol) in benzene (50 ml). The resultant mixture was heated at reflux for 2 hr and kept at 25° overnight, and the resulting solid was extracted with chloroform which was evaporated to give an oil which was triturated with benzene to give crude anilinotriphenylphosphonium bromide (4.42 g, 0.010 mol, 50%, mp 112–120°). Two recrystallizations from methanol–ethyl acetate gave white crystals: mp 201–202°; ir ($CHCl_3$) 3.40 (s), 3.65 (m), 6.25 (m), 6.70 (m), 6.90 (m), 8.20 (m), 8.92 (s), 10.30 (s), and 14.90 μ (s); nmr ($CDCl_3$) τ 3.77 (m, 5), 3.20 (m, 15), −0.75 (d, 1, *J* = 9 Hz).

Anal. Calcd for $C_{24}H_{21}BrNP$: C, 66.36; H, 4.84; Br, 18.45; N, 3.22; P, 7.15. Found: C, 66.18; H, 4.96; Br, 18.60; N, 3.41; P, 7.18.

Registry No.—**10**, 26709-95-5; **12**, 26709-96-6; **13a**, 26710-02-1; **14**, 26709-97-7; **15**, 26709-98-8; **27** (+), 26709-55-7; **27** (−), 26709-61-5; **28**, 26709-56-8; **29**, 26731-54-4; **30** (±), 20108-75-2; **30** (−), 13153-89-4; **32**, 26731-55-5; **35** (*dl*), 2328-23-6; **35** (+), 17170-48-8; **35** (−), 1515-99-7; **36a**, 14182-01-5; **36b**, 26709-60-4; **38**, 26697-55-2; **40**, 6395-93-3; **43**, 26710-00-9; **44**, 451-40-1; methyldiphenylphosphine, 1486-28-8; 5,5-dimethyl-3-bromocyclohexanone, 13271-49-3.

Acknowledgments.—We are indebted to Professor Kurt Mislow for prepublication data on optically active phosphines, and Professor D. B. Denney for helpful data in this area. We wish to thank the National Science Foundation for a grant toward the purchase of the Varian time averaging computer and spin decoupler, the National Institutes of Health for a grant used to purchase a Varian A-60A nmr spectrometer, and Professor Grace Borowitz for aid with ^{31}P nmr spectra.

(41) One of the methods used by us is found in K. E. DeBruin and K. Mislow, *J. Amer. Chem. Soc.*, **91**, 7393 (1969). Our error is greater (*ca.* 10%).

(42) The phosphine oxides and ketones resulting from these hydrolyses were identical with genuine samples (ir, nmr, and melting point).

The Reactions of Phosphorus Esters with Phenylmagnesium Bromide

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Received May 27, 1968

The reactions of a variety of different phosphorus esters with phenylmagnesium bromide were investigated in tetrahydrofuran. For a structurally similar series of substituted phosphonates the order of reactivity was found to be *p*-ClPhP(=O)(OEt)$_2$ > PhP(=O)(OEt)$_2$ > *p*-CH$_3$PhP(=O)(OEt)$_2$ > EtP(=O)(OEt)$_2$. These results support the theory that electron-withdrawing substituents increase the susceptibility of the phosphorus atom to nucleophilic attack. Since the ground state energies of these esters appear to be similar, it seems reasonable that electrophilic substituents stabilize the transition state. On the other hand, in structurally dissimilar phosphorus esters, the order of reactivity was observed to be Ph$_2$P(=O)OEt > PhP(=O)(OEt)$_2$ > (EtO)$_3$P(=O)-OEt > EtP(=O)(OEt)$_2$ > (EtO)$_3$P(=O). Infrared spectral evidence indicates that the P=O bond strengths and thus P–O pπdπ overlap in the ground states increase in the reverse orders. Thus, less energy is required to overcome the P=O character in going from the ground state to the transition state of ethyl diphenylphosphinate than of triethyl phosphate. The fact that the order of magnitude of increased reactivity is less in the aliphatic series than in the aromatic series is readily understandable in terms of the different inductive effects on the stability of the transition states. These results are totally consistent with what is known about the effect of substituents on the stability of pentacovalent organophosphorus compounds and the basicity of phosphoryl compounds.

The reactions of phosphorus esters and halides with nucleophilic reagents have been used extensively to synthesize organophosphorus compounds.[1] In contrast, the mechanism of these reactions does not appear to be well understood. For example, nucleophilic displacements on phosphorus in phosphorus esters have been visualized as being facilitated by electron-withdrawing substituents.[2] Whether or not these substituents stabilize the transition state or affect the ground-state energies does not appear to have been established. This problem was first recognized when diethyl phosphonate was found to be much more reactive with regard to methyl and ethyl Grignard reagents than was diethyl phenylphosphonate.[3] Furthermore, the recent finding that either magnesium chloride or bromide retards the reaction of diethyl phenylphosphonate with phenylmagnesium bromide does not clarify the situation.[4] Conceivably, either the magnesium halide–diethyl phenylphosphonate complexes are not formed appreciably in diethyl ether or tetrahydrofuran (THF) in the presence of phenylmagnesium bromide, or, for some other reason, the primary proposal described above fails to explain the relative reactivities of the phosphonate and its complex. In an attempt to answer these questions, the reactions of several similar and different phosphoryl esters with phenylmagnesium bromide were examined in THF at 68°. This system is highly suitable for study for several reasons.[5]

Results

All reactions of the phosphorus esters with phenylmagnesium bromide were carried out under identical conditions because of the difficulties anticipated in determining the rate constants.[2d] The analytical procedure described earlier was used to determine the percentages of the starting ester, the intermediate esters, and the products.[4]

Figure 1 illustrates the effect of electron-withdrawing substituents *vs.* electron-donating substituents on the rate of disappearance of the diethyl phosphonate in its reaction with phenylmagnesium bromide. The infrared spectra of these diethyl phosphonates showed phosphoryl absorptions at nearly the same wavelength indicating that the P=O bond strengths and P=O pπdπ overlap are nearly the same in all four cases.[6] The remaining analytical data for these diethyl phosphonates are presented in Figures 2–5.

Worthy of note is the fact that the *p*-chlorophenyldiphenylphosphine oxide underwent substitution with phenylmagnesium bromide to form triphenylphosphine oxide. Following addition of another equivalent of phenylmagnesium bromide to the reaction mixture, the formation of triphenylphosphine oxide was nearly complete after 24 hr at 68°. Similar displacements of benzene from triphenylphosphine oxide by alkyllithium compounds have been observed previously.[7]

The results of a similar comparative study of triethyl phosphate, diethyl phenylphosphonate, and ethyl diphenylphosphinate are illustrated in Figures 6 and 7. The infrared spectra of these phosphorus esters and triphenylphosphine oxide showed a steady progression of the phosphoryl absorption from 1272 cm^{-1} to 1252 cm^{-1} to 1236 cm^{-1} to 1200 cm^{-1} with increasing substitution of phenyl groups for ethoxy groups. Similarly the phosphoryl absorptions varied for the series triethyl phosphate (1272 cm^{-1}), diethyl ethylphosphonate (1253 cm^{-1}). Figure 8 illustrates the order of reactivity observed for the aliphatic series of phosphorus esters with phenylmagnesium bromide.

O,O-Diethyl phenylthiophosphonate did not react with phenylmagnesium bromide in THF at 68° over a period of 6 hr.

(1) K. D. Berlin, T. H. Austin, M. Peterson, and M. Nagabhushanam, "Topics in Phosphorus Chemistry," Vol. 1, Wiley-Interscience, New York, N. Y., 1964, p 17.

(2) (a) K. D. Berlin and G. B. Butler, *Chem. Rev.*, **60**, 243 (1960); (b) K. D. Berlin, T. H. Austin, and K. L. Stone, *J. Amer. Chem. Soc.*, **86**, 1787 (1964); (c) K. D. Berlin and M. E. Peterson, *J. Org. Chem.*, **32**, 125 (1967); (d) K. D. Berlin and R. U. Pagilagan, *ibid.*, **32**, 129 (1967).

(3) H. R. Hays, *ibid.*, **33**, 3690 (1968).

(4) H. R. Hays, *ibid.*, **33**, 4201 (1968).

(5) Tetrahydrofuran was selected as the solvent because of its higher boiling point and because many of these reactions are heterogeneous in diethyl ether (see ref 2c and 2d). Phenylmagnesium bromide was selected as the Grignard reagent because the reaction products are readily separated and analyzed by gc. The ethyl esters were selected over the methyl esters since the former gave <1% C-alkylation (see ref 2d).

(6) *p*-ClPhP(=O)(OEt)$_2$, 1256 cm^{-1}; PhP(=O)(OEt)$_2$, 1255 cm^{-1}; *p*-CH$_3$PhP(=O)(OEt)$_2$, 1253 cm^{-1}; EtP(=O)(OEt)$_2$, 1253 cm^{-1}. Recorded with a Perkin-Elmer 21 (see ref 9).

(7) D. Seyferth, D. E. Welch, and J. K. Heeren, *J. Amer. Chem. Soc.*, **86**, 1100 (1964).

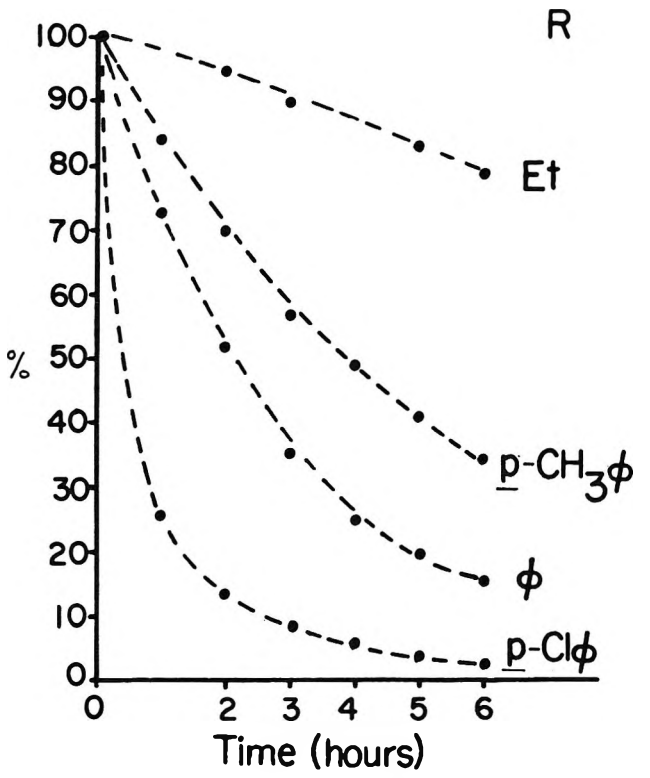


Figure 1.—The per cent of $RP(=O)(OEt)_2$ *vs.* time in the reaction of $RP(=O)(OEt)_2$ with 2PhMgBr in THF at 68°.

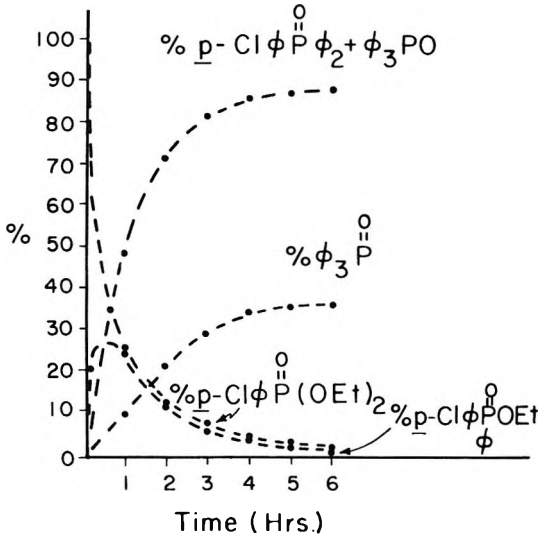
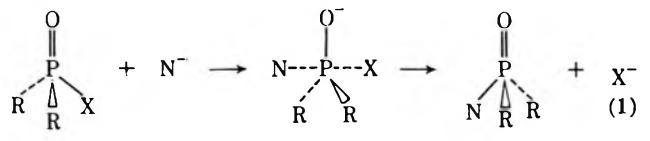


Figure 2.—The reaction of *p*-ClPhP(=O)(OEt)$_2$ with 2PhMgBr in THF at 68°.

Discussion

The reaction of phosphoryl compounds with nucleophiles has been pictured as proceeding *via* a pentacovalent trigonal bipyramidal transition state.[8] Using



this model the results of this investigation can be explained in the following manner in terms of the different effects of substituents on the ground states and the transition states.

The increase in rate of reaction of the four differently substituted diethyl phosphonates with phenylmagne-

(8) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press, New York, N. Y., 1965, pp 53–57.

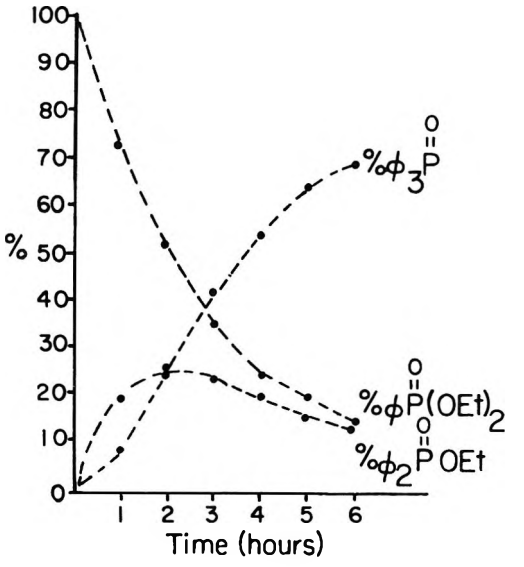


Figure 3.—The reaction of $PhP(=O)(OEt)_2$ with 2PhMgBr in THF at 68°.

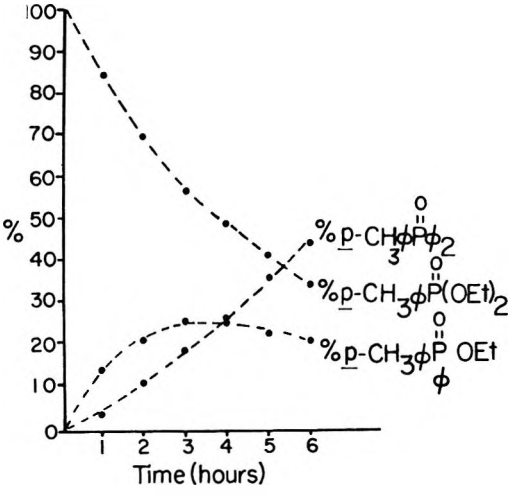


Figure 4.—The reaction of *p*-$CH_3PhP(=O)(OEt)_2$ with 2PhMgBr in THF at 68°.

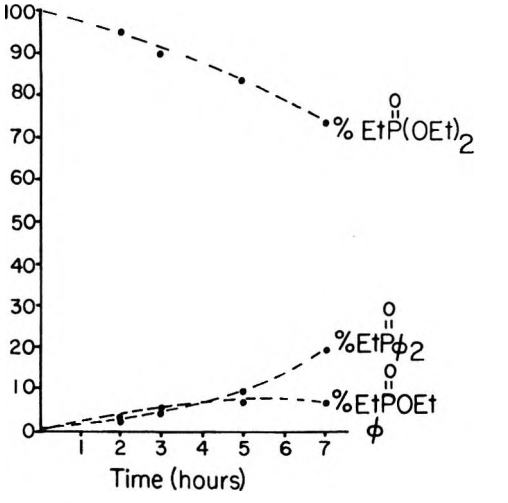


Figure 5.—The reaction of $EtP(=O)(OEt)_2$ with 2PhMgBr in THF at 68°.

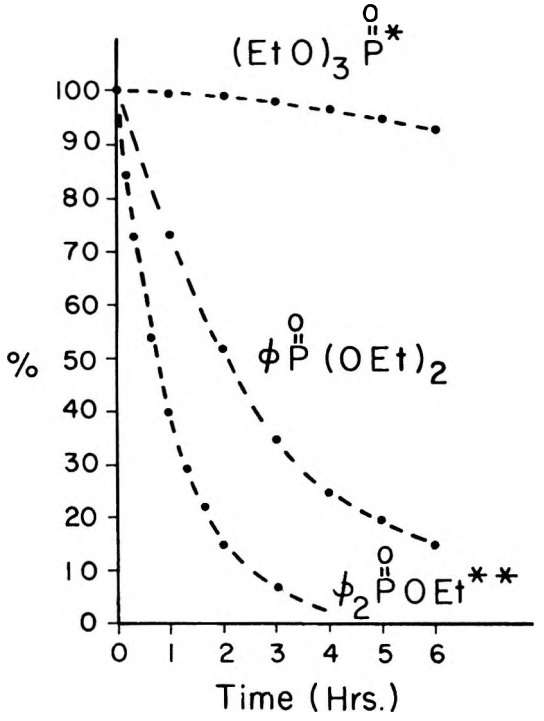


Figure 6.—The per cent of phosphorus ester *vs.* time in the reaction of ester with 2PhMgBr in THF at 68°: *, statistically corrected; **, only 1PhMgBr was used.

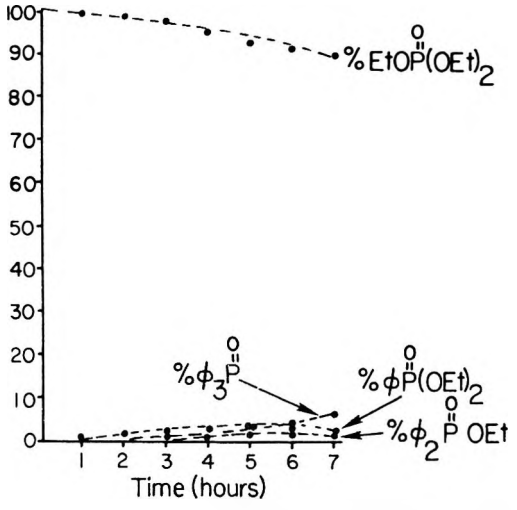


Figure 7.—The reaction of $EtOP(=O)(OEt)_2$ with 2PhMgBr in THF at 68°.

sium bromide is readily seen to parallel the increasingly negative inductive effect of the substituents (Figure 1). Because the four esters are structurally very similar with regard to the central phosphorus atom, these results suggest that the pentacovalent transition state is stabilized by electron-withdrawing substituents. This proposal is not only consistent with the proposal of Berlin and coworkers[2] but also agrees with what is known about stable pentacovalent phosphorus compounds. Thus pentacovalent phosphorus compounds with highly electronegative substituents are markedly more stable than those compounds containing less electronegative substituents.[9] Contingent to this interpretation is the

(9) (a) G. Wittig, "De la chimie du phosphore pentavalent, Composes Organique du Phosphore," Centre National de la Recherche Scientific, 1966, p 145; (b) F. Ramirez, J. F. Pilot, and C. P. Smith, *Tetrahedron*, **24**, 3735 (1968).

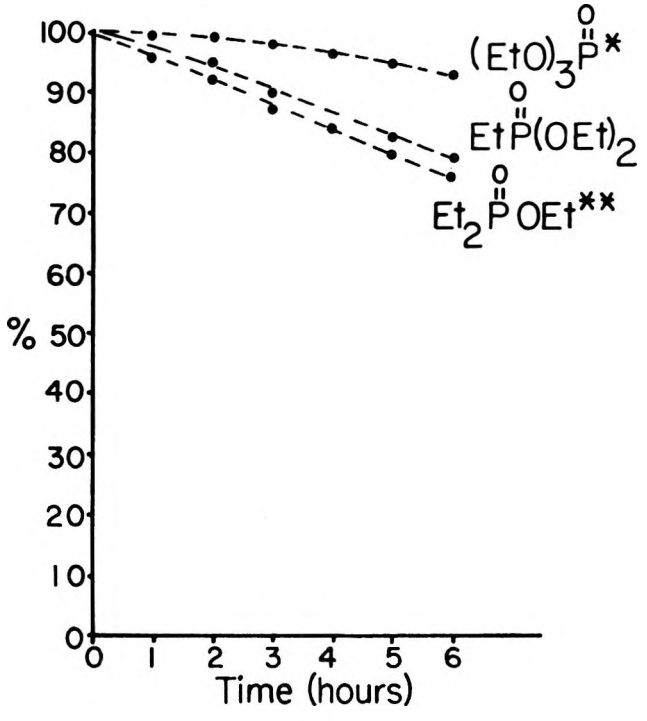


Figure 8.—The per cent of phosphorus ester *vs.* time in the reaction of ester with 2PhMgBr in THF at 68°: *, statistically corrected; **, only 1PhMgBr was used.

belief that the four phosphonate esters have similar ground-state energies. Evidence in support of this belief is the fact that all four of the phosphoryl stretching frequencies which in turn are related to the P=O bond energies and the P=O bond order (in terms of P=O $p\pi d\pi$ overlap)[10] are very nearly the same (± 2 cm^{-1}) for all four of the diethyl phosphonate esters.

In more general terms, the stability of the transition state may also be influenced by factors other than the inductive effect of the substituent on phosphorus. Berlin and Pagilagan[2d] have shown that ethyl diphenylphosphinate and different Grignard reagents react at different rates dependent upon the size of the organic part of the Grignard reagent. That steric factors do not predominate in the preceding series is suggested from the order of reactivity and the fact that a phenyl group is larger than an ethyl group.

In contrast to the four esters described above the order of reactivity of the series of esters, $Ph_2(O=)P$-OEt > $Ph(O=)P(OEt)_2$ > $(EtO)_3(O=)P$, to phenylmagnesium bromide cannot be simply explained by the reasoning described above. If inductive stabilization of the transition state by electron-withdrawing groups were the only factor to consider, the reverse order of reactivity would be expected since the transition state for $(EtO)_3P(=O)$ would be expected to have the lowest energy. This suggests that differences in ground-state energies are the predominant factors in determining the observed order of reactivity in this series. Relatively large differences in ground-state energies in this series would not be surprising in view of the quite different electronic properties of the groups attached to the phosphorus atom. This can be seen more clearly by consideration of the model system shown in eq 1, the P=O

(10) E. L. Wagner, *J. Amer. Chem. Soc.*, **85**, 161 (1963). The phosphoryl absorption frequencies of a wide variety of phosphoryl compounds were shown to correlate very well with the bond orders calculated by the LCAO-MO methods.

bond energies[11] and the P=O stretching frequencies of these three esters. First the model system involves going from a tetrahedral phosphoryl compound with a relatively high degree of P=O $p\pi d\pi$ overlap in the ground state to an anionic pentacovalent transition state in which the negative charge resides largely upon the oxygen atom. In other words the $p\pi d\pi$ overlap between the phosphorus and the phosphoryl oxygen atoms has been greatly diminished if not eliminated in the transition state. Accordingly, any increase in the $p\pi d\pi$ overlap in the phosphoryl group in the ground state, *i.e.*, increase in the phosphoryl bond strength, should markedly increase the activation energy to reach the transition state. The fact that $p\pi d\pi$ overlap in the phosphoryl group is greatest in $(EtO)_3(O{=})P$, next in $Ph(O{=})P(OEt)_2$, and least in $Ph_2(O{=})POEt$, as evidenced by the P=O bond energies[11] and the P=O stretching frequencies, appears consistent with this interpretation of the observed order of reactivity $(EtO)_3(O{=})P < (EtO)_2(O{=})PPh < EtO(O{=})PPh_2$. Inductive stabilization of the transition state by electron-withdrawing groups is important in this series as can be seen below in the comparison with the purely aliphatic esters. However, in the series of $Ph_2(O{=})POEt$, $Ph(O{=})P(OEt)_2$, and $(EtO)_3(O{=})P$, the effect of substituents on the transition state appears of lesser importance than their effect upon the ground state in determining the activation energy.[12]

In the aliphatic series of phosphorus esters the same relative order of reactivity toward phenylmagnesium bromide was observed, *i.e.*, $EtO(O{=})PEt_2 > (EtO)_2(O{=})PEt > (EtO)_3(O{=})P$. This order can also be explained in terms of different ground-state energies as was the case for the aromatic series. However, the order of magnitude of increase in reactivity was not as great as in the aryl series. This is understandable upon consideration of the relative destabilizing effect on the transition state of the electron-donating ethyl group *vs.* the electrophilic phenyl group. This is in spite of even greater decreases in the P=O bond strengths and P=O $p\pi d\pi$ overlap in the aliphatic series than in the aryl series as evidenced by the greater shifts of the P=O stretching frequency to longer wavelengths in going from $(EtO)_3(O{=})P$ to $(EtO)_2(O{=})PEt$ to $EtO(O{=})PEt_2$.

The fact that *O,O*-diethyl phenylthiophosphonate did not react with phenylmagnesium bromide under the same conditions as diethyl phenylphosphonate may be explained in the following manner. From a consideration of the P=S bond energy *vs.* the P=O bond energy, the ground-state energy of the thiophosphonate might be predicted to be larger than that of the phosphonate.[13] However, on the basis of Pauling's electronegativities of sulfur (2.5) and oxygen (3.5), oxygen should stabilize the pentacovalent transition state more than sulfur. This difference in transition energies appears sufficiently great to overcome the difference in ground-state energies.

In view of the fact that electron-withdrawing groups accelerate the reactions of diethyl phosphonates with phenylmagnesium bromide, several questions remain about the manner in which magnesium halides retard the reaction of diethyl phenylphosphonate with phenylmagnesium bromide. If complexation of the phosphonate with magnesium halides occurs as has been suggested, a rate enhancement would be expected on the basis of electronic effects. The fact that a rate decrease is observed suggests one of several alternative effects may predominate. For instance, the highly solvated complex may be hindered to reaction with the Grignard reagent which is also solvated. An alternative explanation is that the mechanism of reaction of the phosphorus ester with the Grignard reagent may require complexation before subsequent reaction. In this case the magnesium halide would compete with the phenylmagnesium bromide for the phosphorus ester. Still another possible explanation is that the phenylmagnesium bromide may be deactivated by complexation with the magnesium halide. At present it is not possible to rule out any of these explanations.

(11) See ref 8, pp 11 and 68.

(12) Several points suggest that the observed order of reactivity is not due to differences in basicity or degree of complexation. First, a separate study [H. R. Hays, *J. Amer. Chem. Soc.*, **91**, 2736 (1969)] indicates ethyl diphenylphosphinate and diethyl phenylphosphonate are completely complexed with the phenylmagnesium bromide under the conditions of the present study. Secondly, the observed order of reactivity $Ph_2(O{=})POEt > Et_2(O{=})POEt$ is exactly opposite of the expected basicity order $Et_2(O{=})POEt > Ph_2(O{=})POEt$. See P. Haake, R. D. Cook, and G. H. Hurse, *ibid.*, **89**, 2650 (1967), and ref 8, p 281. Finally, in the first series of four esters the observed order of reactivity is also exactly the opposite of the anticipated order of basicity.

(13) See ref 8, p 68.

Experimental Section

Starting Materials.—Triethyl phosphate and diethyl ethylphosphonate were obtained commercially. Diethyl phenylphosphonate, ethyl diphenylphosphinate, triphenylphosphine oxide, ethyl diethylphosphinate, and the phenylmagnesium bromide were prepared in an earlier study.[4] *O,O*-Diethyl phenylthiophosphonate was prepared in the same manner as diethyl phenylphosphonate. Diethyl *p*-tolylphosphonate and diethyl *p*-chlorophenylphosphonate were prepared in a separate study.[14] All of the phosphorus esters were freshly distilled and their purity confirmed by gas chromatographic analysis and by their infrared, proton, and phosphorus nmr spectra. The phenylmagnesium bromide was freshly prepared and then analyzed by the double titration method of Vlismas and Parker.[15] The reaction conditions, concentrations, and product analysis were the same as described earlier for the reaction of diethyl phenylphosphonate with phenylmagnesium bromide in THF at 68°.[4] Ethyl diethylphosphinate was so water soluble that repeated extractions of the hydrolysis mixture with diethyl ether followed by drying and concentrating was found to be necessary. Reference samples of the products were prepared in all cases by standard synthesis and their retention times compared with those products of the reactions investigated in this study.

Registry No. —Phenylmagnesium bromide, 100-58-3; *p*-$ClPhP(O)(OEt)_2$, 2373-43-5; $PhP(O)(OEt)_2$, 1754-49-0; *p*-$CH_3PhP(O)(OEt)_2$, 1754-46-7; $EtP(O)(OEt)_2$, 78-38-6; $Ph_2P(O)OEt$, 1733-55-7; $(EtO)_3P(O)$, 78-40-0; $Et_2P(O)OEt$, 4775-09-1; $Ph_3P(O)$, 791-28-6; *p*-ClPhPhP(O)OEt, 4559-69-7; *p*-$CH_3PhP(O)Ph_2$, 6840-28-4; *p*-$CH_3PhPhP(O)OEt$, 26926-25-0; $EtP(O)Ph_2$, 1733-57-9.

Acknowledgment. —The author wishes to express his appreciation to Messrs. J. Adams and B. Banker for their technical assistance and to Drs. D. J. Peterson, C. D. Broaddus, T. J. Logan, and R. G. Laughlin for helpful discussions.

(14) H. R. Hays, *J. Org. Chem.* submitted for publication.

(15) T. Vlismas and R. D. Parker, *J. Organometal. Chem.*, **10**, 193 (1967).

Organic Photochemistry. XII. Further Studies on the Mechanism of Coumarin Photodimerization. Observation of an Unusual "Heavy Atom" Effect[1,2]

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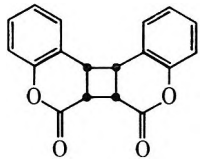
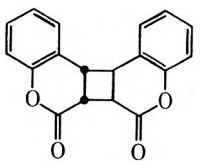
Received June 1, 1970

A detailed study has been made of the photodimerization of coumarin in order to clarify the nature of the mechanism and solvent effects operative in this reaction. Syn head-to-head dimer (IIa) formation has been shown to proceed *via* a singlet precursor and to be markedly enhanced by added sodium perchlorate. The quantum efficiency for IIa formation in acetonitrile is 4.4×10^{-4}. Vapor-pressure osmometry data provide no indication of aggregation in the ground state whereas fluorescence from an excimer species has been observed. A previously proposed mechanism involving such a singlet excimer as a precursor to IIa is invoked. Anti head-to-head dimer (IIb) formation has been shown to be quenched by piperylene (Stern–Volmer slope = 142 M^{-1}) and to reach a maximum efficiency at high concentrations which is less than unity. A mechanism involving one or more intermediates between a monomeric coumarin triplet and photodimer is proposed. Carbon tetrachloride has been shown to be unusually effective in facilitating IIb formation but the effect is not on $^1S \rightarrow {}^1T$ intersystem crossing (ϕ_{ic}). Rather, the fraction of coumarin triplets which successfully go on to dimer is markedly increased. Data for a variety of solvents are reported; in ethyl acetate, $\phi_{ic} = 6 \times 10^{-3}$, $\phi_{r(IIb)} = 5.3 \times 10^{-4}$, $\phi_{r(sens)} = 0.07$ (sensitization by benzophenone), and the rate constant for initial reaction of coumarin triplet with ground state coumarin to form intermediate is 3.5×10^8 l. mol^{-1} sec^{-1}.

Some time ago, we reported[4] on the photodimerization of coumarin (I), in which the major products are the syn and anti head-to-head cyclobutane dimers, IIa and IIb. In that report, we noted a number of



IIa



IIb

interesting features which characterized this reaction[4,5] and made its continued study of considerable general interest. Thus, a remarkable solvent effect is observed whereby IIb is the unique dimer in nonpolar solvents while both IIa and IIb form in polar media. Equally curious was the fact that the syn–anti ratio in polar media is increased by high concentrations and low temperature. Despite this concentration effect, no Beer's law deviation for coumarin ultraviolet absorption spectra is observed. Preliminary studies suggested that formation of the anti dimer but *not* the syn isomer can be quenched by piperylene (photosensitization leads only to the anti product).

To account for these results, we suggested that dimerization to IIa might proceed *via* a singlet excimer (^{1}CC*), with IIb probably arising from the coumarin triplet state. Such a proposal of excimer intermediacy in solution phase photodimerization was, at the time, sufficiently unique[6] and of such potential general import that a search for additional evidence clearly was called for. Furthermore, the nature of the solvent effects, the unanswered questions regarding heavy-atom perturbation of the reaction and catalysis by traces of benzophenone, and the obvious need for quantitative quenching, quantum yield, and rate data all made an extended study of coumarin photodimerization imperative.

Results

IIa Formation.—Earlier work had demonstrated that photodimerization of coumarin is solvent dependent, with IIa being formed only in acetonitrile, dimethylformamide, and methanol among the solvents tried.[4] To confirm that this effect is, in fact, a product of solvent polarity and to test the possibility that photochemical salt effects could be used as a mechanistic probe, we examined the photodimerization of coumarin in acetonitrile containing various concentrations of sodium perchlorate (see Table I).[10] In these and other experiments to be discussed, the coumarin concentration was 0.3 *M* and rigorously dry conditions were maintained. The data confirm a strong dependence of IIa formation on solvent polarity; a smaller, but nevertheless real, enhancement of IIb formation is also observed.

An obvious alternative to excimer formation from monomeric coumarin excited singlet states is the preformation of ground state aggregates which may be directly excited to polymeric excited states.[5] We[4] and others[11] have observed no deviation from Beer's law in the absorption spectra of coumarin. An alternate test for ground state interaction is offered by molecular weight determination; data obtained using vapor pressure osmometry are presented in Table II. The actual molecular weight of coumarin is 146; the average of the data presented in Table II is 1475, within experimental error of the calculated value. There is no apparent solvent effect on the data obtained.

A study of coumarin emission was undertaken with

(1) Abstracted from the Ph.D. Thesis of Richard Hoffman, Purdue University, 1970. Presented at the 159th National Meeting of the American Chemical Society, Feb 23–27, 1970, Houston, Texas.

(2) Part XI: see H. Morrison and W. I. Ferree, Jr., *Chem. Commun.*, 268 (1969).

(3) Author to whom inquiries concerning this paper should be addressed.

(4) H. Morrison, H. Curtis, and T. McDowell, *J. Amer. Chem. Soc.*, **88**, 5415 (1966).

(5) C. H. Krauch, S. Farid, and G. O. Schenck, *Chem. Ber.*, **99**, 625 (1966).

(6) Analogy could be found in the proposal of excimer formation associated with photodimerization of *crystalline* 9-cyanoanthracene,[7] and an "excited complex" as an intermediate leading to the solution-phase photodimerization of anthracene.[8] Competition between excimer formation and photodimerization for 9-methylanthracene had been suggested.[9] A number of proposals of excimer and exciplex intermediacy in photoreactions have since appeared.

(7) B. Stevens, T. Dickinson, and R. R. Sharpe, *Nature*, 877 (1964).

(8) A. Dammers-de-Klerk, *Mol. Phys.*, **1**, 141 (1958).

(9) R. L. Barnes and J. B. Birks, *Proc. Roy. Soc., Ser. A*, **291**, 570 (1966).

(10) A preliminary account of this research has been published: H. Morrison and R. Hoffman, *Chem. Commun.*, 1453 (1968).

(11) C. H. Krauch, personal communication.

TABLE I

EFFECT OF SODIUM PERCHLORATE ON COUMARIN DIMERIZATION IN ACETONITRILE[a]

$NaClO_4$, M	IIa	IIb
0.00	(1.0)	(1.0)
0.01	1.2	
0.02	1.3	
0.03	1.4	
0.05	2.0	
0.10	1.7	1.2
0.30	2.8	
0.50	3.2	
1.00	3.8	
1.25	5.0	1.4
1.50	5.0	
2.00	6.4	1.7

[a] The data are presented as conversions into dimers in salt solutions relative to conversions in pure acetonitrile.

TABLE II

VAPOR PRESSURE OSMOMETRY DATA FOR COUMARIN

Solvent	Concn, M	Mol wt
Acetone	0.025	150
Benzene	0.025	150
	0.025	148
Methanol	0.025	145
	0.025	144
	0.10	148

the hope of finding direct evidence for coumarin excimers. Attempts to obtain fluorescence spectra at room temperature were uniformly unsuccessful, presumably because of the weakness of emission and persistence of trace impurities (others have experienced similar difficulties[12,13]). However, Lamola has been able to detect coumarin fluorescence at 77°K using ethanol and methylcyclohexane glasses.[12] The fluorescence in ethanol is structured with a maximum at 370 mμ. Dilute solutions (10^{-4} M) of coumarin in methylcyclohexane show, in addition to the structured emission, a featureless band with a maximum at 405 mμ. We have subsequently repeated the ethanol observation; for comparison, we chose isopentane as the hydrocarbon glass and observed the long wavelength emission. This long wavelength, unstructured fluorescence is reasonably assigned to excimer emission with the shorter wavelength, structured fluorescence being derived from monomeric coumarin singlets.[12] The absence of coumarin excimer in the ethanol glass is, in all likelihood, a simple consequence of the much higher viscosity (10^{12} *vs.* 10^{4} poise)[14,15] and thus diminished diffusion[15] in the alcohol glass by comparison with the hydrocarbon media.

Quenching experiments using *cis*-piperylene in acetonitrile solutions have shown the formation of IIa to be insensitive to as much as a 0.3 M concentration of the diene; at that concentration, IIb formation is completely quenched (see Figure 1).

The quantum efficiency for formation of IIa was determined in acetonitrile, a solvent in which IIa and IIb are formed with equal efficiency[17] (the measurement was actually made on IIb). The value obtained is $\phi = 4.4 \times 10^{-4}$.

IIb Formation.—Several factors made a more detailed investigation of IIb formation in various solvents desirable. The relative rate of dimerization to this isomer in polar *vs.* nonpolar media had not previously been measured (the same information was lacking for the syn dimer). Also, a small but positive salt effect had been observed for IIb (*cf.* Table I) and a further evaluation of the effect of halogen atoms on the dimerization seemed called for.[10] Along these same lines, our entry into the coumarin system had been motivated by the hope of observing large heavy-atom effects on a photochemical reaction;[4] the initial studies proved inconclusive and warranted extension. Relative solvent efficiencies were determined by suitable turntable studies; these numbers were then put on an absolute basis by a measurement of the quantum efficiency of IIb formation (ϕ_r) in carbon tetrachloride. The data are collected in Table III. A comparison of the acetonitrile, glyme, and ethyl acetate values shows that $\phi_{r(IIb)}$ is essentially independent of solvent polarity; in other words, the high IIb:IIa ratio in nonpolar solvents must be a consequence of a requirement by IIa for polar media. Of greater import are the halocarbon data. As in our earlier study,[4] propyl bromide shows a modest increase over the other solvents. *However, the high value for carbon tetrachloride now unambiguously confirms that halocarbon enhancement of IIb formation exists.*

Quenching studies in ethyl acetate using *cis*-piperylene gave data which have been plotted in the usual Stern–Volmer fashion in Figure 1. ϕ and ϕ_0 represent the quantum efficiencies for formation of IIb in the presence and absence of quencher. The straight line drawn is a least-squares fit of the data and has a slope of 142

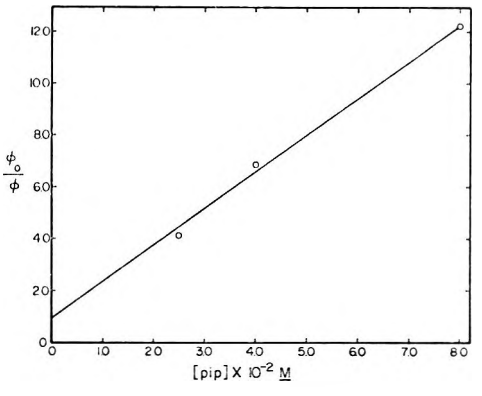


Figure 1.—Stern–Volmer plot of the quenching of IIb formation by *cis*-piperylene in ethyl acetate.

± 5 (std dev). No marked quenching of coumarin fluorescence at low temperature by 0.1 M piperylene was observed. The anti dimer has previously been shown to form upon photosensitized dimerization of coumarin[18] and it appears reasonable that a triplet precursor is involved in the direct irradiation as well.

(12) A. Lamola, personal communication.

(13) C. R. Wheelock, *J. Amer. Chem. Soc.*, **81**, 1348 (1959).

(14) H. Greenspan and E. Fischer, *J. Phys. Chem.*, **69**, 2466 (1965).

(15) J. W. Hilpern, G. Porter, and L. J. Stief, *Proc. Roy. Soc., Ser. A*, **277**, 442 (1964).

(16) We have found efficient (collisional) intermolecular quenching in an isopentane glass can be completely eliminated by placing quencher (10^{-2} M) and quenchee in an ethanol medium: R. Peiffer, unpublished data.

(17) Earlier data,[4] which show a 5:1 ratio of IIb *vs.* IIa in acetonitrile, have been replaced by more recent and accurate measurements.

(18) G. O. Schenck, I. Von Wilucki, and C. H. Krauch, *Chem. Ber.*, **95**, 1409 (1962).

TABLE III

QUANTUM EFFICIENCIES FOR IIb FORMATION IN VARIOUS SOLVENTS[a]

Solvent	$\phi_{r(IIb)}$ Absolute ($\times 10^4$)	$\phi_{r(IIb)}$ Relative
Acetonitrile	4.4	(1.0)[b]
Glyme	4.4	1.0
Ethyl acetate	5.3	1.2
Dioxane	12.	2.7
Toluene[c]	15.	3.5
Propyl bromide	17.	3.9
Carbon tetrachloride	35.	8.0

[a] All data are for 0.30 *M* coumarin. [b] The value for IIa in acetonitrile is 1.0. [c] Substituted for benzene because of the unexplainably wide variation of data using benzene from different sources, even after its extensive purification.

It was, of course, tempting to view the marked enhancement of IIb formation in carbon tetrachloride (Table III) as a manifestation of the heavy-atom effect on $^1S \rightarrow {}^1T$ intersystem crossing which we had been seeking. The net effect would then be increased formation of triplets and a concomitant increase in the triplet (*e.g.*, IIb) dimer. A direct measure of such intersystem crossing (ϕ_{ic}) was made by triplet counting with *cis*-piperylene.[19,20] The data are shown in Table IV. It is evident that the *high efficiency of IIb formation in carbon tetrachloride is not mirrored by an analogous increase in* ϕ_{ic} *in this solvent* (the highest value is, in fact, observed with methanol).

TABLE IV

INTERSYSTEM CROSSING EFFICIENCIES FOR COUMARIN IN VARIOUS SOLVENTS[a]

Solvent	ϕ_{ic} Absolute ($\times 10^3$)	ϕ_{ic} Relative
Ethyl acetate	6.3	0.9
Acetonitrile	7.0	(1.0)
Toluene	9.6	1.4
Carbon tetrachloride	11.	1.6
Methanol	12.	1.7

[a] Coumarin at 0.3 *M*, *cis*-piperylene at 0.10 *M*.

Since IIb appears to be derived from the coumarin triplet state, but coumarin intersystem crossing from $^1S \rightarrow {}^1T$ is not markedly affected by solvent, *the enhancement of reaction observed in carbon tetrachloride must be a result of an increased efficiency of triplet dimerization.* This rather intriguing possibility can be directly tested by examining the quantum efficiency of *sensitized* dimerization to IIb ($\phi_{r(sens)}$) as a function of solvent;[24] the data are gathered in Table V. The relative efficiencies presented in Table V correlate well with the order previously noted for IIb formation (Table III); *appreciable enhancement in carbon tetrachloride is now observed as predicted.* Note that the aromatic solvent toluene also shows unusual efficiency and that the $\phi_{r(sens)}$ values appear to be maximized and independent of concentration (Table V, footnote *b*).

TABLE V

SENSITIZED DIMERIZATION TO IIb IN VARIOUS SOLVENTS[a]

Solvent	$\phi_{r(sens)}$ Absolute	$\phi_{r(sens)}$ Relative
Acetonitrile	0.02	(1.0)
Ethyl acetate	0.07	3.5
Toluene[b]	0.23	11.5
Carbon tetrachloride	0.30	15.0

[a] Solutions were 0.3 *M* in coumarin; benzophenone was used as sensitizer. [b] In one run, the coumarin concentration was raised to 2.0 *M* without effect on $\phi_{r(sens)}$.

Finally, experimental conditions were devised to test the validity of the double energy transfer hypothesis put forward by Hammond, Stout, and Lamola.[25] These workers had observed marked enhancement of coumarin photodimerization in the presence of small amounts of benzophenone, and suggested singlet energy transfer from coumarin to benzophenone was followed by a triplet–triplet back transfer to the coumarin. We irradiated coumarin in the presence of 0.006 *M* benzophenone using filters to assure that coumarin absorbed 99.9% of the incident light. The results are shown in Table VI, where $\phi'_{r(IIb)}$ refers to the quantum efficiency measured for solutions containing traces of nonabsorbing benzophenone. Previous $\phi_{r(IIb)}$ data from Table III are relisted for purposes of comparison. Table VI

TABLE VI

PHOTODIMERIZATION OF COUMARIN TO IIb IN SOLUTIONS CONTAINING TRACES OF NONABSORBING BENZOPHENONE

Solvent	$\phi'_{r(IIb)}$ $\times 10^2$	$\phi_{r(IIb)}$ $\times 10^2$
Ethyl acetate	1.3	0.53
Toluene	2.0	1.2
Carbon tetrachloride	3.5	3.5

demonstrates that the large (factor of ten), previously observed[25,4] enhancement of IIb formation by small amounts of benzophenone was an artifact caused by direct excitation of benzophenone molecules and not a consequence of double energy transfer.[25] Under our conditions, absorption is restricted almost entirely to coumarin and only slight increases are observed. That the increase in ethyl acetate is indeed real, although small, was shown by measuring ϕ_{ic} for coumarin in the presence of (nonabsorbing) benzophenone. The value found, 14×10^{-3}, compares to the value of 6.3×10^{-3} in the absence of benzophenone. The difference between these numbers represents the percentage (*ca.* 1%) of the incident photons which eventually gives rise to triplets through the intermediacy of the benzophenone, either by singlet transfer from coumarin or by light leakage into the benzophenone or both.

Discussion

The pertinent facts regarding IIa formation are now as follows. Coumarin solutions give no positive evidence of aggregation when tested by Beer's law and molecular weight studies. The syn dimer, IIa, is derived

(19) A. A. Lamola and G. S. Hammond, *J. Chem. Phys.*, **43**, 2129 (1965).

(20) The validity of such a probe for a solvent effect on ϕ_{ic} derives from the fact that benzophenone gives a solvent *independent* rate for sensitized isomerization of piperylene[21] (and stilbene[22]). In addition, there is evidence the the photostationary state for sensitized piperylene isomerization is likewise solvent independent.[23]

(21) R. Kleopfer, these laboratories, unpublished data.

(22) S. G. Cohen, M. D. Saltzman, and J. B. Guttenplan, *Tetrahedron Lett.*, 4321 (1969).

(23) P. J. Wagner and J. D. Buchek, *J. Amer. Chem. Soc.*, **91**, 5090 (1969).

(24) The assumption being made here is that benzophenone's intersystem crossing efficiency ($\phi_{ic} = 1$) is independent of solvent; the data cited in ref 20 support such an assumption.

(25) G. S. Hammond, C. A. Stout, and A. A. Lamola, *J. Amer. Chem. Soc.*, **86**, 3103 (1964).

from the coumarin singlet state (*e.g.*, the reaction is not quenchable with piperylene) and must be formed *via* an intermediate and/or transition state involving a "sandwiched," head-to-head configuration of coumarin molecules. Since no other singlet dimer is formed to any appreciable extent, this intermediate–transition state is particularly favorable. The syn dimer requires high concentrations of coumarin for its formation, since the IIa:IIb ratio in methanol can be reversed by dilution; low temperatures increase the amount of IIa formed relative to IIb. Formation of IIa is quite inefficient ($\phi = 4.4 \times 10^{-4}$ in acetonitrile) and, since intersystem crossing is minimal ($\phi_{ic} = 8.8 \times 10^{-3}$ in acetonitrile), the overwhelmingly dominant process(es) for the coumarin singlet state involves decay to the ground state. Finally, the existence of coumarin excimers has now been confirmed through luminescence experiments.

It is our feeling that the above cited data continue to support our proposal that IIa formation proceeds through the intermediacy of coumarin singlet excimers, and an appropriate mechanism is outlined in eq 1–6.[26] $^1CC^*$ represents the excimer species; the low efficiency of dimerization and intersystem crossing requires that the rates of steps 2 and/or 6 far exceed those of 3 and 5.[27]

$$C \xrightarrow{h\nu} {}^1C^* \quad (1)$$

$${}^1C^* \longrightarrow C \quad (2)$$

$${}^1C^* \longrightarrow {}^3C^* \quad (3)$$

$${}^1C^* + C \rightleftharpoons {}^1CC^* \quad (4)$$

$${}^1CC^* \longrightarrow \text{IIa} \quad (5)$$

$${}^1CC^* \longrightarrow 2C \quad (6)$$

Of considerable interest is the fact that IIa formation is favored by a high dielectric medium, whereas excimer emission is observed in hydrocarbon glasses. If excimers are involved, the requirement for polarity must then be *not* at the excimer forming step 4, but at the dimerization stage 5. That is to say, excimer formation occurs in all media but is unproductive in all save the highly polar solvents.[28]

The anti dimer, IIb, is now clearly established as a product of the coumarin triplet state. However, the fact that the efficiency of sensitized dimerization to IIb was unchanged by a sevenfold increase in coumarin concentration (Table V, footnote *b*), requires that unimolecular triplet radiationless decay is *not* the factor responsible for the limiting $\phi_{r(sens)}$ being less than unity (*e.g.*, 0.23 in toluene). That is to say, for coumarin, as for several other molecules actively discussed recently, one or more intermediates must precede formation of the dimer.[23,29,30] The fraction of intermediate which goes on to dimer rather than decaying to the coumarin ground state then represents the limiting, *concentration independent*, quantum efficiency for formation of IIb. The mechanism (which extends the above 1–6 for the singlet state) is outlined in eq 7–11; eq 7 is parenthesized since we have just argued that this step is negligible at the concentrations of coumarin studied. $^3C_2^*$ represents a bimolecular triplet intermediate formed by the reaction of a coumarin triplet monomer with a coumarin ground state species. The nature (and number) of these intermediates is a matter of conjecture. Cole has proposed a triplet excimer precursor for IIb;[27b] Wagner and Bucheck[23] have proposed that the triplet dimerization of cyclopentenone and cyclohexenone proceed *via* an initial charge-transfer complex followed by formation of a 1,4 diradical. The latter authors argue that the rate of intermediate formation (6.6×10^8 for cyclopentenone; 1.1×10^8 for cyclohexenone) is too rapid to be associated with direct formation of the diradical. To the extent that this argument has validity it must equally well be applied to the coumarin case since our values for that rate constant are remarkably similar (see below). It is hard to say whether a charge-transfer complex or a triplet excimer would better accomodate the highly stereospecific triplet dimerization, or, in fact, to what extent such a differentiation has meaning.

$$({}^3C^* \longrightarrow C) \quad (7)$$

$${}^3C^* + C \longrightarrow {}^3C_2^* \quad (8)$$

$${}^3C_2^* \longrightarrow \text{IIb} \quad (9)$$

$${}^3C_2^* \longrightarrow 2C \quad (10)$$

$${}^3C^* + Q \longrightarrow C + {}^3Q^* \quad (11)$$

Some fascinating solvent effects have turned up in this study which warrant further comment. To facilitate discussion, the pertinent data are recollected in Table VII. To begin with, the first column shows data abstracted from Table III, whereby carbon tetrachloride is unusually effective in giving rise to IIb formation. This effectiveness is *not* mirrored by enhancement of intersystem crossing, however; in fact, coumarin intersystem crossing in methanol is more efficient than in carbon tetrachloride (*cf.* Table IV). (*These data make clear the necessity for unambiguous proof of enhanced* $^1S \rightarrow {}^1T$ *intersystem crossing in halocarbon solvents, before the assumption of such a "heavy-atom" effect is invoked as a rationale for facile triplet photodimerization.*[31])

TABLE VII

COMPILED QUANTUM EFFICIENCIES FOR COUMARIN

Solvent	$10^3 \phi_{r(IIb)}$	$10^3 \phi_{ic}$	$\phi_{r(sens)}$
Acetonitrile	0.44	7.0	0.02
Ethyl acetate	0.53	6.3	0.07
Toluene	1.5	9.6	0.24
Carbon tetrachloride	3.5	11.	0.30

(26) It should be made clear that 1% aggregation in acetonitrile (which would be unobservable experimentally) combined with a ϕ of 0.04 for *aggregate photodimerization* would suffice to give an overall ϕ of 4×10^{-4} as observed. However, in the absence of direct evidence in its favor, we can see no purpose in including such a hypothesis in the proposed mechanism. Further studies related to this point are in progress.

(27) (a) Cole[27b] has proposed that photocleavage of singlet coumarin may be responsible for the considerable energy wastage. (b) R. S. Cole, *Diss. Abstr.*, **29**, 933-B (1968).

(28) Even in such media, however, the quantum efficiency date require that for coumarin decay *via* steps 2 and/or 6 far outweighs steps 3 and 5.

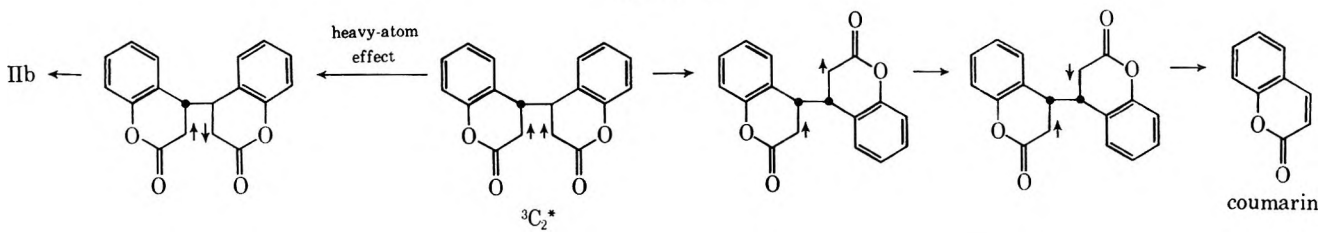
(29) C. DeBoer, *J. Amer. Chem. Soc.*, **91**, 1855 (1969).

(30) See also (a) P. J. Wagner and D. J. Bucheck, *J. Amer. Chem. Soc.*, **90**, 6530 (1968); (b) P. de Mayo, A. A. Nicholson, and M. F. Tchir, *Can. J. Chem.*, **47**, 711 (1969); (c) P. J. Wagner and D. J. Bucheck, *ibid.*, **47**, 713 (1969); (d) R. O. Loutfy, P. de Mayo, and M. F. Tchir, *J. Amer. Chem. Soc.*, **91**, 3985 (1969).

(31) One system for which such additional study was warranted is acenaphthylene photodimerization, wherein halocarbon effects have been noted and attributed to enhanced $^1S \rightarrow {}^1T$ intersystem crossing.[32] In fact, we observe a 20-fold increase in ϕ_{ic} for acenaphthylene in going from toluene to carbon tetrachloride as solvent.[21]

(32) D. O. Cowan and R. L. Drisko, *J. Amer. Chem. Soc.*, **89**, 3068 (1967); I. M. Hartmann, W. Hartmann, and G. O. Schenck, *Chem. Ber.*, **100**, 3146 (1967).

SCHEME I



Carbon tetrachloride's ability to enhance formation of IIb does show up in the quantum efficiencies for sensitized dimerization ($\phi_{r(sens)}$) which, at the concentrations being used (*cf.* Table V, footnote *b*), must represent the fractions of coumarin triplets which productively lead to dimer, *e.g.*, $k_9/(k_9 + k_{10})$.[33-35] A possible explanation for a "heavy-atom" effect at this stage of the reaction can be derived if one assumes that $^3C_2$* is a triplet 1,4 diradical (see above). Such a diradical should, in part, undergo bond closure to form dimer *via* an intersystem crossing step *but such closure should also have to compete with rotation about the central (initially formed) carbon–carbon bond.*[36] The rotated diradical would be geometrically unable to close to dimer and could only undergo cleavage to give back two coumarin molecules (again simultaneous with an intersystem crossing step).

Thus, any enhancement of closure at the initial diradical stage should shorten the lifetime of that species, reduce bond rotation, and result in a net enhancement in dimer formation. Since closure is essentially an intersystem crossing process, external heavy atoms might facilitate bond formation and increase the efficiency of the product forming step. The proposal is summarized in Scheme I. With respect to Scheme I, it is interesting to note that the efficiency with which the diradical partitions to dimer in the "normal" solvents is comparable to values previously observed for thymine (4%)[30a] and dimethylthymine (3%),[21] but well below that reported for cyclopentenone (36%) and cyclohexenone (74%).[23]

There is no *a priori* reason for the effect being proposed here to be limited to *external* heavy atoms or even to dimerization. For example, it has been reported[37] that sensitized cycloaddition of maleic anhydride to *cis*-dichloroethylene gives two cycloadducts in which the cis orientation of the vicinal chlorine atoms is maintained. In this case, bond rotation in a hypothetical diradical intermediate would have been expected to give some *trans*-dichloro product and this unexpected retention of stereochemistry may be a result of an internal heavy-atom effect. A variety of triplet reactions thought to proceed through diradical intermediates are currently being tested in order to evaluate the generality of these observations.

An estimate of the rate constant for formation of the initial intermediate (k_8) can be made from the piperylene quenching data. The slope of the Stern–Volmer plot is equal to $k_{11}/k_8[C] + k_7$ or, at the concentrations of coumarin employed (see above), $k_{11}/k_8[C]$. With a slope of 142 l. mol^{-1}, a coumarin concentration of 0.3 *M*, and a calculated k_{11} (assuming diffusion control) of 1.5×10^{10} l mol^{-1} sec^{-1}, k_8 becomes equal to 3.5×10^8 l. mol^{-1} sec^{-1} (in ethyl acetate). This is the same range as the rate constants calculated for the dimethylthymine (7×10^7, ethyl acetate),[21] cyclopentenone (1.1×10^8, acetonitrile),[23] and cyclohexenone (6.6×10^8, acetonitrile)[23] systems.

Experimental Section

Materials—Coumarin and benzophenone (both from Eastman) were used as received. Acetonitrile (Baker analytical reagent), benzene (bulk grade, thiophene free), and toluene (Baker reagent) were dried batchwise over calcium hydride and distilled. Carbon tetrachloride (Baker spectral grade and Mallinckrodt spectral and analytical reagent grades), ethyl acetate (Matheson Coleman and Bell, anhydrous 99.5%), *n*-hexane (Phillips spectral grade), propyl bromide (Matheson Coleman and Bell, analytical reagent grade), and methanol (Fisher spectral grade) were treated with Fisher Type 4A molecular sieve and distilled.

Glyme (Ansul Co.) and dioxane (Matheson Coleman and Bell spectroquality) were freed of peroxides by refluxing 100 ml of solvent per gram of $SnCl_2 \cdot 2H_2O$ for 2 hr, dried over calcium hydride, and distilled. A negative test with 2% KI and HCl was taken to indicate these ethers to be peroxide free. *cis*-Piperylene (Chemical Samples Co). was distilled immediately prior to use and was glpc pure cis isomer.

Spectral and Physical Data.—Infrared spectra were obtained *via* chloroform or acetonitrile solutions on a Beckman IR-8. Ultraviolet spectra were obtained from a Bausch and Lomb 505, a Cary 14, or a Cary 15. Melting points were from a Fisher–Johns hot stage. Vapor pressure osmometry analyses were by Dr. C. S. Yeh of this department. All glpc data were obtained on a Varian Aerograph Model 90-P chromatograph linked to a Leeds and Northrup Co. Speedomax H recorder with a disk integrator. Emission measurements were done on an Aminco–Bowman spectrophotofluorometer Model 4-8202 and recorded on a Sargent recorder Model SR.

Irradiation Equipment.—Most comparative runs were done on on a turntable device holding eight 25-mm-o.d. photolysis tubes. This turntable rotated the tubes about a 450-W, Hanovia type L mercury arc lamp set in a water cooled, quartz immersion well. The turntable and tubes were in a constant temperature water bath maintained at 30°. Cylindrical filters (30–32 mm o. d. × 20 cm long) fitted around the lamp provided short wavelength cutoff. The most common filter was Kimble Flint Glass (0% transmission at 305 mμ; 50% transmission at 315 mμ; transparent beyond 345 mμ).

A Rayonet photochemical reactor, Model RPR-100, and a motor driven turntable, Model MGR-100, both purchased from the Southern New England Ultraviolet Co., were used in some experiments. This reactor contains 16 vertically mounted ultraviolet lamps arranged in a circle. Two different sets of lamps were used: RPR-300 Å, and RPR-3500 Å. The reactor has a cooling fan and the temperature inside the chamber is maintained at a constant 34° during irradiation. In some cases,

(33) The high values for toluene throughout Table VII are anomalous; the possibility is always present that trace impurities are responsible (*cf.* Table III, footnote *c*).

(34) An alternate represention of $k_9/(k_9 + k_{10})$ should be $\phi_{r(IIb)}/\phi_{ic}$. In fact, $\phi_{r(sens)} \cong \phi_{rIIb}/\phi_{ic}$ in carbon tetrachloride but the identity does not hold for several of the other solvents. The differences are outside experimental error and their origin is under investigation.

(35) There is no evidence for a change in reaction mechanism in carbon tetrachloride; the residue after solvent evaporation still gives almost quantitative amounts of coumarin and anti dimer.

(36) A number of reports in the literature support such a hypothesis; representative examples are P. D. Bartlett and N. A. Porter, *J. Amer. Chem. Soc.*, **90**, 5317 (1968); M. Jones, Jr., and R. H. Levin, *ibid.*, **91**, 6411 (1969); E. L. Allred and R. L. Smith, *ibid.*, **91**, 6766 (1969); N. J. Turro and P. A. Wriede, *ibid.*, **92**, 320 (1970).

(37) R. Steinmetz, W. Hartmann, and G. O. Schenck, *Chem. Ber.*, **98**, 3854 (1965).

the turntable was replaced by a double chambered quartz vessel mounted in a jig for accurately reproducing the position of the vessel between actinometric and photolytic runs. Whenever this vessel was used, the outer chamber of the vessel contained 600 ml of a saturated solution of $NiSO_4$ in water and the entire vessel was surrounded by a Pyrex tube. With this filtering, the (uranyl oxalate) actinometry solution and the reaction mixture both absorbed all of the incident light. The inner chamber (with an insert to reduce the volume) held 300 ml of solution and the level of the filter solution was 1 in. above the level of this reaction solution. The path length of the filter solution was 10 mm and that of the reaction solution was 11 mm. After a number of actinometric measurements were taken in the quartz well, it was found that the intensity of the 3500 Å lamps decreases from an initial high of 3.0×10^{17} $h\nu$/sec to a constant value of $2.38 \pm 0.1 \times 10^{17}$ $h\nu$/sec in about 6 hr. This lower value is then constant for at least 149 hr.

A Bausch and Lomb high-intensity grating monochromator (No. 33-86-25-05) was used in one determination. The reaction vessel was a water jacketed cell with flat quartz faces, a 6-cm path length, and 60-ml volume. The cell contents were stirred with a magnetic stirrer.

Analytical Procedure.—The procedure for IIb analysis was a modification of that previously described.[4] The reaction mixture was sublimed prior to chromatography in order to remove unreacted coumarin and authentic IIb was prechromatographed on the silica column in order to eliminate final traces of water. Hydrolysis of IIb is the major obstacle to accurate analysis and every effort must be made to prevent contact of the reaction mixture with moisture. Overall yields in these reactions were approximately 95% with conversions kept to less than 25%.

Typical Salt Effect Tube.—A typical tube for studying salt effects contained 2.2 g of coumarin, an appropriate amount of $NaClO_4$, and sufficient acetonitrile to make a total volume of 45 ml. A concentrated solution was prepared by weighing the dried $NaClO_4$ into a volumetic flask and filling to volume with acetonitrile. This was then used as a stock solution, diluting as desired in the photolysis tube. All tubes were degassed by bubbling argon through them for 1 hr and irradiated in the turntable about the 450-W mercury lamp. The data are in Table VIII.

TABLE VIII
SALT EFFECT DATA

Run[a] no.	[$NaClO_4$], M	IIa, mg	IIb, mg
1		96	58
2		87	55
3		92	99
4		110	139
4		117	
5		113	119
5		117	111
1	0.01	114	79
1	0.02	126	58
1	0.04	139	90
2	0.05	174	88
2	0.10	104	101
3	0.10	158	
2	0.30	243	89
2	0.50	282	65
2	1.00	332	79
3	1.25	433	150
2	1.50	438	140
4	2.00	710	221
4	2.00	632	134
5	2.00	753	207
5	2.00		202

[a] All samples in a given run were irradiated together.

Quenching by Piperylene.—A typical reaction mixture contained 2.2 g of coumarin and 45 ml of solvent. After degassing, distilled *cis*-piperylene was added to the solution by weighing a syringe before and after the addition. If isomerization of the diene was to be observed by glpc, 0.220 ml of *n*-hexane was also added to the tube to serve as an internal standard. The data are collected in Table IX.

TABLE IX
QUENCHING OF IIb FORMATION BY *cis*-PIPERYLENE IN ETHYL ACETATE[a]

[Piperylene], M	IIb, mg	ϕ_0/ϕ
0	99.2	
0	96.4	
0.025	22.1	4.4
0.025	25.3	3.9
0.040	14.2	6.9
0.040	14.4	6.8
0.080	8.0	12.2

[a] Samples were irradiated for 120 hr using the high-pressure lamp and a soft glass filter.

Determination of $\phi_{r(IIb)}$.—This reaction was run in a Rayonet reactor (with 3500 Å lamps) in the quartz well. The reaction mixture contained 300 ml of carbon tetrachloride and 13.16 g of coumarin (0.30 M). The solution was irradiated for 74 hr and 6 min at an intensity of $2.37 \pm 0.04 \times 10^{17}$ $h\nu$/sec for a total of 0.105 einsteins. The IIb isolated was 108 mg (3.7×10^{-4} mol); therefore the quantum yield of dimerization of coumarin to IIb in carbon tetrachloride is 3.5×10^{-3}.

Determination of ϕ_{ic}.—The reaction was run in the Rayonet reactor (3500 Å lamps) with the quartz well. The reaction mixture contained 13.16 g of coumarin (0.30 M), 2.087 g of *cis*-piperylene (0.10 M), 1.32 ml of *n*-hexane, and 300 ml of carbon tetrachloride. Irradiation for 139 hr at an initial intensity of 2.55×10^{17} $h\nu$/sec (lamp on 3 hr) and a final intensity of 2.38×10^{17} $h\nu$/sec gave a weighed average of 2.38×10^{17} $h\nu$/sec (lamps decay to this constant value after about 6 hr and remain constant). The per cent trans isomer was 3.9 and 4.1% (average 4.0 ± 0.1%).

Since the reaction initially contained 3.07×10^{-2} mol of *cis*-piperylene, 4% trans isomer represents 1.23×10^{-3} mol. As the quantum yield for cis → trans isomerization is 0.55, 2.23×10^{-3} mol of coumarin triplets were quenched. The total incident energy was 0.198 einsteins and the quantum efficiency for intersystem crossing for coumarin in carbon tetrachloride is therefore 1.1×10^{-2}.

Determination of Relative ϕ_{ic} Values.—This study was made using the Rayonet reactor (3500 Å lamps) and its associated turntable. Pyrex photolysis tubes provided the high-energy cutoff (0% transmission at 280 mμ; 50% transmission at 310 mμ).

The relative quantum efficiency of intersystem crossing of coumarin was measured by observing the isomerization of piperylene according to the method of Lamola and Hammond.[19] The isomerization was measured by glpc on a 20 ft, 20%, β,β′-oxydipropionitrile on Chromosorb W (acid washed) column, which was cooled in an ice bath. The helium flow was 110 cc/min. The internal standard used, *n*-hexane, showed that no loss of piperylene occurred.

Pure *cis*-piperylene was used at a concentration (0.1 M) which would quench greater than 90% of the dimerization to IIb. Since piperylene absorbs no light of wavelength longer than 280 mμ (at 0.1 M), the coumarin absorbed all of the incident energy (none of the solvents absorb in the region of 310–360 mμ).

Each tube in the reaction contained 2.2 g of coumarin (0.33 M), 0.340 g of *cis*-piperylene (0.10 M), 220 μl of *n*-hexane, and 45 ml of solvent. Duplicate tubes were irradiated with each of the following solvents: acetonitrile, methanol, toluene, and carbon tetrachloride.

The injections for each tube gave four values of the per cent *trans*-piperylene for each solvent. The values and an average value (after 10 hr of irradiation) were: acetonitrile, 4.5, 5.5, 5.0, and 5.1% (average of the best three was 5.2 ± 0.3%); methanol, 9.5, 9.8, 9.4, and 8.7% (average 9.6 ± 2%); toluene, 8.4, 7.3, 7.5, and 7.8 (average 7.5 ± 0.3%); carbon tetrachloride, 8.4, 8.2, 8.6, and 8.4% (average 8.4 ± 0.2%). The relative ϕ_{ic}'s were: acetonitrile, 1.0; methanol, 1.7; toluene, 1.4; carbon tetrachloride, 1.6.

In a similar run, carbon tetrachloride and ethyl acetate were compared (but this time with the 3000 Å lamps in the Rayonet). The per cent of trans isomer found in ethyl acetate were 3.6 and 3.5% for an average of 3.6%, in carbon tetrachloride 6.5 and 6.1% for an average of 6.3 ± 0.2%. The relative ϕ_{ic}'s (on the same

scale as above) were: ethyl acetate, 0.9; carbon tetrachloride, 1.6.

Determination of $\phi_{r(sens)}$.—To determine the sensitized quantum yield of IIb formation ($\phi_{r(sens)}$), the Bausch and Lomb monochrometer apparatus was used. The grating was set at 366 mμ and the exit slit was opened to 3.4 mm. A 70-min irradiation of 60 ml of standard actinometry solution (done before and after the reaction) gave about 5% decomposition of oxalic acid. The initial intensity was 4.03×10^{16} $h\nu$/sec and the final intensity was 4.15×10^{16} $h\nu$/sec for an average of $4.09 \pm 0.06 \times 10^{16}$ $h\nu$/sec.

For the reaction, 2.656 g of coumarin (0.303 *M*), 1.110 g of benzophenone (0.101 *M*), and 60 ml of carbon tetrachloride were degassed for 1 hr with nitrogen and then irradiated (with stirring) for 8 hr. Benzophenone absorbs all of the incident energy at this wavelength and concentration (at 366 mμ $\epsilon_{\phi 2co}$ 50; ϵ_{cou} 0.11). The IIb isolated was 173 mg (0.593 mmol), thus giving $\phi_{r(sens)} = 0.30$

Determination of Relative $\phi_{r(sens)}$ Values.—This determination was made using the 450-W mercury arc lamp–turntable system. A corex filter was used and soft glass tubes were irradiated for 3 hr. Table X shows the initial contents of the tubes and the amounts of IIb isolated after the reaction.

TABLE X

RESULTS OF $\phi_{(sens)}$ (RELATIVE) EXPERIMENT

Solvent	Coumarin, g	Benzophenone, g	IIb, g
Toluene	2.215		(0.012)[a]
Toluene	2.215	0.0496	0.842
Ethyl acetate	2.250		(0.004)
Ethyl acetate	2.225	0.0489	0.272
Acetonitrile	2.225		(0.004)
Acetonitrile	2.237	0.0491	0.086
Carbon tetrachloride	2.219		0.028
Carbon tetrachloride	2.192	0.0497	1.090

[a] Parenthesized values are estimates based on the carbon tetrachloride value of 28.

From the amounts of IIb formed and the ϕ_r and $\phi_{r(sens)}$ values for carbon tetrachloride, it was calculated that benzophenone absorbed 0.012 einsteins and coumarin absorbed 0.27 einsteins of light during the irradiation.

Determination of $\phi'_{r(IIb)}$.—The apparatus for this experiment was the Rayonet reactor with 3500 Å lamps and the quartz well with $NiSO_4$ and Pyrex filters. Coumarin absorbs >99.88% of the incident light under the conditions of the reaction which were 13.16 g of coumarin (0.30 *M*), 0.337 g of benzophenone (0.006 *M*), and 300 ml of ethyl acetate.

The irradiation time was 62 hr, 25 min. The initial intensity was 2.31×10^{17} $h\nu$/sec and the final intensity was 2.49×10^{17} $h\nu$/sec, for an average of $2.40 \pm 0.9 \times 10^{17}$ $h\nu$/sec. The IIb isolated was 34 mg (1.16×10^{-4} mol), $\phi'_{r(IIb)} = 1.3 \times 10^{-3}$.

Comparable experiments were run with carbon tetrachloride and toluene as solvents. The data here were 9 mg of IIb ($\phi'_{r(IIb)} = 3.1 \times 10^{-3}$) and 13 ± 3 mg of IIb ($\phi'_{r(IIb)} = 2 \pm 1 \times 10^{-3}$), respectively.

Determination of ϕ_{ic} for Coumarin, Trace of Benzophenone Present.—The apparatus for this experiment was the Rayonet reactor (with 3500 Å lamps) and the quartz well. The reaction mixtue contained 13.184 g of coumarin (0.30 *M*), 2.049 g of *cis*-piperylene (0.10 *M*), 1.3 ml of *n*-hexane, 0.349 g of benzophenone (0.006 *M*), and 300 ml of ethyl acetate. Since the intensity of the lamps in this system was 2.4×10^{17} $h\nu$/sec in every previous determination, this value was assumed. The irradiation was carried out for 95 hr giving a total energy absorbed by coumarin of 0.136 einsteins.

Initially the ratio of standard to piperylene was 1.00:2.44. After irradiation, the ratio in two trials was 1.00:2.42, showing no loss of piperylene. The per cent of trans isomer found in two trials was 3.5 and 3.7% for an average of 3.6 ± 1% trans (1.08×10^{-3} mol) which implies quenching of 1.96×10^{-3} mol of coumarin triplets. Thus ϕ_{ic} was found to be 1.4×10^{-2}.

Registry No.—I, 91-64-5; IIa, 5248-11-3; IIb, 5248-12-4.

Acknowledgments.—We are grateful to the Public Health Service (Grant No. CA-10733, National Cancer Institute) and the Purdue Research Foundation (David Ross Fellowship to R. H., 1967–1969) for generous support of this research. We also wish to thank Dr. Angelo Lamola for kindly making his emission data available to us.

4-Thio-D-arabinofuranosylpyrimidine Nucleosides[1]

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Received February 13, 1970

Reaction of 2,3,5-tri-*O*-benzoyl-4-thio-β-D-arabinofuranosyl bromide (II) with the appropriate trimethylsilylated pyrimidine has led to the preparation and isolation of the α-D and β-D forms of 1-(4-thio-D-arabinofuranosyl)uracils (Va and Vb) and the β-D forms of thymine VIIb and cytosine IXb. The synthesis of IXb has also been accomplished by ammonolysis of 1-(2,3,5-tri-*O*-benzcyl-4-thio-β-D-arabinofuranosyl)-4-thiouracil (X).

1-(β-D-Arabinofuranosyl)cytosine has been shown to possess significant carcinostatic activity,[2,3] as well as a broad spectrum antiviral activity[4-9] *in vitro* against DNA viruses. Here we describe the preparation of the nucleoside analog in which the ring oxygen of the sugar moiety is replaced by a sulfur atom. The syntheses of 1-(4-thio-β-D-arabinofuranosyl)thymine (VIIb) and both anomers of 1-(4-thio-D-arabinofuranosyl)uracil (Va and Vb) are also described.

The synthesis of methyl 4-thio-β-D-arabinofuranoside from D-glucose has been reported.[10] This compound is

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(1) This work was supported by the National Institutes of Health, Education and Welfare Grant No. IROI AM 11463, Journal Paper No. 3979, of the Purdue Agricultural Experiment Station, Lafayette, Ind. 47907.

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converted to 2,3,5-tri-*O*-benzoyl-4-thio-β-D-arabinofuranosyl bromide (II) according to a procedure given by Ness and Fletcher.[11] Assignment of the β-D configuration to the major product formed is based on its being more levorotatory than the minor product α-D-III. Also, the greater coupling constant *J* for the β-D anomer is consistent with the cis relationship of the hydrogen atoms on C-1 and C-2.

Displacement of bromide ion from II by trimethylsilyl derivatives[12] of uracil and thymine leads to the formation of anomeric mixtures of the benzoylated nucleosides, which are separated chromatographically. Nishimura and Shimizu[13] have used similar procedures in their synthesis of the anomeric pyrimidine nucleosides of D-arabinofuranose. Debenzoylation is achieved by treatment of the blocked nucleosides with sodium in methanol.

1-(4-Thio-β-D-arabinofuranosyl)cytosine (IXb) is prepared by two methods. Reaction of II with bis(trimethylsilyl)-*N*-acetylcytosine yields a mixture of the anomeric forms of the blocked nucleosides, from which the β-D anomer (VIIIb) crystallizes. The other method of producing this nucleoside involves thiation[14] of 1-(2,3,5-tri-*O*-benzoyl-4-thio-β-D-arabinofuranosyl)uracil (IVb) to its 4-thiouridine analog X. This derivative, upon treatment with methanolic ammonia, gives 1-(4-thio-β-D-arabinofuranosyl)cytosine (IXb).

It has been observed,[15] previously, that the optical rotatory relationship of the anomeric pyrimidine nucleosides do not obey Hudson's isorotation rules. These exceptions to Hudson's rules have been found to hold for the anomeric D-arabinofuranosyluracils[13] and is further supported by the optical rotatory dispersion (ORD) measurements on a large number of pyrimidine nucleosides.[16] The anomeric configuration of the nucleosides described here cannot be assigned from ORD measurements since both anomers show positive Cotton effects in blocked and unblocked forms. Tentative anomeric configurations are assigned on the basis that the β-D anomer is expected in greatest yield. Far less significant is the observation that benzoylated β-D anomers have had, in our hands, the slowest chromatographic mobilities on silica gel G in solvent C.

Experimental Section

Analytical Methods.—Purity of products was determined by thin layer chromatography (tlc) on silica gel G[17] coated glass plates (5 × 13 cm) irrigated with (a) benzene–ethyl acetate (6:1), (b) hexane–ethyl acetate (4:1), (c) benzene–ethyl acetate (10:1), (d) chloroform–acetone (15:1), (e) chloroform–acetone (30:1), and (f) chloroform–acetone (9:1). Solvent ratios are based on volumes. Components were located by spraying with 5% sulfuric acid in ethanol and heating until permanent char spots were visible. Melting points were determined on a Fisher–Johns apparatus and are corrected. Nuclear magnetic resonance (nmr) spectra were obtained with a Varian Associates A-60 instrument. Evaporations were done under diminished pressure with a bath temperature below 40°. Absorption chromatography was made on silica gel.[18] Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter.

Methyl 2,3,5-Tri-*O*-benzoyl-4-thio-β-D-arabinofuranoside (I).—To a stirred, ice-cooled solution of methyl 4-thio-β-D-arabinofuranoside (9 g, 0.05 mol) in 100 ml of dry pyridine was added benzoyl chloride (23.26 g, 0.165 mol) dropwise over a period of 30 min. Benzoylation was complete in 2 hr as monitored by tlc in solvent A. The reaction mixture was poured into 600 ml of ice and water under stirring and stirring continued for 2 hr at which time the mixture was extracted with 500 ml of chloroform. The chloroform extract was washed sequentially with water, 2 *N* hydrochloric acid until slightly acidic, 1 *N* sodium hydroxide solution until slightly alkaline, and water until neutral. The chloroform solution so washed was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under diminished pressure to obtain 25 g of pure syrup methyl 2,3,5-tri-*O*-benzoyl-4-thio-β-D-arabinofuranoside (I): $[\alpha]^{25}D$ −174.3° (*c* 1.05, $CHCl_3$). Compound I was used directly for the preparation of the bromo sugar.

Anomeric 2,3,5-Tri-*O*-benzoyl-4-thio-D-arabinofuranosyl Bromides (II and III).—To a stirred solution of compound I (25 g) in 125 ml of glacial acetic acid was added 125 ml of 32% (w/w) hydrogen bromide in glacial acetic acid. The reaction mixture was stirred for 20 min at 25° during which time the entire mass solidified. This was diluted with 750 ml of dry methylene chloride. The solution was poured into 2.5 l. of ice and water and the organic layer was quickly washed sequentially with water, a 10% aqueous sodium bicarbonate solution, and water. The washed methylene chloride solution was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under diminished pressure at a bath temperature of 30°. The residue solidified when concentrated and was recrystallized from methylene chloride–hexane (75 ml:300 ml). Needle-shaped crystals of 2,3,5-tri-*O*-benzoyl-4-thio-β-D-arabinofuranosyl bromide (II) separated: yield 22 g; mp 126°; $[\alpha]^{25}D$ −171° (*c* 1, CH_2Cl_2).

Anal. Calcd for $C_{26}H_{21}BrO_6S$: C, 57.67; H, 3.91; Br, 14.56; S, 6.05. Found: C, 57.80; H, 4.03; Br, 14.58; S, 6.05.

Further concentration of the mother liquors produced 5 g more of II to give a total yield of 27 g. Additional concentration produces a small amount of the α-D anomer III: $J_{1,2}$ = 4.5 cps for II and 0 cps for III.

Anomeric 1-(2,3,5-Tri-*O*-benzoyl-4-thio-D-arabinofuranosyl)-uracils (IVa and IVb).—A stirred mixture of 5.41 g (0.01 mol) of compound II and 3.84 g (0.015 mol of bis(trimethylsilyl)uracil was heated on an oil bath at 130–135° for 3 hr in a current of dry nitrogen. During this time the bromo sugar II disappeared as indicated by tlc in solvent B. The yellowish gummy product was refluxed for 20 min with 50 ml of 95% ethanol. After evaporation of the solvent under diminished pressure, the residue was taken into benzene and refluxed for 5 min and filtered. The filtrate was concentrated to a brownish yellow syrup which was applied to a silica gel column (40 × 1.5 cm) prepared in benzene. The column was eluted with 1 l. of benzene, which removed the olefinic contaminants. The column was then eluted with solvent C and the nucleoside fractions collected on a fraction collector. The nucleoside fractions containing both α-D and β-D anomers IVa and IVb were combined and concentrated to a foam (1.3 g) which was dissolved in 20 ml of hot ethyl acetate. On cooling, pure 1-(2,3,5-tri-*O*-benzoyl-4-thio-β-D-arabinofuranosyl)uracil (IVb) crystallized as small needles: yield 2.1 g; mp 208–209°; $[\alpha]^{25}D$ −13.8° (*c* 1, $CHCl_3$); ORD (*c* 0.004, $CHCl_3$) $[\phi]_{275}$ +4100°, $[\phi]_{247}$ −21,800°.

Anal. Calcd for $C_{30}H_{24}N_2O_8S$: C, 62.93; H, 4.22; N, 4.89; S, 5.60. Found: C, 63.03; H, 4.25; N, 4.87; S, 5.86.

The filtrate after separation of the β-D anomer IVb when examined by tlc in solvent D (plate developed three times) showed the presence of more β-D anomer (minor) and the α-D anomer (major). By repeated silica gel chromatography using solvent E as eluent the α-D anomer IVa (550 mg, 8.7%) and 300 mg more of the β-D anomer IVb were collected. Total yield of 1-(2,3,5-tri-*O*-benzoyl-4-thio-β-D-arabinofuranosyl)uracil (IVb) was 2.4 g, 42%. The α-D anomer IVa was recrystallized from ethanol: mp 127–128°; $[\alpha]^{25}D$ +12.3° (*c* 1, $CHCl_3$); ORD (*c* 0.004, $CHCl_3$) $[\phi]_{287}$ +14,900°, $[\phi]_{262}$ −29,500°.

Anal. Found: C, 62.92; H, 4.40; N, 4.77; S, 5.87.

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1-(4-Thio-α-D-arabinofuranosyl)uracil (Va).—To a solution of 50 mg of sodium in 10 ml of neat methanol was added a solution of compound IVa (700 mg) in 30 ml of warm neat methanol. This was stirred at 25° for 18 hr. The reaction mixture was deionized using methanol-washed Amberlite IR 120 (H^+) resin and filtered. The filtrate was concentrated under diminished pressure to a solid which was triturated with absolute ether to remove methyl benzoate and filtered. The precipitate was recrystallized from neat methanol to yield 266 mg of 1-(4-thio-α-D-arabinofuranosyl)uracil (Va): mp 214–215°; $[\alpha]^{25}D$ +57.7° (*c* 1, H_2O); uv $\lambda_{max}^{H_2O}$ mμ (ε, pH) 265 (10,000, 3.2), 265 (10,700, 7.0), 265 (9600, 9.6), 267 (8600, 14.0); ORD (*c* 0.004, $CHCl_3$) $[\phi]_{285}$ +9740°, $[\phi]_{251}$ −14,430°,

Anal. Calcd for $C_9H_{12}N_2O_5S$: C, 41.49; H, 4.65; N, 10.77; S, 12.33. Found: C, 41.58; H, 4.83; N, 10.86; S, 12.11.

1-(4-Thio-β-D-arabinofuranosyl)uracil (Vb).—The β-D anomer was debenzoylated in a manner similar to that used for the α-D-anomer. 1-(4-Thio-β-D-arabinofuranosyl)uracil (Vb) was crystallized from neat methanol to yield 600 mg: mp 194–195°; $[\alpha]^{25}D$ +117.8° (*c* 1, H_2O); uv $\lambda_{max}^{H_2O}$ mμ (ε, pH) 264 (10,700, 3.2), 264 (10,400, 7.0), 264 (11,400, 9.6), 266 (9200, 14.0); ORD (*c* 0.004, $CHCl_3$) $[\phi]_{286}$ +4740°, $[\phi]_{262}$ −4410°.

Anal. Found: C, 41.26; H, 4.65; N, 10.71; S, 12.09.

Anomeric 1-(4-Thio-D-arabinofuranosyl)thymines (VIIa and VIIb).—In a procedure similar to that described above for 1-(2,3,5-tri-*O*-benzoyl-4-thio-D-arabinofuranosyl)uracils, the bromo sugar II (5.41 g, 0.01 mol) was condensed with bis(trimethylsilyl)-thymine (4.05 g, 0.015 mol). After chromatographic purification on silica gel, 3.1 g of the anomeric 1-(2,3,5-tri-*O*-benzoyl-4-thio-D-arabinofuranosyl)thymines (VIa and VIb) was obtained. Debenzoylation with a catalytic amount of sodium methoxide followed by deionization with methanol-washed Amberlite IR 120 (H^+) resin gave the anomeric mixture of 1-(4-thio-D-arabinofuranosyl)thymines (VIIa and VIIb). Crystallization from neat methanol gave 0.76 g (27.7%) of pure 1-(4-thio-β-D-arabinofuranosyl)thymine (VIIb): mp 209–210°; $[\alpha]^{25}D$ +136° (*c* 1, H_2O); uv $\lambda_{max}^{H_2O}$ mμ (ε, pH) 270 (10,900, 3.2), 270 (10,400, 7.0), 270 (10,200, 9.6), 271 (8500, 14.0); ORD (*c* 0.004, $CHCl_3$) $[\phi]_{290}$ +10,900°, $[\phi]_{247}$ −22,600°.

Anal. Calcd for $C_{10}H_{14}N_2O_5S$: C, 43.78; H, 5.14; N, 10.22; S, 11.69. Found: C, 44.26; H, 5.05; N, 10.40; S, 11.93.

Anomeric 1-(2,3,5-Tri-*O*-benzoyl-4-thio-D-arabinofuranosyl)-*N*-acetylcytosines (VIIIa and VIIIb).—Bis(trimethylsilyl)-*N*-acetylcytosine and the bromo sugar II (5.41 g, 0.01 mol) were condensed as described for 1-(2,3,5-tri-*O*-benzoyl-4-thio-D-arabinofuranosyl)uracils. After chromatographic purification using solvent F, the nucleoside fractions were collected to give 1.5 g of the mixture of the α-D and β-D anomers VIIIa and VIIIb. A thin layer chromatogram developed five times in solvent D showed the two distinct anomers. Recrystallization from ethyl acetate gave 1.23 g of 1-(2,3,5-tri-*O*-benzoyl-4-thio-β-D-arabinofuranosyl)-*N*-acetylcytosine (VIIIb): mp 226–227°; $[\alpha]^{25}D$ +15.8° (*c* 1, $CHCl_3$); ORD (*c* 0.004, $CHCl_3$) $[\phi]_{267}$ +19,000°, $[\phi]_{248}$ −27,700°.

Anal. Calcd for $C_{32}H_{27}O_8N_3S$: C, 62.63; H, 4.44; N, 6.85; S, 5.22. Found: C, 62.41; H, 4.42; N, 6.80; S, 5.43.

1-(4-Thio-β-D-arabinofuranosyl)cytosine (IXb).—A solution of compound VIIIb (1.2 g) in 50 ml of absolute methanol was saturated with dry NH_3 gas at 0° and kept in the refrigerator for 2 days. The mixture was then evaporated to dryness and triturated with dry ether three times to remove benzamide and methyl benzoate. The residual solid was recrystallized from dry methanol to give 450 mg of 1-(4-thio-β-D-arabinofuranosyl)cytosine (IXb): mp 210–211°; $[\alpha]^{25}D$ +143° (*c* 1, H_2O). uv $\lambda_{max}^{H_2O}$ mμ (ε, pH) 280 (12,100, 3.2), 274 (9700, 7.0), 274 (10,600, 9.6), 275 (9600, 14).

Anal. Calcd for $C_9H_{13}O_4N_3S$: C, 41.69; H, 5.05; N, 16.20; S, 12.38. Found: C, 41.45; H, 5.07; N, 16.19; S, 12.40.

1-(2,3,5-Tri-*O*-benzoyl-4-thio-β-D-arabinofuranosyl)-4-thiouracil (X).—A mixture containing 6.292 g (0.011 mol) of IVb, 10.77 g of phosphorus pentasulfide, and 150 ml of reagent grade pyridine was refluxed for 5 hr. About half of the pyridine was removed under diminished pressure and the dark brown colored solution was poured into stirred water where compound X started solidifying. The solid product was filtered and the precipitate was taken into chloroform and filtered from insoluble material. The chloroform solution was washed twice with water and dried over anhydrous sodium sulfate. After filtration the chloroform solution was concentrated to a yellow solid foam which was crystallized from hot ethanol to give 4.96 g of compound X as yellow needles: mp 156–157°; $[\alpha]^{24}D$ +6.4° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{30}H_{24}O_7N_2S_2$: C, 61.21; H, 4.11; N, 4.76; S, 10.89. Found: C, 61.37; H, 4.11; N, 4.89; S, 10.86.

1-(4-Thio-β-D-arabinofuranosyl)cytosine (IXb).—Compound X (1.178 g, 0.002 mol) was treated with 160 ml of anhydrous methanolic ammonia (previously saturated at −5 to 0°) in a sealed tube at 110–115° for 18 hr. After the tube was opened, the contents were transferred to a round-bottomed flask and concentrated under reduced pressure to a solid. The solid was triturated with ether to remove benzamide and the residual solid dissolved in hot methanol and decolorized with charcoal. The methanolic solution was filtered and then concentrated under diminished pressure to a solid which was recrystallized from hot methanol to give 0.37 g of compound IXb: mp 210–211°; $[\alpha]^{25}D$ +143° (*c* 1, H_2O).

Registry No.—I, 26527-29-7; II, 26527-30-0; III, 26527-31-1; IVa, 26527-32-2; IVb 26527-33-3; Va, 26527-34-4; Vb, 26527-35-5; VIIb, 26527-36-6; VIIIb, 26527-37-7; IXb, 26599-17-7; X, 26527-38-8.

The Synthesis of (±)-Hexahydropronuciferine and Related Compounds[1]

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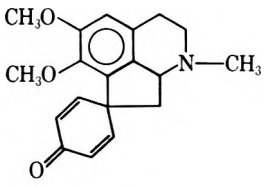
Received May 18, 1970

In an effort to develop a new synthetic approach to the proaporphine alkaloids, a method for effecting the conversion of a suitably substituted 1-indanone to a hexahydrocyclopent[*ij*]isoquinoline has been developed. Bobbitt's modification of the Pomeranz–Fritsch reaction applied to 4,5-dimethoxy-1-indanone affords the corresponding cyclopentisoquinoline (**5**) in acceptable yield. By the same procedure demethoxydeoxystepharine (**11**) was prepared from spiroindanone (**7**), which was in turn synthesized in three steps from 2-bromoanisole and ethyl cyanocyclohexylidineacetate. This procedure was extended to the total synthesis of (±)-hexahydrostepharine (**26**) by subjecting spiroindanone (**12**) to the modified Pomeranz–Fritsch reaction. The indanone was prepared from 4-cyano-2,3-dimethoxycyclohexanone (**14**) by reduction to the hydroxy aldehyde (**19**), homologation, and oxidation to the requisite acetic acid (**24**) followed by polyphosphoric acid cyclization. Methylation of **26** gave (±)-hexahydropronuciferine (**27**).

The proaporpine alkaloids, of which pronuciferine (**1**) is a typical example, constitute a relatively small, but important, group of alkaloids.[2] The structural features of the basic skeleton of these alkaloids pose two



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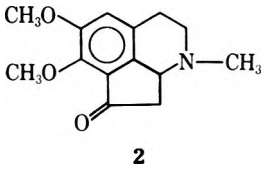

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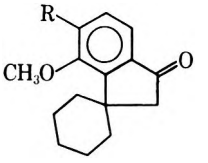
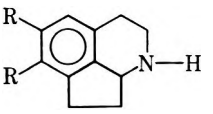
major obstacles to their synthesis, which are, first, the formation of a suitably substituted C-7a quaternary carbon atom[3] and, second, the synthesis of the requisite hexahydrocyclopent[*ij*]isoquinoline. Both these problems were overcome simultaneously in the biogenetic type syntheses of these alkaloids by the oxidation of appropriate benzylisoquinoline precursors;[4] however, the yields are very low. The stepwise total synthesis of pronuciferine reported by Bernauer[5] utilized the cyclopentisoquinolone **2** as a starting material, with the cyclohexadienone ring constructed by more or less standard techniques.

In an effort to devise an alternative synthetic approach to these alkaloids, it was felt that a reversal of Bernauer's route, namely synthesis of an appropriately substituted indanone (for example **3**) containing the quaternary C-7a carbon but lacking the heterocyclic ring, might prove promising. Since compounds related to **3** appeared *a priori* to be less than readily available, and in view of the inherent perversity of the Pomeranz–Fritsch reaction,[6] various model syntheses directed toward the conversion of simple indan derivatives to compounds **4** and **5** were undertaken.

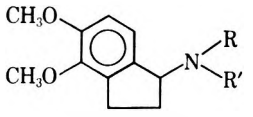
The successful conversion of *N*-benzylglycine derivatives to 4-oxotetrahydroisoquinolines has been reported;[7] however, the attempted cyclization of a number of N-substituted *N*-(4,5-dimethoxyindanyl)glycine derivatives (**6**) failed to yield any identifiable products.[8]



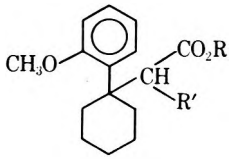
3, R = OCH_3
7, R = H



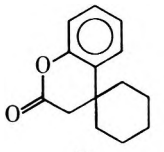
4, R, R = H
5, R, R = OCH_3



6, R = $CH_2C_6H_5$ or CHO; R′ = CH_2CO_2H or CN



8, R = C_2H_5; R′ = CN
9, R; R′ = H



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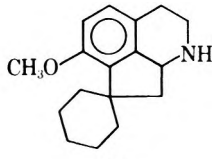

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The desired conversion of 4,5-dimethoxy-1-indanone to **5** in 54% yield was finally accomplished by means of Bobbitt's modification of the Pomeranz–Fritsch reaction.[9] Initial attempts to carry out this reaction failed; however, when the reaction was carried out under scrupulously anhydrous conditions with the exclusion of oxygen the conversion of the indanone to **5** proceeded smoothly.[10] The nmr spectrum of **5** was in accord with the assigned structure, with the aromatic proton appearing as a singlet at δ 6.45. The benzyl and methylene protons adjacent to nitrogen appeared as a complex multiplet in the δ 2.2–3.2 region. The benzylic methine proton adjacent to nitrogen was a triplet at δ 3.77, partially obscured by the methoxyl singlets.

With a method in hand for converting indanones to cyclopent[*ij*]quinolines, approaches to the preparation of an indanone containing an appropriate spirocyclo-

* To whom correspondence should be addressed.

(1) (a) A preliminary communication describing a portion of this work appeared in *Tetrahedron Lett.*, 5243 (1969). (b) Abstracted in part from the Ph.D. Dissertation of C. E. Opliger, Clemson University, Dec 1969. (c) This work was supported in part by Career Development Award GM-5433 from the National Institutes of Health.

(2) K. L. Stuart and M. P. Cava, *Chem. Rev.*, **68**, 321 (1968).

(3) The numbering system is that suggested by the authors in ref 2.

(4) (a) D. H. R. Barton and T. Cohen, *Festschr. Prof. Dr. Arthur Stoll Siebzigsten Geburtstag*, 117 (1957); (b) A. H. Jackson and J. A. Martin, *J. Chem. Soc. C*, 2222 (1966).

(5) (a) K. Bernauer, *Experientia*, **20**, 380 (1964); (b) K. Bernauer, *Helv. Chim. Acta*, **51**, 1120 (1968).

(6) W. J. Gensler, *Org. React.*, **6**, 191 (1951).

(7) (a) G. Grethe, H. L. Lee, M. Uskokovic, and A. Brossi, *J. Org. Chem.*, **33**, 491 (1968); (b) B. Umezawa, O. Hoshino, and Y. Yamanashi, *Tetrahedron Lett.*, 933 (1969).

(8) The preparation and reactions of these compounds are described in ref 1b.

(9) J. M. Bobbitt, A. S. Steinfeld, K. H. Weisgrabber, and S. Dutta, *J. Org. Chem.*, **34**, 2478 (1969), and earlier papers in this series.

(10) W. H. Perkin and R. Robinson, *J. Chem. Soc.*, **105**, 2376 (1914), have found that Schiff bases of various indanones are exceedingly sensitive to water.

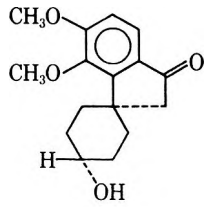
hexane system were explored. The obvious approach to this system is the preparation of an appropriately substituted 1-arylcyclohexaneacetic acid. A method which has been used successfully for the formation of quaternary centers similar to this is the cuprous chloride catalyzed reaction of a Grignard reagent with an unsaturated ester.[11] In an effort to utilize this route, attempts were made to prepare the Grignard reagent derived from 2,3-dimethoxybromobenzene. Although it has been stated that this compound forms a Grignard reagent in a normal manner,[12] this work could not be repeated.[13] Since the immediate goal was the development of a general synthetic method, an attempt was made to prepare the demethoxy derivative of **3** (**7**), which appeared to be available from the reaction of 2-methoxyphenylmagnesium bromide and ethyl cyclohexylideneacetate. However, even in the presence of cuprous chloride, the only product isolated from this reaction had the formula $C_{22}H_{26}O_3$, with the infrared spectrum showing the absence of carbonyl absorption. The nmr showed the presence of a vinyl proton and six methoxyl protons, indicating that instead of adding 1–4 to the conjugated system, a normal reaction with the ester had occurred.

When, however, the cuprous chloride catalyzed reaction of 2-methoxyphenylmagnesium bromide with ethyl cyanocyclohexylideneacetate was carried out, a compound $C_{18}H_{23}NO_3$ was obtained in 73% yield which had the spectral characteristics expected for **8**. Prolonged, vigorous, basis hydrolysis with concomitant decarboxylation afforded 1-(2-methoxyphenyl)cyclohexaneacetic acid (**9**).[14]

Polyphosphoric acid cyclization of **9** gave a mixture of two compounds, one of which was soluble in hot, 10% base and was recovered on acidification. This, the major product of the reaction (63% yield), showed carbonyl absorption at 5.68 μ in the infrared, and the nmr spectrum indicated the lack of a methoxyl peak and the presence of four aromatic protons. On the basis of these data, and a formula of $C_{14}H_{16}O_2$, this compound must be the lactone **10** resulting from demethylation and cyclization. Chromatography of the base insoluble portion of the reaction mixture gave 11% yield of a compound, $C_{15}H_{18}O_2$, which showed carbonyl absorption at 5.85 μ in the infrared and the nmr spectrum was that predicted for a compound of structure **7**. Bobbitt's modification of the Pomeranz–Fritsch reaction again proceeded smoothly to afford 2-methoxy-10-deoxo-8,9,11,12-tetrahydrostepharine (**11**) in 64% yield.[15]

This synthetic approach to the proaporphine alkaloids successfully overcomes the conversion of an indanone to the requisite hexahydrocyclopent[*ij*]-isoquinoline synthesis, but owing to the failure of 2,3-dimethoxybromobenzene in the Grignard reaction, an alternative synthesis of the requisite indanone (**12**) had to be developed.

Utilizing steps paralleling those reported,[16] 2,3-dimethoxyphenylacetonitrile (**13**)[17] was converted to



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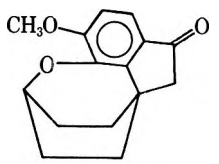

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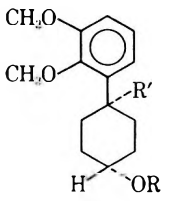
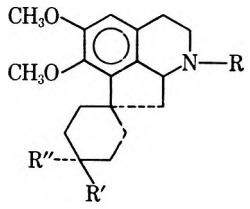


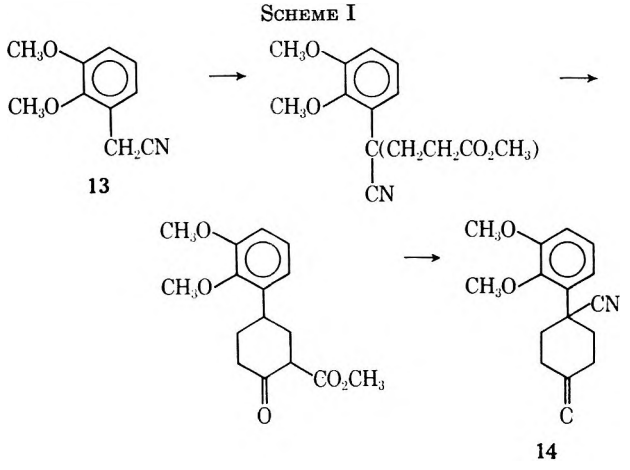
15, R = H; R′ = CN
16, R = $C_6H_5CH_2$; R′ = CN
17, R = $CH_2C_6H_5$; R′ = HC = NH
18, R = $CH_2C_6H_5$; R′ = CHO
19, R = H; R′ = CHO
20, R = H; R′ = CH_2NH_2
21, R = $OCOCH_3$; R′ = CHO
22, R = $OCOCH_3$; R′ = CH = $CHOCH_3$
23, R = $OCOCH_3$; R′ = CH_2CHO
24, R = $OCOCH_3$; R′ = CH_2CO_2H



26, R; R′ = H; R″ = OH
27, R = CH_3; R′ = H; R″ = OH
28, R = CH_3; R′ = OH; R″ = H

4-cyano-4(2,3-dimethoxyphenyl)cyclohexanone (**14**) by the sequence outlined in Scheme I.

SCHEME I



13

14

The various reactions leading to **12** required the protection of the carbonyl group in **14**, and reduction to the alcohol appeared to be a most promising method of accomplishing this goal. Treatment of **14** with sodium borohydride gave **15** as the only isolable product in 72% yield. The assignment of stereochemistry for the hydroxyl group is based on the nmr spectrum which shows the carbinol proton as a broad multiplet at δ 3.57, indicating an equatorial hydroxyl. Since $-\Delta G_{C_6H_5}$ is in excess of 2 kcal/mol while $-\Delta G_{CN}$ is less than 0.3 kcal/mol,[18] the dimethoxyphenyl group in **15** should exist largely in the equatorial conformation, while the nitrile would be axial.[19] The attempted conversion of **15** to the benzyl ether **16** by conventional methods[20]

(11) J. W. Huffman and T. W. Bethea, *J. Org. Chem.*, **30**, 2956 (1965).
(12) G. Holmberg, *Acta Chem. Scand.*, **8**, 728 (1954).
(13) J. A. Barltrop and J. S. Nicholson, *J. Chem. Soc.*, 2524 (1951), also report the failure of this halide to react normally with magnesium.
(14) Less vigorous hydrolysis of **8** gave the amide corresponding to **9**.
(15) As in the case of 4,5-dimethoxyindanone, the classical Pomeranz–Fritsch reaction failed to afford any of the desired product.
(16) N. Hazama, H. Irie, T. Mizutani, T. Shingu, M. Takada, S. Uyeo, and A. Yoshitake, *J. Chem. Soc. C*, 2947 (1968).
(17) R. Delaby, G. Tsatsas, and M. C. Jendrot, *Bull. Soc. Chim. Fr.*, 1830 (1956).
(18) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 435–444.
(19) In the isomer of **15** with the hydroxyl cis to the aromatic ring, the phenyl group would still be equatorial since $-\Delta G_{OH} = 0.6$ kcal/mol and $-\Delta G_{OH} + -\Delta G_{CN} = 0.8$ kcal/mol, still significantly less than $-\Delta G_{C_6H_5}$.
(20) (a) D. A. Prins, *Helv. Chim. Acta*, **40**, 1621 (1957); (b) R. L. Whistler and S. Hirase, *J. Org. Chem.*, **26**, 4600 (1961).

failed, apparently due to solubility factors; however, treatment of the alcohol with benzyl bromide, potassium *tert*-butoxide, *tert*-butyl alcohol, and dimethylformamide smoothly afforded the desired ether.

In an effort to prepare a suitable precursor for **12**, the controlled lithium aluminum hydride reduction of **16** to the imine **17** followed by hydrolysis to the aldehyde **18** was attempted. This sequence afforded **18**; however, reduction was incomplete and the isolation of the product difficult. In order to circumvent this problem, the direct reduction of **14** with lithium aluminum hydride was carried out to give, after hydrolysis, aldehyde **19** in 55% yield, accompanied by 4% of the primary amine **20**. The assignment of stereochemistry to this compound is based on the same nmr arguments employed in the discussion of **15**; however, subsequent experiments (*vide infra*) indicate that there may well have been a small percentage of the isomeric alcohol present in the reduction product.

The acetate of **19** (**21**) smoothly underwent the Wittig reaction with methoxymethylenetriphenylphosphorane to give the enol ether **22**. The nmr spectrum of **22** showed two overlapping AB quartets, one at δ 4.17 and 5.86 (J = J Hz), the other at δ 5.14 and 6.21 (J = 13 Hz), corresponding to the cis and trans isomers, respectively, of **22**. The mixture of isomeric enol ethers on treatment with perchloric acid in ether[21] gave the requisite aldehyde **23**. Oxidation of **23** with Jones reagent[22] in acetone afforded the substituted phenylpropionic acid **24**, the direct precursor of ketone **12**.

Although some lactonization of **24** under acidic cyclization conditions was predicted by analogy to the model synthesis described previously, the presence of a methoxyl group para to the site for cyclization to the indanone was expected to increase the relative amount of **12** in the reaction mixture. This was indeed the case, and it was found that on treatment of **24** with polyphosphoric acid at 65°, **12** was obtained in 40% yield. The use of more vigorous cyclization conditions led to the formation of a compound which showed only a single carbonyl peak in the infrared at 5.88 μ and was devoid of hydroxyl absorption. The nmr spectrum of this material showed an aromatic AB quartet, indicating cyclization to an indanone, but only one methoxyl peak at δ 4.00. On the basis of these spectral data, this compound was assigned the cyclic ether structure **25**, analogous to that suggested by Pfeifer for a compound obtained by reaction of oreoline with acid.[23]

Conversion of **12** to (±)-10-hydroxy-8,9,11,12-tetrahydrostepharine (**26**) was effected as described above using Bobbitt's modification of the Pomeranz–Fritsch reaction. The crude product from the isoquinoline synthesis was a mixture of three compounds, all with very similar R_f values on tlc, but with one of three components of the mixture predominating. The nmr spectrum of the crude product was consistent with that predicted for **26** and showed an aromatic singlet at δ 6.77, a one proton triplet at 4.12 for the benzylic methine proton, a six proton methoxyl singlet at δ 3.80, and the axial carbinol proton as a broad multiplet centered at δ 3.67. Although some efforts were made to purify this material (see Experimental Section), they were not successful on a small scale, and it was converted to the known *N*-methyl derivative[5,24] (**27**) for characterization. Eschweiler–Clarke methylation gave a mixture of several compounds; however, the recently reported N-methylation procedure of Cava and Buck[25] gave (±)-10-hydroxy-8,9,11,12-tetrahydropronuciferine (**27**), identical with a sample prepared by Bernauer.[5,24] Although both the free base and hydrochloride of **27** prepared by the above procedure and that prepared by Bernauer are identical, tlc of our material showed a trace of a second compound with an R_f value identical with that of the 10 epimer of **27** (**28**). This may be due to a small quantity of an impurity in **27**, which coincidentally has the same R_f value as **28**, but is probably due to the presence of a small amount of **28**, which arises from the reduction of **14** to the stereoisomer of **19** (see above) at an earlier stage in the synthesis. Although there was no direct evidence for the presence of isomeric compounds in the precursors of **27**, the possibility that small amounts of C-10 epimers are present cannot be precluded.

(21) G. W. Wittig, W. Boll, and K. Kruck, *Chem. Ber.*, **95**, 2514 (1962).

(22) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, pp 143–144.

(23) (a) I. Mann and S. Pfeifer, *Pharmazie*, **22**, 124 (1967). (b) Compound **25** was characterized only by spectral means, since it was obtained in very small quantities while efforts were being made to find optimum conditions for the cyclization of **24** to **12**.

Experimental Section[26]

4,5-Dimethoxy-1-indanone.—4,5-Dimethoxy-1-indanone was prepared after the method of Koo.[27] From 17.2 g of 2,3-dimethoxydihydrocinnamic acid was obtained 10.4 g (67.0%) of 4,5-dimethoxy-1-indanone, sublimed at 105–115° (0.04 mm): mp 74° (lit.[10] 74–75° and 82°); nmr 2.62, 3.10 (m, 4 H, CH_2-CH_2), 3.95 and 3.98 (s, 6 H, OCH_3), 7.04 (d, J = 9 Hz, 1 H, H-7), 7.55 (d, J = 9 Hz, 1 H, H-8).

5,6-Dimethoxy-1,2,3,7,8,8a-hexahydrocyclopent[*ij*]isoquinoline (5).—A mixture of 0.398 g of 4,5-dimethoxy-1-indanone, 5 ml of dry toluene, and 0.840 g of aminoacetal was stirred and heated at reflux for 42 hr under a water separator in a system flushed with nitrogen. A positive pressure of nitrogen was maintained during the entire reaction. A second portion of 0.271 g of aminoacetal was added to the reaction mixture, and heating was continued for 24 hr. After the reaction mixture was evaporated and dried *in vacuo*, the brown oily residue was dissolved in 10 ml of absolute ethanol (3A molecular sieves). To a mixture of 50 mg of platinum oxide in 5 ml of absolute ethanol (3A molecular sieves), which was prereduced, was added the dissolved oily residue. The reduction was carried out at room temperature and pressure with hydrogen passed through a Dry Ice–acetone condenser and was completed in 2.5 hr. After the catalyst was collected on a Celite pad and washed with ethanol, the filtrate was evaporated *in vacuo* at room temperature. The dried residue was dissolved in 15–20 ml of ether and was added to 20 ml of ice cold 10 *N* hydrochloric acid. The cold mixture was extracted with ether and stored at room temperature overnight. After the dissolved ether was removed *in vacuo*, 0.206 g of 5% palladium on carbon was added to the acidic solution, which was reduced to room temperature and pressure for 24 hr or until reduction was completed. The catalyst was collected on a Celite pad, and the filtrate was evaporated *in vacuo* at 40–50°, giving a yellow viscous mass. After the mass was dissolved in ethanol and evaporated to dryness several times, it solidified. The residue was dissolved

(24) We would like to thank Dr. Bernauer for comparison samples of compounds **27** and **28**.

(25) M. P. Cava and K. T. Buck, *Tetrahedron*, **25**, 2795 (1969).

(26) All melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were taken as potassium bromide disks or liquid films on sodium chloride plates using a Perkin-Elmer Model 137 spectrophotometer and are reported in microns. Ultraviolet spectra were taken in 95% ethanol using a Perkin-Elmer Model 202 spectrophotometer and are reported as λ_{max} in millimicrons (log ϵ) except where the units are specified. Nuclear magnetic resonance spectra were obtained from a Varian Associates A-60 nuclear magnetic resonance spectrophotometer in deuteriochloroform unless stated otherwise. All spectra are reported in ppm relative to tetramethylsilane. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(27) J. Koo, *J. Amer. Chem. Soc.*, **75**, 189 (1953).

in water, and the solution was extracted with methylene chloride, made basic with concentrated ammonium hydroxide, filtered, and extracted with methylene chloride. The organic extract was washed with water, 10% sodium hydroxide, and water, dried over sodium sulfate, evaporated, and dried *in vacuo* giving 0.25 g (54.5%) of **5**, mp 81–93°. The free base could not be induced to crystallize satisfactorily from any of several solvent systems and purification was effected through the picrate. A portion of the picrate was dissolved in sodium hydroxide and extracted with methylene chloride. The washed and dried extract was evaporated and dried *in vacuo*, giving the free base: mp 90–95°; ir 3.11; uv (neutral) 208 (4.69), 230 (4.15), 2.85 (3.49); uv (base) 284 (3.49); uv (acid) 208 (4.76), 228 (4.30), 253 (3.83), 285 (3.57); nmr (C_6D_6) 1.52 (t, J = 10 Hz, 2 H, Ar CH_2CH_2CH), 2.53 (m, 6 H, Ar CH_2CH_2N– and Ar CH_2), 3.52, 3.77 (s, 6 H, OCH_3), 3.77 (t, 1 H, NHCH), 6.45 (s, 1 H, Ar H). The analytical sample was characterized as the picrate and crystallized from ethanol as yellow-brown needles, mp 230–235° dec.

Anal. Calcd for $C_{19}H_{20}N_4O_9$: C, 50.90; H, 4.50; N, 12.50. Found: C, 50.70; H, 4.50; N, 12.37.

Cyclohexylidenebis(2-methoxyphenyl)carbinol.—In a dry system a mixture of 0.058 g of magnesium, a crystal of iodine, and 0.448 g of *o*-bromoanisole in 2 ml of dry ether was warmed until the magnesium was consumed. The reagent was transferred to an addition funnel and diluted with 8–10 ml of dry ether. The Grignard solution was added dropwise over 10 min to a stirred mixture of 0.336 g of ethyl cyclohexylideneacetate[28] and 0.30 g of cuprous chloride in 5 ml of dry ether. The reaction mixture was heated at reflux for 2 hr and then hydrolyzed with 10% ammonium chloride solution and extracted with ether. The ether extract was washed with saturated sodium bicarbonate and water, and dried. Removal of the solvent gave a mixture of oil and crystals which on trituration with ether–petroleum ether gave 0.104 g (25%) of solid, mp 131–133.5°. The analytical sample crystallized from ether–hexane as white needles: mp 132.5–133.5°; ir 2.30; nmr 1.52, 2.18 [m, 10 H, $(CH_2)_5$], 3.62 (s, 6 H, OCH_3), 4.75 (s, 1 H, OH), 5.78 (s, 1 H, =CH–), 7.25 (m, 8 H, Ar H). After the sample was shaken with deuterium oxide, the peak at 4.75 disappeared.

Anal. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 78.23; H, 7.52.

Ethyl α-Cyano-1-(2′-methoxyphenyl)cyclohexaneacetate (8).—To a mixture of 7.36 g of magnesium turnings, 100 ml of dry ether, and a crystal of iodine was added 11.9 g of *o*-bromoanisole. After the reaction had started, the mixture was diluted with 100 ml of dry ether. A solution of 44.2 g of o-bromoanisole in 60 ml of dry ether was added dropwise to maintain reflux and the resulting mixture was heated at reflux for 60 min. The cooled *o*-methoxyphenylmagnesium bromide solution was filtered into an addition funnel and added dropwise over 75 min to a stirred heterogeneous mixture of 48.7 g of ethyl cyanocyclohexylideneacetate,[29] 0.84 g of cuprous chloride, and 300 ml of dry ether. The gummy mixture was heated at reflux for 60 min, cooled to 0°, and hydrolyzed with 600 ml of 10% ammonium chloride. After the aqueous layer was extracted with ether, the combined extracts were washed with 1 *N* hydrochloric acid and with water. Evaporation of the dried solvent *in vacuo* gave a yellow semisolid residue. Crystallization from methanol gave 54.4 g (73.4%) of crystalline product, mp 89–96°, in two crops. The analytical sample, mp 97–98°, was recrystallized from methanol: ir 4.50, 5.78; nmr 0.93 (t, J = 7 Hz, 3 H, CH_3CH_2), 3.82 (s, 3 H, OCH_3), 3.83 (q, J = 7 Hz, 2 H, CH_3CH_2O), 3.60 [s, $CH(CO_2)$-CH], 7.20 (m, 4 H, Ar H).

Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.69; H, 7.53; N, 4.57.

1-(2′-Methoxyphenyl)cyclohexaneacetic Acid (9).—To a stirred, heated mixture of 48.8 g of potassium hydroxide and 190 ml of diethylene glycol flushed continuously with a slow stream of nitrogen was added 33.5 g of ethyl α-cyano-1-(2′-methoxyphenyl)cyclohexaneacetate (**8**). The mixture was heated at 175–185° for 35 hr, cooled, poured into an ice–water slurry, and extracted with ether. The cold aqueous basic solution was acidified with concentrated hydrochloric acid and extracted with ether. The extract was washed, dried, and evaporated *in vacuo*, giving 26.0 g (98.8%) of crude acid, mp 95–105°. The analytical sample crystallized from ether–hexane: mp 106–107°; ir 5.88, 5.99 sh, 6.29, 6.38; nmr 1.17, 2.08 [m, 10 H, $(CH_2)_5$], 2.90 (s, 2 H, CH_2CO_2H), 3.84 (s, 3 H, OCH_3), 7.16 (m, 4 H, Ar H).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.56; H, 8.16.

When the reaction mixture was heated less than 20 hr, partial hydrolysis was observed. The basic ether extract was washed and dried. Removal of the solvent gave crude 1-(2′-methoxyphenyl)cyclohexaneacetamide, mp 96–98°. The analytical sample crystallized from ethanol–hexane: mp 100–101°; ir 3.03, 3.21, 6.04; nmr 1.30, 2.08 [10 H, $(CH_2)_5$], 2.87 (s, 2 H, CH_2CONH_2), 3.92 (s, 3 H, OCH_3), 7.23 (m, 4 H, Ar H).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.86; H, 8.61; N, 5.70.

Spiro[cyclohexane-1,3′-(4′-methoxyindan-1′-one)] (7).—To 320 g of polyphosphoric acid at 90–100° was added 20.0 g of pulverized 1-(2′-methoxyphenyl)cyclohexaneacetic acid, and the mixture was stirred at 90–100° for 1.5 hr. The dark red mixture was poured into 1200 ml of ice–water slurry and extracted with ether. The ether extract was washed with water, and the ether was removed *in vacuo*. To the tarry residue were added 40 g of potassium hydroxide, 340 ml of methanol, and 60 ml of water. The mixture was heated at reflux for 3–4 hr in a nitrogen atmosphere, cooled, and diluted with water. The methanol was removed *in vacuo*, and the aqueous mixture was extracted with ether. The organic layer was washed, dried, and evaporated *in vacuo*, giving 4.86 g (27.0%) of residue, which was dissolved in benzene–hexane, 1:1, and chromatographed on alumina. Elution with benzene gave 1.92 g of spiro[cyclohexane-1,3′-(4′-methoxyindan-1′-one)]. The analytical sample crystallized from ether as colorless rectangular crystals: mp 119°; ir 5.85; uv (neutral) 211 (4.17), 226 (4.30), 256 (3.81), 312 (3.42); uv (base) 256 (3.85), 310 (3.57); nmr 2.60 (s, 2 H, CH_2C=O), 3.92 (s, 3 H, OCH_3), 7.17 (m, 3 H, Ar H).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.83. Found: C, 78.22; H, 7.86.

The aqueous basic layer was acidified and extracted with ether. The ether extract was washed, dried, and evaporated *in vacuo*, giving 11.6 g (63.0%) of the δ-lactone of 1-(2′-hydroxyphenyl)-cyclohexaneacetic acid (**10**). The analytical sample was obtained by distillation as a viscous colorless oil: bp 117–120° air bath, (0.07 mm); $n^{23.5}D$ 1.5569; ir 5.68; nmr 1.67 [m, 10 H, $(CH_2)_5$], 2.78 (s, 2 H, CH_2CO), 7.20 (m, 4 H, Ar H).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.68; H, 7.58.

Almost complete lactone formation was observed with polyphosphoric acid at room temperature for 1.5 hr and at 150° for 3 min, as well as with a mixture of phosphorus oxychloride, phosphoric acid, and phosphorus pentoxide heated at reflux for 1.5 hr.

2-Demethoxy-10-deoxo-8,9,11,12-tetrahydrostepharine (11).—A mixture of 0.247 g of spiro[cyclohexane-1,3′-(4′-methoxyindan-1′-one)], 0.858 g of distilled aminoacetal, and 5 ml of dry toluene was stirred and heated at reflux over a water separator for 48 hr in a system flushed and maintained under a slight positive pressure of nitrogen. A second portion of 0.570 g of aminoacetal was added, and heating was continued for 24 hr. The light yellow solution was evaporated and dried *in vacuo* at room temperature, giving a viscous oil. This oil was dissolved in 10 ml of absolute ethanol (3A molecular sieves) and added to a mixture of 5 ml of absolute ethanol and 0.037 g of platinum oxide which was prereduced. The reduction was carried out with hydrogen passed through a Dry Ice–acetone condenser at room temperature and pressure. After 11.2 ml of hydrogen was consumed in 3.25 hr, the reduction ceased and a coating was observed on the catalyst. An additional 0.040 g of platinum oxide was added, and reduction was completed in 3 hr. The reduction mixture was filtered through a Celite pad, and the filtrate was evaporated and dried *in vacuo* at 35–60°. The residue was dissolved in 15 ml of ether, cooled to 0°, and added to 20 ml of 6 *N* hydrochloric acid at 0°. The mixture was stirred and allowed to stand at room temperature overnight. The aqueous–ether mixture was filtered, and the ether was concentrated *in vacuo* at room temperature to 15 ml. To the solution were added 15 ml of ethanol and 0.210 g of 5% palladium on charcoal and the mixture was reduced at room temperature and pressure for 6 hr or until the theoretical uptake of hydrogen was observed. After the catalyst was collected on a Celite pad, the filtrate was concentrated *in vacuo* at room temperature to approximately 3 ml. The white precipitate which formed was collected, washed with water, and dried *in vacuo* giving 0.186 g (63.7%) of 2-demethoxy-10-deoxy-8,9,11,12-tetra-

(28) C. Ruchardt, S. Eichler, and P. Panse, *Angew. Chem.*, **75**, 858 (1953).

(29) A. C. Cope, C. M. Hoffman, C. Wycoff, and E. Hardenbergh, *J. Amer. Chem. Soc.*, **63**, 3452 (1941).

hydrostepharine hydrochloride (11 hydrochloride), mp 244–256° dec. The methylene chloride extract from the acidic filtrate was evaporated, giving an additional 0.053 g (19.3%), mp 245–264° dec. A 0.073-g portion of the salt was stirred with 5–10 ml of water, adjusted to pH 10 with sodium hydroxide, and extracted with methylene chloride. The organic layer, which was washed and dried with sodium sulfate, was evaporated and dried *in vacuo*, giving 61 mg of free base which solidified after standing: mp 93–100°; ir 3.09, 6.20, 6.30; uv (neutral) 208 (4.43), 230 (3.85), 280 (3.17); uv (acid) 208 (4.43), 230 (3.83), 280 (3.17); uv (base) 280 (3.17); nmr (hexadeuteriobenzene), 2.88 (m, 6 H, Ar CH_2CH_2N– and CH_2CHN), 3.48 (s, 3 H, OCH_3), 3.90 (t, 1 H, NCHAr), 6.60 (d, J = 9 Hz, 1 H, H-2), 6.93 (d, J = 8 Hz, 1 H, H-1). The analytical sample of the hydrochloride was recrystallized from methylene chloride by dilution with dry ether, giving white needles, mp 254–259°.

Anal. Calcd for $C_{17}H_{24}NOCl$: C, 69.49; H, 8.25; N, 4.77; Cl, 12.01. Found: C, 69.26; H, 8.47; N, 5.03; Cl, 12.31.

2,3-Dimethoxyphenylacetonitrile.—2,3-Dimethoxyphenylacetonitrile was prepared by a modification of the method used for the preparation of 3-ethoxy-3-methoxybenzonitrile.[16] To a mixture of 86.0 g of 2,3-dimethoxybenzyl alcohol and 150 ml of dry benzene in a dry system was added a solution of 140 ml of thionyl chloride in 150 ml of dry benzene over 20 min at room temperature. After the reaction mixture was heated at reflux for 3 hr, the benzene and excess thionyl chloride were removed *in vacuo*. To the azeotropically dried residue in 300 ml of ethanol was added a solution 96.5 g of potassium cyanide in 300 ml of water at room temperature. The mixture was heated at reflux for 8 hr. After the solution was evaporated *in vacuo* at 100° to one-half the original volume, the aqueous layer was extracted with benzene. The organic extract was washed, dried over 4A molecular sieves, and evaporated *in vacuo* to a black viscous oil. Distillation of the crude nitrile gave 63.1 g (69.8%) of colorless liquid: bp 82–95° (0.13–0.15 mm) [lit.[17] 154–161° (13 mm)]; ir 4.45; nmr 3.65 (s, 2 H, CH_2), 3.80 (s, 6 H, OCH_3), 7.50 (m, 3 H, Ar H).

Dimethyl 4-Cyano-4-(2′,3′-dimethoxyphenyl)pimelate.—To a mixture of 60 g of 2,3-dimethoxyphenylacetonitrile, 160 ml of methyl acrylate, and 160 ml of dry *tert*-butyl alcohol heated at reflux under a nitrogen atmosphere was added rapidly a solution of 67.5 ml of 35% methanolic Triton B and 75 ml of dry *tert*-butyl alcohol. After heating the reaction mixture at reflux for 4.5 hr, 100 ml of solvent was distilled off. The remaining solvent was removed *in vacuo* at 100°, and the residue was dissolved in methylene chloride. After the organic mixture was washed with 1.5 *N* hydrochloric acid and water and dried over 4A molecular sieves, evaporation of the methylene chloride *in vacuo* gave 110 g (93.0%) of light yellow viscous oil. Distillation of an 80-g portion of the crude pimelate gave 73.7 g (91.9%) of fluorescent blue-green syrupy oil [bp 175–220° (0.10–035 mm)] which eventually crystallized. The analytical sample was obtained by distillation and crystallized during transfer: bp 187–192° air bath (0.10–0.12 mm); mp 55–57°; ir 4.50 w, 5.77; nmr 2.38 (m, 8 H, CH_2) 3.58 (s, 6 H, CH_3OCO), 3.83, 3.88 (s, 6 H, Ar OCH_3), 6.95 (m, 3 H, Ar H).

Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 62.06; H, 6.74; N, 3.87.

Methyl 5-Cyano-5-(2′,3′-dimethoxyphenyl)-2-oxycyclohexanecarboxylate.—To a stirred mixture of 31.2 g of 50% sodium hydride washed with dry toluene in a dry nitrogen atmosphere in 1.9 l. of dry toluene was added 69.7 g of dimethyl 4-cyano-4-(2′,3′-dimethoxyphenyl)pimelate in 400 ml of dry toluene. The mixture was stirred vigorously with a mechanical stirrer and heated at reflux for 5 hr. The cooled mixture was diluted cautiously with 200 ml of 6 *N* acetic acid and 200 ml of water. After the toluene layer was collected, the aqueous layer was extracted with toluene. The combined extracts were washed with aqueous sodium bicarbonate and then with water. The dried toluene extract was evaporated *in vacuo*, giving 57.1 g (85.5%) of a crystalline residue, mp 99–100°. The analytical sample was crystallized from absolute ethanol, giving colorless crystals: mp 103–104°; ir 4.48 w, 5.98, 6.15; uv (neutral) 222 (3.95), 255 (3.94); uv (acid) 221 (3.97), 254 (3.97); uv (base) 283 (4.19); nmr 2.37 (m, 6 H, CH_2), 3.19 (d, J = 15.5 Hz, 1 H, CHCO), 3.67 (s, 3 H, CH_3OCO), 3.79 (s, 3 H, Ar OCH_3), 3.93 (s, 3 H, Ar OCH_3), 6.84 (m, 3 H, Ar H).

Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.61; H, 6.14; N, 4.38.

1-(2′,3′-Dimethoxyphenyl)-4-oxocyclohexanecarbonitrile (14).—A mixture of 57.1 g of crude methyl 5-cyano-5-(2′,3′-dimethoxyphenyl)-2-oxocyclohexanecarboxylate, 900 ml of glacial acetic acid, and 500 ml of 10% sulfuric acid was heated at reflux for 7 hr. After the acidic mixture was extracted with benzene, the extract was washed with saturated sodium bicarbonate and with water and the benzene distilled off. Crystallization of the crude product from methanol gave 34.3 g (77.5%) of colorless crystals, mp 132–135°. The analytical sample crystallized from absolute ethanol: mp 136–137°; ir 4.50, 5.83; uv (neutral and acid) 218 sh (3.90), 278 (3.31); nmr 2.38 (m, 8 H, CH_2), 3.84, 4.00 (s, 6 H, OCH_3), 6.95 (m, 3 H, Ar H).

Anal. Calcd for $C_{16}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.52; H, 6.69; N, 5.34.

1-(2′,3′-Dimethoxyphenyl)-4-hydroxycyclohexanecarbonitrile (15).—To a stirred mixture of 10.0 g of **14** and 700 ml of absolute ethanol was added 3.50 g of sodium borohydride over 5–10 min at room temperature. The mixture was stirred for 3.5 hr at room temperature, diluted with 200 ml of water, and stirred for 0.5 hr. After the ethanol was removed *in vacuo* at elevated temperature, the residue was diluted with water and extracted with methylene chloride. Evaporation of the washed and dried extract and crystallization from acetone–hexane, 1:1, gave 7.2 g (72.0%) of crystals in two crops, mp 169–171°. The analytical sample crystallized from acetone–hexane as white crystals: mp 171–172°; ir 3.08, 4.48; uv (neutaal) 218 sh (3.98), 278 (3.33); uv (acid) 218 sh (3.95), 278 (3.39); uv (base) 278 (3.50); nmr 1.97 (s, 1 H, OH), 2.08 (m, 8 H, CH_2), 3.57 (m, 1 H, CHOH), (s, 6 H, OCH_3), 6.93 (m, 3 H, Ar H); with the addition of D_2O the peak at 1.97 disappeared.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.09; H, 7.32; N, 5.33.

4-Benzyloxy-1-(2′,3′-dimethoxyphenyl)cyclohexanecarbonitrile (16).—A stirred solution of 5.7 g of potassium *tert*-butoxide and 40 ml of dry *tert*-butyl alcohol was cooled to 2–4° in a system protected from atmospheric moisture and flushed with dry nitrogen. When the mixture began to freeze, 10 ml of dry *N*,*N*-dimethylformamide was added at 2–4°, and then a mixture of 6.5 g of 1-(2′,3′-dimethoxyphenyl)-4-hydroxycyclohexanecarbonitrile and 50 ml of *N*,*N*-dimethylformamide was added. To the mixture was added a solution of 6.0 ml of benzyl bromide in 30 ml of *N*,*N*-dimethylformamide at 2–4° over 25 min, and the mixture was stirred at 2–4° for an additional 40 min. The light yellow mixture was gradually warmed to room temperature and stirred for 3.5 hr. The mixture was poured into 250 g of ice–water and the precipitate was collected, washed, and dried *in vacuo*, mp 87–89°. Crystallization from methanol gave 7.8 g (87.8%) of white needles: mp 93–94°; ir 4.47 w; nmr 2.25 (m, 8 H, CH_2), 3.43 (m, 1 H, OCH), 3.87 (s, 3 H, OCH_3), 4.02 (s, 3 H, OCH_3), 4.61 (s, 2 H, $C_6H_5CH_2O$), 6.98 (m, 3 H, Ar H), 7.36 (m, 5 H, C_6H_5).

Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.22; H, 7.06; N, 3.92.

4-Benzyloxy-1-(2′,3′-dimethoxyphenyl)cyclohexanecarboxaldehyde (18).—To a mixture of 10 ml of dry tetrahydrofuran and 10.7 mg of lithium aluminum hydride were added 0.221 g of 4-benzyloxy-1-(2′,3′-dimethoxyphenyl)cyclohexanecarbonitrile (16) and 3 ml of tetrahydrofuran and the reaction mixture was heated at reflux for 5.75 hr. Tlc showed starting material present in an aliquot of the reaction mixture. After an additional 0.010 g of lithium aluminum hydride was added, the mixture was heated at reflux for 3.75 hr. The excess hydride was decomposed with 1 *N* sodium hydroxide, and the tetrahydrofuran was removed *in vacuo*. The residue was partially dissolved in 1 *N* sodium hydroxide and extracted with chloroform. The chloroform extract was washed with ice-cold 1 *N* hydrochloric acid, saturated sodium bicarbonate, and water, dried, and evaporated *in vacuo*, giving 172 mg (76.0%) of a brown oil containing starting material and aldehyde. After the acidic wash solution was made basic and extracted with chloroform, the chloroform extract was evaporated *in vacuo*. The residue was hydrolyzed with 5 ml of 50% acetic acid containing 0.15 ml of concentrated sulfuric acid at 100° for 40 min. The mixture was diluted with water and extracted with chloroform. Evaporation of the washed and dried chloroform gave 0.025 g (11.1%) of an oil. An infrared spectrum shows the oil to be a mixture of aldehyde (5.73 μ) and aldimine (6.03 μ). The extracted hydrolysis solution was made basic and extracted with chloroform. Negligible residue was found in the chloroform extract. The aldehyde was characterized as the 2,4-dinitrophenylhydrazone derivative, which was prepared and isolated from the 0.172 g of the crude material. After repeated recrystallizations from ethanol–water, mp 135–

136° was obtained: ir 3.02, 6.16; nmr 1.77, 2.62 (m, 8 H, CH_2), 3.43 (m, 1 H, CHO), 3.73, 3.78 (s, 6 H, OCH_3), 4.54 (s, 2 H, $C_6H_5CH_2O$), 6.94 (m, 3 H, ArH), 7.25 (s, 5 H, C_6H_5), 7.70, 7.75, 8.14, 8.19 [doublet of doublets, J = 7 or 8 Hz, J = 10 Hz, 3 H, 2,4-$(NO_2)_2$ArH], 10.95 (s, 1 H, C=H).

Anal. Calcd for $C_{28}H_{30}N_4O_7$: C, 62.91; H, 5.66; N, 10.48. Found: C, 62.74; H, 5.74; N, 10.36.

1-(2′,3′-Dimethoxyphenyl)-4-hydroxycyclohexanecarboxaldehyde (19).—A mixture of 0.708 g of lithium aluminum hydride and 300 ml of dry 1,2-dimethoxyethane (glyme) was stirred and cooled to 10° in a system protected from atmospheric moisture and continuously purged with dry nitrogen. To the cold mixture was added a mixture of 5.50 g of 1-(2′,3′-dimethoxyphenyl)-4-oxocyclohexanecarbonitrile (**14**) in 100 ml of glyme over 7 min. A white precipitate formed 15 min after heating was started, and the heterogeneous mixture was heated at reflux for 5 hr. The mixture was cooled to 10°, decomposed with 2.5 N sodium hydroxide, and stirred 30 min at 10°. The supernatant liquid was decanted and evaporated *in vacuo* at 35–40° and the residue dissolved in chloroform. After the chloroform solution was extracted with 400 ml of ice-cold 1 N hydrochloric acid, the washed and dried organic layer was evaporated *in vacuo* giving 2.09 g of an oil.

Residual chloroform in the hydrochloric acid wash layer was removed *in vacuo* at 30–45°, and after the mixture was stored at room temperature overnight, a precipitate was observed in the acidic solution. The acidic mixture was made basic and cooled to 10°, and the white precipitate was collected, washed, and dried, giving 2.89 g (51.7%) of 1-(2′,3′-dimethoxyphenyl)-4-hydroxycyclohexanecarboxaldehyde (**19**), mp 143–146°. The analytical sample crystallized from methylene chloride–ether: mp 141–146°; ir 3.09, 3.71 w, 5.82; nmr, 1.85 (m, 8 H, CH_2), 3.50 (m, 1 H, CHOH), 3.68 and 3.76 (s, CH_3, OCH_3), 6.85 (m, 3 H, Ar H), 9.60 (s, 1 H, CH=O).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.45; H, 7.84.

After extraction of the basic filtrate with chloroform, the extract was evaporated, and the residue was heated in 300 ml of 50% acetic acid containing 30 drops of concentrated sulfuric acid at 100° for 2 hr. The acidic mixture was diluted with water and extracted with chloroform. The washed and dried extract was evaporated *in vacuo* giving 0.16 g (3.0%) of recrystallized **19**, mp 144–148°.

After the acidic layer was made basic and extracted with chloroform, the washed and dried extract was evaporated giving 0.23 g (4.1%) of crude 4-aminomethyl-4-(2′,3′-dimethoxyphenyl)cyclohexanol (**20**), mp 109–117°. The amine was characterized as its picrate. The analytical sample crystallized from ethanol as yellow needles: mp 204–205°; ir 3.20, 6.12.

Anal. Calcd for $C_{21}H_{26}N_4O_{10}$: C, 51.01; H, 5.30; N, 11.33. Found: C, 51.21; H, 5.44; N, 11.30.

Considerable reduction of the nitrole to the amine was observed when glyme distilled from lithium aluminum hydride was used in the preceding procedure.

1-(2′,3′-Dimethoxyphenyl)-4-acetoxycyclohexanecarboxaldehyde (21).—A mixture of 2.17 g of 1-(2′,3′-dimethoxyphenyl)-4-benzyloxycyclohexanecarboxaldehyde (**18**), 10.8 ml of pyridine, and 3.6 ml of acetic anhydride was stirred at room temperature for 12 hr. The light tan solution was diluted with 36 ml of methanol, stirred for 2 hr, and evaporated *in vacuo* giving 2.44 g (97.3%) of **21**, mp 103–106°. The analytical sample crystallized from methanol: mp 109–111°; ir 3.64 w, 5.79; uv (neutral, acid, and base) 278 (3.43); nmr 1.97 (s, 3 H CH_3CO), 2.02 (m, 8 H, CH_2), 3.67, 3.77 (5,6 H, OCH_3), 4.76 (m, 1 H, $CHOCOCH_3$), 6.82 (m, 3 H, Ar H), 9.55 (s, 1 H, CH=O).

Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.49; H, 7.19.

1-(2′,3′-Dimethoxyphenyl)-4-acetoxycyclohexaneacetaldehyde (23).—A suspension of 15.3 g of methoxymethyltriphenylphosphonium chloride[30] and 324 ml of freshly distilled tetrahydrofuran was stirred vigorously in a system previously dried and flushed with dry nitrogen. After the protected mixture was cooled to −10°, 28.3 ml of *n*-butyllithium (1.6 N) was added over 30 min. The deep red mixture was gradually warmed to room temperature and stirred for 2.6 hr. After the deeply colored solution was cooled to −10°, a solution of 5.84 g of 1-(2′,3′-dimethoxyphenyl)-4-acetoxycyclohexanecarboxaldehyde (**21**) in 60 ml of freshly distilled tetrahydrofuran was added over 15 min. The mixture was stirred at −10° for 30 min, room temperature for 8 hr, and at reflux for 5 hr. The cooled solution was evaporated and dried *in vacuo*. The foamy residue was triturated with eight 100-ml portions of dry ether. After the decantate was filtered and washed with water, 0.1 N hydrochloric acid, water, and dried over 4A molecular sieves, the ether was evaporated, giving 8.2 g of a viscous brown mass which contained the partially deacetylated enol-ether. To a stirred solution of 32 ml of dry pyridine and 8.2 g of the crude enol-ether was added 10.5 ml of acetic anhydride at room temperature, and the mixture was stirred overnight. The mixture was diluted with 100 ml of methanol and stirred at room temperature for 2 hr. After removal of the solvents *in vacuo* at 60–80°, the residue was dissolved in ether. The organic layer was washed with water, 0.1 N hydrochloric acid, saturated sodium bicarbonate, and water, and dried over 4A molecular sieves, evaporated, and dried *in vacuo*, giving 7.6 g of crude, fully acetylated enol-ether (**22**). To a column of alumina packed in hexane was added a solution of the crude enol-ether in benzene–hexane, 1:1. The desired product was found in the fractions eluted with benzene–hexane, 1:1, and benzene. After the solvents were removed *in vacuo*, 3.88 g of **22** was obtained as a light yellow oil: ir 5.78, 6.04; nmr 2.05 (s, 3 H, CH_3CO_2–), 3.40 and 3.55 (s, 3 H = $CHOCH_3$), 3.83, 3.85, and 3.99 (s, 6 H, Ar OCH_3), 4.17 and 5.14 (d, J = 7 and 13 Hz, 1 H, =CH–), 5.86 and 6.21 (d, J = 7 and 13 Hz, 1 H, =CH), 6.96 (m, 3 H, Ar H).

To a stirred solution of 3.31 g of enol-ether in 100 ml of ether was added 20 ml of 40% perchloric acid at room temperature, and the solution was heated at reflux for 30 min. The reaction mixture was diluted with water and extracted with ether. After the organic layer was washed with saturated sodium bicarbonate and water and was dried, the ether was evaporated giving 2.75 g (86.0%) of 1-(2′,3′-dimethoxyphenyl)-4-acetoxycyclohexaneacetaldehyde (**23**) as a light yellow viscous oil, which was converted to the acid without purification. The aldehyde was characterized as the 2,4-dinitrophenylhydrazone which crystallized from ethanol: mp 183–184°; ir 3.03, 5.76; nmr 2.07 (s, 3 H, CH_3CO_2, and m, 8 H, CH_2), 3.00 (d, J = 6 Hz, 2 H, CH_2C=N), 3.85 and 3.88 (s, 6 H, OCH_3), 4.73 (m, 1 H, CHO), 7.00 (m, 3 H, Ar H), 7.77 (d, J = 9 Hz, 1 H), 8.20, 8.25 (doublet of doublets, J = 9 Hz, 1 H), 9.00 (d, J = 3 Hz, 1 H), 10.73 (singlet, 1 H, CH=N).

Anal. Calcd for $C_{24}H_{28}N_4O_8$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.58; H, 5.69; N, 11.18.

1-(2′,3′-Dimethoxyphenyl)-4-acetoxycyclohexaneacetic Acid (24).—To a solution of 2.16 g of 1-(2′,3′-dimethoxyphenyl)cyclohexaneacetaldehyde (**23**) and 150 ml of reagent grade acetone at 10° was added a slight excess of Jones reagent. The mixture was stirred for 5 min, warmed to 15–20°, and stirred for 35 min. After the mixture was diluted with 50 ml of water, 10% aqueous sodium sulfite was added until the yellowish-red color was discharged. The aqueous acetone layer was decanted evaporated *in vacuo* at 30–35° until most of the acetone was removed. The residue was taken up in methylene chloride and then washed with four 25-ml portions of 5% sodium hydroxide, followed by water. After drying, the organic extracts were evaporated and dried *in vacuo* giving 0.88 g (38.2%) of an unidentified viscous yellow oil.

The 5% sodium hydroxide and water wash solutions were combined, back-washed with methylene chloride, acidified at 0° with concentrated hydrochloric acid, and extracted with methylene chloride. The organic extract was washed with water, dried, evaporated, and dried *in vacuo*, giving 0.94 g (41.3%) of partially hydrolyzed crystalline acid, mp 136–160°. The acid was dissolved in 15 ml of dry pyridine, 6 ml of acetic anhydride were added at room temperature, and the solution was stirred at room temperature for 17 hr. After the mixture was hydrolyzed with 1.5 ml of water at 0° for 1 hr, it was evaporated *in vacuo* at room temperature giving an oily brown residue. The residue was dissolved in methylene chloride, and the solution was washed with 1 N hydrochloric acid and water, dried, evaporated, and dried *in vacuo*, giving 1.02 g (49.3%) of **24** as a foamy solid. The foamy mass crystallized from ether–hexane, giving 0.67 g of 1-(2′,3′-dimethoxyphenyl)-4-acetoxycyclohexaneacetic acid as white crystals, mp 114–120°. The analytical sample crystallized from hexane–ether as white needles: mp 121–123°; ir 5.78; nmr 2.07 (s, 3 H, CH_3CO_2), 2.88 (s, 2 H, CH_2CO_2N), 3.87, 3.90 (s, 6 H, OCH_3), 4.83 (m, 1 H, CHO), 6.95 (m, 3 H, Ar H).

Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.13; H, 7.25.

(30) G. Wittig and M. Schlosser, *Chem. Ber.*, **94**, 1373 (1961).

Spiro[4-hydroxycyclohexane-1,3′-(4′,5′-dimethoxyindan-1′-one] (12).—To 20 g of polyphosphoric acid was added 0.348 g of pulverized 1-(2′,3′-dimethoxyphenyl)-4-acetoxycyclohexaneacetic acid. After the solid was thoroughly dispersed in the polyphosphoric acid, the mixture was heated in an oil bath at 64–65° for 30 min. The mixture was stirred every 4–5 min and gradually turned a brownish red. The mass was cooled in an ice bath and hydrolyzed with 150 ml of an ice–water slurry. After the mixture was extracted with methylene chloride, the organic layer was washed with water, dried, and evaporated to a viscous residue. The residue was heated at reflux with a mixture of 36 ml of methanol, 12 ml of water, and 4.8 g of potassium hydroxide for 2 hr in a system continuously flushed with nitrogen. After the methanol was removed from the cooled solution *in vacuo*, the aqueous mixture was diluted with 20 ml of water and was extracted with methylene chloride. The washed and dried extract was evaporated and dried *in vacuo*, giving 0.115 g (40.2%) of indanone as a greenish-brown amorphous mass. One crystallization from ether–hexane gave 0.068 g (24.5%) of pure material, mp 166–168°. The analytical sample was obtained by filtration through a column containing 2 g of alumina and elution with benzene–ethyl acetate, 1:1. Recrystallization from ether–hexane gave the analytical sample: mp 167–169°; ir 2.88, 5.78, 6.24, 6.34; uv (neutral) 203 (4.18), 231 (4.24), 281 (4.04); uv (acid) 199 (4.34), 231 (4.24), 281 (4.04); uv (base) 281 (4.04); nmr 1.33–2.50 (m, 8 H, CH_2), 2.62 (s, 2 H, CH_2CO), 3.67, 3.83 (m, 1 H, CHOH), 3.95, 3.98 (s, 6 H, OCH_3), 7.02 (d, J = 9 Hz, 1 H, Ar H), 7.56 (d, J = 9 Hz, 1, H, Ar H).

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.33; H, 7.25.

The aqueous basic layer was acidified and extracted with methylene chloride. The organic extract was washed with water, dried, and evaporated. The residue was dried *in vacuo*, giving 0.116 g (40.6%) of crude lactone (ir 2.91, 5.63) which was not characterized in detail.

(±)-10-Hydroxy-8,9,11,12-tetrahydrostepharine (26).—A mixture of 0.063 g of spiro-4-hydroxycyclohexane-1,3′-(4′,5′-dimethoxyindan-1′-one) (24), 1.1 g of distilled aminoacetal, and 4 ml of dry toluene (excluding the water separator volume) was heated at reflux for 72 hr in a system previously dried and flushed with dry nitrogen. A slight positive nitrogen pressure was maintained during the reaction. The excess reagent and solvent were removed *in vacuo*, and the viscous residue was dried *in vacuo* overnight. After 0.027 g of platinum oxide in 5 ml of absolute ethanol was reduced with hydrogen passed through a Dry Ice condenser, the Schiff base was dissolved in 12 ml of absolute ethanol and added to the prereduced catalyst. The mixture was reduced at room temperature and pressure until the theoretical uptake of hydrogen was observed. Usually, the reduction was completed in 4–6 hr. After the reduction mixture was filtered through a Celite pad, the filtrate was evaporated *in vacuo* at 30–40° to an oily residue. The light brown residue was dissolved in 10–15 ml of dry ether and cooled in an ice bath. The cold ether solution was added to 15 ml of ice-cold 6 N hydrochloric acid, and the mixture was stored at room temperature overnight. After the mixture was extracted with three 5-ml portions of ether, the dissolved ether was removed *in vacuo*, first with a water aspirator, and then with an oil pump connected to two sets of Dry Ice and sodium hydroxide traps. When the volume had been reduced to approximately 10 ml, 10 ml of 1:1 ethanol–concentrated hydrochloric acid was added. To this solution was added 0.077 g of 5% palladium on charcoal, and reduction was carried out at room temperature and pressure. Reduction was stopped when the theoretical uptake of hydrogen was observed (6 hr). After the reaction mixture was filtered through a Celite pad, the filtrate was concentrated *in vacuo* at room temperature. The concentrated solution was diluted with 10–20 ml of water, cooled to 0°, and made basic with concentrated sodium hydroxide. The basic solution was extracted with methylene chloride. After the methylene chloride was washed with water, dried over anhydrous sodium sulfate, and evaporated, the residue was dried *in vacuo* giving 0.055 g (81.2%) of **26** as a light yellow foam: mp 30–66°; ir 2.95; nmr (CD_3CN) 1.35–2.00 [m, 8 H, (CH_2)], 2.70 (m, 6 H, $ArCH_2CH_2N$ and CH_2CHN), 3.58–3.75 (m, 1 H, CHOH), 3.80 (s, 6 H, OCH_3), 4.12 (t, J = 7 Hz, 1 H, CH_2CHN), 6.77 (s, 1 H, Ar H). Tlc showed two minor spots in addition to one major component.

Attempts were made to purify a portion of the free base or hydrochloride for analysis but were unsuccessful. Tlc showed two or three spots still present in the free base after chromatography.

(±)-10-Hydroxy-8,9,11,12-tetrahydropronuciferine (27).—To a mixture of 0.030 g of 10-hydroxy-8,9,11,12-tetrahydrostepharine (26), 1.2 ml of chloroform, and 0.2 ml of dry pyridine at 0° was carefully added 0.14 ml of ethyl chloroformate in a system protected from atmospheric moisture. The mixture was heated at reflux on a steam bath for 5 min and evaporated to a viscous residue. After the residue was dissolved in methylene chloride, the organic solution was washed with 10% hydrochloric acid, 10% sodium bicarbonate, and water, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 0.039 g (95.1%) of red residue.

To a slurry of 0.050 g of lithium aluminum hydride in 1.5 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride) at 0° was added the crude amide dissolved in 1.5 ml of dry tetrahydrofuran.

After the mixture was heated at reflux for 2 hr, it was cooled to 0°, and the excess hydride was destroyed at 0° with 10% sodium hydroxide. The granular mixture was filtered and washed with tetrahydrofuran. After the tetrahydrofuran was removed *in vacuo*, at 35–50°, the residue was dissolved in methylene chloride, and the solution was washed with water and dried over anhydrous sodium sulfate. The solvent was removed and the residue dried *in vacuo*, giving 0.020 mg (64.7%) of **27** as a foamy solid, mp 48–58°. Tlc showed a mixture of four components. The mixture, 0.017 g, was purified by column chromatography on 3.3 g of Biorad neutral alumina (activity II). The product was eluted from the column with a 2% methanol–ether solution. After 7 ml was collected in six fractions, the remaining 100 fractions were collected in 0.2-ml portions. Tlc was used to monitor the elution products. From fractions 16–56 was obtained 0.0055 g of **27**. An infrared spectrum of this material was identical with that of Bernauer's sample of the free base (hydroxyl, 2.95 μ).[5,24] The R_f value on tlc was identical with the R_f value of Bernauer's sample; however, there was a trace of a faster moving component present which had an R_f value identical with that of the 10 epimer of **41** (**42**). Fractions 26–56 (0.00238) were converted to the hydrochloride and recrystallized twice from methanol–ether, mp 209–219° dec, mmp with Bernauer's sample 203–214°. The decomposition point of this compound is indefinite at best and appears to be a function of the rate of heating. The material prepared in this work was not obtained in sufficient quantity to permit exhaustive purification of the base hydrochloride. An infrared spectrum of the hydrochloride (hydroxyl, 2.95 μ), was identical with that of Bernauer's sample of (±)-10-hydroxy-8,9,11,12-tetrahydropronuciferine hydrochloride.[5,24]

Registry No.—**5**, 26709-68-2; **5** picrate, 26679-48-3; **7**, 26709-69-3; **8**, 26709-70-6; **9**, 26709-71-7; **9** amide, 26709-72-8; **10**, 26709-73-9; **11**, 26697-49-4; **11** HCl, 26697-50-7; **12**, 26681-39-0; **14**, 26709-74-0; **15**, 26681-40-3; **16**, 26686-05-5; **18** 2,4-DNP, 26686-06-6; **19**, 26686-07-7; **20**, 26681-41-4; **20** picrate, 26681-42-5; **21**, 26681-43-6; **22**, 26681-44-7; **23**, 26681-45-8; **24**, 26681-46-9; **26**, 26681-47-0; **27**, 25926-57-2; 4,5-dimethoxy-1-indanone, 6342-80-9; cyclohexylidenebis-(2-methoxyphenyl)carbinol, 26709-76-2; 2,3-dimethoxyphenylacetonitrile, 4468-57-9; dimethyl 4-cyano-4-(2′,3′-dimethoxyphenyl)pimelate, 26709-78-4; methyl 5-cyano-5-(2′,3′-dimethoxyphenyl)-2-oxocyclohexenecarboxylate, 26709-79-5; **23** 2,4-DNP, 26686-09-9.

Synthetic Intermediates Potentially Useful for the Synthesis of Tetrodotoxin and Derivatives. III.[1] Synthesis of a Key Lactone Intermediate from Shikimic Acid

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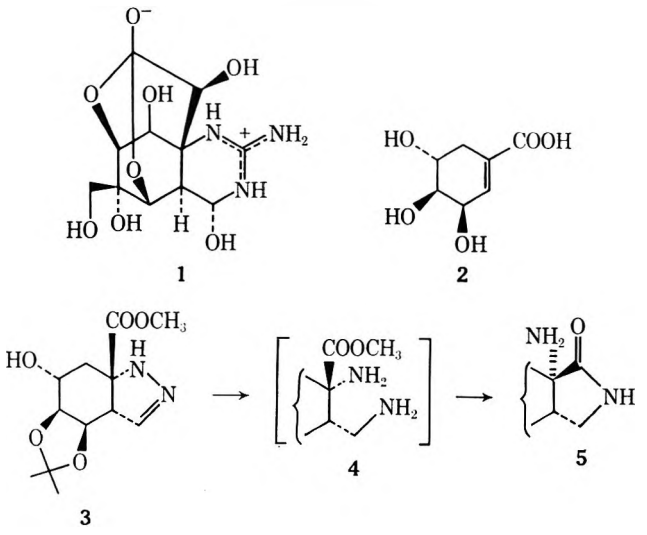
Received July 8, 1970

Toward the goal of synthesizing from shikimic acid a pyrazoline intermediate in which the two-carbon angular substituent is tied back through formation of a lactone to the carbocyclic ring (see lactone **60**), diazo ketone **9** was prepared. This substance together with those epoxypyrazolines obtained by the reaction of diazomethane with amides **16** and **17** and ester **18** all failed in their mission. Reaction of pyrazolines **27** and **3**, however, with methanesulfonyl chloride led to novel mesylate derivatives **32** and **33**, the latter affording the oxygen-bridged cyclopropane **36** upon reaction with hot acetic anhydride. The synthetic goal was realized through chain extension of intermediate **3** in which the pyrazoline ring was already in place, a sequence which avoided the undesirable formation of epoxy derivatives at the α position on the side chain (see below). In order for the final ring closure to a lactone to take place, it was found necessary to reduce the α-keto function of amide **45**, producing alcohol **59**. This last substance upon treatment with hot pyridine–water smoothly cyclized to the desired key lactone intermediate **60**.

We describe in this paper further progress toward the synthesis of the Japanese puffer fish (*Fugu*) and California newt neuropoison tetrodotoxin (**1**)[2] (Scheme I) and

SCHEME I

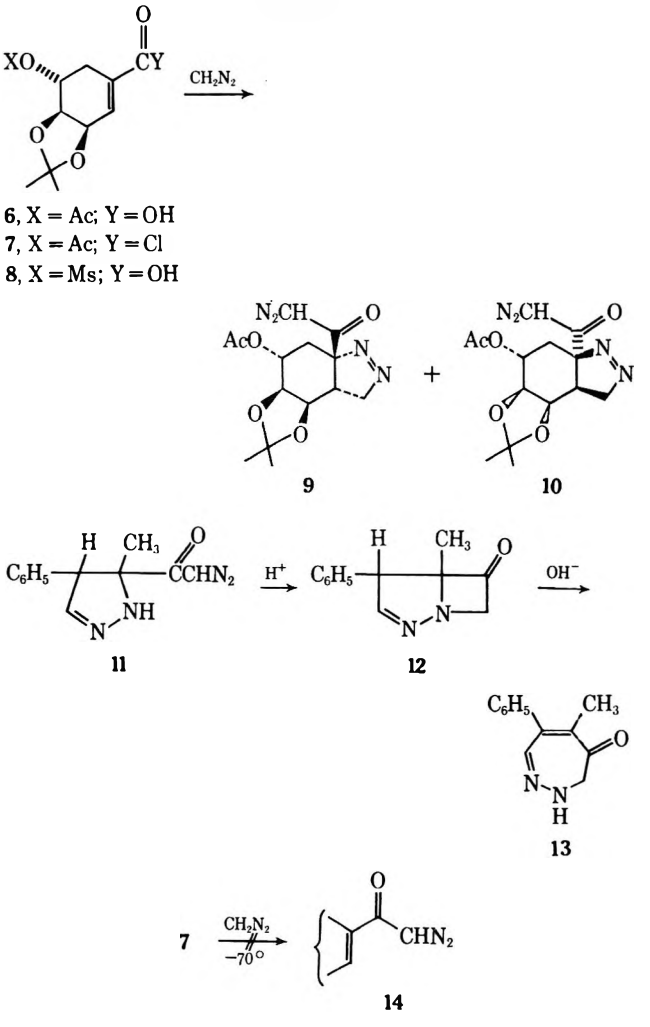


closely related structural derivatives utilizing the readily available natural shikimic acid (**2**) as a starting point. In particular, the chemistry leading to the synthesis of key lactone intermediate **60** is herewith disclosed.

In part II[1] of this series we described the synthesis of pyrazoline **3** from shikimic acid and outlined a plan for the conversion of the pyrazoline ring of **3** into a cyclic guanidine moiety by way of reduction to the 1,3-diamine **4** and subsequent condensation with cyanamide or nitroguanidine. Progress toward this goal, however, became quickly thwarted when attempts to obtain the diamine **4** resulted in a mixture which probably contained the lactam **5**. It became clear that conversion of the pyrazoline ring to the cyclic guanidine must necessarily be accomplished after the side chain is "tied back" to the carbocyclic ring through formation of a lactone or two-thirds ortho ester.

Since in our plan the carboxy group of shikimic acid (**2**) was destined to become the two-carbon angular substituent of tetrodotoxin, it was necessary to convert the carboxy carbon atom into a two-carbon appendage which might then be tied back. It appeared that the reaction of diazomethane with a suitably protected acid chloride would not only provide a two-carbon functionalized appendage but moreover introduce the required pyrazoline ring in the same step. To this end acid **6**[1] (Scheme II) was converted into the acid chlo-

SCHEME II



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(1) Part II: J. F. W. Keana and C. U. Kim, *J. Org. Chem.*, **35**, 1093 (1970).

(2) R. B. Woodward, *Pure Appl. Chem.*, **9**, 49 (1964), and references cited therein.

ride **7** with thionyl chloride and then allowed to react with excess diazomethane. Column chromatography afforded pure oily pyrazolines **9** in 65% yield and **10** in 25% yield.[3,4]

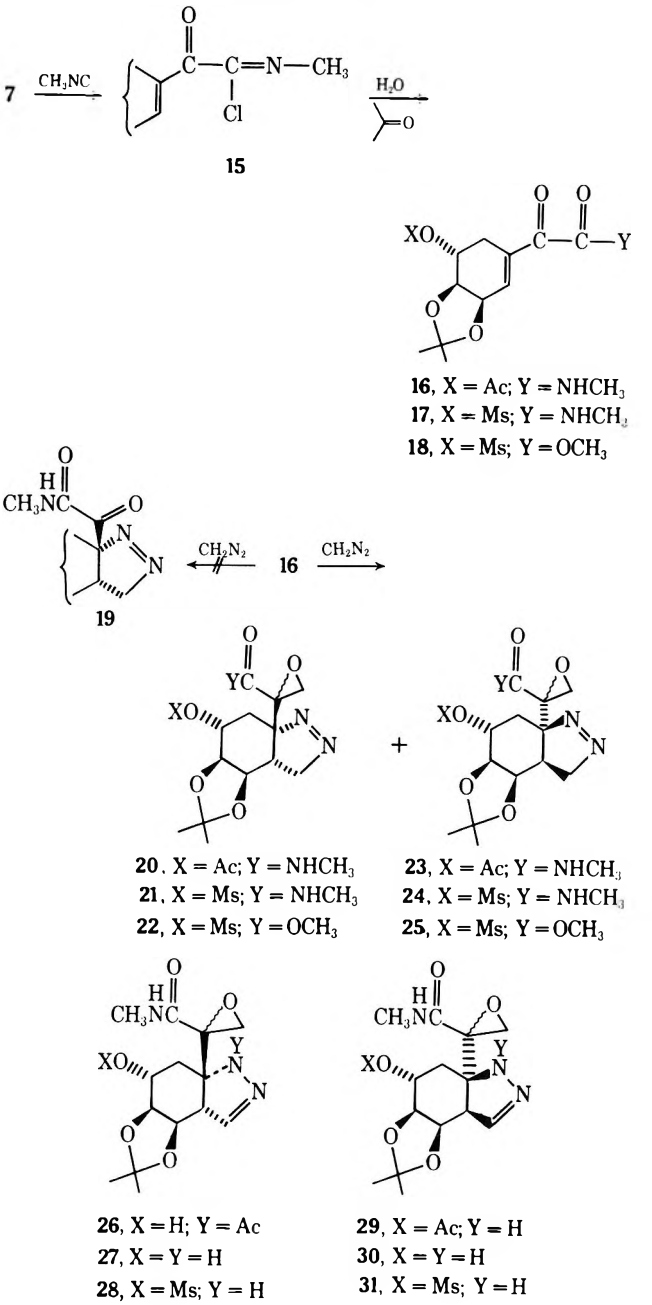
Although simple diazo ketones can be transformed into a variety of functional groups, often in high yield,[5] all attempts to convert the α-diazo ketone function of pyrazoline **9** into an α-halo ketone, a ketoaldehyde, or a keto acid utilizing conventional methods[5] consistently met with failure. It is likely that the pyrazoline ring became involved in a manner analogous to that observed by Moore[6] where the action of acid on pyrazoline **11** led to heterocycle **12**, base treatment of which produced **13**.

The sequence was then attempted stepwise since Moore,[7] for example, was able to add successfully only 1 equiv of diazomethane to α-methylcinnamoyl chloride to obtain the corresponding α,β unsaturated diazo ketone in good yield. However, our acid chloride **7** or the corresponding 5-mesyloxy derivative led to a mixture of diazoketopyrazolines and starting acid chloride even when deficiencies of diazomethane were employed at $-70°$. Apparently once the unsaturated diazo ketone is formed it reacts with more diazomethane at a much faster rate than does starting acid chloride **7**, and thus it was not possible in our series to prepare the unsaturated diazo ketone **14**.

At this point it occurred to us that the elegant general α-ketoamide synthesis recently developed by Ugi[8] utilizing the reaction between acid chlorides and isocyanides might be applicable to α,β-unsaturated acid chlorides. Thus acid chloride **7** was allowed to react with methyl isocyanide, affording an adduct tentatively represented as imidoyl chloride **15** (Scheme III) in near quantitative yield. The adduct could be hydrolyzed quantitatively to ketoamide **16**. In a completely analogous sequence, mesylate **17** (see below) was also prepared from acid **8**.

Having introduced the desired side chain, we then allowed diazomethane to react with ketoamide **16**, a reaction which led not to the desired pyrazoline **19** but instead to a mixture of epoxypyrazolines **20** and **23** in which diazomethane had added to the α-keto carbonyl group as well, probably nonstereoselectively. Formation of the epoxides could not be suppressed even by reaction of **16** at $-70°$ with 1 equiv of diazomethane. Chromatographic separation was difficult, affording only minor pyrazoline **23** in nearly pure form in 14% yield.[3] It could be estimated from the nmr spectrum of the mixture that major pyrazoline **20** was produced in about 50% yield.

SCHEME III



Experience gained in the one-carbon side chain pyrazoline series[1] suggested that pyrazolines **20** and **23** might well suffer isomerization to the Δ^2-pyrazoline series and with, in the case of pyrazoline **20**, concommitant OAc → NAc migration upon treatment with toluenesulfonic acid in refluxing benzene. Indeed, when the mixture was so treated and the resulting products chromatographed, *N*-acetate **26**, mp 195–196°, was isolated in 24% yield, based on starting ketoamide **16**. The structure of **26** followed from the ir spectrum which showed a new sharp strong band at 1620 cm^{-1} (=N—NAc)[1] and the nmr spectrum which displayed a three-proton singlet at δ 2.23 (NAc).[1] In order for a OAc → NAc migration to occur, the C-6 acetoxy group and the pyrazoline ring must be cis to one another. Minor pyrazoline **29** could not be obtained in pure form from this chromatography.

In another series of experiments the mixture of pyrazolines **20** and **23** was treated with sodium methoxide

(3) The stereochemical assignment of the newly formed pyrazoline ring as either α or β is partially or entirely based on the following considerations (see part II[1] of this series). The isomer resulting from cis addition of diazomethane to the least hindered side of the double bond (side opposite the acetonide moiety) would be expected to predominate. This isomer and its Δ^2 analog invariably had the longer retention time upon chromatography over silica gel than did the other. Secondly, if the Δ^1-pyrazoline ring is cis to the acetonide moiety the chemical shift difference between the two singlets observed for the acetonide moeity is about 4 Hz, whereas this difference is about 8 Hz if the Δ^1-pyrazoline ring is trans to the acetonide moeity.[1]

(4) Complete spectral data on all pertinent compounds are found in the Experimental Section. All compound names and structures, excepting tetrodofoxin (**1**), are given without regard to absolute configuration.

(5) For a review of α-diazo ketone reactions, see F. Weygand and H. J. Bestmann, *Angew. Chem.*, **72**, 535 (1960).

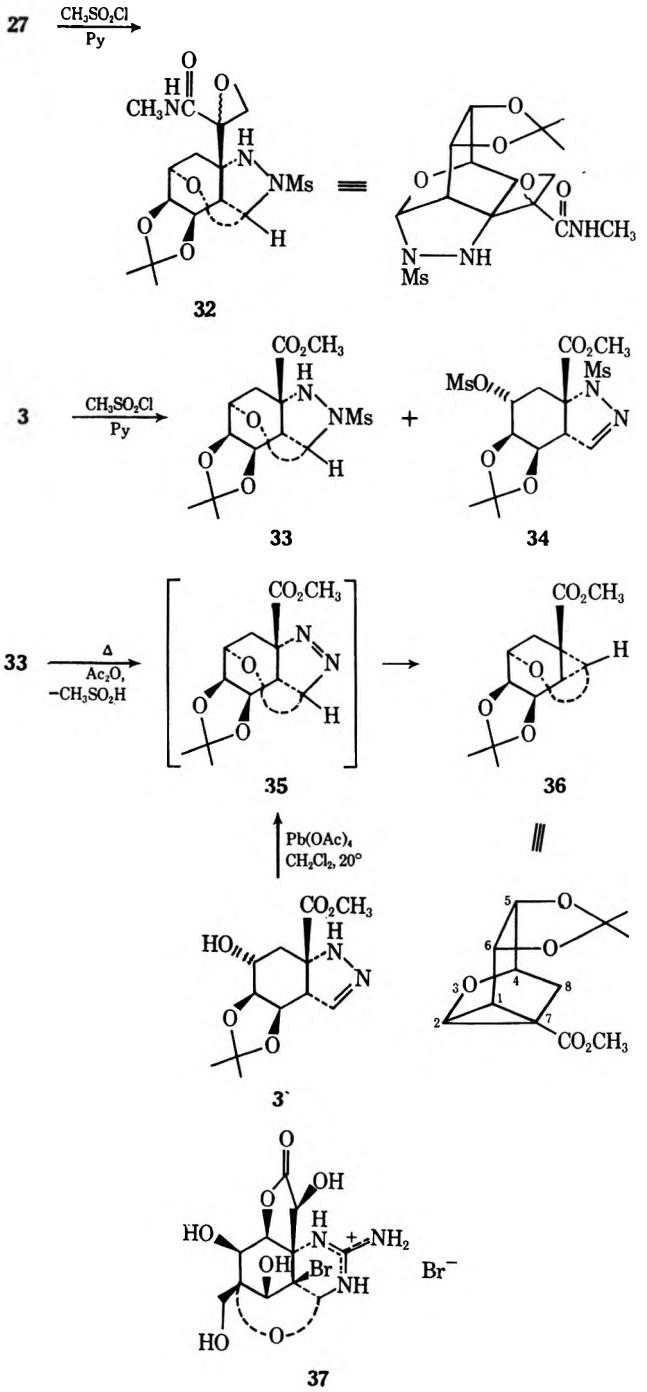
(6) J. A. Moore, W. F. Holton, and E. L. Wittle, *J. Amer. Chem. Soc.*, **84**, 390 (1962); J. A. Moore and L. J. Pandya, *J. Org. Chem.*, **29**, 336 (1964).

(7) J. A. Moore, *ibid.*, **20**, 1607 (1955).

(8) I. Ugi and U. Fetzer, *Chem. Ber.*, **94**, 1116 (1961).

in methanol, cleaving the acetates and isomerizing the double bond into the 2 position. Chromatographic separation of this mixture afforded first pure minor pyrazoline **30**,[3] mp 176–177°, in 13% yield followed by oily predominant isomer **27** in 26% yield. This latter material was converted into crystalline mesylate derivative **32**, mp 183–185° (Scheme IV), the structure of which for some time remained a mystery.

SCHEME IV



Elemental analysis and mass spectral data revealed that **32** was a monomesylate derivative of **27**. The nmr spectrum of **32** displayed the C-3 proton as a doublet (J = 4.0 Hz) at δ 5.60. The C-3 proton in all the Δ^2-pyrazolines of our series appeared at δ 6.6–7.0; thus **32** was not simply the *N*- or *O*-mesylate of Δ^2-pyrazoline **27**. The *O*-mesylate **28**, prepared by another route (see below), displayed the expected one-proton doublet (J = 1.5 Hz) at δ 6.72 for the C-3 proton. The ir spectrum of **32** was not revealing since other functional groups in the substance masked the crucial OH and C=N regions.

Confirming evidence was obtained from a study of the mesylation of pyrazoline **3**.[1] Treatment of **3** with methanesulfonyl chloride in pyridine followed by a chromatography led to a crystalline monomesylate derivative, mp 126–128°, which was assigned structure **33** and an oily dimesylate derivative **34**. Mesylate **33**, like **32**, displayed in its nmr spectrum a one-proton doublet (J = 3.0 Hz) at δ 5.60 assigned to H-3. The ir spectrum displayed weak absorption at 3400 cm^{-1} (NH or OH) but no absorption at ~1650 cm^{-1} (C=N). Dimesylate **34**, on the other hand, displayed H-3 as the expected doublet (J = 1.5 Hz) at δ 6.90 and showed as well weak C=N absorption at 1650 cm^{-1}.

Treatment of monomesylate **33** with methanesulfonyl chloride in pyridine led quantitatively to starting material, clearly indicating that **33** was not an intermediate on the way to dimesylate **34**. It is our interpretation that initial mesylation on the oxygen atom of **3** (or **27**) is competitive with attack on the pyrazoline ring. Once the simple *O*-mesylate is produced, the hydroxyl is now protected and the substance suffers further rapid attack on N-1 to produce dimesylate **34**. However, if initial attack occurs on the pyrazoline ring, it is the less hindered N-2 which is attacked with concomitant addition of the juxtaposed (in several conformations) C-6 hydroxy group to the C=N group, affording monomesylate **32** (or **33**). An analogous transannular addition of a suitably juxtaposed hydroxy group to a C=N linkage was observed in the instance of bromoanhydrotetrodoic lactone hydrobromide (**37**) by Woodward.[2]

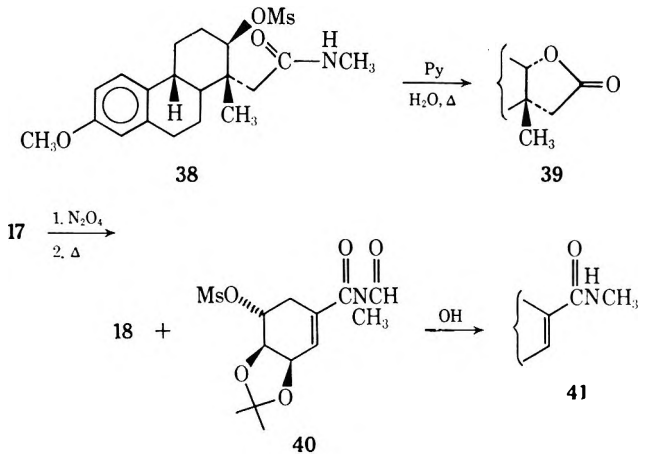
Mesylate **33** also resisted the action of acetic anhydride in pyridine, but when treated with refluxing acetic anhydride a most interesting elimination ensued, producing in high yield a crystalline ester, mp 105–106°, assigned structure **36** on the basis of elemental analysis and spectral data.[4] It seems reasonable that the first step toward **36** might be a thermal elimination of methanesulfinic acid to produce Δ^1-pyrazoline **35** which then suffers rapid loss of nitrogen, producing cyclopropane **36**. It is well known that Δ^1-pyrazolines in which the nitrogen atoms are attached to carbon atoms capable of providing good stabilization for a free radical at that site readily thermally eliminate nitrogen to afford the corresponding cyclopropane.[9] Cyclopropane (**36**) had been obtained earlier by us (unpublished) when ester **3** was treated with lead tetraacetate in dichloromethane with the aim of producing a Δ^1-3-acetoxy derivative.[10] It is not possible to conclude with certainty from the above discussion that the mesylate groups in **32** and **33** are in fact located on N-2 rather than N-1; however, since *N*-acetate **44** (see below), for example, shows no tendency toward addition of the C-6 hydroxy group to the C=N linkage, it is likely that structures **32** and **33** are correct for the substances described.

Because of the low yields and difficult chromatographic separations encountered in the C-6 acetate series above we formulated a new plan which envisioned an intramolecular displacement of the mesylate group

(9) See, *inter alia*, R. Crawford and G. Erickson, *J. Amer. Chem. Soc.*, **89**, 3907 (1967); D. E. McGreer and W. Wu, *Can. J. Chem.*, **45**, 461 (1967).
(10) J. P. Freeman, *J. Org. Chem.*, **29**, 1379 (1964).

in mesylate **21** by the oxygen atom of the amide carbonyl group, a process related to that effected recently by Ireland[11] with the conversion of mesylate **38** to lactone **39** (Scheme V). This scheme eventually proved successful in modified form (see below).

SCHEME V



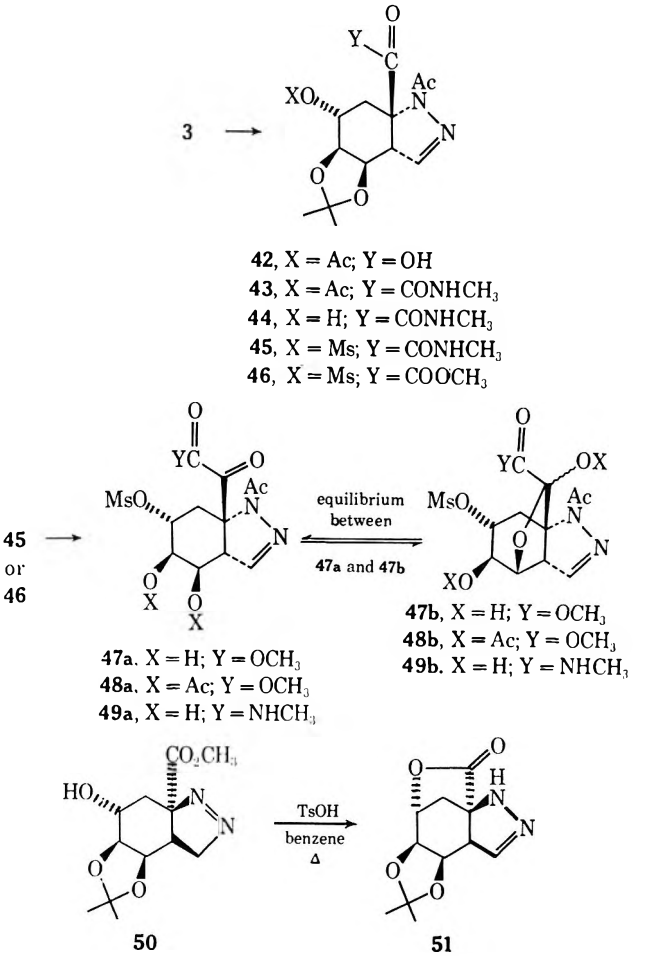
Reaction of diazomethane with mesylate ketoamide **17** (see above) produced, after chromatography, an inseparable oily mixture of pyrazolines **21** and **24** which was isomerized to the readily separable Δ^2-pyrazoline series through refluxing benzene containing toluenesulfonic acid. The oily predominant isomer (by nmr) could be isolated in 18% yield after rechromatography and was assigned structure **28**.[3] The minor isomer **31**, obtained in 10% yield, was characterized only by spectra. The low yield of pure pyrazoline **28** precluded extensive study on the cyclization to a lactone. The substance was subjected to the action of refluxing dimethylformamide, sodium hydride in tetrahydrofuran, and sodium methoxide in methanol, none of which led to useful material.

At this point it was decided to explore the reactions of the two-carbon side chain α-keto ester series. The action of dinitrogen tetroxide[12] on mesylate amide **17** followed by a period of heating in benzene smoothly led to methyl ester **18**, obtainable in an overall yield of 70% from the acetonide of shikimic acid (**2**) without purification of any intermediates. Also produced in 15% yield along with ester **18** was *N*-methylformamide **40**. Treatment of **40** with sodium hydroxide in methanol afforded *N*-methylamide **41**, mp 130–131°, in 60% yield. The origin of **40** is not clear at this time.

Not surprisingly, ester **18** behaved toward diazomethane in a manner analogous to that of ketoamide **17**. Chromatography of the resulting mixture of pyrazolines **22** and **25** afforded the predominant (by nmr) pure oily pyrazoline **22** in 38% yield. Unfortunately, attempted hydrolysis of **22** with cold methanolic sodium hydroxide led only to poorly resolved mixtures in which the epoxide appeared to have suffered ring opening and the pyrazoline ring perhaps a comparable fate. Thus we were led to explore yet another synthetic permutation, the ultimately successful one toward our goal, namely, one in which the angular carbomethoxy group of a suitable intermediate was chain-extended after the pyrazoline ring had been introduced and protected.

This last approach began with pyrazoline **3**, readily available from shikimic acid in 75% overall yield. Treatment (Scheme VI) of **3** with aqueous sodium hydroxide in methanol afforded the corresponding acid which, without purification, was converted into diacetate **42** in 83% overall yield by acetic anhydride in pyridine. The action of thionyl chloride on acid **42** led to the corresponding acid chloride which was immediately allowed to react with methyl isocyanide.[8] The resulting adduct was hydrolyzed in aqueous acetone to afford after chromatography pure oily amide **43** in 56% overall yield from ester **3**.

SCHEME VI



In order to introduce a good leaving group at the 6 position the OAc of diacetate **43** was selectively hydrolyzed by treatment with 1.1 equiv of aqueous sodium hydroxide in methanol at 0°, producing alcohol **44**, mp 118–122°. The reaction of **44** with methanesulfonyl chloride in pyridine led to mesylate **45** as a white foam. We were now in a position to attempt an intramolecular displacement of the mesylate group (see above). The reaction proved unsuccessful once again, perhaps for the following reasons: (a) the strain involved with formation of the lactone bridge which would contain two sp^2-hybridized carbon atoms; (b) the unfavorable interaction of the bridge with the nearby cis acetonide moiety; (c) an extremely unfavorable position of equilibrium between the two chair conformers of amide **45**, only one of which can cyclize.

(11) R. E. Ireland, D. A. Evans, D. Glover, G. M. Rubottom, and H. Young, *J. Org. Chem.* **34**, 3717 (1969).

(12) E. H. White, *J. Amer. Chem. Soc.*, **77**, 6008 (1955).

The amide **45** was next converted into ester **46**, mp 153–154°, by the action of dinitrogen tetroxide[11] followed by heat. It was hoped that mild basic hydrolysis of **46** would lead to the corresponding acid which might undergo cyclization to the desired lactone. However, as in the case of ester **22** above, mild hydrolysis attempts on ester **46** led only to bad mixtures, the nmr spectra of which were not promising.

It was possible that removal of the acetonide grouping might allow cyclization to proceed. Toward this goal ester **46** was treated with methanolic hydrogen chloride, affording diol **47**, a substance which readily led to triacetate **48** (see below) by treatment with acetic anhydride in pyridine. Diol **47** was recovered unchanged from treatment with toluenesulfonic acid in refluxing benzene, conditions which readily afforded lactone **51** from ester **50**.[1] From the fact that diol **49**, prepared from amide **47** by the action of methanolic hydrogen chloride, displayed only weak ir absorption at ~1730 cm^{-1} due to the α-keto grouping and that diol **54** (see below) displayed no absorption in this region, it appeared that the failure of the above cyclization attempt likely resulted from existence of both diols **47** and **49** largely in the hemiketal forms **47b** and **49b**, respectively. In this regard it is possible that the structure of triacetate **48** is **48b** rather than **48a**. Spectra do not permit a clear distinction to be made.

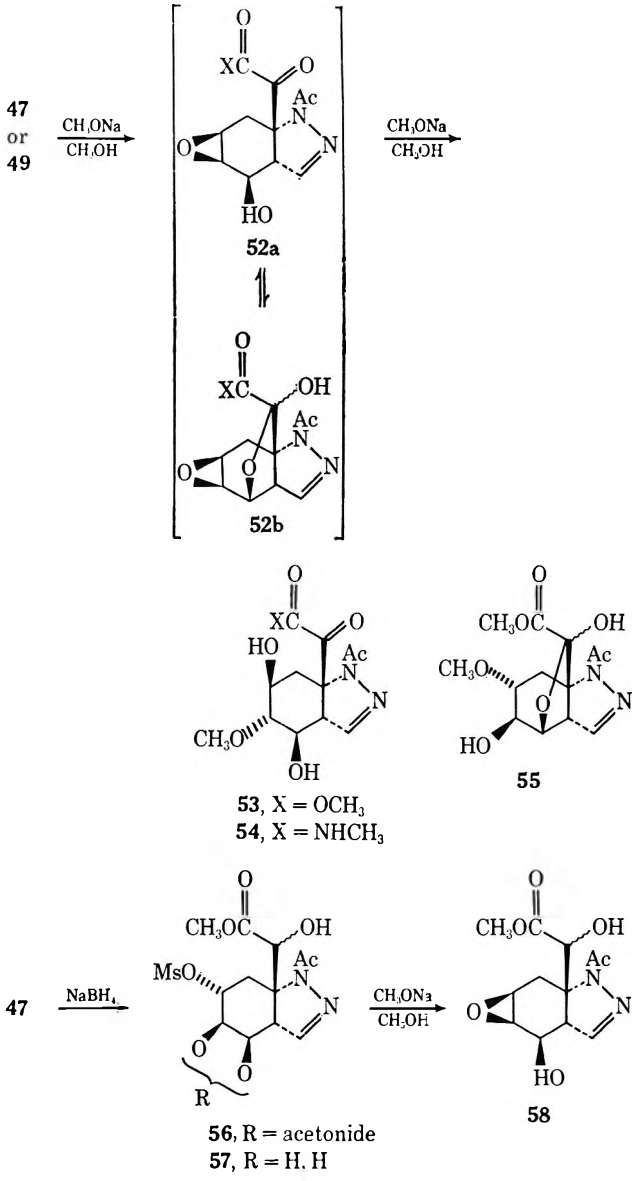
The probable existence of the hemiketal forms suggested an alternative route toward stereospecific inversion of the maverick oxygen function at C-6 *via* an epoxide intermediate. Indeed, treatment of diol **47** with sodium methoxide in methanol smoothly led undoubtedly (see below) *via* epoxide **52** (Scheme VII) to diol **53**, mp 212–216°, in 74% overall yield from diol **47**. Treatment of **53** with acetic anhydride in pyridine afforded the corresponding oily triacetate. Diol **49** in an analogous manner led to amide **54**.

Diol **53** appeared to be stereochemically homogeneous and was assigned the indicated stereochemistry based on the following considerations. Epoxide intermediate **52** would be expected to be opened by methoxide ion in a trans diaxial manner and if the ring opening takes place by attack of methoxide on the hemiketal form **52b**, then diol **53** should be produced stereospecifically. Chemical evidence in support of the 1,3-diol structure **53** was found in the observed resistance of **53** toward formation of an acetonide under conditions which readily converted shikimic acid (**2**) into its acetonide. This is negative evidence, however, and resistance to acetonide formation could be a result of an unusually stable hemiketal form **55** of the isomeric 1,2-diol.

Diol **53** was next subjected to the action of toluenesulfonic acid in refluxing toluene, conditions more vigorous than those used to prepare lactone **51**.[1] Starting **53** was recovered quantitatively. This experiment would suggest that diol **53** exists largely in the hemiketal form and thus formation of a lactone is not feasible. It now appeared necessary that the keto grouping on the side chain in all these intermediates must be reduced to the corresponding alcohol, analogous to the situation in tetrodotoxin, before formation of a lactone or two-thirds ortho ester may proceed.

Reduction of ester **46** with 1.5 equiv of sodium borohydride in ethanol at 0° (conditions which minimized overreduction to the corresponding diol[13]) produced

SCHEME VII

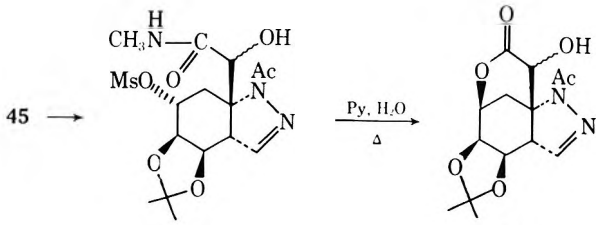


alcohol **56** in 50% yield. The action of methanolic hydrogen chloride on **56** led to triol **57** which, without purification, was treated with sodium methoxide in methanol to give epoxide **58**, an isolable substance which was characterized. Epoxide **58** was subjected to the action of toluenesulfonic acid in refluxing benzene–tetrahydrofuran, conditions which unexpectedly led only to recovered starting material.

Reduction of mesylate amide **45**, on the other hand, proceeded with sodium borohydride in ethanol in high yield to alcohol **59** which was probably a mixture of stereoisomers at the newly introduced center of asymmetry. This time treatment of **59** with refluxing pyridine–water[11] led smoothly to lactone **60** in near quantitative yield. The structure of the long sought after lactone **60** followed from elemental analysis, the mass spectrum which displayed a prominent parent ion at *m/e* 310.1154, the nmr spectrum which showed no mesylate or methylamide groupings, and the ir spectrum which displayed strong absorption at 1750 cm^{-1}, ex-

(13) See, *inter alia*, V. Boekelheide and R. J. Windgassen, *J. Amer. Chem. Soc.*, **81**, 1456 (1959); J. E. G. Barnett and P. W. Kent, *J. Chem. Soc.*, 2743 (1963).

pected for a six-membered lactone. With the lactone **60** in hand the stage is at last set for final elaboration to a toxin derivative.



Experimental Section[14]

4β,5β-Dihydroxy-6α-acetoxy-8β-diazoacetyl-4,5,6,7,8,9β-hexahydro-3(*H*)-indazole 4,5-Acetonide (9) and 4β,5β-Dihydroxy-6α-acetoxy-8α-diazoacetyl-4,5,6,7,8,9α-hexahydro-3(*H*)-indazole 4,5-Acetonide (10).—Acid chloride **7** was prepared by treatment of acid **6**[1] with excess boiling thionyl chloride followed by removal of the excess reagent under vacuum. A solution of 3.00 g (10.9 mmol) of crude acid chloride **7** (reddish oil) in 20 ml of ether was added dropwise to a solution of 2.0 g (47 mmol) of diazomethane in 90 ml of ether at 0°. The solution was allowed to stir for 60 min at 25° and then evaporated *in vacuo* affording 3.8 g of a yellow oil. Chromatography over 80 g of silica gel and elution with chloroform afforded 890 mg (25%) of **10** as a yellow oil. Although molecular distillation of **10** at *ca.* 10^{-5} mm in a 110° oil bath failed to afford an acceptable analytical specimen (see analysis), the mass, nmr, and ir spectra were completely consistent with those expected for **10**: nmr δ 1.25 (s, 3, acetonide methyl), 1.35 (s, 3, acetonide methyl), 1.8–3.3 (m, 3, H-7, 9), 1.90 (s, 3, acetate), 3.8–5.2 (m, 5, H-3, 4, 5, 6), 5.83 (s, 1, $-CHN_2$); ir ($CHCl_3$) 3000 (w), 2130 (s), 1635 cm^{-1} (s); uv max (EtOH) 322 mμ (ε 372); mass spectrum *m/e* 307 (loss of a methyl[15]), 297, 279, 269, 177.

Anal. Calcd for $C_{14}H_{18}N_4O_5$: C, 52.17; H, 5.63. Found: C, 51.43; H, 5.58.

Continued elution with the same solvent system afforded 2.3 g (65%) of **9** as a yellow oil: nmr δ 1.25 (s, 3, acetonide methyl), 1.42 (s, 3, acetonide methyl), 1.89 (s, 3, acetate), 2.0–3.1 (m, 3, H-7, 9), 3.8–5.2 (m, 5, H-3, 4, 5, 6), 5.83 (s, 1, $-CHN_2$); ir ($CHCl_3$) 3000 (w), 2130 (s), 1745 (s), 1645 cm^{-1} (s); uv max (EtOH) 325 mμ (ε 370); mass spectrum *m/e* 322 (parent ion), 307 (loss of a methyl), 280, 279, 177.

Molecular distillation (10^{-5} mm at 110°) of **35** afforded the analytical specimen as a yellow hard oil.

Anal. Calcd for $C_{14}H_{18}N_4O_5$: C, 52.17; H, 5.63. Found: C, 51.78; H, 5.33.

Methyl Isocyanide.—The procedure of Casanova[16] was followed exactly. From 15.0 g (0.25 mol) of *N*-methylformamide (Aldrich Chemical Co.) and 129 g (1.00 mol) of quinoline there was obtained 3.86 g (36%, based on *N*-methylformamide) of methyl isocyanide. This substance was dried and redistilled prior to use.

(3′β,4′β-Dihydroxy-5′α-acetoxycyclohexene-1′-yl)glyoxylic Acid *N*-Methylamide 3′,4′-Acetonide (16).—Following the procedure of Ugi,[8] to a solution of 121 mg (2.95 mmol) of methyl isocyanide in 2 ml of dry tetrahydrofuran at 0° was added a solution of 500 mg (1.83 mmol) of acid chloride **7** in 2 ml of dry tetrahydrofuran under nitrogen. The solution was allowed to stir for 10 hr at 25° and then the solvent was evaporated, affording 570 mg (~100%) of imidoyl chloride **15** as a dark oil, suitable for further reactions: nmr δ 1.45 (s, 6, two methyls of acetonide), 2.00 (s, 3, acetate), 2.2–2.8 (m, 2, H-6′), 3.50 (s, 3, methyl of imine), 4.0–5.4 (s, 3, H-3′, 4′, 5′), 7.00 (broad s, 1, H-2′); ir ($CHCl_3$) 3000 (w), 1750 (s), 1680 (s), 1650 cm^{-1} (s).

A solution of 1.45 g (4.60 mmol) of **15** in 12 ml of acetone–water (1:1) was stirred for 60 min at 0° and then 386 mg of sodium bicarbonate was added. The solution was extracted with 15 ml of chloroform three times. Removal of dried solvent afforded 1.36 g (~100%) of **16** as a slightly yellow oil, suitable for further reactions. Molecular distillation at *ca.* 10^{-5} mm in a 80–90° oil bath afforded the analytical specimen as a colorless hard oil: nmr δ 1.35 (s, 6, two methyls of acetonide), 2.00 (s, 3, acetate), 2.0–2.8 (m, 2, H-6′), 2.87 d, *J* = 5.0 Hz, 3, amide methyl), 4.0–5.2 (m, 3, H-3′, 4′, 5′), 7.0–7.4 (broad, 1, –NH), 7.60 d, *J* = 1 Hz, 1, H-2′); ir ($CHCl_3$) 3500 (w), 3000 (w), 1745 (s), 1700 (s), 1680 (s), 1540 cm^{-1} (m); mass spectrum *m/e* 297 (parent ion), 282 (loss of a methyl), 237 (loss of *N*-methylamide).

Anal. Calcd for $C_{14}H_{19}NO_6 \cdot {}^1/_2H_2O$: C, 54.90; H, 6.53; N, 4.58. Found: C, 54.81; H, 6.29; N, 4.48.

(3′β,4′β-Dihydroxy-5′α-mesyloxycyclohexene-1′-yl)glyoxylic Acid *N*-Methylamide 3′,4′-Acetonide (17).—Acid **8**[1] was converted into the corresponding acid chloride by treatment with excess boiling thionyl chloride followed by removal of the excess reagent under vacuum. To a solution of 4.0 g (12.3 mmol) of the acid chloride in 3 ml of dry tetrahydrofuran at 0° was added a solution of 2.6 g (65 mmol) of methyl isocyanide in 2 ml of tetrahydrofuran under nitrogen. The solution was allowed to stir for 12 hr at 25° and then all the solvent was removed *in vacuo*, affording ~4.5 g of dark oil which was treated with 10 ml of acetone–water (1:1) at 0° for 30 min. Then 1.01 g (12.0 mmol) of sodium bicarbonate was added and all was extracted with chloroform (three 20-ml portions). Removal of the dried chloroform afforded 3.7 g of an orange-colored oil which was chromatographed over 5.0 g of silica gel. Elution with ether afforded ~2.5 g (68%) of **17** as a slightly yellow foam: nmr δ 1.45 (s, 3, acetonide methyl), 1.48 (s, 3, acetonide methyl), 2.2–3.0 (m, 2, H-6′), 2.90 (d, *J* = 5.0 Hz, 3, amide methyl), 3.15 (s, 3, mesylate), 4.0–5.2 (m, 3, H-3′, 4′, 5′), 7.0–7.5 (broad, 1, –NH), 7.5–7.7 (m, 1, H-2′); ir ($CHCl_3$) 3460 (m), 1700 (s), 1680 (s), 1570 cm^{-1} (s); mass spectrum *m/e* 333 (parent ion), 318 (loss of a methyl), 275 (loss of *N*-methylamide).

Molecular distillation of **17** at ~10^{-5} mm in a 120° oil bath afforded the analytical specimen as a hard oil.

Anal. Calcd for $C_{13}H_{19}NO_7S \cdot {}^1/_2H_2O$: C, 45.62; H, 5.85; N, 4.10. Found: C, 45.56; H, 5.46; N, 3.69.

A benzene solution of **17** was refluxed (water separator) for 60 min. Evaporation of the benzene afforded a colorless oil which was exposed to high vacuum to produce a white foam which was dried at 56° (~0.1 mm) for 20 hr to give the analytical specimen.

Anal. Calcd for $C_{13}H_{19}NO_7S$: C, 46.84; H, 5.70. Found: C, 46.63; H, 5.32.

2-[4′β,5′β-Dihydroxy-6′α-acetoxy-4′,5′,6′,7′,8′,9′α-hexahydro-3′(*H*)-indazole-8′α-yl]acrylic Acid *N*-Methylamide 2,3-Epoxide 4′,5′-Acetonide (23).—A solution of 400 mg (1.35 mmol) of α-ketoamide **16** in 1 ml of methanol was added to a solution of 170 mg (4.0 mmol) of diazomethane in 10 ml of ether at 0°. The solution was allowed to stir for 30 min at 0° and then all solvent was removed *in vacuo*, affording 460 mg of a yellow oil which was chromatographed over 8.0 g of silica gel. Elution with 0.2% methanol in chloroform afforded 69 mg (14%) of almost pure (by nmr) minor isomer **23** as a colorless oil followed by 370 mg of an oily mixture of **23** and **20** (~3:7 by nmr). Pyrazoline **23** displayed the following: nmr δ 1.37 (s, 3, acetonide methyl), 1.43 (s, 3, acetonide methyl), 2.10 (s, 3, acetate), 2.0–2.6 (m, 2, H-7′), 2.78 (d, *J* = 4 Hz, 3, methyl of amide), 2.7–3.2 (m, 3, H-9′ and epoxide methylene), 3.0–5.3 (m, 5, H-3′, 4′, 5′, 6′), 6.0–6.7 (broad, 1, –NH); ir ($CHCl_3$) 3500 (m), 1735 (s), 1680 (s), 1540 cm^{-1} (m); mass spectrum *m/e* 338 (loss of a methyl[15]), 310. The analytical specimen of **23** was obtained by molecular distillation (10^{-5} mm) at 100–110° as a colorless hard oil.

Anal. Calcd for $C_{16}H_{23}N_3O_6$: C, 54.38; H, 6.56. Found: C, 54.81; H, 6.47.

2-[1′-Acetyl-4′β,5′β,6′α-trihydroxy-4′,5′,6′,7′,8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]acrylic Acid *N*-Methylamide 2,3-Epoxide 4′,5′-Acetonide (26).—A solution of 2.7 g (9.1 mmol) of α-ketoamide **16** in 1 ml of methanol and 3 ml of ether was added dropwise to a solution of 1.2 g (28.6 mmol) of diazomethane in 50 ml of ether at 0°. The solution was allowed to stir for 30 min at 0°; then all the solvent was removed *in vacuo*, affording 3.5 g of a yellow oil which was chromatographed over 40 g of silica gel. Elution with 0.3% methanol in chloroform afforded ~1.4 g of a colorless oily mixture of **20** and **23** by nmr.

The mixture was dissolved in 10 ml of benzene containing 40 mg of *p*-toluenesulfonic acid and then refluxed for 2 hr under nitrogen. Removal of the benzene afforded a reddish oil which was chromatographed over 7 g of silica gel. Elution with 2% methanol in chloroform afforded ~250 mg (24, based on **16**) of

(14) The preamble of the Experimental Section of part II[1] applies here. The drying agent used throughout was anhydrous magnesium sulfate.

(15) Acetonides frequently do not show a parent ion. See J. A. McCloskey and M. J. McClelland, *J. Amer. Chem. Soc.*, **87**, 5090 (1965).

(16) J. Casanova, R. E. Schuster, and N. D. Werner, *J. Chem. Soc.*, 4280 (1963).

26 as a yellow oil which, by scratching in ether, crystallized slowly. Recrystallization from chloroform–ether afforded 60 mg of **26** as white needles: mp 195–196°; nmr δ 1.34 (s, 3, acetonide methyl), 1.42 (s, 3, acetonide methyl), 2.0–3.0 (m, 2, H-7′), 2.21 (s, 3, methyl of -NAc), 2.69 (d, J = 4.5 Hz, 3, methyl of amide), 2.80 (d, J = 4 Hz, 1, epoxide proton), 3.00 (d, J = 4 Hz, 1, epoxide proton), 3.7–5.0 (m, 4, H-4′, 5′, 6′, 9′), 6.85 (d, J = 1.5 Hz, 1, H-3′), 6.6–6.8 (broad, 1, -NH); ir ($CHCl_3$) 3500 (m), 3020 (m), 1675 (s), 1620 (m), 1550 cm^{-1} (m); mass spectrum m/e 353 (parent ion), 338 (loss of methyl), 295 (loss of -(O=)C-NHCH$_3$), 253 (loss of -(O=)C—C(=O)NHCH$_3$).

Anal. Calcd for $C_{16}H_{23}N_3O_6 \cdot {}^1/_4CHCl_3$: C, 50.90; H, 6.14; N, 10.95. Found: C, 51.00; H, 6.40; N, 10.35.

Recrystallization of **26** from ethyl acetate gave white needles, mp 195°, which were also analyzed.

Anal. Calcd for $C_{16}H_{23}N_3O_6$: C, 54.38; H, 6.56. Found: C, 54.49; H, 6.20.

2-[4′β,5′β,6′α-Trihydroxy-4′,5′,6′,7′,8′,9′α-hexahydro-1′(*H*)-indazole-8′α-yl]acrylic Acid *N*-Methylamide 2,3-Epoxide 4′,5′-Acetonide (30) and 2-[4′β,5′β,6′α-Trihydroxy-4′,5′,6′,7′,8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]acrylic Acid *N*-Methylamide 2,3-Epoxide 4′,5′-Acetonide (27).—A solution of 980 mg (3.30 mmol) of α-ketoamide **16** in 2 ml of dry tetrahydrofuran was added to a solution of 148 mg (3.30 mmol) of diazomethane in 7 ml of ether at −78°. The solution was allowed to stir for 15 min at −78°; then all the solvent was removed *in vacuo*, affording 1.16 g of a yellow oil. The oil was dissolved in 10 ml of dry methanol containing 216 mg (4.00 mmol) of sodium methoxide and the solution was stirred for 14 hr at 25° under nitrogen. The solution was acidified with 2% hydrochloric acid at 0° and then a small portion of sodium bicarbonate was added until pH 9 ∼ 10. Removal of solvent afforded a residue which was digested with several 20-ml portions of chloroform. Removal of the chloroform gave 778 mg of a yellow oil which was chromatographed over 15 g of silica gel. Elution with 1% methanol in chloroform afforded 133 mg (13%) of crystalline **30**. Recrystallization from chloroform and ether afforded 54 mg of white needles: mp 175–176°; nmr δ 1.32 (s, 3, acetonide methyl), 1.47 (s, 3, acetonide methyl), 1.4–2.3 (m, 2, H-7′), 2.68 (d, J = 4.0 Hz, 1, epoxide proton), 2.95 (d, J = 4.0 Hz, 1, epoxide proton), 2.84 (d, J = 5.0 Hz, 3, methyl of amide), 3.5–4.9 (m, 4, H-4′, 5′, 6′, 9′), 6.82 (d, J = 1.0 Hz, 1, H-3′), 6.5–6.8 (broad, 1, -NH), 7.5–7.8 (broad, 1, -NH); ir ($CHCl_3$) 3450 (m), 3350 (w), 1675 (s), 1580 cm^{-1} (m); mass spectrum m/e 311 (parent ion) 295 (loss of a methyl), 253, 211 (loss of -(O=)C—C(=O)NH—CH$_3$). The analytical specimen was prepared by recrystallization of **30** from ethyl acetate to give white needles, mp 176–177°.

Anal. Calcd for $C_{14}H_{21}N_3O_5$: C, 54.01; H, 6.80; N, 13.50. Found: C, 54.02; H, 6.80; N, 13.04.

Continued elution with 3% methanol in chloroform afforded 260 mg (26%, based on α-ketoamide **16**) of **27** as a slightly yellow oil (see next experiment): nmr δ 1.32 (s, 3, acetonide methyl), 1.48 (s, 3, acetonide methyl), 2.0–2.8 (m, 2, H-7′), 2.79 (d, J = 5.0 Hz, 3, methyl of amide), 2.80 (d, J = 4.5 Hz, 1, epoxide proton), 3.17 (d, J = 4.5 Hz, 1, epoxide proton), 3.3–5.0 (m, 4, H-4′, 5′, 6′, 9′), 5.0–5.5 (broad, 1, -NH), 6.72 (d, J = 2.0 Hz, 1, H-3′), 6.7–6.9 (broad, 1, -NH); ir ($CHCl_3$) 3450 (m), 3350 (w), 1675 (s), 1570 cm^{-1} (m); mass spectrum m/e 311 (parent ion), 253, 225, 211.

2-[4′β,5′β,6′α-Trihydroxy-2′-methanesulfonyl-3′α→6′α-oxa-2′,3′,4′,5′,6′,7′,8′,9′β-octahydro-1′(*H*)-indazol-8′β-yl]acrylic Acid *N*-Methylamide 2,3-Epoxide 4′,5′-Acetonide (32).—A solution of 160 mg (0.540 mmol) of pyrazoline **27** and 137 mg (1.20 mmol) of methanesulfonyl chloride in 1.5 ml of dry pyridine was allowed to stir for 14 hr at 25° under nitrogen. Removal of pyridine and excess of methanesulfonyl chloride by high vacuum gave a reddish viscous oil which was dissolved into 5 ml of chloroform and washed with 2% hydrochloric acid at 0°. Removal of the dried chloroform afforded 134 mg of a yellow oil which was chromatographed over 3.0 g of silica gel. Elution with chloroform gave 88 mg (42%) of crystalline **32**: mp 180–184°; nmr δ 1.37 (s, 3, acetonide methyl), 1.67 (s, 3, acetonide methyl), 2.3–2.8 (m, 2, H-7′), 2.82 (d, J = 4.5 Hz, 3, methyl of amide), 2.84 (d, J = 5 Hz, 1, epoxide proton), 2.97 (d, J = 5 Hz, 1, epoxide proton), 3.05 (s, 3, mesylate), 3.1–4.8 (m, 4, H-4′, 5′, 6′, 9′), 5.60 (d, J = 4.0 Hz, 1, H-3′), 6.2–6.9 (broad, 1, -NH), 6.55 (broad s, 1, -NH); ir ($CHCl_3$) 3500 (w), 3320 (w), 1680 (s,)1750 cm^{-1} (m); mass spectrum m/e 389 (parent ion), 374 (loss of a methyl), 310, 294, 281. Recrystallization from ethyl acetate afforded the analytical specimen of **32**, mp 183–185°, as white needles.

Anal. Calcd for $C_{15}H_{23}N_3O_7S$: C, 46.27; H, 5.91; N, 10.79. Found: C, 46.30; H, 6.04; N, 10.69.

2-Mesyl-4β,5β,6α-trihydroxy-3α→6α-oxa-8β-carbomethoxy-2,3,4,5,6,7,8,9β-octahydro-1(*H*)-indazole 4,5-Acetonide (33) and 1-Mesyl-4β,5β-dihydroxy-6α-mesyloxy-8β-carbomethoxy-4,5,6,7,-8,9β-hexahydro-1(*H*)-indazole 4,5-Acetonide (34).—A solution of 102 mg (0.380 mmol) of alcohol **3** in 1 ml of pyridine was cooled to 0° and then 130 mg (1.14 mmol) of methanesulfonyl chloride was added under nitrogen. The solution was allowed to stir for 15 hr at 25° and then almost all the solvent was removed by high vacuum affording a residue which was dissolved in 5 ml of chloroform and washed with 3% hydrochloric acid at 0°. Removal of dried chloroform afforded 88 mg of a yellow oil which was chromatographed over 3.0 g of silica gel. Elution with chloroform–carbon tetrachloride (1:1) afforded 48 mg (37%) of crystalline **33**. Recrystallization from ethyl acetate–ether afforded 21 mg of **33** as white needles: mp 126–128°; nmr δ 1.33 (s, 3, acetonide methyl), 1.44 (s, 3, acetonide methyl), 1.5–2.2 (m, 2, H-7), 3.09 (s, 3, mesylate), 3.0–3.2 (m, 1, H-9), 3.80 (s, 3, methyl ester), 4.0–4.8 (m, 3, H-4, 5, 6), 5.1–5.3 (broad s, 1, NH), 5.60 (d, J = 3 Hz, 1, H-3); ir ($CHCl_3$) 3400 (w), 3000 (w), 1745 (s), 1340 cm^{-1} (s); mass spectrum m/e 348 (parent ion), 333 (loss of a methyl), 289 273.

Anal. Calcd for $C_{13}H_{20}N_2O_7S$: C, 44.83; H, 5.75; N, 8.05. Found: C, 44.87; H, 5.59; N, 8.44.

Continued elution with chloroform afforded 18 mg of **34** as a slightly yellow oil: nmr δ 1.32 (s, 3, acetonide methyl), 1.50 (s, 3, acetonide methyl), 1.4–1.7 (m, 2, H-7), 3.10 (s, 3, mesylate), 3.20 (s, 3, mesylate), 3.0–3.2 (m, 1, H-9), 3.88 (s, 3, methyl ester), 4.0–5.2 (m, 3, H-4, 5, 6), 6.90 (d, J = 1.5 Hz, 1, H-3); ir ($CHCl_3$) 3000 (w), 1745 (s) 1350 cm^{-1} (s); mass spectrum m/e 426 (parent peak), 411 (loss of a methyl), 367, 333.

Anal. Calcd for $C_{14}H_{22}N_2O_9S_2$: C, 39.43 H, 5.16. Found: C, 39.50; H, 5.11.

3-Oxa-(5*S*,6*R*)-dihydroxy-7-carbomethoxytricyclo[2.2.2.0^{2,7}]-octane 5,6-Acetonide (36).—Following Freeman's procedure,[10] 150 mg (0.550 mmol) of **3** in 1 ml of methylene chloride was added at 25° to a solution of 267 mg (0.605 mmol) of lead tetraacetate in 2 ml of methylene chloride under nitrogen. The solution was allowed to stir for 60 min at 25° and then 1.5 ml of water was added. The organic layer was filtered through Celite 535 and washed with 4 ml of water followed by 2 ml of 10% aqueous sodium bicarbonate. Removal of the dried solvent afforded 130 mg of crude crystalline **36** which was chromatographed over 3.0 g of silica gel. Elution with carbon tetrachloride afforded 75 mg (56%) of **36** as white needles, mp 105–106°. Recrystallization from carbon tetrachloride–hexane produced the analytical specimen as white needles: mp 105–106°; nmr δ 1.30 (s, 3, acetonide), 1.50 (s, 3, acetonide), 2.0–2.4 (m, 3, H-1, 8), 3.70 (s, 3, methyl ester), 3.8–4.2 (m, 1, H-4), 4.2–4.7 (m, 3, H-2, 5, 6); ir (CCl_4) 3000 (m), 1745 cm^{-1} (s); mass spectrum m/e 240 (parent ion), 224 (loss of an oxygen), 208.

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.59; H, 6.70.

In another experiment, a solution of 63 mg (0.18 mmol) of **33**, mp 124–128°, in 2 ml of acetic anhydride was heated at reflux for 60 min under nitrogen. Removal of acetic anhydride by high vacuum afforded a reddish oil which was chromatographed over 3.0 g of silica gel. Elution with carbon tetrachloride–chloroform (1:1) afforded 36 mg of crude crystals. Recrystallization from carbon tetrachloride–hexane afforded 12 mg of **36** as white needles, mp 104–106°, identical with the product of the lead tetraacetate reaction with **3** (see above) as evidenced by ir, nmr, and mixture melting point behavior.

2-[4′β,5′β-Dihydroxy-6′α-mesyloxy-4′,5′,6′,7′,8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]acrylic Acid *N*-Methylamide 2,3-Epoxide 4′,5′-Acetonide (28).—A solution of diazomethane (9 mmol) in 15 ml of ether was added to a solution of 1.2 g (3.6 mmol) of amide **17** in 5 ml of tetrahydrofuran at 0°. The solution was allowed to stir for 30 min at 0° and then all the solvent was removed *in vacuo*, affording 1.4 g of a yellow oil. This oily mixture was refluxed in benzene with 10 mg of *p*-toluenesulfonic acid for 60 min under nitrogen to give 1.3 g of a crude oily mixture of **28** and **31**. A 980-mg sample (2.52 mmol) of the isomerized oily mixture was chromatographed over 20 g of silica gel. Elution with chloroform afforded ∼100 mg (10%, based on amide **17**) of an unisomerized oily mixture of **21** and **24**. Continued chloroform elution afforded 100 mg (10%) of pure (by nmr) oily pyrazoline **31**: nmr δ 1.39 (s, 3, acetonide methyl), 1.55 (s, 3, acetonide methyl), 1.8–2.2 (m, 2, H-7′), 2.79 (d, J = 5 Hz, 3, methyl of

amide), 2.8–3.2 (m, 3, probably H-9′ and epoxide proton), 3.10 (s, 3, mesylate), 3.7–4.7 (m, 3, H-4′, 5′, 6′), 5.6–5.8 (broad, 1, –NH), 6.7 (d, J = 1.0 Hz, 1, H-3′), 6.7–6.9 (broad, 1, –NH); ir ($CHCl_3$) 3450 (m), 3000 (w), 1675 (s), 1570 cm^- (m).

Elution with 1% methanol in chloroform afforded ~150 mg of an oily mixture of **28** and **31** followed by 220 mg (22%) of almost pure desired pyrazoline **28**. Rechromatography of this fraction over 3.0 g of silica gel afforded 107 mg of pure oily **28**: nmr δ 1.37 (s, 3, acetonide methyl), 1.52 (s, 3, acetonide methyl), 2.0–2.8 (m, 2, H-7′), 2.83 (d, J = 5.0 Hz, 3, methyl of amide), 2.85 (d, J = 5 Hz, 1, epoxide proton), 3.10 (s, 3, mesylate), 3.18 (d, J = 5 Hz, 1, epoxide proton), 3.6–3.8 (m, 1, H-9′), 4.0–5.1 (m, 3, H-4′, 5′, 6′), 5.7–6.2 (broad, 1, –NH), 6.5–7.0 (broad, 1, –NH), 6.72 (d, J = 1.5 Hz, 1, H-3′); ir ($CHCl_3$) 3450 (m), 1670 (s), 1575 cm^{-1} (m). The mass spectrum of pure **28** displayed no peaks above m/e 150.

Oily **28** was digested with hexane and evaporated to give a foam which was crushed to a powder, dried at 56° in high vacuum, and analyzed.

Anal. Calcd for $C_{15}H_{23}N_3O_7S$: C, 46.27; H, 5.91. Found: C, 46.02; H, 5.89.

Dinitrogen Tetroxide.—Following the procedure of White,[12] nitrogen dioxide, prepared from air and nitric oxide (Matheson), was trapped at −78° affording the dinitrogen tetroxide as a pale blue solid.

Methyl (3′β,4′β-Dihydroxy-5′α-mesyloxycyclohexene-1′-yl)-glyoxylate 3′,4′-Acetonide (18).—To a solution of 760 mg (2.28 mmol) of amide **17** in 10 ml of chloroform containing 450 mg (5.50 mmol) of anhydrous sodium acetate at 0° was added a cold solution of 1.8 g (19.5 mmol) of dinitrogen tetroxide in 10 ml of chloroform. The reaction mixture was allowed to stir for 15 hr at 0° and then 40 ml of cold water was added with good stirring. The chloroform layer was separated and washed with 5% sodium bicarbonate at 0°. Removal of the dried chloroform afforded 850 mg (100%) of crude N-nitroso derivative which was dissolved in 10 ml of dry benzene and heated at reflux for 4 hr. The benzene was removed *in vacuo*, affording 750 mg of a yellow oil, suitable for further reactions. Chromatography of the oil over silica gel and elution with chloroform–carbon tetrachloride (1:1) afforded a colorless foam which was dried at 56° in high vacuum to give the analytical specimen: nmr δ 1.42 (s, 3, acetonide methyl), 1.48 (s, 3, acetonide methyl), 2.5–3.0 (m, 2, H-6′), 3.23 (s, 3, mesylate), 3.92 (s, 3, methyl ester), 4.7–5.1 (m, 3, H-3′, 4′, 5′), 6.9–7.1 (m, 1, H-2′); ir ($CHCl_3$) 3000 (w), 1745 (s), 1690 (s), 1645 cm^{-1} (m); mass spectrum m/e 334 (parent ion), 319 (loss of a methyl), 275 (loss of –(O=)$COCH_3$).

Anal. Calcd for $C_{13}H_{18}O_8S$: C, 46.70; H, 5.38. Found: C, 46.25; H, 5.44.

(3′β,4′β-Dihydroxy-5′α-mesyloxycyclohexene-1′-yl)glyoxylic Acid N-Formyl-N-methylamide 3′,4′-Acetonide (40).—In one experiment, amide **17** was prepared from 1.0 g (4.7 mmol) of the acetonide of shikimic acid without purification of any intermediates. Chromatography of the crude product over 10 g of silica gel afforded ~900 mg (60%, overall) of amide **17** by elution with chloroform–carbon tetrachloride (1:1). Continued elution with the same solvent system afforded 200 mg (18%) of **40** as a colorless oil. Rechromatography over silica gel afforded a colorless foam which was dried at 56° in high vacuum to give the analytical specimen: nmr δ 1.41 (s, 3, acetonide methyl), 1.50 (s, 3, acetonide methyl), 2.6–2.9 (m, 2, H-6′), 3.14 (s, 3, mesylate or amide methyl), 3.17 (s, 3, mesylate or amide methyl), 4.2–5.0 (m, 3, H-3′, 4′, 5′), 6.1–6.3 (m, 1, H-2′), 9.26 (s, 1, formyl proton); ir ($CHCl_3$) 3000 (w), 1730 (m), 1675 cm^{-1} (s); mass spectrum m/e 333 (parent ion), 318 (loss of a methyl), 199.

Anal. Calcd for $C_{13}H_{19}NO_7S \cdot {}^1/_2H_2O$: C, 45.62; H, 5.85; N, 4.10. Found: C, 45.49; H, 5.58; N, 3.84.

(3′β,4′β-Dihydroxy-5′α-mesyloxycyclohexene-1′-yl)glyoxylic Acid N-Methylamide (41).—A solution of 0.19 ml of 1.0 N sodium hydroxide was added to a solution of 63 mg (0.19 mmol) of the amide **40** in 0.5 ml of methanol at 0° under nitrogen. The solution was allowed to stir for 12 hr at 25° and then neutralized with hydrochloric acid at 0°. The neutral solution was extracted with 3 ml of chloroform three times. Removal of the dried chloroform afforded 60 mg of yellow oil which was chromatographed over 2.0 g of silica gel. Elution with chloroform afforded 34 mg (59%) of **41** as white needles. Recrystallization from ether–methylene chloride afforded the analytical specimen as white needles: mp 130–131°; nmr δ 1.42 (s, 3, acetonide methyl), 1.50 (s, 3, acetonide methyl), 2.5–2.9 (m, 2, H-6′), 2.90 (d, J = 5.0 Hz, 3, amide methyl), 3.17 (s, 3, mesylate), 4.1–5.0 (m, 3, H-3′, 4′, 5′), 6.0–6.5 (broad, 1, –NH), 6.5–6.7 (m, 1, H-2′); ir ($CHCl_3$) 3500 (m), 3000 (w), 1680 (s), 1650 (m), 1580 cm^{-1} (m); mass spectrum m/e 305 (parent ion), 290 (loss of a methyl), 248, 230.

Anal. Calcd for $C_{12}H_{19}NO_6S$: C, 47.21; H, 6.23; N, 4.59. Found: C, 47.41; H, 6.28; N, 4.51.

[4′β,5′β-Dihydroxy-6′α-mesyloxy-4′,5′,6′,7′,8′,9′β-hexahydro-3′(*H*)-indazole-8′β-yl]acrylic Acid Methyl Ester 2,3-Epoxide 4′,5′-Acetonide (22).—A solution of diazomethane (6 mmol) in 10 ml of ether was added to a solution of 345 mg (1.03 mmol) of methyl ester **18** in 5 ml of dry tetrahydrofuran at 0°. The solution was allowed to stir for 2 hr at 0°; then all the solvent was removed *in vacuo*, affording 360 mg of a yellow oil which was chromatographed over 10 g of silica gel. Elution with chloroform afforded 150 mg (38%, based on ester **18**) of almost pure pyrazoline **22** as a yellow oil. Rechromatography afforded a colorless oil which was dissolved in small amount of methylene chloride and exposed to high vacuum to give a white foam which was dried in high vacuum at 56° for 3 hr to afford the analytical specimen: nmr δ 1.33 (s, 3, acetonide methyl), 1.47 (s, 3, acetonide methyl), 2.0–2.8 (m, 2, H-7′), 2.9–3.2 (m, 1, H-9′), 3.0 (s, 3, mesylate), 3.04 (d, J = 5 Hz, 1, epoxide proton), 3.28 (s, J = 5 Hz, 1, epoxide proton), 3.75 (s, 3, methyl ester), 4.2–5.0 (m, 5, H-3′, 4′, 6′); ir ($CHCl_3$) 3000 (w), 1745 cm^{-1} (s); mass spectrum m/e 390 (parent ion), 375 (loss of a methyl), 359, 347.

Anal. Calcd for $C_{15}H_{22}N_2O_8S$: C, 46.15; H, 5.64; N, 7.18. Found: C, 46.50; H, 5.53; N, 6.87.

1-Acetyl-4β,5β-dihydroxy-6α-acetoxy-8β-carboxy-4,5,6,7,8,9β-hexahydro-1(*H*)-indazole 4,5-Acetonide (42).—To a solution of 720 mg (2.70 mmol) of ester **3** in 5 ml of methanol was added 3.5 ml of 1.0 N NaOH at 0° under nitrogen. The solution was allowed to stir for 4 hr at 25°; then 240 mg (4.00 mmol) of acetic acid was added. Almost all the solvent was removed by high vacuum affording a slightly yellow viscous oil which was dissolved in 3% methanol in chloroform (15 ml) and dried. Removal of the solvent afforded 782 mg of a clear colorless oil which was dissolved in 5 ml of dry pyridine, cooled to 0° under nitrogen, and then treated with 1.22 g of acetic anhydride. The reaction was allowed to stir for 15 hr at 25°; then almost all the solvent was removed by high vacuum affording a slightly yellow viscous oil which was dissolved in 20 ml of chloroform and washed with 5 ml of 3% hydrochloric acid followed by 5 ml of water. Removal of the dried chloroform afforded 760 mg (83%, based on ester **3**) of **42** as a white foam which was pure enough for further reactions. The analytical specimen was prepared by silica gel column chromatography and elution with chloroform to give a colorless white foam: nmr δ 1.33 (s, 3, acetonide), 1.50 (s, 3, acetonide), 2.00 (s, 3, OAc), 2.31 (s, 3, NAc), 2.5–2.7 (m, 2, H-7), 4.0–5.2 (m, 4, H-4, 5, 6, 9), 6.92 (d, J = 1.5 Hz, 1, H-3), 8.83 (broad s, 1, acid proton); ir ($CHCl_3$) 3500–2300 (broad), 1750 (s), 1670 (s), 1620 cm^{-1} (m); mass spectrum m/e 325 (loss of a methyl[15]), 296 281, 279.

Anal. Calcd for $C_{15}H_{20}N_2O_7 \cdot 1/2H_2O$: C, 51.60; H, 6.03; N, 8.03. Found: C, 51.73; H, 6.29; N, 8.23.

[1′-Acetyl-4′β,5′β-dihydroxy-6′α-acetoxy-4′,5′,6′,7′,8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]glyoxylic Acid N-Methylamide 4′,5′-Acetonide (43).—A solution of 740 mg (2.18 mmol) of diacetate **42** in 7 ml of thionyl chloride was heated at reflux for 60 min. Removal of the solvent afforded 764 mg of the corresponding oily acid chloride which was dissolved in 4 ml of dry tetrahydrofuran, cooled to 0° under nitrogen, and then treated with 900 mg (22.0 mmol) of methyl isocyanide in 1 ml of tetrahydrofuran. The reaction was allowed to stir for 12 hr at 25°; then all the solvent was removed *in vacuo*, affording 830 mg of crude adduct as a yellow foam: nmr δ 1.32 (s, 3, acetonide), 1.47 (s, 3, acetonide), 2.00 (s, 3, OAc), 2.18 (s, 3, NAc), 2.2–2.9 (m, 2, H-7′), 3.40 (s, 3, NCH_3), 4.0–5.2 (m, 4, H-4′, 5′, 6′, 9′), 7.10 (d, J = 1.5 Hz, 1, H-3′); ir ($CHCl_3$) 3000 (m), 1740 (s), 1670 (s), 1620 cm^{-1} (m).

A solution of 830 mg of crude adduct in 5 ml of acetone and 5 ml of water was stirred for 10 hr at 0° and then 168 mg of sodium bicarbonate was added. The solution was diluted with 10 ml of water and extracted with 15 ml of chloroform five times. Removal of the dried chloroform afforded 733 mg of yellow oil which was chromatographed over 10 g of silica gel. Elution with chloroform afforded 600 mg (56%, based on ester **3**) of oily α-ketoamide **43**. Oily **43** containing traces of methylene chloride was exposed to high vacuum to give a white foam which was dried at 56° in high vacuum and analyzed: nmr δ 1.32 (s, 3, acetonide), 1.45 (s, 3, acetonide), 2.00 (s, 3, OAc), 2.24 (s, 3,

NAc), 2.2–2.8 (m, 2, H-7'), 2.83 (d, J = 5.0 Hz, 3, amide methyl), 4.2–4.4 (m, 2, H-4', 6'), 4.75 (m, 1, H-9), 4.8–5.1 (m, 1, H-5'), 7.02 (d, J = 1.5 Hz, 1, H-3), 7.0–7.2 (broad, 1, -NH); mass spectrum m/e 382 (loss of a methyl[15]), 366, 353; ir ($CHCl_3$) 3450 (w), 3000 (m), 1740 (s), 1670 (s), 1620 (m), 1570 cm^{-1} (m).

Anal. Calcd for $C_{17}H_{23}N_3O_7 \cdot {}^1/_2H_2O$: C, 52.29; H, 6.15; N, 10.79. Found: C, 52.23; H, 6.11; N, 10.68.

[1'-Acetyl-4'β,5'β,6'α-trihydroxy-4',5',6',7',8',9'β-hexahydro-1'(*H*)-indazole-8'β-yl]glyoxylic Acid *N*-Methylamide 4',5'-Acetonide (44).—A solution of 2.1 g (5.3 mmol) of diacetate **43** in 15 ml of methanol was cooled to 0°; then 5.8 ml of 1.0 *N* NaOH was added dropwise by syringe under nitrogen. The reaction was allowed to stir for 30 min at 0°; then four drops of acetic acid was added to neutralize the solution. Almost all the solvent was removed by high vacuum to give a yellow viscous oil which was digested with 30 ml of 10% methanol in chloroform. Removal of the dried solvent afforded 2.1 g of crude alcohol **44** as a yellow oil. A 200-mg sample was chromatographed over 3.0 g of silica gel. Elution with 2% methanol in chloroform afforded 146 mg of slightly yellow crystalline **44**. Recrystallization from chloroform afforded white needles, mp 75–77°, recrystallization of which from benzene afforded fine white needles, mp 92–95° (see analytical results). Sublimation at 0.1–0.2 mm in a 170° oil bath afforded solvent free powder-like crystals: mp 118–122°; nmr δ 1.32 (s, 3, acetonide), 1.47 (s, 3, acetonide), 2.29 (s, 3, NAc), 2.8–3.1 (m, 3, H-7' and -OH), 2.87 (d, J = 5.0 Hz, 3, amide methyl), 4.0–4.9 (m, 4, H-4', 5', 6', 9'), 7.10 (d, J = 1.5 Hz, H-3'), 7.0–7.3 (broad, 1, -NH); ir ($CHCl_3$) 3800–3100 (broad), 3000 (w), 1730 (m), 1690 (s), 1640 (m), 1620 (m), 1570 cm^{-1} (m); mass spectrum m/e 339 (parent ion), 324 (loss of methyl), 311, 282, 281, 263.

Anal. [White needles (mp 75–77°) from chloroform and dried at 56° in high vacuum for 20 hr.] Calcd for $C_{15}H_{21}N_3O_6 \cdot {}^3/_4CHCl_3$: C, 44.05; H, 4.55; N, 9.80. Found: C, 43.42; H, 5.08; N, 10.02.

Anal. [White needles (mp 92–95°) from benzene and dried at 56° in high vacuum for 20 hr.] Calcd for $C_{15}H_{21}N_3O_6 \cdot {}^1/_3C_6H_6$: C, 55.88; H, 6.34; N, 11.50. Found: C, 56.06; H, 6.20; N, 11.47.

Anal. [Sublimed powder-like crystals (mp 118–122°).] Calcd for $C_{15}H_{21}N_3O_6$: C, 53.06; H, 6.24; N, 12.38. Found: C, 52.39; H, 6.14; N, 12.29.

[1'-Acetyl-4'β,5'β-dihydroxy-6'α-mesyloxy-4',5',6',7',8',9'β-hexahydro-1'(*H*)-indazole-8'β-yl]glyoxylic Acid *N*-Methylamide 4',5'-Acetonide (45).—A solution of 125 mg (0.350 mmol) of alcohol **44** in 1 ml of pyridine was cooled to 0° and then 130 mg (1.15 mmol) of methanesulfonyl chloride was added under nitrogen. The reaction was allowed to stir for 17 hr at 25° and then almost all the solvent was removed by high vacuum affording a viscous reddish oil which was dissolved in 10 ml of chloroform and washed with 1 ml of 3% hydrochloric acid then 1 ml of water. Removal of the dried chloroform afforded 120 mg (80%) of mesylate **45** as a yellow foam, suitable for further reactions. This yellow foam was chromatographed over 3.0 g of silica gel. Elution with chloroform afforded 97 mg (64%) of pure white foam: nmr δ 1.32 (s, 3, acetonide), 1.47 (s, 3, acetonide), 2.30 (s, 3, NAc), 2.3–2.8 (m, 2, H-7'), 2.87 (d, J = 5.0 Hz, 3, amide methyl), 3.05 (s, 3, mesylate), 4.2–5.1 (m, 4, H-4', 5', 6', 9'), 7.08 (d, J = 1.5 Hz, 1, H-3'), 7.0–7.2 (broad, 1, -NH); ir ($CHCl_3$) 3500 (m), 3000 (m), 1730 (m), 1690 (s), 1650 (m), 1620 cm^{-1} (m); mass spectrum m/e 417 (parent ion), 402 (loss of a methyl), 341, 331, 315.

Anal. Calcd for $C_{16}H_{23}N_3O_8S$: C, 46.04; H, 5.51; N, 10.07. Found: C, 46.00; H, 5.64; N, 9.65.

Methyl [1'-Acetyl-4'β,5'β-dihydroxy-6'α-mesyloxy-4',5',6',7',-8',9'β-hexahydro-1'(*H*)-indazole-8'β-yl]glyoxylate 4',5'-Acetonide (46).—To a solution of 230 mg (0.550 mmol) of mesylate **45** in 5 ml of chloroform at 0° was added 500 mg (5.50 mmol) of dinitrogen tetroxide in 5 ml of cold chloroform under nitrogen. The solution was allowed to stir for 18 hr at 0° and then 5 ml of cold water was added. The organic layer was separated and washed with 5% sodium bicarbonate. Removal of dried chloroform afforded 240 mg of the *N*-nitroso derivative as a slightly yellow oil. A solution of the *N*-nitroso derivative in 5 ml of dry benzene was refluxed for 3 hr and then the benzene was removed *in vacuo*, affording 230 mg (100%) of ester **46** as a yellow oil which crystallized upon addition of one drop of methanol. Recrystallization from methanol afforded 160 mg (70%) of white plates: mp 153–154°; nmr δ 1.32 (s, 3, acetonide), 1.45 (s, 3, acetonide), 2.25 (s, 3, NAc), 2.2–2.8 (m, 2, H-7'), 2.98 (s, 3, mesylate), 3.84 (s, 3, methyl ester), 4.0–5.0 (m, 4, H-3', 4', 5', 9'), 6.90 (d, J = 1.0 Hz, H-3'); ir ($CHCl_3$) 3000 (w) 1740 (s), 1690 (m), 1660 (m), 1620 cm^{-1} (m); mass spectrum m/e 418 (parent ion), 403 (loss of a methyl), 367, 361, 331, 315, 289, 273.

Anal. Calcd for $C_{16}H_{22}N_2O_9S$: C, 45.93; H, 5.26; N, 6.69. Found: C, 45.84; H, 5.07; N, 6.92.

Methyl [1'-Acetyl-4'β,5'β-dihydroxy-6'α-mesyloxy-4',5',6',-7',8',9'β-hexahydro-1'(*H*)-indazole-8'β-yl]glyoxylate (47).—A solution of 180 mg (0.43 mmol) of mesylate **46**, mp 153–154°, in 4 ml of chloroform–methanol (1:1) was cooled to 0° and then 3 ml of methanol containing ~300 mg of hydrogen chloride was added. The reaction was allowed to stir for 3 hr at 25° and then all the solvent was removed *in vacuo* affording 155 mg of a slightly yellow oil which was chromatographed over 3.0 g of silica gel. Elution with 2% methanol in chloroform afforded 112 mg (69%) of **47** as a pure white foam which was dried at 56° in high vacuum for 20 hr to give the analytical specimen: nmr ($CD_3(O{=})CCD_3$) δ 2.20 (s, 3, NAc), 2.8–3.5 (m, 2 or 3, assignment not clear), 3.18 (s, 3, mesylate), 3.80 (s, 3, methyl ester), 3.7–5.2 (m, 5 or 6, assignment not clear), 7.30 (d, J = 1.0 Hz, 1, H-3'); mass spectrum m/e 291 (loss of (O=)C—C(=O)OCH_3), 249, 231.

Anal. Calcd for $C_{13}H_{18}N_2O_9S \cdot {}^1/_2H_2O$: C, 40.31; H, 4.90; N, 7.23. Found: C, 40.11; H, 4.60; N, 6.99.

Methyl [1'-Acetyl-4'β,5'β-diacetoxy-6'α-mesyloxy 4',5',6',7'-8',9'β-hexahydro-1'(*H*)-indazole-8'β-yl]glyoxylate (48).—To a solution of 67 mg (0.18 mmol) of mesylate **47** in 1 ml of pyridine at 0° was added 55 mg (0.54 mmol) of acetic anhydride under nitrogen. The reaction was allowed to stir for 12 hr at 25° and then almost all the solvent was removed by high vacuum affording a viscous slightly yellow oil which was dissolved in 5 ml of chloroform and washed with 3% hydrochloric acid at 0°. Removal of the dried chloroform afforded 76 mg of a colorless oil which was chromatographed over 3.0 g of silica gel. Elution with chloroform afforded 62 mg of white foam which was dried at 56° for 12 hr under high vacuum to give the analytical specimen: nmr δ 1.7–2.3 (m, 2, H-7'), 2.08 (s, 6, two OAc), 2.26 (s, 3, NAc), 3.08 (s, 3, mesylate), 3.89 (s, 3, methy ester), 3.9–4.2 (m, 1, H-9'), 4.7–5.8 (m, 3, H-4', 5', 6'), 7.05 (d, J = 1.5 Hz, 1, H-3'); ir ($CHCl_3$) 3000 (m), 1730 (s), 1685 (s), 1650 (s), 1610 cm^{-1} (m); mass spectrum m/e 446, 315, 279, 272.

Anal. Calcd for $C_{17}H_{22}N_2O_{11}S$: C, 44.18; H, 4.76; N, 6.06. Found: C, 44.38; H, 4.96; N, 5.76.

[1'-Acetyl-4'β,5'β-dihydroxy-6'α-mesyloxy-4',5',6',7',8',9'β-hexahydro-1'(*H*)-indazole-8'β-yl]glyoxylic Acid *N*-Methylamide (49).—To a solution of 50 mg (0.12 mmol) of mesylate **45** in 1 ml of methanol at 0° was added 1 ml of methanol containing ~100 mg of hydrogen chloride. The reaction was allowed to stir for 3 hr at 25° and then all the solvent was removed *in vacuo* affording 40 mg of a yellow foam. Chromatography over silica gel and elution with 2% methanol in chloroform afforded a foam which was dried at 56° in high vacuum and analyzed: nmr (D_2O) δ 1.7–2.2 (m, 2, H-7), 2.25 (s, 3, NAc), 2.70 (s, 3, methyl of amide), 3.20 (s, 3, mesylate), 3.5–4.7 (m, ~4, H-4', 5', 6', 9'), 7.3 (d, J = 1.0 Hz, 1, H-3'); ir (CH_3CN) 1730 (w), 1690 (s), 1660 (s), 1620 cm^{-1} (w); mass spectrum m/e 291 (loss of (O=)-C—C(=O)$NHCH_3$), 249, 231.

Anal. Calcd for $C_{13}H_{19}N_3O_8S \cdot {}^1/_2CHCl_3$: C, 37.07; H, 4.46. Found: C, 37.42; H, 4.49.

Methyl [1'-Acetyl-4'β,6'β-dihydroxy-5'α-methoxy-4',5',6',7',-8',9'β-hexahydro-1'(*H*)-indazole-8'β-yl]glyoxylate (53).—To a solution of 117 mg (0.310 mmol) of diol **47** in 3 ml of dry methanol at 0° was added 55 mg (0.93 mmol) of sodium methoxide under nitrogen. The reaction was allowed to stir for 30 min at 0° and then four drops of acetic acid was added (pH 6). Almost all the solvent was removed *in vacuo* affording a slightly yellow oil which was digested with 20 ml of 3% methanol in chloroform and filtered through Celite 535. Removal of the dried solvent afforded 120 mg (containing sodium acetate) of a yellow oil which was chromatographed over 3.0 g of silica gel. Elution with 2% methanol in chloroform afforded 72 mg (74%) of white powder-like crystals. Recrystallization from benzene afforded 44 mg of white needles: mp 212–216° dec; nmr δ 1.4–2.2 (m, 2, H-7'), 2.32 (s, 3, NAc), 2.6–3.2 (broad s, 2 OH, exchangeable with D_2O), 3.50 (s, 3, methoxy group), 3.5–4.8 (m, 4, H-4', 5', 6', 9'), 3.85 (s, 3, methyl ester), 7.20 (d, J = 1 Hz, 1, H-3'); ir ($CHCl_3$) 3500–3100 (broad), 3000 (m), 1750 (s), 1680 (s), 1620 cm^{-1} (m); mass spectrum m/e 255, 213, 195, 194.

Anal. Calcd for $C_{13}H_{18}N_2O_7$: C, 49.68; H, 5.77; N, 8.91. Found: C, 49.35; H, 5.52; N, 8.60.

Methyl [1′-Acetyl-4′β,6′β-diacetoxy-5′α-methoxy-4′,5′,6′,7′,-8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]glyoxylate (not shown).—A solution of 46 mg (0.15 mmol) of diol **53** in 1 ml of pyridine was cooled to 0° and then 73 mg (0.72 mmol) of acetic anhydride was added under nitrogen. The reaction was allowed to stir for 12 hr at 25°. Almost all the solvent was removed by high vacuum affording a yellow viscous oil which was dissolved in 5 ml of chloroform and washed with 3% hydrochloric acid at 0°. Removal of dried chloroform afforded 53 mg (90%) of the triacetate as a colorless oil: nmr δ 1.3–1.9 (m, 2, H-7′), 2.17 (s, 6, two OAc), 2.30 (s, 3, NAc), 3.50 (s, 3, methoxy group), 3.85 (s, 3, methyl ester), 4.5–5.3 (m, 4, H-4′, 5′, 6′, 9′), 6.95 (d, J = 1.5 Hz, 1, H-3′); ir ($CHCl_3$) 3000 (m), 1750 (s), 1690 (s), 1620 cm^{-1} (m). Chromatography over silica gel and elution with chloroform afforded a pure white foam which was dried at 56° in high vacuum for 20 hr and analyzed.

Anal. Calcd for $C_{17}H_{22}N_2O_9 \cdot {}^1/_4CHCl_3$: C, 48.36; H, 5.19; N, 6.54. Found: C, 48.17; H, 5.15; N, 6.28.

[1′-Acetyl-4′β,6′β-dihydroxy-5′α-methoxy-4′,5′,6′,7′,8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]glyoxylic Acid *N*-Methylamide (54).—To a solution of 45 mg (0.12 mmol) of diol **49** in 1 ml of methanol at 0° was added 24 mg (0.48 mmol) of sodium methoxide under nitrogen. The reaction was allowed to stir for 30 min at 0° and then two drops of acetic acid was added. Removal of all the solvent afforded a residue which was digested with 10% methanol in chloroform and filtered through Celite 535. Removal of the dried solvent gave a 50-mg residue which was chromatographed over 3.0 g of silica gel. Elution with 2% methanol in chloroform afforded 16 mg of **54** as a white oil. Rechromatography over silica gel and elution with 1% methanol in chloroform afforded the analytical specimen as a colorless oil: nmr δ 1.4–1.9 (m, 2, H-7′), 2.25 (s, 3, NAc), 2.91 (d, J = 5.0 Hz, 3, methyl of amide), 3.0–3.2 (m, 3, H-9′ and two –OH), 3.48 (s, 3, methoxy group), 3.5–4.8 (m, 3, H-4′, 5′, 6′), 6.3–6.7 (broad, 1, –NH), 7.15 (d, J = 1 Hz, 1, H-3′); ir ($CHCl_3$) 3500 (m), 3000 (w), 1685 (s), 1620 (m), 1570 cm^{-1} (m); mass spectrum m/e 313 (parent ion), 279, 255, 213.

Anal. Calcd for $C_{13}H_{19}N_3O_6 \cdot H_2O$: C, 47.13; H, 6.39; N, 12.68. Found: C, 47.39; H, 6.03; N, 12.49.

Methyl 2-Hydroxy-2-[1′-acetyl-4′β,5′β-dihydroxy-6′α-mesyloxy-4′,5′,6′,7′,8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]acetate 4′,5′-Acetonide (56).—A solution of 80 mg (0.19 mmol) of **46** in 1 ml of tetrahydrofuran was added at 0° to a solution of 2.80 mg (0.075 mmol) of sodium borohydride in 1 ml of ethanol. The solution was allowed to stir for 60 min at 0° and then almost all the solvent was removed *in vacuo*. The white oily residue was treated with 1 ml of ice-cold 5% hydrochloric acid and extracted with 5 ml of chloroform three times. Removal of the dried solvent afforded 80 mg of colorless oil which was chromatographed over 3.0 g of silica gel. Elution with chloroform afforded 41 mg (50%) of **56** as a colorless oil. Rechromatography over silica gel and elution with chloroform afforded a white foam which was dried at 56° in high vacuum to give the analytical specimen: nmr δ 1.32 (s, 3, acetonide), 1.48 (s, 3, acetonide), 2.2–2.9 (m, 2, H-7′), 2.30 (s, 3, *N*-acetate), 2.99 (s, 3, mesylate), 3.72 (s, 3, methyl ester), 4.2–4.9 (m, 5, H-2, 4′, 5′, 6′, 9′), 6.90 (d, J = 1.5 Hz, 1, H-3′); ir ($CHCl_3$) 3600–3200 (broad), 3000 (m), 1745 (s), 1725 (s), 1645 (s), 1610 cm^{-1} (m); mass spectrum m/e 420 (parent ion), 405 (loss of a methyl), 363, 361, 331.

Anal. Calcd for $C_{16}H_{24}N_2O_9S$: C, 45.71; H, 5.71. Found: C, 45.57; H, 5.81.

Methyl 2-Hydroxy-2-[1′-acetyl-4′β-hydroxy-4′,7′,8′,9′β-tetrahydro-1′(*H*)-indazole-8′β-yl]acetate 5′β,6′β-Epoxide (58).—To a solution of 40 mg (0.09 mmol) of **56** in 0.5 ml of methanol at 0° was added 1 ml of methanol containing 50 mg of hydrogen chloride. The solution was allowed to stir for 3 hr at 25° and then all the solvent was removed *in vacuo* affording 38 mg of triol **57** as a colorless hard oil: nmr (CD_3OD) δ 1.3–1.7 (m, 2, H-7′), 2.30 (s, 3, *N*-acetate), 2.8–3.0 (m, ~2, assignment not clear), 3.12 (s, 3, mesylate), 3.5–4.6 (m, ~5, assignment not clear), 3.77 (s, 3, methyl ester), 7.10 (d, J = 1.0 Hz, 1, H-3′).

The triol was dissolved in 1 ml of methanol at 0° and then 16 mg (0.30 mmol) of sodium methoxide was added under nitrogen. The solution was allowed to stir for 20 min at 0° and then one drop of acetic acid was added to neutralize the solution. Almost all the solvent was removed *in vacuo* affording a yellow oily residue which was digested with 10 ml of 3% methanol in chloroform and filtered through Celite 535. Removal of the solvent afforded 40 mg of a slightly yellow oil which was chromatographed over 3.0 g of silica gel. Elution with 1% methanol in chloroform afforded 27 mg of **58** as a colorless hard oil: nmr 1.5–2.4 (m, 2, H-7′), 2.30 (s, 3, *N*-acetate), 3.0–4.2 (m, 6 or 7, assignment not clear), 3.79 (s, 3, methyl ester), 7.0–7.2 (m, 1, H-3′); ir ($CHCl_3$) 3600–3300 (broad), 3000 (s), 1750 (s), 1680 (s), 1620 cm^{-1} (s); mass spectrum m/e 284 (parent ion), 253, 242, 225, 207, 195. The exact molecular weight as determined by high resolution mass spectrometry was 284.0995 (calcd for $C_{12}H_{16}N_2O_6$: 284.1004).

2-Hydroxy-2-[1′-acetyl-4′β,5′β-dihydroxy-6′α-mesyloxy-4′,5′,-6′,7′,8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]acetic Acid *N*-Methylamide 4′,5′-Acetonide (59).—A solution of 110 mg (0.264 mmol) of amide **45** in 1 ml of tetrahydrofuran was added at 0° to a solution of 33 mg (0.39 mmol) of sodium borohydride in 2 ml of ethanol. The solution was allowed to stir for 3 hr at 25° and then almost all the solvent was removed *in vacuo* affording a yellow viscous oil which was treated with 3% hydrochloric acid at 0°. The acidic solution was extracted with 5 ml of chloroform three times. Removal of dried chloroform afforded 112 mg of **59** as a slightly yellow oil which was chromatographed over 3.0 g of silica gel. Elution with 1% methanol in chloroform afforded 80 mg (73%) of pure **59** as a white foam: nmr δ 1.37 (s, 3, acetonide), 1.50 (s, 3, acetonide), 1.9–2.7 (m, 2, H-7′), 2.32 (s, 3, *N*-acetate), 2.81 (d, J = 5.0 Hz, 3, amide methyl), 3.02 (s, 3, mesylate), 4.1–5.2 (m, 4, H-4′, 5′, 6′, 9′), 6.55 (s, 0.6, H-2), 6.75 (s, 0.4, H-2), 7.05 (d, J = 1.0 Hz, 1, H-3′), 7.0–7.2 (broad, 1, –NH–); ir ($CHCl_3$) 3500 (w), 3400–3100 (broad), 3000 (w), 1680 (s), 1620 (m); mass spectrum m/e 404 (loss of a methyl[15]), 361, 350, 341, 331, 323. Rechromatography over silica gel afforded a white foam which was dried at 56° for 20 hr to give the analytical specimen.

Anal. Calcd for $C_{16}H_{25}N_3O_8S$: C, 45.82; H, 5.97. Found: C, 45.31; H, 6.12.

2-Hydroxy-2[1′-acetyl-4′β,5′β,6′β-trihydroxy-4′,5′,6′,7′,8′,-9′β-hexahydro-1′(*H*)-indazole-8′β-yl]acetic Acid 1→6′β-Lactone 4′,5′-Acetonide (60).—A solution of 34 mg (0.08 mmol) of **59** in 1 ml of pyridine containing 100 mg of water was heated at 100–110° for 12 hr under nitrogen. Almost all the solvent was removed by high vacuum affording a reddish residue which was dissolved in 10 ml of chloroform and washed with 3% hydrochloric acid at 0°. Removal of the dried solvent afforded 25 mg of **60** as a colorless oil. Chromatography over silica gel and elution with chloroform afforded lactone **60** as a white foam: nmr δ 1.33 (s, 3, acetonide), 1.55 (s, 3, acetonide), 2.31 (s, 3, *N*-acetate), 2.6–3.2 (m, 2, H-7′ and OH), 3.7–4.8 (m, 4, H-4′, 5′, 6′, 9′), 5.50 (s, 1, H-2), 6.90 (d, J = 1.0 Hz, 1, H-3′); ir ($CHCl_3$) 3600–3300 (broad), 3000 (m), 1750 (s), 1680 (s), 1620 cm^{-1} (m); mass spectrum m/e 310 (parent ion), 295 (loss of a methyl), 265, 252, 235.

Anal. Calcd for $C_{14}H_{18}N_2O_6 \cdot H_2O$: C, 51.22; H, 6.14. Found: C, 51.71; H, 6.17.

The exact molecular weight as determined by high resolution mass spectrometry was 310.1154 (calcd for $C_{14}H_{18}N_2O_6$: 310.1160).

Registry No.—**9,** 26681-48-1; **10,** 26681-49-2; **15,** 26681-50-5; **16,** 26681-51-6; **17,** 26681-52-7; **18,** 26681-53-8; **22,** 26681-54-9; **23,** 26681-55-0; **26,** 26681-56-1; **27,** 26681-57-2; **28,** 26681-58-3; **30,** 26681-59-4; **31,** 26681-60-7; **32,** 26681-61-8; **33,** 26681-62-9; **34,** 26681-63-0; **36,** 26681-64-1; **40,** 26731-47-5; **41,** 26681-20-9; **42,** 26681-21-0; **43,** 26681-22-1; **44,** 26681-23-2; **45,** 26681-24-3; **46,** 26731-48-6; **47a,** 26681-25-4; **47b,** 26681-36-7; **48a,** 26681-26-5; **48b,** 26681-37-8; **49a,** 26681-27-6; **49b,** 26681-38-9; **53,** 26681-28-7; **54,** 26681-29-8; **56,** 26681-30-1; **57,** 26681-31-2; **58,** 26681-32-3; **59,** 26681-33-4; **60,** 26681-34-5; methyl (1′-acetyl-4′β,6′β-diacetoxy-5′α-methoxy-4′,5′,6′,7′,8,′9′β-hexahydro-1′(*H*)-indazole-8′β-yl)glyoxylate, 26681-35-6.

Acknowledgments.—The authors thank the National Science Foundation (GP 10736) and the National Institutes of Health (5-R01-NS-07586-03) for support of this work and Hoffmann–LaRoche for a generous gift of shikimic acid.

The Copper-Catalyzed Decomposition of Some Dimethylphosphono-Substituted Diazoalkanes

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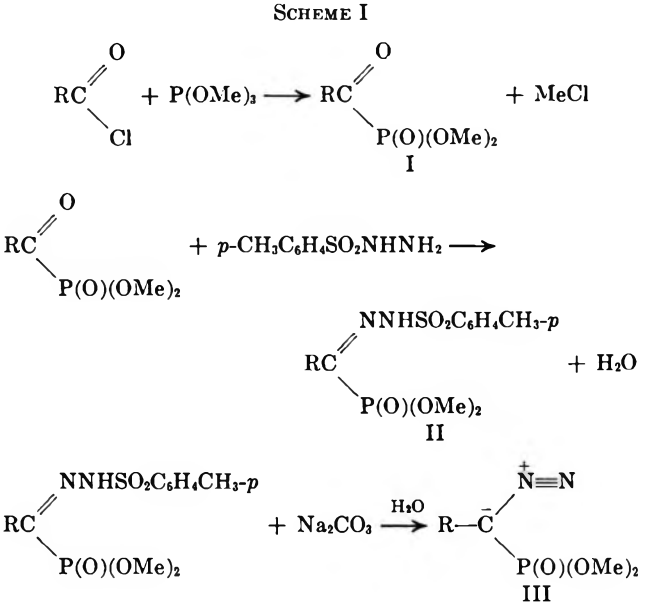
Received July 31, 1970

A number of dimethylphosphono-substituted diazoalkanes having the general formula $RC(N_2)P(C)(OMe)_2$ (R = alkyl, cycloalkyl, and substituted vinyl) have been prepared by the action of aqueous base on the corresponding *p*-toluenesulfonylhydrazone precursor. Copper powder catalyzed the decomposition of these diazo compounds to give a carbenoid which then underwent intramolecular rearrangement, the course of which varied depending on the nature of "R." The dimethylphosphono group was unaffected during these reactions.

There has been much interest recently in phosphorus-substituted diazoalkanes. Horner and coworkers[1] prepared the first such compound, $PhC(N_2)P(O)Ph_2$, in 1961. Kreutzkamp, *et al.*,[2] prepared $N_2CHP(O)Ph_2$ in 1965 by the direct diazotization of the amine $H_2NCH_2P(O)Ph_2$ and in 1967 we reported on the synthesis of dimethylphosphono-substituted diazo compounds *via* the base-induced decomposition of the *p*-toluenesulfonylhydrazone derivatives of α-ketophosphonates (see Scheme I) and on the copper-catalyzed addition of $PhCP(O)(OMe)_2$ to olefins using the diazoalkane precursor.[3] Petzold and Henning[4] have described the synthesis of a variety of phosphorus-substituted diazoalkanes by transdiazotization with *p*-toluenesulfonyl azide, a procedure also used by Regitz, *et al.*,[5,6] in the preparation of such phosphorus compounds. Notable were the photolyses of $Ph_2P(O)C(N_2)R$ compounds carried out by the latter workers, in which migrations of a phenyl group from phosphorus to the carbenic carbon atom were observed.[7,8] Very recently Regitz and Anschütz prepared the parent compound $N_2CHP(O)(OEt)_2$ in low yield.[9,10]

SCHEME I

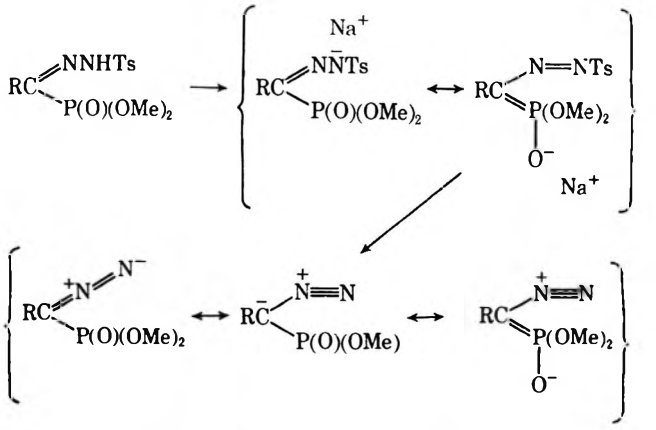


In the present paper we extend the scope of the chemistry of phosphorus-substituted diazoalkanes and carbenoids with a report concerning the synthesis and copper-catalyzed decomposition of a number of dimethylphosphono-substituted diazoalkanes of type $(MeO)_2P(O)C(N_2)R$, where R = alkyl, cycloalkyl, and substituted vinyl. Compounds of this type have not been reported previously.

Results and Discussion

Trimethyl phosphite underwent the Michaelis–Arbuzov reaction smoothly with the appropriate acid chlorides to give the corresponding α-ketophosphonates in high yield.[11] The compounds of this class prepared during the course of this study are listed in Table I. These reactive ketones readily formed *p*-toluenesulfonylhydrazones (Table II).

The great facility of the latter reaction at room temperature is evidence of the contribution of the phosphoryl group to the stability of the anion and of the resulting diazo compound after expulsion of the *p*-toluenesulfinate anion, in much the same way as that reported for α-diazocycloalkanones.[12] The en-



* To whom correspondence should be addressed.

(1) L. Horner, H. Hoffmann, H. Ertel, and G. Klahre, *Tetrahedron Lett.*, 9 (1961).

(2) N. Kreutzkamp, E. Schmidt-Samoa, and A. K. Herberg, *Angew. Chem.*, **77**, 1138 (1965).

(3) D. Seyferth, P. Hilbert, and R. S. Marmor, *J. Amer. Chem. Soc.*, **89**, 4811 (1967).

(4) G. Petzold and H. G. Henning, *Naturwissenschaften*, **54**, 469 (1967).

(5) M. Regitz, W. Anschütz, and A. Liedhegener, *Chem. Ber.*, **101**, 3734 (1968).

(6) M. Regitz and W. Anschütz, *ibid.*, **102**, 2216 (1969).

(7) M. Regitz, W. Anschütz, W. Bartz, and A. Liedhegener, *Tetrahedron Lett.*, 3171 (1968).

(8) M. Regitz, H. Scherer, and W. Anschütz, *ibid.*, 753 (1970).

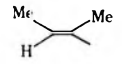
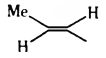
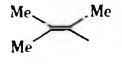
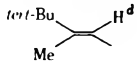
(9) M. Regitz and W. Anschütz, *Justus Liebigs Ann. Chem.*, **730**, 194 (1969).

(10) We have prepared the dimethyl ester, $N_2CHP(O)(OMe)_2$, in good yield by direct diazotization of dimethyl aminomethylphosphonate and have successfully generated the carbenoid by copper powder catalysis and added it to several olefins: D. Seyferth and R. S. Marmor, *Tetrahedron Lett.*, 2493 (1970).

(11) K. D. Berlin, D. M. Hellwege, and M. Nagabhushanam, *J. Org. Chem.*, **30**, 1265 (1965). These authors prepared a number of diethyl α-ketophosphonates in 73–88% yield, an improvement over previous reports.

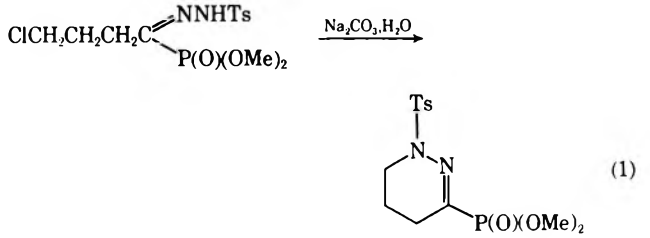
(12) L. Friedman and H. Shechter, *J. Amer. Chem. Soc.*, **83**, 3159 (1961).

TABLE I
DIMETHYL ACYLPHOSPHONATES

$RC(O)P(O)(OMe)_2$ R =	Yield, %	Bp, °C (mm)	$n^{25}D$	ν (C=O), cm^{-1}	Nmr δ, ppm	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found
Ia CH_3	90	82–86 (6.5)	1.4229			...[a]			
Ib n-C_5H_{11}	86	75.5 (0.12)–73.5 (0.07)	1.4339	1695	0.7–1.8 (m, 9), 2.75 (t, 2, J = 7 Hz), 3.78 (d, 6, J = 10.5 Hz)	46.15	46.11	8.23	8.46
Ic $(CH_3)_2CH$	97	53 (0.12)	1.4257	1690	1.13 (d, 6, J = 6.5 Hz), 3.05 (septuplet with fine splitting, 1, J = 6.5 Hz), 3.77 (d, 6, J = 11.5 Hz)	40.00	40.23	7.27	7.28
Id $(CH_3)_3C$	95	76 (2.1)–78 (2.0)	1.4280	1685	1.25 (s, 9), 3.80 (d, 6, J = 10.5 Hz)	43.30	42.92	7.79	7.82
Ie CH_3OCH_2	100 (crude)	Decomposes		1705		...[b]			
If $Cl(CH_2)_3$	88	110 (0.13)–120 (0.15)	1.4560	1695	2.05 (quintet, 2, J = 7 Hz), 2.92 (t, 2, J = 7 Hz), 3.56 [t (partially buried), 2, J = 7 Hz], 3.80 (d, 6, J = 10.5 Hz)	33.58	33.68	5.64[c]	5.70[c]
Ig c-C_3H_5	88	66–67 (0.02)	1.4543	1675	1.17 (d, 4, J = 6.5 Hz), 2.5–2.9 (m, 1), 3.80 (d, 6, J = 11 Hz)	40.45	40.36	6.23	6.22
Ih c-C_4H_7	84	82.5 (0.07)	1.4532	1690	1.5–2.5 (m, 7), 3.79 (d, 6, J = 11 Hz)	43.75	43.64	6.82	6.79
Ii c-C_5H_9	89	72–75 (0.05)	1.4588	1690	1.4–2.1 (m, 8), 3.1–3.6 (m, 1), 3.83 (d, 6, J = 11 Hz)	46.60	46.50	7.33	7.25
Ij c-C_6H_{11}	87	80–82 (0.05)	1.4680	1685	0.9–2.1 (m, 10), 2.5–3.0 (m, 1), 3.75 (d, 6, J = 11 Hz)	49.08	49.10	7.78	7.68
Ik 	82	79–84 (0.02)	1.4710	1645 (1625, C=C)	1.78 (s, 3), 2.02 (d, 3, J = 7 Hz), 3.79 (d, 6, J = 11.5 Hz), 7.65 (quintet with fine splitting, 1, J = 7 Hz)	43.75	43.63	6.82	6.84
Il 	79	86 (0.23)–100 (0.46)	1.4729	1660 (1600, C=C)	2.03 (s, 3), 2.20 (s, 3), 3.78 (d, 6, J = 11 Hz), 6.62 (finely split s, 1)	43.75	43.69	6.82	6.90
Im 	92	80–86 (0.22)	1.4678	1650 (1590, C=C)	1.7–2.0 (m, 9), 3.82 (d, 6, J = 11.5 Hz)	46.60	46.62	7.33	7.42
In 	91	99 (0.13)–102 (0.18)	1.4740	1655 (1585, C=C)	1.20 (s, 9), 2.18 (s, 3), 3.78 (d, 6, J = 10 Hz), 6.63 (s, 1)	51.27	51.12	8.18	8.21

[a] M. I. Kabachnik and P. A. Rossitskaya, *Bull. Acad. Sci. USSR*, 364 (1945); *Chem. Abstr.*, 40, 4688 (1946). [b] Attempted purification gave decomposition, so the product was converted directly to the *p*-toluenesulfonylhydrazone. [c] Calcd for Cl: 16.52. Found: 16.68. [d] See Experimental Section for preparation of the acid chloride.

hanced stabilization of the diazoalkane imparted by the phosphoryl group can be explained on the basis of resonance forms of the type shown, where the P=C bond is of the (p → d) π type. Evidence for such P–C π bonding had been reported previously by Berlin and Burpo[13] for acylphosphonates. It was possible to fractionally crystallize compounds IIi and IIj to give both syn and anti isomers. Our assignments are based solely on their differing solubility in diethyl ether, as demonstrated quite generally by Regitz.[5] On treatment with aqueous sodium carbonate at room temperature these *p*-toluenesulfonylhydrazones underwent a remarkably facile Bamford–Stevens type of elimination[14] to give the diazoalkane, with the exception of IIf which underwent cyclization (eq 1).



(1)

The diazoalkanes prepared in this manner are listed in Table III. Their thermal stability varied considerably. Some could be distilled at reduced pressure and isolated in analytical purity, *e.g.*, dimethyl α-diazo-*n*-hexylphosphonate, bp 82° (44 mm), and dimethyl α-diazocyclohexylmethylphosphonate, bp 89° (0.15 mm). Others, such as dimethyl α-diazocyclopropylmethylphosphonate underwent spontaneous decomposition, while dimethyl α-diazocyclobutylmethylphosphonate decomposed partially under the reaction conditions and could not be obtained in analytical purity. All were yellow to orange colored liquids.

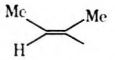
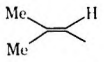
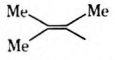
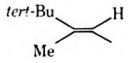
Although our major interest was in the copper-catalyzed decomposition of these diazoalkanes, a few other reactions of $MeC(N_2)P(O)(OMe)_2$ were examined. This compound reacted with acetic acid to give the expected ester, with triphenylphosphine to give the phosphazine, and with $PhHgCCl_2Br$-derived dichlorocarbene to give the dichloroolefin[15] (Scheme II).

Alkyl-Substituted Diazomethylphosphonates.—Five alkyl-substituted diazomethylphosphonates were prepared (IIIa–e in Table III), and their decomposition in benzene solution in the presence of copper powder was

(13) K. D. Berlin and D. H. Burpo, *J. Org. Chem.*, **31**, 1304 (1966).
(14) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).
(15) D. Seyferth, J. D. H. Paetsch, and R. S. Marmor, *J. Organometal. Chem.*, **16**, 185 (1969).

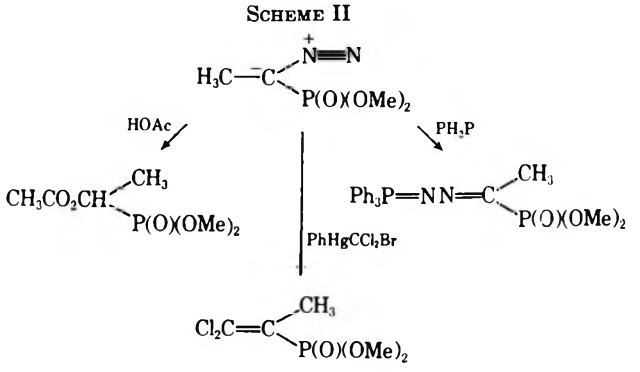
TABLE II

p-TOLUENESULFONYLHYDRAZONES

R in RCP(O)(OMe)$_2$	Yield, %	Mp, °C	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
IIa CH_3	91[a]	183 dec	41.25	41.12	5.35	5.19		
IIb *n*-C_5H_{11}	73[a] 67[b]	106–107	47.86	48.05	6.69	6.82	7.44	7.40
IIc $(CH_3)_2CH$	86[b]	181–182 dec	44.82	44.93	6.08	5.83	8.04	8.32
IId $(CH_3)_3C$	66[b]	88.5–89.5	46.40	46.57	6.40	6.67	7.73	7.41
IIe CH_3OCH_2	46[b]	157.0–157.5 dec	41.14	41.30	5.47	5.68	8.00	8.10
IIf $Cl(CH_2)_3$	81[a]	140–141	40.79	40.79	5.27	5.33		
IIg *c*-C_3H_5	87[a]	201–202 dec	45.08	45.41	5.53	5.47	8.09	8.09
IIh *c*-C_4H_7	64[a]	169.5–171.0 dec	46.66	46.71	5.87	5.61	7.78	7.68
IIi *c*-C_5H_9 (syn)	72[c]	67–68	48.12	48.10	6.19	6.06	7.48	7.52
(anti)		145–146	48.12	48.11	6.19	6.12	7.48	7.31
IIj *c*-C_6H_{11} (syn)	92[c]	82.5–83.0	49.47	49.48	6.49	6.49	7.21	7.23
(anti)		167–168 dec	49.47	49.50	6.49	6.51	7.21	7.32
IIk 	85[b]	155–156 dec	46.66	46.60	5.87	5.89		
III 	57[b]	115.0–115.5	46.66	46.55	5.87	5.80	7.78	7.79
IIm 	58[b]	84–85	48.12	48.40	6.19	6.34	7.48	7.58
IIn 	65[b]	118.0–118.5	50.73	51.05	6.76	6.83	6.96	7.19

[a] Prepared in methanol. [b] Prepared in tetrahydrofuran with hydrochloric acid. [c] Prepared in methanol with hydrochloric acid.

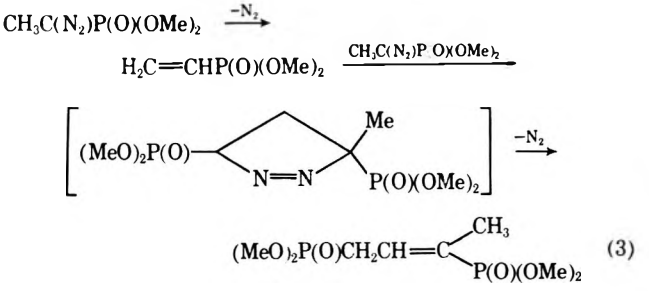
SCHEME II



studied. When the diazo compounds had available α hydrogens (IIIa–c,e), hydride migration occurred and the expected α,β-unsaturated phosphonate ester was produced (eq 2). Thus *n*-$C_5H_{11}C(N_2)P(O)(OMe)_2$ gave

$$XCH_2C(N_2)P(O)(OMe)_2 \longrightarrow XCH_2\dot{C}P(O)(OMe)_2 \longrightarrow XCH{=}CHP(O)(OMe)_2 \quad (2)$$

n-$C_4H_9CH{=}CHP(O)(OMe)_2$ in 79% yield, $Me_2CHC(N_2)P(O)(OMe)_2$ gave $Me_2C{=}CHP(O)(OMe)_2$ in 87% yield, and *trans*-$MeOCH{=}CHP(O)(OMe)_2$ was produced in 87% yield from $MeOCH_2C(N_2)P(O)(OMe)_2$. Such rearrangements are typical of alkyl carbenes containing an α-H substituent.[16] In the case of $CH_3C(N_2)P(O)(OMe)_2$, however, the expected product, dimethyl vinylphosphonate, was isolated in only trace amounts, the major product being a high-boiling oil derived from the 1,3-dipolar addition of as yet undecomposed diazo compound with the dimethyl vinylphosphonate produced (eq 3). The structure of the product



(3)

is based on the pmr spectrum which shows one vinyl proton and on the observed uptake of 1 mol of hydrogen on hydrogenation. The other diazo compounds (IIIb,d,e) did not undergo 1,3-dipolar addition side reactions during their decomposition to any appreciable extent, although high-boiling oils were found in small amounts in all cases. Presumably, dimethyl vinylphosphonate, having no β-alkyl substituents, undergoes 1,3-dipolar addition more readily. Vinylphosphonate esters have been reported to undergo 1,3-dipolar addition reactions.[17] We have found that all of the stable dimethylphosphono-substituted diazoalkanes react with ethyl acrylate to give Δ^2-pyrazolines, but these tended to decompose rather readily to give mixtures of cyclopropyl compounds and olefins which could be resolved only with difficulty.

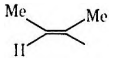
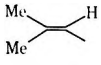
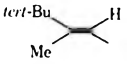
Several attempts to capture an intermediate carbene or carbenoid from $CH_3C(N_2)P(O)(OMe)_2$ with cyclohexene were unsuccessful. It would appear that here also the intramolecular rearrangement of the carbene or carbenoid is faster than any possible intermolecular reaction with an olefin.

In the case of the copper-catalyzed decomposition of $Me_3CC(N_2)P(O)(OMe)_2$, a compound with no α-

(16) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, Chapter 3.

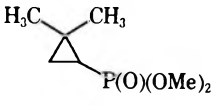
(17) A. N. Pudovik and R. D. Gareev, *Zh. Obshch. Khim.*, **34** 3942 (1964); **38**, 1291 (1968).

TABLE III
DIMETHYLPHOSPHONO-SUBSTITUTED DIAZOALKANES

R in $RC(N_2)P(O)(OMe)_2$	Yield, %	Bp, °C (mm)	$n^{25}D$	ν (C=N=N)	Nmr (δ) ppm (in CCl_4)	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found
IIIa CH_3[a]	44	50–52 (0.20)	1.4583	2080	1.83 (d, 3, J = 10 Hz), 3.73 (d, 6, J = 11.5 Hz)	29.27	29.57	5.53	5.55
IIIb n-C_5H_{11}	85	82 (0.44)	1.4555	2080	0.7–1.1, 1.1–1.6, 1.9–2.5 (m, 11), 3.75 (d, 6, J = 12 Hz)	43.63	43.86	7.78	7.91
IIIc $(CH_3)_2CH$	72	50 (0.11)	1.4545	2075	1.14 (d, 6, J = 6.5 Hz), 2.0–2.6 (m, 1), 3.65 (d, 6, J = 11.5 Hz)	37.50	38.09	6.82	6.87
IIId $(CH_3)_3C$	64	41.5 (0.10)	1.4562	2070	1.20 (s, 9), 3.69 (d, 6, J = 11.7 Hz)	40.77	40.97	7.73	7.51
IIIe CH_3OCH_2	71	56–58 (0.10)	1.4610	2085	3.27 (s, 3), 3.68 (d, 6, J = 11 Hz), 4.03 (d, 2, J = 12 Hz)	30.93	30.99	5.71	5.74
IIIh c-C_4H_7	80 (undistilled)	Decomposes[b]		2070	1.7–2.5 (m, 7), 3.63 (d, 6, J = 11.5 Hz)	41.18	42.88	6.42	6.72
IIIi c-C_5H_9	80	84 (0.20)	1.4800	2070	1.1–2.7 (m, 9), 3.62 (d, 6, J = 12 Hz)	44.03	44.49	6.93	6.91
IIIj c-C_6H_{11}	82	85 (0.10)–89 (0.15)	1.4841	2070	0.9–2.1 (m, 11), 3.66 (d, 6, J = 11.5 Hz)	46.54	46.70	7.38	7.34
IIIk 	12 (crude)	Undergoes ring closure		2070					
IIIl 	37 (crude)	Decomposes		2070					
IIIm 	4 (crude)	Decomposes		2075					
IIIn 	100 (crude)	Decomposes		2070					

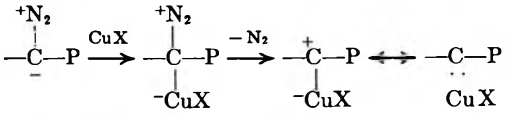
[a] Also prepared in 32% yield was $CH_3C(N_2)P(O)(OEt)_2$, an orange oil, bp 49° (0.14 mm), $n^{25}D$ 1.4503. *Anal.* Calcd for $C_6H_{13}N_2O_3P$: C, 37.50; H, 6.82. Found: C, 37.43; H, 6.93. Nmr (CCl_4) 1.32 (t, 6, J = 7.0 Hz, CH_3 of OEt), 1.82 [d, 3, J = 9.8 Hz, $CH_3C(N_2)$], 3.97 and 4.11 ppm [2 quartets, 4, J (HCCH) = 7.0 Hz, J (HCOP) = 8.5 Hz, CH_2 of OEt]. [b] Violent decomposition occurred on one attempted distillation.

hydrogen substituents, two products were formed. One, $Me_2C{=}C(Me)P(O)(OMe)_2$ (obtained in 81% yield), resulted from methyl migration in $Me_3CCP(O)(OMe)_2$ to the carbenic carbon atom; the other, a cyclopropane (IV, obtained in 9% yield), resulted from



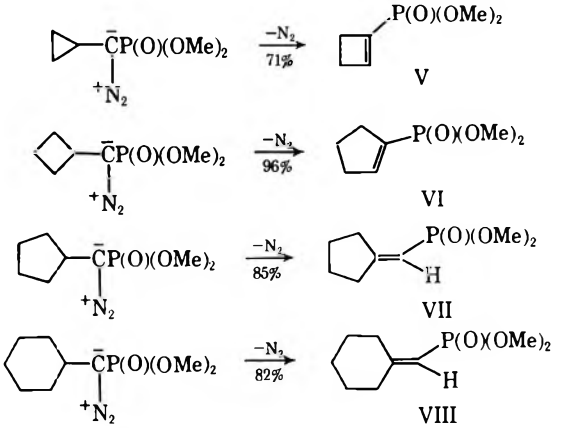
IV

intramolecular insertion of the carbene into a β-CH bond. The relative amounts of these products changed significantly when the diazoalkane was decomposed by photolysis in ether solution, and a third product was formed. In this reaction the olefin was formed in 49% yield, the cyclopropane in 21% yield, and dimethyl neopentylphosphonate in 13% yield. This change in product ratio, especially the increase in the amount of cyclopropane formed, suggests to us that the copper-catalyzed decomposition involves a complexed carbene in which there is less carbene character and some carbonium ion character at the α-carbon atom.[18]



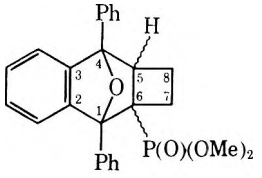
Cycloalkyl-Substituted Diazomethylphosphonates.—The precursors for the dimethyl esters of cyclopropyl-, cyclobutyl-, cyclopentyl-, and cyclohexyldiazomethylphosphonates were prepared. The last two diazoalkanes could be isolated as pure compounds, the cyclobutyl derivative only in impure form; the cyclopropyl compound decomposed during the course of its preparation.

The cycloalkyl-substituted compounds with the three- and four-membered rings underwent ring enlargement, *i.e.*, alkyl migration, exclusively, even though an α-hydrogen atom was available, while the cyclopentyl- and cyclohexyl-substituted compounds gave products with an exocyclic double bond and no products of ring enlargement. The fact that with the latter two diazo compounds hydrogen migration was observed (*vs.* ring enlargement in the case of the cyclopropyl and cyclobutyl compounds) very likely is due to ring strain effects in the derivatives containing the three- and four-membered rings.



(18) The "copper metal catalyzed" decomposition of diazoalkanes is generally believed to be induced by small amounts of copper(I) salts present at the copper metal surface. We have found CuCl and $Cu(acac)_2$ to be effective in catalyzing decomposition of $N_2CHP(O)(OMe)_2$ but cyclopropane yields were highest when copper powder was used.[10]

In the pmr spectrum of the hydrogenation product of V, the ring proton signals were found downfield from where they would be expected for a cyclopropyl compound. Cyclobutene V underwent a Diels–Alder reaction with 1,3-diphenylisobenzofuran to give IX. The formation of the cyclobutene V is an interesting result in view of the experiments of Wiberg and Lavanish[19] who observed two different modes of decomposi-

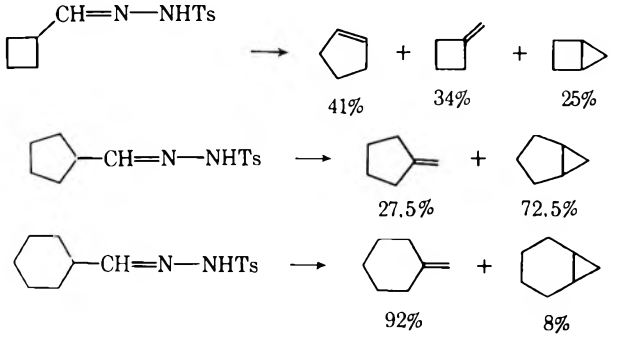


IX

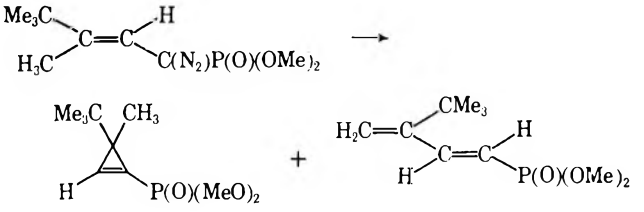
tion of cyclopropyldiazomethane depending on the solvent. In aprotic media cyclobutene was obtained; in protic solvents the product was bicyclobutane. In our case it is entirely possible that dimethyl bicyclobutylphosphonate was the initial product formed in the aqueous medium used, but that its strained ring system was destabilized by the dimethylphosphono group, resulting in rearrangement to V.

The proof of structure of VI is based on comparison of the hydrogenated product, dimethyl cyclopentylphosphonate, and the acid resulting from its saponification with authentic samples. That ring enlargement had not occurred in the case of VII and VIII was demonstrated by direct comparison of the products of their hydrogenation followed by saponification with authentic samples of dimethyl cyclohexylphosphonate and cycloheptylphosphonate and their derived phosphonic acids. These were quite different in their physical and spectral properties.

A comparison with the behavior of the unsubstituted cyclobutyl-, cyclopentyl-, and cyclohexylcarbenes is of interest.[20] It would appear that the introduction of the $P(O)(OMe)_2$ group has a profound effect on the course of the carbene chemistry observed. The major effect seems to involve steric hindrance to intramolecular C–H insertion in these cyclic systems.

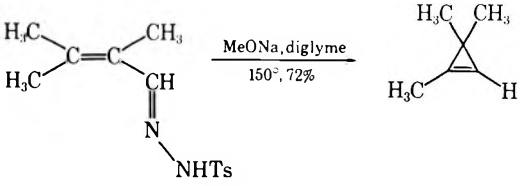


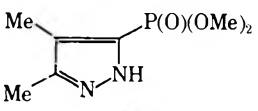
Vinyl-Substituted Diazomethylphosphonates.—The vinyl-substituted diazo compound *cis*-$MeCH{=}C(Me)$-$C(N_2)P(O)(OMe)_2$ underwent slow cyclization at room temperature to give the pyrazole X. However, such ring closure could be prevented by the introduction of a second β-alkyl substituent on the C=C bond. The compounds $Me_2C{=}CHC(N_2)P(O)(OMe)_2$, $Me_2C{=}C(Me)C(N_2)P(O)(OMe)_2$, and $Me_3C(Me)C{=}CHC(N_2)P(O)(OMe)_2$ could be isolated, but they were too thermally unstable to survive distillation. The first underwent copper-catalyzed decomposition to give only tars and unidentified high-boiling oils, while the yield of the second was too low (4%) to permit its detailed study. The last compound was obtained in high yield and underwent smooth copper-catalyzed decomposition to a mixture of a cyclopropene (arising from intramolecular addition) and a *trans*-diene. No *cis*-diene was present, as indicated by pmr and glc.



A 3-day reaction time gave an 86:14 mixture of the cyclopropene and diene in 64% yield; after 6 days the cyclopropene to diene ratio was changed to 40:60 and the total product yield had decreased to 34%. The diene was formed for the most part by decomposition of the cyclopropene under the reaction conditions. A control experiment with the cyclopropene showed its complete conversion to the diene after it had been stirred with copper powder in benzene for 1 week. Also, attempted resolution of the cyclopropene–diene mixture by glc resulted in thermal conversion to the diene, and, indeed, a pure sample of the diene was obtained by preparative glc of this mixture.

The possibility that the cyclopropene was formed by thermal decomposition of an intermediate Δ^1-pyrazole rather than by a direct intramolecular carbene addition to the C=C bond has not been ruled out. Also, it is possible that at least some of the diene arose by another pathway: migration of the α-vinylic hydrogen atom to form an allene which then rearranged to the 1,3-diene and/or polymerized. It should be noted that Closs and Closs[21] have observed the formation of a cyclopropene from an unsaturated diazoalkane.





X

Experimental Section

General Comments.—All reactions involving preparation or use of the dimethylphosphono-substituted diazoalkanes were carried out under an atmosphere of prepurified nitrogen. Infrared spectra were recorded using Perkin-Elmer Infracord 237B and 337 grating spectrophotometers, pmr spectra using Varian A60 or T60 spectrometers. Chemical shifts are given in ppm downfield from internal TMS (δ units). Melting points were measured using a Mel-Temp or Büchi melting point apparatus and are un-

(19) K. B. Wiberg and J. M. Lavanish, *J. Amer. Chem. Soc.*, **88**, 365 (1966).

(20) W. Kirmse, "Carbene, Carbenoide und Carbenanaloge," Verlag Chemie, Weinheim, Germany, 1969, pp 146–147.

(21) G. L. Closs and L. E. Closs, *J. Amer. Chem. Soc.*, **83**, 2015 (1961).

corrected. All gas–liquid partition chromatography (glc) was carried out using an F & M 700 gas chromatograph.

Preparation of Dimethyl α-Ketoalkylphosphonates.—A solution of the appropriate acyl halide (X mmol) in 2.5X ml of diethyl ether was stirred under nitrogen in a flask equipped with a condenser, a dropping funnel, and a magnetic stirring assembly at *ca.* 0°. Trimethyl phosphite (1.05X mmol, distilled before use) was added dropwise over a 20–60-min period, depending on the reaction scale. The reaction mixture was stirred overnight at room temperature and subsequently the solvent was removed on the steam bath under a stream of dry nitrogen. The residual oil was distilled using a Vigreux column. The product obtained in general was analytically pure. The compounds prepared are listed in Table I.

Preparation of α-Ketoalkylphosphonate *p*-Toluenesulfonylhydrazones.—A solution of equimolar amounts of the appropriate dimethyl α-ketoalkylphosphonate and *p*-toluenesulfonylhydrazine was set aside at room temperature for 24 hr and then concentrated and the residue was allowed to crystallize. In some cases, as indicated in Table II, better yields were obtained when hydrochloric acid was added and the reactants were mixed at 0°. Tetrahydrofuran was the preferred solvent for other acid-catalyzed reactions, as indicated in Table II. The compounds prepared are listed in Table II. Recrystallization from methanol or aqueous methanol gave pure samples for microanalysis.

Preparation of α-Diazoalkylphosphonates.—To a solution of sodium carbonate (1.2X mmol) in 2X ml of water was added the appropriate dimethyl α-ketoalkylphosphonate *p*-toluenesulfonylhydrazone (X mmol). The resulting solution was stirred until no more diazo compound was forming, as indicated by the intensity of the yellow color of the reaction mixture. For compounds IIIa and b (*cf.* Table III), ether was present in a two-phase system and was replaced every few hours with fresh solvent. For compounds IIIc, i, j, l, m, and n, hexane was used in this manner. The reaction varied from *ca.* 24 to 72 hr. The aqueous layer then was extracted with dichloromethane until it was colorless and the combined organic layers were dried ($MgSO_4$) and evaporated using a rotary evaporator to give the crude diazoalkane. The product was dissolved in a small amount of diethyl ether and eluted through a short column containing neutral alumina, and then was concentrated and distilled (short path). If the chromatography was omitted, the diazo compounds decomposed partially on attempted distillation. In some cases, the microanalyses were not inside the acceptable range because of the relative instability of some of these compounds. However, the pmr spectra even in those cases indicated an acceptable degree of purity.

1-*p*-Toluenesulfonyl-3-dimethylphosphono-Δ²-tetrahydropyridazine.—Attempted conversion of the *p*-toluenesulfonylhydrazone derivative $ClCH_2CH_2CH_2C(=NNHTs)P(O)(OMe)_2$ to a diazo compound by the above method resulted in separation of a heavy, colorless oil after 5 min. The reaction mixture was stirred for 8 hr, and then extracted with a 100-ml and then two 50-ml portions of chloroform. The combined, dried organic layers were evaporated to leave an oil which solidified to a white solid after being kept overnight in high vacuum. A 97% yield (13.24 g) of the cyclic product was obtained, mp 82–83°. Slow recrystallization from ethyl acetate gave an analytical sample: mp 82.0–82.5°; ir (Nujol) 1360, 1350, 1260, 1165, 1130, 1045, 1020, 790, 730 cm^{-1}; nmr ($CDCl_3$) δ 1.8–2.5 (m, 4), 2.42 (s, 3), 3.44 (t, 2, J = 5.5 Hz), 3.77 (d, 6, J = 11.5 Hz), 7.35 and 7.78 ppm [two d, 4, J (both) = 8.5 Hz].

Anal. Calcd for $C_{13}H_{19}N_2O_5PS$: C, 45.08; H, 5.53; N, 8.09. Found: C, 44.89; H, 5.72; N, 8.09.

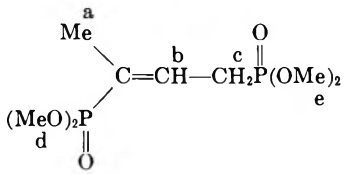
Copper-Catalyzed Decomposition of Dimethyl α-Diazoalkylphosphonates.—A mixture of dimethyl α-diazoalkylphosphonate (50 mmol), copper powder (2.5 g from J. T. Baker Co., "purified grade"), and 120 ml of benzene was stirred under nitrogen at room temperature for 24 hr and then refluxed until colorless or nearly so. The solution was filtered through Celite, evaporated using a rotary evaporator, and short-path distilled. Redistillation in most cases gave pure product.

Hydrogenation of the Products of the Decomposition of the Dimethyl α-Diazoalkylphosphonates.—To a solution of the olefinic decomposition product (10 mmol) in 10 ml of absolute ethanol under nitrogen was added 200 mg of 10% palladium on charcoal. The flask was swept with hydrogen and stirred very vigorously for 24–48 hr under hydrogen balloon pressure at room temperature. The flask then was swept with nitrogen and the reaction mixture was filtered through Celite. The filtrate was evaporated at reduced pressure and the residual oil short-path distilled to give pure product. Hydrogenation went to completion in all cases, as indicated by ir and nmr spectra.

Saponification of Dimethyl Alkylphosphonates.—A solution of the dimethyl alkylphosphonate (4.0 mmol) in 25 ml of concentrated HCl was heated at reflux for 5–7 hr and then placed in the refrigerator. If the product separated, the mixture was filtered and the product dried. When the product did not separate, the acid mixture was concentrated to a small volume and dried *in vacuo* in a desiccator over KOH flakes.

The monoaniline salt of these alkylphosphonic acids was prepared by adding an excess of aniline to an ether solution of the acid, filtering the voluminous precipitate, washing with ether, and recrystallizing from ethanol.

Tetramethyl 2-Butylene-1,3-diphosphonate.—Decomposition of $CH_3C(N_2)P(O)(OMe)_2$ by the general procedure gave the title compound, bp 124° (0.11 mm)–137° (0.25 mm), as a pale yellow oil in 51% yield. Redistillation gave very pale yellow liquid: bp 111–113° (0.03 mm); $n^{25}D$ 1.4642; ir (liquid film)



1615 (w), 1250 (s, P=O), 1180 (m), 1030 cm^{-1} (s, POC); nmr (CCl_4) δ 1.30 (d of d, J (b,c) = 7 Hz, J_P = 18 Hz, c of major isomer), 1.1–3.2 (m, 5, a and c), 3.7 (m of d, 12, d and e), 5.8–6.8 ppm (m, 1, b).

Anal. Calcd for $C_8H_{18}O_6P_2$: C, 35.30; H, 6.67. Found: C, 35.36; H, 6.61.

Hydrogenation of this product gave tetramethyl 1-methyltrimethylenediphosphonate in 76% yield as a pale yellow oil: bp 113–115° (0.05 mm); $n^{25}D$ 1.4560; ir (liquid film) 1240, 1030, 820, 790 cm^{-1}; nmr (CCl_4) δ 0.9–2.6 (m with maximum peaks at 1.08, 1.27, 1.38, and 2.20, 8), 3.7 ppm (m of d with maximum d at 3.68, J = 10.5 Hz, 12).

Anal. Calcd for $C_8H_{20}O_6P_2$: C, 35.04; H, 7.35. Found: C, 35.18; H, 7.21.

Saponification of the hydrogenation product afforded a glassy free acid which formed a crystalline dianiline salt, mp ~167° (with sharp softening at 160°). The analysis suggested that the product was the dihydrate.

Anal. Calcd for $C_{16}H_{30}N_2O_8P_2$: C, 43.64; H, 6.87; N, 6.36. Found: C, 43.53; H, 6.22; N, 6.45.

An authentic sample was prepared by saponification (and conversion of the acid to the dianiline salt) of tetraethyl 1-methyltrimethylenediphosphonate. The latter was obtained by the Michaelis–Arbuzov reaction between triethyl phosphite and 1,3-dibromobutane; bp 139° (0.03 mm), $n^{25}D$ 1.4450.

Anal. Calcd for $C_{12}H_{28}O_6P_2$: C, 43.63; H, 8.54. Found: C, 43.44; H, 8.43.

The dianiline salt obtained in this manner showed the same melting behavior, and a mixture melting point with the dianiline salt from the sequence described above was not depressed.

Dimethyl 1-Hexenylphosphonate.—Decomposition of *n*-C_5H_{11}-$C(N_2)P(O)(OMe)_2$ gave this compound in 79% yield as a colorless liquid, bp 63° (0.11)–61° (0.07 mm). Redistillation gave pure material: bp 57° (0.07 mm), 61° (0.03 mm); $n^{25}D$ 1.4450; ir (liquid film) 1635 (m, C=C), 1250 (s, P=O), 1030 cm^{-1} (s, POC); nmr (neat) δ 0.7–1.1, 1.1–1.6 (m, 7), 2.0–2.4 (m, 2), 3.63 (d, 6, J = 11.0 Hz), 5.3–6.1, 6.3–7.2 ppm (m, 2).

Anal. Calcd for $C_8H_{17}O_3P$: C, 49.99; H, 8.92. Found: C, 50.13; H, 8.90.

Hydrogenation of this product gave dimethyl *n*-hexylphosphonate in 94% yield: bp 56–57° (0.10 mm); $n^{25}D$ 1.4292 (lit.[22] bp 121–123°; $n^{20}D$ 1.4276); ir (liquid film) 1245 (s, P=O), 1205 (m), 1180 (m), 1055 (s), 1030 (s, POC), 825 (s), 810 cm^{-1} (s); nmr (CCl_4) δ 0.7–1.9 (m with maximum signals at 0.84 and 1.34, 13), 3.62 ppm (d, 6, J = 11 Hz). Saponification of the hydrogenation product afforded a 97% yield of *n*-hexylphosphonic acid, mp 104.5–106° (lit.[23] mp 104.5–106°).

Dimethyl β,β-Dimethylvinylphosphonate.—Decomposition of $Me_2CHC(N_2)P(O)(OMe)_2$ by the general procedure gave this

(22) A. E. Canavan, B. F. Dowden, and C. Eaborn, *J. Chem. Soc.*, 331 (1962).

(23) G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **67**, 1180 (1945).

compound as a colorless liquid, bp 75–76° (2.6 mm), n^{25}D 1.4502, in 87% yield. Prolonged exposure to air gave rise to unknown impurities.

Ir (liquid film) 1645 (s, C=C), 1250 (s, P=O), 1185 (m), 1060 (s), 1035 cm^{-1} (s, POC); nmr (CCl_4) δ 1.92 (s, 3), 2.05 (d, 3, J_P = 2.5 Hz), 3.60 (d, 6, J = 11.5 Hz), 5.32 ppm (d with fine splitting, 1, J = 18 Hz).

Anal. Calcd for $C_6H_{13}O_3P$: C, 43.90; H, 7.98. Found: C, 43.72; H, 8.33.

Hydrogenation of this ester gave dimethyl isobutylphosphonate in 78% yield: bp 66° (3.2 mm); n^{25}D 1.4206; ir (liquid film) 1260 (s, P=O), 1245 (s), 1185 (m), 1060 (s), 1035 cm^{-1} (s); nmr (CCl_4) δ 1.03 (d, 6, J = 7 Hz), 1.1–2.4 (m with maximum peaks at 1.38, 1.50 and 1.82, 3), 3.66 ppm (d, 6, J = 11.5 Hz).

Anal. Calcd for $C_6H_{15}O_3P$: C, 43.37; H, 9.10. Found: C, 43.20; H, 9.11.

Dimethyl Trimethylvinylphosphonate and Dimethyl 2,2-Dimethylcyclopropylphosphonate.—Copper-catalyzed decomposition of $Me_3CC(N_2)P(O)(OMe)_2$ gave a mixture of these compounds, bp 80° (3.6 mm), n^{25}D 1.4540, in 89% yield. Glc (4 ft Lac 728 at 125°) showed the ratio of the olefinic to the cyclopropyl product to be 9:1, with retention times of 13.0 and 9.6 min, respectively.

Anal. Calcd for $C_7H_{15}O_3P$: C, 47.19; H, 8.49. Found (for the mixture): C, 47.37; H, 8.54.

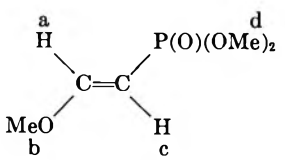
Photolysis of the diazoalkane (10 mmol) in 160 ml of dry ether under nitrogen with a Hanovia 140-W high-pressure mercury ultraviolet lamp in a quartz flask for 45 hr resulted in a colorless solution which on concentration and short-path distillation at 73.5° (2.3 mm)–78° (2.5 mm) afforded 1.44 g (81%) of product mixture, n^{25}D 1.4464. Glc analysis indicated the presence of three products in the (area) ratio of 13:26:61 with retention times (conditions as above) of 7.0, 10.2, and 13.8 min, respectively. The second and third products were the cyclopropane and the olefin, respectively.

Dimethyl 2,2-dimethylcyclopropylphosphonate was collected by glc and was identified by comparison with an authentic sample prepared by the copper-catalyzed addition of $HCP(O)(OMe)_2$ (*via* the diazoalkane) to isobutylene.[10]

Dimethyl trimethylvinylphosphonate showed the following principal bands in its ir spectrum (liquid film): 1630 (m, C=C), 1260 (s, P=O), 1225 (s), 1180 (m), 1025 (s, POC), 855 (s), 820 (s), 770 (s), 630 cm^{-1} (s); nmr (CCl_4) δ 1.63 (upfield peak of buried doublet, 1.5), 1.84 (s, 4.5), 2.13 (finely split s, 3), 3.61 (d, 6, J = 11 Hz). Hydrogenation of this phosphonate ester gave dimethyl α,β-dimethylpropylphosphonate, bp 65° (2.1 mm)–68° (2.5 mm), n^{25}D 1.4300, in 87% yield. This compound was saponified and the resulting acid was converted to the monoaniline salt in 91% overall yield. Recrystallization from ethanol gave pure material, mp 141–143° (with prior softening).

Anal. Calcd for $C_{11}H_{20}NO_3P$: C, 53.87; H, 8.22; N, 5.71. Found: C, 53.86; H, 8.27; N, 5.76.

***trans*-Dimethyl β-Methoxyvinylphosphonate.**—Decomposition of $MeOCH_2C(N_2)P(O)(OMe)_2$ gave this phosphonate ester: bp 52° (0.04 mm); n^{25}D 1.4506; 87% yield; ir (liq film) 1615 (s, C=C), 1250 (s, P=O), 1225 (s), 1185 (m), 1055 (s), 1030 (s), 830 cm^{-1} (s); nmr (CCl_4) δ 3.58 (d, 6, J = 12 Hz, d), 3.72 (s, 3, b, coincidental overlap with downfield peak of d doublet), 4.68 [d of d, 1; J (c,P) = 9 Hz, c], 7.09 ppm [d of d, 1, J (a,c) = 13.5 Hz, J (a,P) = 12 Hz, a].



Anal. Calcd for $C_5H_{11}O_4P$: C, 36.15; H, 6.68. Found: C, 36.21; H, 6.93.

Hydrogenation of this compound gave dimethyl β-methoxyethylphosphonate: bp 51° (0.23 mm); n^{25}D 1.4230; 70% yield; ir (liquid film) 1255 (s), 1230 (s, P=O), 1185 (s), 1115 (s), 1050 (s), 1030 (s), 830 cm^{-1} (s); nmr (CCl_4) δ 1.95 [d of t, 2, J (HCCH) = 7.5 Hz, J_P = 19 Hz], 3.27 (s, 3), 3.51 (t, partially buried beneath POMe doublet), 3.65 ppm [d, 8 (including 3.51 signal, J = 11 Hz)].

Anal. Calcd for $C_5H_{13}O_4P$: C, 35.72; H, 7.79. Found: C, 35.79; H, 8.05.

Dimethyl Δ^1-Cyclobutenylphosphonate.—Formation of this compound occurred spontaneously during the attempted conversion of c-$C_3H_5C(NNHTs)P(O)(OMe)_2$ to c-$C_3H_5C(N_2)P(O)(OMe)_2$ by the general procedure for preparing diazo compounds. Extraction of the aqueous carbonate solution with dichloromethane gave, after drying with sodium sulfate, evaporating at reduced pressure, and short-path distilling, a 71% yield of colorless liquid: bp 84° (2.8 mm); n^{25}D 1.4596; ir (liquid film) 1580 (m, C=C), 1260 (s, P=O), 1030 cm^{-1} (s, POC); nmr (neat) δ 2.70 (s, 4), 3.69 (d, 6, J = 11.5 Hz), 6.88 ppm (d, 1, J = 5 Hz).

Anal. Calcd for $C_6H_{11}O_3P$: C, 44.45; H, 6.84. Found: C, 44.56; H, 6.86.

Hydrogenation of this product gave dimethyl cyclobutylphosphonate in 86% yield: bp 67–70° (1.8 mm), n^{25}D 1.4442; ir (liquid film) 1240 (s, P=O), 1180 (s), 1030 (s, POC), 815 cm^{-1} (s); nmr (CCl_4) δ 1.8–2.6 (m with maximum peak at 2.13, 7), 3.64 ppm (d, 6, J = 10 Hz).

Anal. Calcd for $C_6H_{13}O_3P$: C, 43.90; H, 7.98. Found: C, 43.79; H, 8.06.

Saponification of this hydrogenation product afforded an oil which could not be crystallized. An aniline derivative could be prepared: mp 163–165° (methanol–ether); ir (Nujol) 3060 (sh, NH), 2610 (m, POH), 1185 (m), 1110 (s, P=O), 1025 cm^{-1} (s).

Anal. Calcd for $C_{10}H_{16}NO_3P$: C, 52.40; H, 7.03. Found: C, 52.12; H, 7.08.

Bromination of the cyclobutenylphosphonate in carbon tetrachloride gave on short-path distillation a 32% yield of dimethyl 1,2-dibromocyclobutylphosphonate, bp 94° (0.08 mm)–107° (0.16 mm), n^{25}D 1.5261. Redistillation gave pure material: bp 93° (0.05 mm), n^{25}D 1.5260; ir (liquid film) 1265 (s, P=O), 1185 (m), 1030 cm^{-1} (s, POC); nmr (CCl_4) δ 2.4–3.3 (m, 4), 3.85 and 3.87 (two d, 6, both J = 11 Hz), 4.5–5.2 ppm (m, 1).

Anal. Calcd for $C_6H_{11}Br_2O_3P$: C, 22.38; H, 3.44; Br, 49.64. Found: C, 22.30; H, 3.52; Br, 49.86.

Reaction of 5.6 mmol of the cyclobutenylphosphonate with 5.0 mmol of 1,3-diphenylisobenzofuran in 10 ml of xylene at reflux under nitrogen for 8.5 hr gave, after evaporation at reduced pressure, a solid residue which was extracted with hot hexane and diethyl ether to leave 0.15 g of white powder, mp 232–234°. Slow recrystallization from ethyl acetate gave white nuggets, mp 239–240°. The infrared spectrum of this material showed that the dimethylphosphono substitutent was not present, and its is believed that this solid was the dimer of 1,3-diphenylisobenzofuran. Evaporation of the hexane and ether extracts and recrystallization of the residue from ethyl acetate gave 0.35 g of white crystals of the desired adduct IX. Another recrystallization from ethyl acetate gave an analytical sample, mp 169–170°. The ir spectrum (Nujol) showed the P=O stretch at 1250 and the POC frequency at 1055 cm^{-1}: nmr ($CDCl_3$) δ 1.6–2.8 (m, cyclobutyl H, 5), 3.34 and 3.47 (two d, 6, both J = 11 Hz), 6.9–8.0 ppm (m, 14, aryl).

Anal. Calcd for $C_{26}H_{26}O_4P$: C, 72.21; H, 5.83. Found: C, 72.40; H, 6.19.

Dimethyl Δ^1-Cyclopentenylphosphonate.—Decomposition of c-$C_4H_7C(N_2)P(O)(OMe)_2$ by the general procedure gave this compound, bp 75–78° (0.70 mm), n^{25}D 1.4676, in 96% yield. Redistillation at 85–87° (1.7 mm) gave a center cut sample with n^{25}D 1.4669: ir (liquid film) 1605 (m, C=C), 1250 (s, P=O), 1175 (m), 1080 (s), 1050 (s), 1025 (s, POC), 815 cm^{-1} (s); nmr (CCl_4) δ 1.8–2.3 (m, 2), 2.3–2.8 (m with maximum peak at 2.50, 4), 3.63 (d, 6, J = 11.5 Hz), 6.60 ppm (d with fine splitting, 1, J = 11 Hz).

Anal. Calcd for $C_7H_{13}O_3P$: C, 47.73; H, 7.44. Found: C, 47.82; H, 7.93.

Hydrogenation of this product gave dimethyl cyclopentylphosphonate: bp 57° (0.35 mm); n^{25}D 1.4518; 88% yield; ir (liquid film) 1240 (s, P=O), 1185 (m), 1060 (s), 1030 (s, POC), 820 cm^{-1} (s); nmr (CCl_4) δ 1.4–2.1 (m with maximum peak at 1.60, 9), 3.67 ppm (d, 6, J = 11 Hz).

Anal. Calcd for $C_7H_{15}O_3P$: C, 47.19; H, 8.49. Found: C, 47.36; H, 8.55.

Saponification of the hydrogenation product gave a 93% yield of cyclopentylphosphonic acid, mp 122–122.5°. Several recrystallizations from benzene–heptane raised the melting point to a constant 123.0–123.5°.

Anal. Calcd for $C_5H_{11}O_3P$: C, 40.00; H, 7.39. Found: C, 39.92; H, 7.32.

Authentic dimethyl cyclopentylphosphonate and cyclopentylphosphonic acid were prepared from cyclopentylphosphonyl dichloride (available from the oxidative chlorophosphonation of cyclopentane).[24] The ester had identical ir and nmr spectra with the product described above and had $n^{25}D$ 1.4511. The authentic acid had mp 122–122.5° and was undepressed on admixture with the above acid.

Bromination of the dimethyl cyclopentenylphosphonate in carbon tetrachloride gave dimethyl 1,2-dibromocyclopentylphosphonate, bp 107° (0.15 mm)–124° (0.07 mm) (short-path distillation), which crystallized in the receiver to material with mp 62–68.5°. Recrystallization from petroleum ether gave silky white needles, mp 72.5–73.0°.

Anal. Calcd for $C_7H_{13}Br_2O_3P$: C, 25.02; H, 3.90; Br, 47.57. Found: C, 25.22; H, 4.11; Br, 47.80.

Dimethyl Cyclopentylidenemethylphosphonate.—Decomposition of c-$C_5H_9C(N_2)P(O)(OMe)_2$ by the general procedure gave this compound: bp 67° (0.08 mm); $n^{25}D$ 1.4750, 85% yield; ir (liquid film) 1640 (m, C=C), 1245 (s, P=O), 1180 (m), 1050 (s), 1030 (s), 875 (s,) 820 cm^{-1} (s); nmr (CCl_4) δ 1.5–2.0 (m with maximum peak at 1.68, 4), 2.2–2.9 (m, 4), 3.60 (d, 6, J = 10 Hz), 5.47 ppm (finely split d, 1, J_P = 17 Hz).

Anal. Calcd for $C_8H_{15}O_3P$: C, 50.52; H, 7.95. Found: C, 50.38; H, 7.89.

Hydrogenation of this product gave dimethyl cyclopentylmethylphosphonate: bp 74° (0.40 mm); $n^{25}D$ 1.4538; 88% yield; ir (liquid film) 1250 (s, P=O), 1185 (m), 1055 (s), 1030 (s), 840 cm^{-1} (s); nmr (CCl_4) δ 0.9–2.4 (m with maximum peaks at 1.58 and 1.88, 11), 3.63 ppm (d, 6, J = 11 Hz).

Anal. Calcd for $C_8H_{17}O_3P$: C, 49.99; H, 8.92. Found: C, 49.84; H, 8.82.

Saponification of the hydrogenated ester gave fluffy white crystals of cyclopentylmethylphosphonic acid, mp 169–170°.

Anal. Calcd for $C_6H_{13}O_3P$: C, 43.90; H, 7.98. Found: C, 43.61; H, 8.09.

Dimethyl cyclohexylphosphonate and cyclohexylphosphonic acid, the other possible products if the initial diazo compound decomposition had given dimethyl cyclohexenylphosphonate, were prepared for comparison from cyclohexylphosphonyl dichloride.[24] Dimethyl cyclohexylphosphonate had bp 66° (0.17 mm)–61° (0.12 mm), $n^{25}D$ 1.4533, but *different* ir and nmr spectra from dimethyl cyclopentylmethylphosphonate. Cyclohexylphosphonic acid melted at 164–165°, close to the melting point of cyclopentylmethylphosphonic acid, but a mixture melting point was depressed to 110–120°.

Dimethyl Cyclohexylidenemethylphosphonate.—Copper-catalyzed decomposition of c-$C_6H_{11}C(N_2)P(O)(OMe)_2$ gave the product: bp 76° (0.07 mm); $n^{25}D$ 1.4812; 82% yield; ir (liquid film) 1640 (s, C=C), 1245 (s, P=O), 1180 (m), 1050 (s), 1030 (s), 875 (s) and 820 cm^{-1} (s); nmr (CCl_4) δ 1.4–1.9 (m with maximum peak at 1.61, 6), 2.1–2.8 (m, 4), 3.60 (d, 6, J = 11 Hz), 5.22 ppm (broad d, 1, J_P = 19 Hz).

Anal. Calcd for $C_9H_{17}O_3P$: C, 52.93; H, 8.39. Found: C, 52.98; H, 8.39.

Hydrogenation of this compound gave dimethyl cyclohexylmethylphosphonate: bp 66° (0.09 mm); $n^{25}D$ 1.4598; 85% yield; ir (liquid film) 1250 (s, P=O), 1185 (m), 1055 (s), 1030 (s), 835 (s), 810 cm^{-1} (s); nmr (CCl_4) δ 0.7–2.2 (m with maximum peak at 1.68, 13), 3.63 ppm (d, 6, J = 11 Hz).

Anal. Calcd for $C_9H_{19}O_3P$: C, 52.41; H, 9.29. Found: C, 52.13; H, 9.20

Saponification of the hydrogenation product gave white crystals of cyclohexylmethylphosphonic acid, mp 199.5–200.5°, in 93% yield.

Anal. Calcd for $C_7H_{15}O_3P$: C, 47.19; H, 8.49. Found: C, 47.03; H, 8.41.

Authentic dimethyl cycloheptylphosphonate and cycloheptylphosphonic acid were prepared for comparison from cycloheptylphosphonyl dichloride (available from oxidative chlorophosphonation of cycloheptane[24]). Both of these compounds were different (spectral and physical properties) from the dimethyl cyclohexylmethylphosphonate and cyclohexylmethylphosphonic acid obtained above. These cycloheptylphosphorus derivatives are new compounds: dimethyl cycloheptylphosphonate, bp 72–73° (0.09 mm); $n^{25}D$ 1.4670; ir (liquid film) 1260 (s), 1230 (s), 1185 (m), 1030 (s), 815 (s), and 785 cm^{-1} (s); nmr (CCl_4) δ 1.1–2.4 (m with maximum peak at 1.57, 13), 3.64 ppm (d, J = 11 Hz).

Anal. Calcd for $C_9H_{19}O_3P$: C, 52.41; H, 9.29. Found: C, 52.60; H, 9.47.

Cycloheptylphosphonic acid melted at 106–107°.

Anal. Calcd for $C_7H_{15}O_3P$: C, 47.19; H, 8.49. Found: C, 46.98; H, 8.69.

A derivative, the monoaniline salt, was prepared as well, mp 166–168° (with prior softening).

Anal. Calcd for $C_{13}H_{22}NO_3P$: C, 57.55; H, 8.18; N, 5.16. Found: C, 57.74; H, 8.35; N, 5.06.

3,4-Dimethyl-5-(dimethylphosphono)pyrazole (X).—The formation of this compound occurred during the conversion of *cis*-MeCH=C(Me)C(NNHTs)P(O)(OMe)$_2$ to the diazoalkane by the general procedure for preparing diazo compounds. The crude diazoalkane, *cis*-MeCH=C(Me)C(N$_2$)P(O)(OMe)$_2$, changed on standing from an orange hexane-soluble oil to a white water-soluble solid, the pyrazole. The latter was isolated in 65% yield. Recrystallization from water gave white nuggets: mp 141–142° (with prior softening); ir (Nujol) 3170 (s, NH), 3120 (s, NH), 3050 (s), 1680 (broad, w), 1455 (s), 1355 (s), 1245 (s, P=O), 1230 (s), 1195 (s), 1040 (s), 1015 (s), 835 (s), 790 cm^{-1} (s); nmr (DMSO-d_6) δ 2.06 (s, 3), 2.18 (s, 3), 3.68 (d, 6, J = 12 Hz), and 10.94 ppm (broad s, 1).

Anal. Calcd for $C_7H_{13}N_2O_3P$: C, 41.18; H, 6.42; N, 13.72. Found: C, 40.97; H, 6.39; N, 13.70.

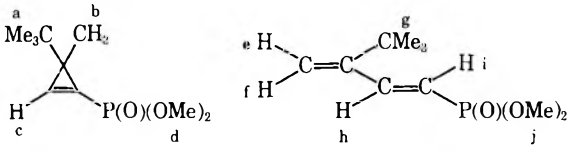
Dimethyl 3-Methyl-3-*tert*-butylcyclopropenylphosphonate and *trans*-Dimethyl 3-*tert*-Butyl-1,3-butadienylphosphonate.—Copper-catalyzed decomposition of Bu^t(Me)C=CHC(N$_2$)P(O)(OMe)$_2$ was carried out as usual except that the benzene solution of the diazo compound was stirred at room temperature for a longer time before being refluxed. When it had been stirred for 6 days, a product mixture was obtained at 61–63° (0.06 mm) as a pale yellow oil. A large amount of viscous oil was left behind. This residue began to distil at *ca.* 150° (0.7 mm) and then turned black and decomposed. Redistillation of the product (short-path) at 61–63° (0.04 mm) gave a 34% yield of product mixture, $n^{25}D$ 1.4610. The nmr spectrum suggested that a 60:40 mixture of the *trans*-diene and the cyclopropene (based on the relative areas of the dimethylphosphono and the *tert*-butyl signals) was present. The high $J_{h,i}$ coupling constant of 17.0 Hz suggests the *trans*-diene isomer, and the absence of other olefinic signals ruled out the presence of a significant amount of the cis isomer. Attempted glc purification (Lac 728 at 150°) of the distillate gave only a single peak at 14.7 min retention time. Collection of this product gave a liquid with the identical ir spectrum as the unpassed product mixture except for the complete absence of the 1690-cm^{-1} band.

Repetition of this experiment with a 3-day reaction time at room temperature gave a 64% yield of yellow product mixture at 61–65° (0.10 mm) which nmr analysis showed to be an 86:14 mixture of cyclopropene and *trans*-diene, respectively, $n^{25}D$ 1.4542.

A control experiment with this 86:14 product mixture showed that stirring in benzene solution at room temperature in the presence of copper powder for 7 days and 1 hr at reflux caused complete conversion of the cyclopropene to the diene and polymer. Distillation afforded a sample of the pure *trans*-diene.

Anal. Calcd for $C_{10}H_{19}O_3P$: C, 55.03; H, 8.78. Found for the 60:40 mixture of *trans*-diene and cyclopropene: C, 55.01; H, 8.74. Found for the pure diene: C, 54.80; H, 8.77.

Data for methyl 3-methyl-3-*tert*-butylcyclopropenylphosphonate are: ir (major band) (liquid film) 1690 cm^{-1} (s, C=C);[25] nmr ($CDCl_3$) (by subtraction of diene resonances from those of cyclopropene–diene mixture) δ 0.87 (s, 9, a), 1.23 (d, 3, J_P = 2.7 Hz, b), 3.78 (d, 6, J = 11.5 Hz, d), 8.27 ppm (d, 1, J_P = 4 Hz, c).[25]



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(25) Long-range splitting has been observed in the nmr spectra of cyclopropenes. Also, there is a great variance in the C=C absorption frequency in the infrared spectra of reported cyclopropene compounds: G. L. Closs, W. A. Böll, H. Heyn, and V. Dev, *ibid.*, **90**, 173 (1968).

Data for *trans*-dimethyl 3-*tert*-butyl-1,3-butadienylphosphonate are: ir (liquid film) 1620 (w, C=C), 1600 (w, C=C), 1250 (s, P=O), 1215 (m, *tert*-Bu), 1180 (m), 1055 (s), 1030 (s, POC), 960 (w, diene), 920 cm^{-1} (sh, *tert*-Bu); nmr ($CDCl_3$) δ 1.13 (s, 9, g), 3.63 (d, 6, J = 11 Hz, j), 5.01 (s, 1, e or f), 5.24 (s, 1, e or f), 5.90 (d of d, 1, J_P = 19.5 Hz, $J_{h,i}$ = 17 Hz, i), 7.23 ppm (d of d, 1, J_P = 22.5 Hz, $J_{h,i}$ = 17 Hz, h).

Dimethyl α-Acetoxyethylphosphonate.—A solution of MeC(N_2)P(O)(OMe)$_2$ (10.5 mmol) and acetic acid (10.5 mmol) in 15 ml of diethyl ether was heated slowly on the steam bath. As the last of the ether solvent boiled off, a violent reaction occurred and a pale yellow, sweet-smelling oil remained behind. This was distilled (trap-to-trap) and the distillate was purified by glc (10% General Electric Co. SE-30 at 163°) to give as the major product $CH_3CH(OAc)P(O)(OMe)_2$: $n^{25}D$ 1.4379; ir (liquid film) 1770 (s), 1750 (s), 1260 (s), 1220 (s), 1180 (s), 1025 (s), and 830 cm^{-1} (s).

Anal. Calcd for $C_6H_{13}O_5P$: C, 36.74; H, 6.68. Found: C, 36.94; H, 6.45.

Dimethyl α-Diazoethylphosphonate and Triphenylphosphine.—The diazo compound (7.8 mmol) and triphenylphosphine (7.8 mmol) were stirred in ether solution under nitrogen at room temperature for 69 hr. Removal of the ether at reduced pressure was followed by recrystallization of the residue from benzene–heptane to give 210 mg (15%) of short white needles of $Ph_3P{=}N{-}N{=}C(Me)P(O)(OMe)_2$. Another recrystallization gave an analytical sample, mp 136.5–137.5°. The compound decomposed slowly at room temperature: nmr ($CDCl_3$) δ 2.24 (d, 3, J = 10.7 Hz), 3.48 (d, 6, J = 10.5 Hz), 7.1–7.8 ppm (m, 15); ir (Nujol) 1245 (s, P=O), 1110 (s, P=N), 1035 cm^{-1} (s, POC).

Anal. Calcd for $C_{22}H_{24}N_2O_3P_2$: C, 61.97; H, 5.67. Found: C, 61.93; H, 5.85

***trans*-3,4,4-Trimethyl-2-pentenoyl Chloride.**—*trans*-Ethyl 3,4,4-trimethyl-2-pentenoate was prepared by the Wadsworth–Emmons modification[26] of the Wittig reaction between triethyl phosphonoacetate and pinacolone in refluxing toluene and saponified to the acid in 61% overall yield, mp 83.5–84.5° (lit.[27] mp 84–85°). The acid on reaction with thionyl chloride gave the desired acid chloride in 94% yield: bp 42–43° (1.0 mm); a colorless liquid; ν (C=O) 1775 cm^{-1}; ν (C=C) 1595 cm^{-1}.

Anal. Calcd for $C_8H_{13}ClO$: C, 59.81; H, 8.16. Found: C, 59.90; H, 8.20.

Registry No.—Ia, 17674-28-1; Ib, 26583-87-9; Ic, 6918-58-7; Id, 6918-59-8; Ie, 26583-90-4; If, 26583-92-5; Ig, 26583-92-6; Ih, 26583-93-7; Ii, 26583-94-8; Ij, 1490-12-6; Ik, 26583-96-0; Il, 26583-97-1; Im, 26583-98-2; In, 26583-99-3; IIa, 26584-00-9; IIb, 26584-01-0; IIc, 26584-02-1; IId, 26584-03-2; IIe, 26584-04-3; IIf, 26584-05-4; IIg, 26584-06-5; IIh, 26584-07-6; IIi (syn), 26584-08-7; IIi (anti), 26584-09-8; IIj (syn), 26584-10-1; IIj (anti), 26584-11-2; IIk, 26584-12-3; IIl, 26630-74-0; IIm, 26584-13-4; IIn, 26584-14-5; IIIa, 26584-15-6; IIIb, 26579-98-6; IIIc, 26579-99-7; IIId, 26580-00-7; IIIe, 26580-01-8; IIIh, 26580-02-9; IIIi, 26580-03-0; IIIj, 26580-04-1; IIIk, 26584-16-7; IIIl, 26580-05-2; IIIm, 26580-06-3; IIIn, 26630-75-1; 1-*p*-toluenesulfonyl-3-dimethylphosphono-Δ^2-tetrahydropyridazine, 26580-07-4; tetramethyl 2-butylene-1,3-diphosphonate, 26630-76-2; tetramethyl 1-methyltrimethylenediphosphonate, 26580-08-5; tetramethyl 2-butylene-1,3-diphosphonate (dianiline salt), 26580-09-6; tetraethyl 1-methyltrimethylene diphosphonate, 26580-10-9; dimethyl 1-hexenylphosphonate, 23897-48-5; dimethyl *n*-hexylphosphonate, 6172-92-5; dimethyl β,β-dimethylvinylphosphonate, 26580-13-2; dimethyl isobutylphosphonate, 26580-14-3; dimethyl trimethylvinylphosphonate, 26580-15-4; dimethyl 2,2-dimethylcyclopropylphosphonate, 26580-16-5; dimethyl α,β-dimethylpropylphosphonate, 6172-91-4; dimethyl α,β-dimethylpropylphosphonate (monoaniline salt), 26580-18-7; *trans*-dimethyl β-methoxyvinylphosphonate, 26584-17-8; dimethyl β-methoxyethylphosphonate, 26119-43-7; dimethyl Δ^1-cyclobutenylphosphonate, 26580-20-1; dimethyl cyclobutylphosphonate, 26580-21-2; dimethyl cyclobutylphosphonate (aniline salt), 26580-22-3; dimethyl 1,2-dibromocyclobutylphosphonate, 26584-80-23-4; IX, 26630-77-3; dimethyl Δ^1-cyclopentenylphosphonate, 26580-24-5; dimethyl cyclopentylphosphonate, 26580-25-6; cyclopentylphosphonic acid, 6869-04-1; dimethyl 1,2-dibromocyclopentylphosphonate, 26580-27-8; dimethyl cyclopentylidenemethylphosphonate, 26580-28-9; dimethyl cyclopentylmethylphosphonate, 26580-29-0; cyclopentylmethylphosphonic acid, 26580-30-3; dimethyl cyclohexylidenemethylphosphonate, 26580-31-4; dimethyl cyclohexylmethylphosphonate, 26580-32-5; cyclohexylmethylphosphonic acid, 16016-55-0; dimethyl cycloheptylphosphonate, 26580-34-7; cycloheptylphosphonic acid, 26580-35-8; cycloheptylphosphonic acid (monoaniline salt), 26580-36-9; X, 26580-37-0; dimethyl 3-methyl-3-*tert*-butylcyclopropenylphosphonate, 26580-38-1; *trans*-dimethyl 3-*tert*-butyl-1,3-butadienylphosphonate, 26584-18-9; dimethyl α-acetoxyethylphosphonate, 17036-86-1; $Ph_3P{=}N{-}N{=}C(Me)P(O)(OMe)_2$, 16965-79-0; *trans*-3,4,4-trimethyl-2-pentenoyl chloride, 26584-19-0.

Acknowledgments.—The authors are grateful to the U. S. Public Health Service (Grant CA-08278) for generous support of this work.

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The Importance of Steric Inhibition of Resonance in the Mass Spectral Cleavage of Benzophenones

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Received June 5, 1970

The intensity of the benzoyl ion, *m/e* 105, in the mass spectra of some para-monosubstituted benzophenones was compared with the intensity of this ion in benzophenones where the para substituent is flanked by two bromo substituents in the 3 and 5 positions. Consideration of the scatter in the Hammett plot expected for multiple substitution does not alter the conclusion that the dimethylamino group acts very nearly the same in the presence and in the absence of two adjacent bromo substituents.

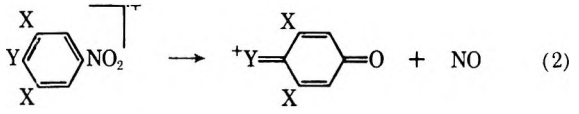
This study extends the analysis of substituent effects on ion intensities with a search for steric inhibition of resonance of the dimethylamino substituent by flanking groups. It was observed some years ago that relative intensities of the *m/e* 105 ion, presumably $C_6H_5CO^+$, in the spectra of singly substituted benzophenones can be correlated remarkably well with Hammett σ constants.[2] If the intensities of benzoyl ions in each spectrum $[A^+]$, divided by the intensities of the molecular ions from which they are formed $[M^+]$, are plotted as the ratio $Z = [A^+]/[M^+]$ against substituent constants, then eq 1 is obeyed very well, with a ρ value of

$$\log (Z/Z_0) = \rho\sigma \qquad (1)$$

1.01.[2] Other plots for data collected for other systems have been prepared;[3] sometimes a good correlation is obtained, sometimes not. More sophisticated arguments than the original kinetic interpretation[2] have now been advanced to explain these results,[4-8] and it now appears that the benzophenone system fits the Hammett equation so well because of the coincident magnitudes of many factors which influence reactivity in one of several ways: either the factors correlate well in Hammett plots, or else they are quite independent of Hammett constants and produce only a uniform influence on intensity, or else they have an effect tending to destroy the correlation but are insignificant when compared to the effects which tend to produce an overall correlation. Hence the benzophenone system should give a tight correlation because of an appropriate dependence of ionization potentials and appearance potentials on substituent constants, a proper distribution of ion energies after electron impact, and a lack of competing reactions which would tend to destroy the correlation, so that rates of processes and amounts of ions produced by decomposition reflect the fundamental effect of the substituents on electron density.

For singly substituted benzophenones the correlation is sufficiently good to be of excellent predictive value; ortho substituent effects derived from the mass spectra of ortho-substituted benzophenones[9] produce essentially the same Hammett-type constants as data for the same substituents obtained from gas-phase pyrolyses of esters.[10] Likewise, one can take advantage of the excellent correlation of singly substituted benzophenones to test the loss of correlation predicted for multiply substituted benzophenones as a result principally of the introduction of more reaction pathways competing with the formation of benzoyl ion.[11] It appears that, as expected, a loss of correlation does occur for doubly substituted benzophenones, but the standard deviation of points from the line does not increase so greatly as to preclude the extraction of information about fundamental substituent effects from an ion-intensity plot.

Consequently, it is possible to examine this well-behaved system for steric inhibition of resonance. Steric inhibition of resonance has been studied for another mass spectral reaction, eq 2, where the effect of



(2)

the para electron donor on the formation of the product ion is in keeping with stabilization of the daughter ion by resonance when X is H; the intensity of the ion increases markedly for Y = OH, OCH_3, NH_2, $N(CH_3)_2$.[12] On the other hand, when X is fairly large, a chloro or bromo substituent[13] or a methyl substituent[14] on either side of a very large para donor like the dimethylamino substituent should prevent stabilization of the product ion by resonance, since the electron donor should be twisted with respect to the plane of the ring, and, in fact, the relative intensity of the product ion is dramatically reduced for the hindered system.

It has been observed empirically that the stability of the product ion is a very important "driving force" in governing the intensities of product peaks in mass spectra.[5b,15] In the case of the nitrobenzenes, the substituents obviously play a very great role in this respect. We have now studied the benzophenone system, in which the stability of the product ion is not determined by a retained substituent in the ion. Thus we may ex-

(1) Research Fellow of the Alfred P. Sloan Foundation, 1969–1971. To whom correspondence should be addressed.

(2) M. M. Bursey and F. W. McLafferty, *J. Amer. Chem. Soc.*, **88**, 529 (1966).

(3) For a review, see M. M. Bursey, *Org. Mass Spectrom.*, **1**, 31 (1968).

(4) (a) R. P. Buck and M. M. Bursey, *ibid.*, **3**, 387 (1970); (b) M. M. Bursey and P. T. Kissinger, *ibid.*, **3**, 395 (1970); (c) M. M. Bursey and M. K. Hoffman, "Mass Spectrometry, 1970," G. W. A. Milne, Ed., Wiley, New York, N. Y., in press.

(5) (a) F. W. McLafferty, *Chem. Commun.*, 956 (1968); (b) F. W. McLafferty and M. M. Bursey, *J. Amer. Chem. Soc.*, **90**, 5299 (1968).

(6) (a) R. S. Ward, R. G. Cooks, and D. H. Williams, *ibid.*, **91**, 2727 (1969); (b) R. G. Cooks, I. Howe, and D. H. Williams, *Org. Mass Spectrom.*, **2**, 137 (1969).

(7) M. S. Chin and A. G. Harrison, *ibid.*, **2**, 1073 (1969).

(8) T. W. Bentley, R. A. W. Johnstone, and D. W. Payling, *J. Amer. Chem. Soc.*, **91**, 3978 (1969).

(9) K. K. Lum and G. G. Smith, *J. Org. Chem.*, **34**, 2095 (1969).

(10) G. G. Smith, K. K. Lum, J. A. Kirby, and J. Posposil, *ibid.*, **34**, 2090 (1969).

(11) M. M. Bursey and C. E. Twine, Jr., *ibid.*, **35**, 2012 (1970).

(12) M. M. Bursey and F. W. McLafferty, *J. Amer. Chem. Soc.*, **88**, 5023 (1966).

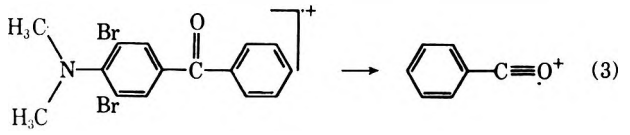
(13) M. M. Bursey, *ibid.*, **91**, 1861 (1969).

(14) M. M. Bursey and M. K. Hoffman, *ibid.*, **91**, 5023 (1969).

(15) F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, New York, N. Y., 1966, p 81.

pect that steric effects are likely to play a more subtle role than in the nitrobenzene system. For example, the removal of direct resonance interaction of the substituent and reaction site might limit the substituent effect approximately to its field or inductive effect. In this case, one might expect the substituent effect to resume that of the meta substituent, where the resonance effect is small and other interactions predominate.

The point of our experiment was to determine whether the regular ion intensity relationship for the m/e 105 ion observed in the mass spectrum of benzophenones[2,9,11] showed deviation from additivity when the dimethylamino group in the para position was blocked by ortho bromo substituents (eq 3). If there is signifi-


(3)

cant steric inhibition of resonance, it will be reflected in an *increase* in the production of m/e 105, for a decrease in electron-donor ability increases the amount of m/e 105 formed. The alteration in the substituent effect may be estimated by comparing the σ values of p-$N(CH_3)_2$ and m-$N(CH_3)_2$, -0.83 *vs.* -0.21, respectively.[16] Since substituent effects in this system are additive,[11] we may assume that the difference between these effects will hold irrespective of further substitution on the ring by the blocking groups. This is of course an oversimplification: the degree of resonance interaction of the dimethylamino group with the ring depends on the angle by which it is twisted out of the plane; the angle depends on the size of the blocking group. For our model, we assume a picture in which, as an extreme, the groups are sufficiently large to effectively remove the typical para resonance interaction.

Thus the alteration in intensities will be given by eq 4. The slope estimate from the correlation of mono-

$$\Delta \log (Z/Z_0) = \rho\Delta\sigma \qquad (4)$$

substituted benzophenones is 1.01;[2] from disubstituted, 0.77.[11] Hence, for alteration of the substituent effect to something approximated by the meta effect, there should be an increase in log Z by 0.48–0.62 log unit.

This increase is predicated upon the accurate prediction of intensities by the Hammett correlation. As we have noted,[11] when there is multiple substitution the scatter increases because of the increase in the number of decomposition routes competing with the production of $C_6H_5CO^+$ from the molecular ion. The standard deviation of points from the line for doubly substituted compounds is 0.15 log unit against σ, 0.06 log unit against σ^+; the standard deviation for singly substituted compounds using the same substituents is 0.06 against σ, 0.07 against σ^+. Thus the expected value of the change in log Z is much larger than the error introduced by the assumption that the substituent effects which tend to destroy the correlation for this fragmentation process are not important. The magnitude of 95% of all deviations from the expected values is, according to statistics, less than twice the standard deviation; consequently, so large a change in log Z, if observed, can be ascribed with high confidence to an alteration in the substituent effect involving electron distribution (*e.g.*, the σ constant for the substituent), not to some other phenomenon such as the introduction of competitive processes, gross alteration of the distribution of energy states, and so forth. In short, interpretation of results is feasible.

(16) The σ values were taken from the tabulation of C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 323 (1964).

Experimental Section

Preparation of Benzophenones.—The compounds were either commercially available or else produced by literature procedures.[17-19] The only new compound was **3,5-dibromo-4-dimethylaminobenzophenone**, which was prepared by the methylation of 4-amino-3,5-dibromobenzophenone[17] with trimethyl phosphate at 60° for 8 hr,[20] and purified by column and thin layer chromatography, after which it had mp 97–98°. It tends to decompose on silica.

Anal. Calcd for $C_{15}H_{13}Br_2NO$: C, 47.04; H, 3.39; monoisotopic mol wt, 380.9363. Found: C, 46.97; H, 3.23; mol wt, 380.9361.

The purity of all samples was checked by agreement of their melting point with reported values and/or thin layer chromatographic homogeneity. If apparent decomposition on the tlc plate was observed (recovered single bands from tlc giving, on repeated chromatography, multiple bands identical with the previous chromatogram), the identity and purity of the desired band were checked by other means. The analytical sample of the 3,5-dibromo-4-dimethylaminobenzophenone was used for the mass spectra, since its purity was crucial.

Mass Spectra.—All the mass spectra were recorded on a Hitachi RMU-6E single-focusing instrument, using 75-eV electrons (emission current 80 μA). The source pressure was always in the range $5-10 \times 10^{-7}$ Torr, with a source temperature at 185 ± 5°. Samples were introduced by the direct-insertion probe, because the data for samples introduced by the heated inlet at 185 ± 5° gave indication of some thermal decomposition, especially for the dibromohydroxy and dibromomethoxy compounds.[21] The reproducibility of peak height ratios was at least 3% for quadruplicate determinations and usually much better (1%).

Results and Discussion

Our results for the "unblocked" and "blocked" compounds are listed in Table I. Their correlation with

TABLE I

RELATIVE INTENSITIES OF $C_6H_5CO^+$ (m/e 105) IN MASS SPECTRA OF SUBSTITUTED BENZOPHENONES

Substituent	Registry no.	Log Z/Z_0	$\Sigma\sigma$[a]	$\Sigma\sigma^+$[a]
4-OH	1137-42-4	−0.27	−0.37	−0.92
4-OCH_3	611-94-9	−0.33	−0.27	−0.78
4-NH_2	1137-41-3	−0.79	−0.66	−1.3
4-$N(CH_3)_2$	530-44-9	−0.47	−0.83	−1.7
3,5-Br_2-4-OH	26733-16-4	+0.29	+0.41	−0.12
3,5-Br_2-4-OCH_3	26733-17-5	+0.50	+0.51	+0.02
3,5-Br_2-4-NH_2	26733-18-6	−0.20	+0.12	−0.5
3,5-Br_2-4-$N(CH_3)_2$	26785-60-3	−0.68	−0.05	−0.90

[a] See ref 16.

substituent constants are illustrated in the figures. Figure 1 shows a plot of relative intensities *vs.* the sum of Hammett σ constants for both the monsubstituted

(17) L. Clarke and G. J. Esselen, Jr., *J. Amer. Chem. Soc.*, **33**, 1135 (1911).

(18) P. J. Montagne, *Recl. Trav. Chim. Pays-Bas*, **41**, 703 (1922).

(19) *Cf.* G. N. Vyas and N. M. Shah, "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed, Wiley, New York, N. Y., 1963, p 836.

(20) *Cf.* J. H. Billman, A. Radike, and B. W. Mundy, *J. Amer. Chem. Soc.*, **64**, 2977 (1942).

(21) There was a small variance in several data points for the disubstituted benzophenones introduced by the direct probe from values reported earlier.[11] The change in the position of points was just outside experimental error, no new trends for these points were noted, and the quantitative conclusions reached earlier[11] are still valid.

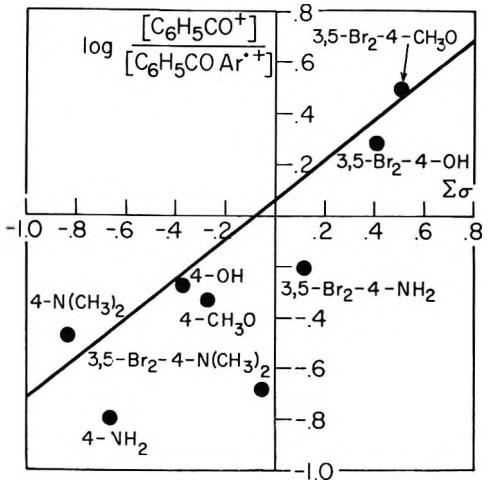


Figure 1.—Correlation of log (Z/Z_0) with σ and $\Sigma\sigma$ for the formation of $C_6H_5CO^+$ from unhindered and hindered benzophenones.

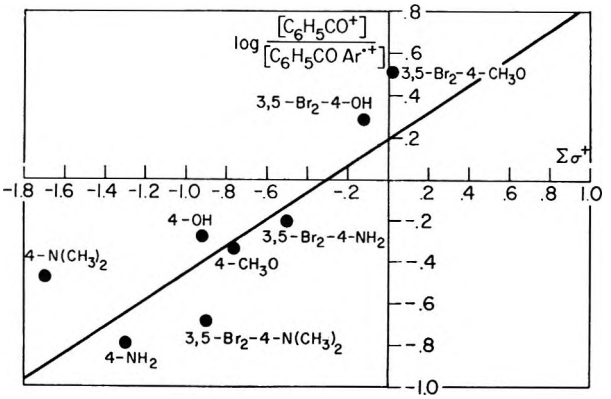


Figure 2.—Correlation of log (Z/Z_0) with σ^+ and $\Sigma\sigma^+$ for the formation of $C_6H_5CO^+$ from hindered and unhindered benzophenones.

and trisubstituted compounds; Figure 2 shows the same data points *vs.* the sum of σ^+ constants. We plot both monosubstituted and trisubstituted compounds in the same graph because the substituent effects are additive,[11] the bromo substituents affecting the orientation only of the dimethylamino group, and because we wish to illustrate at once the behavior of the key substituent, dimethylamino, when it is flanked by large substituents and when it is not. The correlation lines are determined with the exclusion of the point for the dibromodimethylamino compound; only compounds where there can be no steric effect influence the position of the line. Thus the line is not influenced by the dibromodimethylamino compound, the one point whose deviation from the line is the crux of this analysis.

For Figure 1, the plot *vs.* σ values, the slope is 0.78, the standard deviation of seven points from the correlation line is 0.17 log unit, and the correlation coefficient is 0.913. The slope is in reasonable agreement with the value of 1.01 for monosubstituted benzophenones and 0.77 for disubstituted benzophenones. The correlation coefficient is nearly the same as that found for the disubstituted compounds earlier, 0.918,[11] though it might be expected to decrease as a result of less sampling of data in this graph. The standard deviation is larger than the values of 0.09 and 0.15 obtained for monosubstituted and disubstituted compounds earlier.[11]

For Figure 2, the plot *vs.* σ^+ values, the slope is 0.63, the standard deviation of seven points from the correlation line is 0.24, and the correlation coefficient is 0.884. The value of the slope may be compared with values of 0.66 and 0.55 for the slopes of correlation lines found for the monosubstituted[2] and disubstituted[11] benzophenones plotted *vs.* σ^+ constants. As expected from the smaller sampling of data, there is a decrease in the correlation coefficient relative to that for the plot of disubstituted compound values *vs.* σ^+ (0.956) and an increase in standard deviations from previous[11] values (0.11, 0.06). Hence the deviation of data points from predicted values, *i.e.*, points on the correlation line, is in rather good accordance with what was expected.

We are now in a position to comment on the placement of the dibromodimethylamino point on these graphs. The deviation from the correlation line in Figure 1 is −0.70 log unit; in Figure 2 it is −0.29 log unit. The strong inhibition of resonance described earlier would have been expected to raise the point above the line by 0.48 to 0.62 log unit; one may even argue that since the log Z/Z_0 values for the single substituent *m*-Br is also above the correlation line for single substituents,[2] additivity of substituent effects requires that the point should actually be raised even more than 0.48 to 0.62 log unit. Quite obviously the deviation from the correlation line is not so positive as this picture predicts. To a first approximation, then, the picture is invalid.

Considering now the standard deviation of the data in these plots and others previously cited, we find it unlikely that the results can be explained away by two compensating effects, one an increase in the true substituent effect on the reaction in question and the other an opposite variation in intensity resulting from the introduction of new reaction pathways and distortion of energy distributions. The statistics argue strongly against so large a variation due to other causes. The amount by which log (Z/Z_0) would have to be lowered to compensate for so large an increase in the true substituent effect (0.48 to 0.62 log unit), and also lower the point to its actual position below the line, exceeds the standard deviation of the data by more than four times the standard deviation of data points for comparable systems, and must therefore correspond to a situation which exists less than one time in five thousand. The more reasonable picture is that there is in fact very little steric inhibition of resonance of the dimethylamino group by the bromo substituents flanking it in this system; if there is any change in the effect of the dimethylamino group, it is less than can be detected because of statistical problems. Thus more resonance interaction remains in the system than the meta-substitution analogy can approximate, and indeed the para-substitution analogy still predicts results fairly well.

We note that there is a parallel between these results, where the resonance effect of the dimethylamino group cannot be diminished by attempts at twisting it, and the previously reported case of the *p*-phenyl substituent in the benzophenone system.[2] A very strong resonance effect, greater than nearly all solution cases, was noted there in the formation of *m/e* 105, and it was attributed to the ability of the *p*-phenyl substituent to achieved coplanarity with the substituted ring in the molecular ion more easily, since blocking by ortho hydrogens was

apparently very easily overcome. We are continuing our studies by examining the effect of other, larger ortho substituents on the resonance effect of the *p*-phenyl substituent in benzophenones.

In comparison with the result for the hindered nitrobenzenes,[13,14] these two results are startling. In the nitrobenzenes, where one begins with a system without much resonance interaction between substituent and reaction center and produces an ion where resonance stabilization is important, steric inhibition of resonance is easily achieved by flanking groups. Now juxtaposed to this system we have a case where resonance demand is lost in the product ion, yet as measured by substituent effects flanking substituents seem unable to decrease resonance interaction substantially. This latter case is of course one in which the number of free rotors increases throughout the progress of the reaction, while the nitrobenzene rearrangement involves a decreasing number of rotors as the quinonoid ion is formed in the initial stages of the reaction. In the statistical treatment,[22] the energy dependence of rates (and therefore ultimately ion intensities) is then different for the two cases. Even so, it is difficult to draw a fully consistent picture. Apparently resonance effects remain important in spite of blocking in simple cleavages like the formation of *m/e* 105 in benzophenones, fast reactions on the average, but can be blocked in at least some rearrangements, like the nitrobenzene rearrangement, which are on the average several orders of magnitude slower. Perhaps this implies that steric inhibition of resonance takes time to become effective, as if ionization on the nitrogen atom in both systems (or the first transmittal of energy to this site of lowest energy) produces at first a nonequilibrium set of states in which there is enough vibrational energy associated with the dimethylamino group to force a more nearly planar configuration of the substituent and the ring, but then over several hundred vibrational periods equilibrium among vibrational modes over the whole molecule is achieved, and the substituent then no longer can so easily achieve such a small average dihedral angle with the ring.

(22) H. M. Rosenstock, *Advan. Mass Spectrom.*, **4**, 523 (1968), and references contained therein.

Acknowledgments.—We thank the University Research Council of the University of North Carolina at Chapel Hill for help in supporting this work.

Cleavage of α,α'-Dinitrocyclanones

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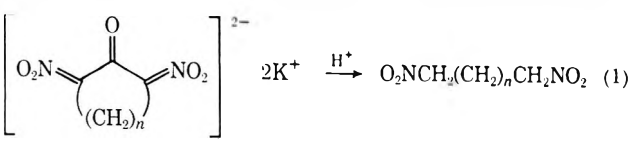
Received April 27, 1970

In aqueous medium at the appropriate pH, potassium salts of α,α'-dinitrocyclanones undergo ring cleavage to the corresponding α,ω-dinitroalkanes in high yield. In methanolic acetic acid, cleavage proceeds without decarboxylation to α,ω-dinitroalkyl methyl esters.

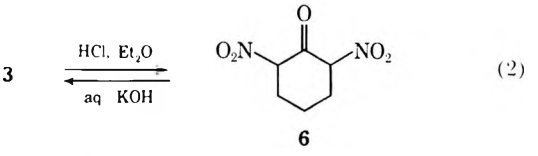
In a preliminary report,[1] we communicated a new ring-opening reaction of potassium 2-keto-3-nitrocycloalkanenitronates which provides a convenient route for the preparation of α,ω-dinitroalkanes. These salts were obtained directly from alkyl nitrate nitration mixtures[2] after acidification with glacial acetic acid and, therefore, were contaminated with potassium acetate. We are now reporting on the results of the reaction with the analytically pure salts, dipotassium 2-keto-1,3-cyclopentanedinitronate (**1**), potassium 2-keto-3-nitrocyclopentanenitronate (**2**), dipotassium 2-keto-1,3-cyclohexanedinitronate (**3**), potassium 2-keto-3-nitrocyclohexanenitronate (**4**), and dipotassium 2-keto-1,3-cycloheptanenitronate[3] (**5**) (eq 1). The purity of these



salts was conveniently determined by nonaqueous titration.[4]

The pure mononitronate salts **2** and **4** were obtained on acidifying aqueous solutions of the corresponding dinitronate salts[3] **1** and **3** at 0° with acetic acid. Compound **4** was also obtained on treating **3** with methanolic glacial acetic acid at 25°. This procedure was not applicable for the preparation of **2** because of its high solubility in methanol.

The high purity of **3** was demonstrated by the fact that it was converted in 93% yield to 2,6-dinitrocyclohexanone (**6**) upon treatment with hydrogen chloride in an ether suspension. Compound **6** was purified by sublimation *in vacuo* and, contrary to a previous report,[5] readily gave a 2,4-DNP derivative in 90% yield. **6** was reconverted into **3** on treatment with aqueous potassium hydroxide (eq 2).



α,ω-Dinitroalkanes.—The results of hydrolytic cleavage of compounds **1**–**6** leading to α,ω-dinitroalkanes are summarized in Table I. At about the same pH, the disalts **1** and **3** gave 1,4-dinitrobutane (**7**) and 1,5-dinitropentane (**8**), respectively, in the same yields as the monosalts **3** and **4**, except that 2 molar equiv of acid was required. However, a significant difference between **1** and **3** was observed on treatment with acetic

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(1) H. Feuer and R. S. Anderson, *J. Amer. Chem. Soc.*, **83**, 2960 (1961).

(2) H. Feuer, J. W. Shepherd, and C. Savides, *ibid.*, **78**, 4364 (1956).

(3) H. Feuer, A. M. Hall, S. Golden, and R. L. Reitz, *J. Org. Chem.*, **33**, 3622 (1968).

(4) H. Feuer and B. F. Vincent Jr., *Anal. Chem.*, **35**, 598 (1963).

(5) H. Wieland, P. Garbsch, and J. J. Chavan, *Justus Liebigs Ann. Chem.*, **461**, 295 (1928).

acid (pH 5). Compound **1** was converted to monosalt **2** in 95.5% yield while **3** was cleaved to **8** in 88% yield. On the other hand at pH ~6 disalt **5** afforded 1,7-dinitrohexane in 91% yield.[3]

The dependence of pH on ring size in the cleavage reaction was also apparent with the monosalts **2** and **4** (Table I).

TABLE I

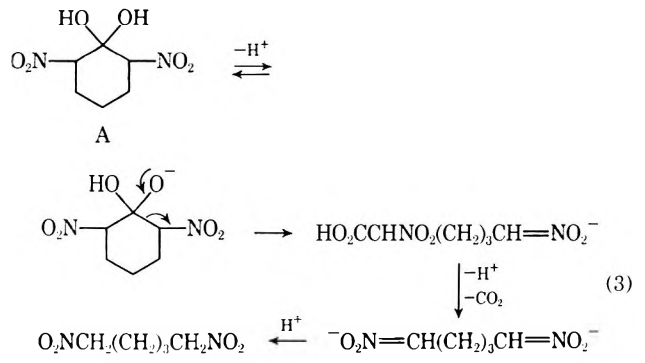
AQUEOUS ACIDIC CLEAVAGE OF POTASSIUM SALTS OF α,α'-DINITROCYCLANONES AND α,α'-DINITROCYCLOHEXANONE TO α,ω-DINITROALKANES[a]

Compd	Acid (equiv)	Initial pH	Final pH	Time, hr	α,ω-DNA,[b] yield, %
1	H_2SO_4 (1.0)	3.5	4.0	5	61.0
1	HCO_2H (2.0)	3.5	4.0	5	82.7
1[c]	CH_3CO_2H (2.0)	5.0	5.0		*d*
2	H_2SO_4 (0.5)	3.5	4.0	5	64.1
2	HCO_2H (1.0)	4.0	5.0	4	84.2
3[e]	H_2SO_4 (2.0)	1.0	1.0	1	*f*
3	H_2SO_4 (1.0)	4.0	4.0	12	70.9
3	CH_3CO_2H (2.0)	5.0	6.0	12	88.1
4	CH_3CO_2H (1.0)	5.0	6.0	12	90.2
4	CO_2 (excess)	6.0	7.0	12	90.5
5[g]	Picolinic (<2.0)	6.0	6.0	12	90.9
6	H_2SO_4 (1.0)	2.0	3.0	12	37.4[h]
6	*i*	3.0	4.0	12	89.1

[a] In all experiments the reaction temperature was 25° unless noted otherwise. [b] DNA, dinitroalkane. [c] The reaction was carried out at 3° for 1 hr and then at 25° for 3 hr. [d] A 95.5% yield of compound **2** was obtained. [e] The reaction temperature was 3°. [f] Compounds **6** (50.6%) and **3** (23.4%) were obtained, the latter after basifying the aqueous layer with potassium hydroxide. [g] See ref 3. [h] There were also obtained **6** (19.4%) and **3** (11.2%). [i] The reaction was carried out in water and the initial pH was taken after a homogeneous solution was obtained (1 hr).

When disalt **3** was treated with sulfuric acid at pH 1 at 3°, the cleavage reaction was exceedingly slow and 74% of **3** was accounted for as uncleaved. Extraction of the aqueous reaction mixture with ether gave 50.6% of **6**. Neutralization of the aqueous layer with potassium hydroxide led to a 23.4% recovery of **3**. Similarly, cleavage of **6** was retarded with sulfuric acid at pH 2–3 because only 37.4% **8** was obtained. On the other hand, compound **6** was cleaved to **8** in 89% yield in water alone.[6]

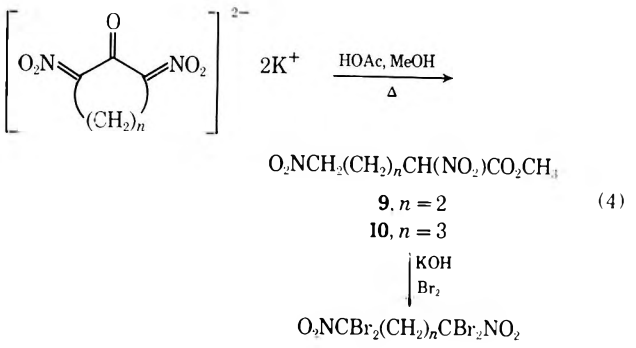
The retardation of the cleavage reaction of α,α'-dinitro ketones at low pH can be readily understood if one postulates[7,8] that the cleavage proceeds *via* an anion formed from a hydrated species "A" through the loss of a proton (eq 3).



(3)

(6) The monosalts **2** and **4** also underwent cleavage in water, in an apparent disproportionation reaction, to give approximately equal amounts of the corresponding α,ω-dinitroalkanes **7** and **8** and disalts **1** and **3**.

α,ω-Dinitroalkyl Esters.—Compounds **1**, **3**, and **6** were cleaved in refluxing methanolic acetic acid without decarboxylation to give, respectively, methyl 2,5-dinitropentanoate (**9**) and methyl 2,6-dinitrohexanoate (**10**) in yields of about 65% (eq 4).[9] The cleavage reaction was also successful with compound **5** as ascertained from infrared and nmr spectra of the crude reaction product. However, attempts to purify the crude ester by glpc or vacuum distillation led to decomposition. The structure of **9** and **10** was confirmed by spectral data and by conversion to the corresponding $\alpha,\alpha,\omega,\omega$-tetrabromo-$\alpha,\omega$-dinitroalkanes on treatment with bromine in alkaline medium (eq 4).



(4)

Compounds **9** and **10** were found to be relatively strong pseudo acids. This property was rather well illustrated by the fact that treating disalt **3** with an equivalent amount of **10** at 25° in anhydrous methanol gave a 96% yield of monosalt **4** and a 90% yield of the monopotassium salt of **10**.

Experimental Section

Potassium 2-Keto-3-nitrocyclopentanenitronate (2).—A solution of dipotassium 2-keto-1,3-cyclopentanedinitronate[3] (**1**) (3.69 g, 14.7 mmol) in 10 ml of water was cooled to 0° and 3 ml of glacial acetic acid was added all at once. Filtering the mixture after 10 min and drying *in vacuo* gave 2.41 g (77.5%) of tan **2**:[10] explosion point 152° (lit.[5] explosion point 154–158°); neutralization[4] equivalent found, 211 (calcd, 212); ir (Nujol) 1645 (C=O), 1658 (C=N), 1550 and 1357 (NO_2), and 1232 and 1160 cm^{-1} (NO_2^-); nmr (DMSO-d_6) δ 5.25 (t with spacing of 7 Hz, 1, $CHNO_2$) and 2.60 (m, 4, CH_2); uv max (95% C_2H_5OH) 212 mμ (log ϵ 3.70), 248 (3.53), 357 (4.14), and 405 (3.58); uv max (H_2O) 224 mμ (log ϵ 3.62), 250 (3.57), and 402 (4.37).

Potassium 2-Keto-3-nitrocyclohexanenitronate (4). A. From Compound 3 and Acetic Acid.—The procedure was similar to that described for **2** except that compound **3**[3] (3.36 g, 15 mmol) was used.

Drying the red solid *in vacuo* gave 1.655 g (92.8%) of **4**:[10] explosion point 214° (lit.[5] explosion point 221°); neutralization equivalent found, 227 (calcd, 226); ir (Nujol) 1651 (C=O), 1658 (C=N), 1534 and 1370 (NO_2), and 1227 and 1152 cm^{-1} (C=NO_2^-); nmr (DMSO-d_6)[11] δ 2.60 (m, 4, $CH_2C{=}NO_2^-$ and CH_2-$CHNO_2$) and 1.70 (m, 2, $CH_2CH_2CH_2$); uv max (95% C_2H_5OH) 214 mμ (log ϵ 3.52), 269 (3.58), and 422 (4.29); uv max (H_2O) 233 mμ (log ϵ 3.37) and 386 (4.35).

B. From Compound 3 and Methyl 2,6-Dinitrohexanoate (10).—To a suspension of **3** (0.676 g, 2.56 mmol) in 60 ml of anhydrous methyl alcohol was added **10** (0.564 g, 2.56 mmol).

Stirring for 1 hr at room temperature and filtering gave 0.556 g (96.0%) of **4**, explosion point 213°.

(7) R. G. Pearson, D. H. Anderson, and L. L. Alt, *J. Amer. Chem. Soc.*, **77**, 527 (1955).

(8) H. Feuer and P. M. Pivawer, *J. Org. Chem.*, **34**, 2917 (1969).

(9) Cleavage of **1** and **3** in anhydrous methanolic hydrogen chloride and of **6** in anhydrous methyl alcohol was found to be slow and gave considerable amounts of starting material. No convenient method was found to separate these from the cleavage products.

(10) No suitable solvent for recrystallization could be found.

(11) The α hydrogen exchanged with the solvent.

Evaporating the filtrate *in vacuo* and slurrying the remaining paste with ether gave after filtering and drying 0.595 g (89.9%) of **potassium 1-carbomethoxy-5-nitropentanenitronate**: mp 132–135° dec; neutralization equivalent found, 253 (calcd, 258); ir (Nujol) 1688 (C=O), 1664 (C=N), 1555 and 1381 (NO_2), and 1255 and 1110 cm^{-1} ($C{=}NO_2^-$); nmr (D_2O) δ 4.59 (m, CH_2NO_2), 3.73 (s, 3, OCH_3), 2.60 (m, 2, $CH_2C{=}NO_2^-$), and 1.75 (m, 4, CH_2); uv max (H_2O) 294 mμ (log ϵ 3.94).

2,6-Dinitrocyclohexanone (6).—Hydrogen chloride was introduced for 1 hr at room temperature into a suspension of disalt **3** (1.437 g, 5.44 mmol) in 200 ml of anhydrous ether. After stirring for an additional 2.5 hr at room temperature, the mixture was filtered and the filtrate was evaporated *in vacuo*. Washing the residue with ether and drying *in vacuo* gave 0.94 g (93.5%) of **2,6-dinitrocyclohexanone (6)**: mp 100–101° (lit.[5] mp 110.5°); ir (Nujol) 1748 (C=O) and 1570 and 1379 (NO_2); nmr (DMSO-d_6) δ 6.10 (m, 2, $CHNO_2$) and 2.3 (m, 6, CH_2); nmr (CH_2Cl_2)[12] δ 5.25 (m, $CHNO_2$), 12.72 (s, OH), and 2.22 (m, CH_2); uv max (CH_3OH) 228 mμ (log ϵ 3.70), 259 (3.63), 321 (3.53), and 422 (4.21).

Anal. Calcd for $C_6H_8N_2O_5$: C, 38.30; H, 4.26; N, 14.90. Found: C, 38.56; H, 4.54; N, 14.94.

2,4-DNP derivative of 6 showed mp 162° dec, ethanol–ethyl acetate; ir (Nujol) 1620 (C=N) and 1560 and 1553 cm^{-1} (NO_2).

Anal. Calcd for $C_{12}H_{12}N_6O_8$: C, 39.13; H, 3.26; N, 22.83. Found: C, 39.26; H, 3.20; N, 22.02.

1,4-Dinitrobutane (7). A. From Compound 1.—To a solution of **1** (2.53 g, 10.1 mmol) in 60 ml of water (pH 7.9) was added 85% formic acid (1.105 g, 20.4 mmol) all at once (pH 3.5). After this had stirred for 5 hr at room temperature the pH was 4.3.

Extracting the solution with ether, evaporating the combined extracts *in vacuo*, and recrystallizing the residue from 95% ethanol gave 1.231 g (82.7%) of compound **7**, mp 30–31° (lit.[13] mp 31–32°).

B. From Compound 2.—By following a similar procedure as described in part A, 1.374 g (6.48 mmol) of **2** and 0.352 g (6.5 mmol) of 85% formic acid afforded 84.2% **7**.

1,5-Dinitropentane (8). A. From Compound 3.—From 2.64 g (9.98 mmol) of **3** and 1.205 g (20.1 mmol) of glacial acetic acid there was obtained 1.423 g (88.1%) of compound **8**: bp 92–93° (0.01 mm); $n^{20}D$ 1.4600 (lit.[13] $n^{20}D$ 1.4601).

B. From Compound 4.—Introducing carbon dioxide for 12 hr into 2.208 g (9.8 mmol) of **4** dissolved in water gave 1.442 g (90.5%) of **8**.

C. From Compound 6.—From 0.605 g (3.3 mmol) of **6** dissolved in 60 ml of water there was obtained 0.475 g (89.1%) of **8**.

Methyl 2,5-Dinitropentanoate (9).—To a suspension of compound **1** (3.20 g, 12.8 mmol) in 80 ml of methanol was added glacial acetic acid (3.84 g, 64 mmol). After the mixture refluxed for 12 hr at 65° the resulting solution was concentrated *in vacuo*, the residue was taken up in ether, and the precipitated potassium acetate was filtered off. Concentrating the filtrate *in vacuo* gave 1.76 g (66.7%) of **methyl 2,5-dinitropentanoate**: bp 130–132° (0.28 mm); $n^{20}D$ 1.4634; ir (Nujol) 1748 (C=O) and 1575, 1567, and 1374 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 5.28 (t with spacing of 6 Hz, 1, $CHNO_2$), 4.52 (m, 2, CH_2NO_2), 3.88 (s, 3, CH_3), and 2.28 (m, 4, CH_2); uv max (CH_3OH) 284 mμ (log ϵ 2.18).

Anal. Calcd for $C_6H_{10}N_2O_6$: C, 34.95; H, 4.85; N, 13.60. Found: C, 34.97; H, 4.61; N, 13.69.

Treating **9** (0.485 g, 2.35 mmol) with aqueous potassium hypobromite gave 0.834 g (76.5%) of 1,1,4,4-tetrabromo-1,4-dinitrobutane, mp 99–100° (hexane) (lit.[2] mp 99–100°).

Methyl 2,6-Dinitrohexanoate (10).—The procedure similar to that described for **9**, except that 2.12 g (8 mmol) of **3** was used, afforded 1.15 g (65.2%) of **methyl 2,6-dinitrohexanoate**: bp 138–140° (0.3 mm); $n^{20}D$ 1.4630; ir (Nujol) 1770 (C=O), and 1575, 1558, and 1380 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 5.19 (t with spacing of 7 Hz, 1, $CHNO_2$), 4.43 (m, 2, CH_2NO_2), 3.86 (s, 3, CH_3), and 2.10 (m, 6, CH_2); uv max (CH_3OH) 268 mμ (log ϵ 1.96).

Anal. Calcd for $C_7H_{12}N_2O_6$: C, 38.18; H, 5.45; N, 12.73. Found: C, 38.46; H, 5.55; N, 12.86.

Registry No.—**1**, 12286-73-6; **2**, 26717-79-3; **3**, 12286-74-7; **4**, 26785-71-7; **6**, 26785-72-8; **6**, 2,4-DNP derivative, 26736-24-3; **7**, 4286-49-1; **8**, 6848-84-6; **9**, 26736-27-6; **10**, 26074-70-4; 1-carbomethoxy-5-nitropentanenitronate, 26736-29-8.

Acknowledgment.—We are indebted to the Office of Naval Research for the financial support of the work.

(12) By integration of signal areas it was estimated that in this solvent, **6** was enolized to the extent of 75%.

(13) H. Feuer and G. Leston, *Org. Syn.*, **34**, 37 (1954).

The Stereochemistry of Halogenation of Cyclohex-4-ene-1,2-dicarboxylic Acids

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Received April 22, 1970

trans-Cyclohex-4-ene-1,2-dicarboxylic acid gives on bromination the product of trans-diaxial addition. A product of similar stereochemistry is obtained on reacting the same acid with bromine chloride. The cis diacid yields with bromine chloride a trans-addition product with the bromine cis to the carboxyl group. It is inferred that the cis acid forms a bromomium ion cis to the carboxyl group. A series of halolactones can be prepared from the halogenated compounds. *cis,cis*-3-Phenylcyclohex-4-ene-1,2-dicarboxylic acid, its salt, and mono- and dimethyl ester give direct lactonization on treatment with bromine.

Remote polar substituents exert an influence on the rates[1] and the steric course of electrophilic addition to cyclohexenes.[2] The electrophile enters generally trans to an electron-withdrawing substituent,[2] but a cis epoxidation of the anhydride of I was observed.[3] This was ascribed to the boat conformation of this anhydride[3] or to a complex formation with the peracid,[2] in view of the different steric course of the epoxidation of the ester I.[2]

Halolactonization of cyclohexene-1- and -2-acetic acids gave *cis*-γ-lactones with the halogen trans to the lactone ring.[4] The reason for this stereospecificity could have been a result of a stereospecific halonium ion formation trans to the carboxylate group or simply a consequence of the unreactivity of the cis halonium ion with the carboxylate group in the side chain, due to the strain that would be created by formation of a trans lactone. The *cis*-halonium ion would in this case revert to the olefin, which could then yield a reactive *trans*-halonium ion. Bromination of cyclohex-3-enecarboxylic

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(1) H. Kwart and L. J. Miller, *J. Amer. Chem. Soc.*, **83**, 4552 (1961).

(2) H. B. Henbest, *Proc. Chem. Soc.*, 159 (1963).

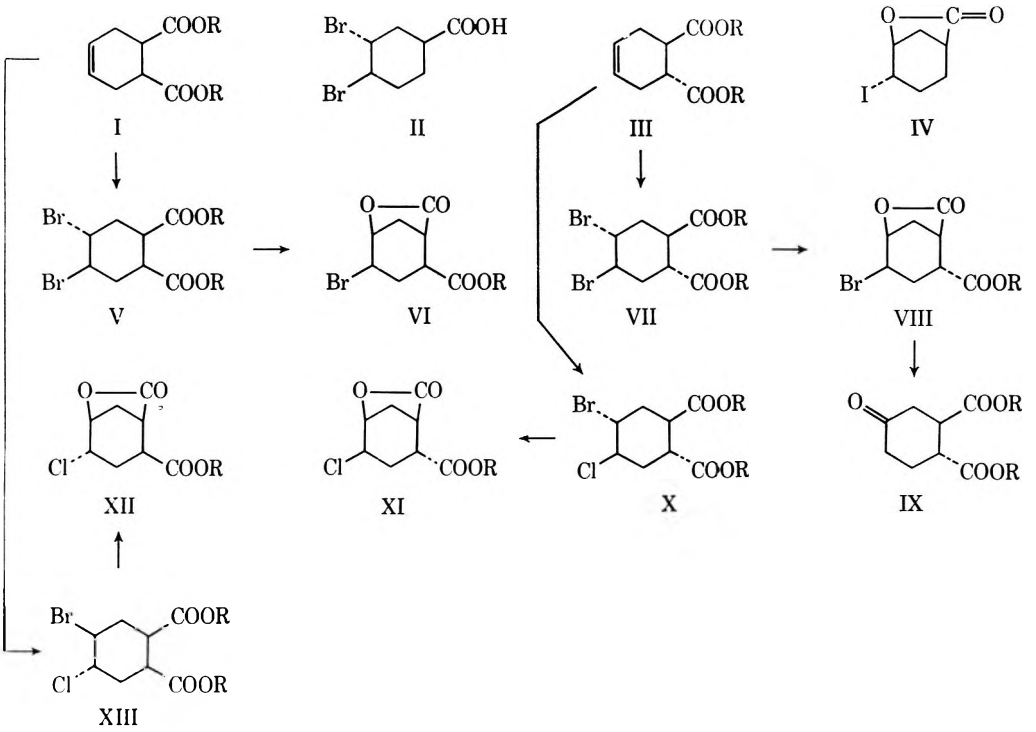
(3) A. P. Gray, D. E. Heitmeier, and H. Krauss, *J. Amer. Chem. Soc.*, **84**, 89 (1962).

(4) J. Klein, *ibid.*, **81**, 3611 (1959).

acid gave only one isomer (II) of the possible adducts.[5,6] However, no conclusions can be drawn on the specificity of the bromonium ion formation, since any of these, either cis or trans, would give the same product by trans-diaxial opening[7-10] if the carboxyl maintained an equatorial conformation during the reaction. Symmetric halogens are therefore of no use in solving this problem. We decided, therefore, to study the addition of bromine chloride to *trans*-IIIa and *cis*-cyclohex-4-ene-1,2-dicarboxylic acid (Ia). The dicarboxylic acids were chosen to diminish the number of possible adducts. Addition of bromine chloride to cyclohexenes and steroids was already found to proceed in a trans-diaxial manner[11-13] through a chair-like transition state.[10,11,13,14] A preliminary attempt to react cyclohex-3-enecarboxylic acid with iodine chloride has shown the unsuitability of this reagent for our study, since the obtained chloroiodo adduct[15] gave on treatment with sodium bicarbonate the known[5] iodolactone IV. This compound could be obtained only by a reversal of the chloroiodo compound either to the iodonium ion or to the starting olefin with subsequent trans iodolactonization.

The halogenations were carried out also with the methyl esters Ib and IIIb and with the corresponding anhydrides. The structures of the halogenated products obtained from the acids were determined by heating with triethylamine (1 equiv to each carboxyl group) in 1,2-dimethoxyethane (DME). It was assumed that the lactones obtained in this reaction are a product of an intramolecular substitution by the carboxylate of the halogen trans to this group. This assumption seems to be correct, since lactonization in these conditions of Va, obtained[16] by bromination of Ia, gave the same lactone VIa as obtained previously in aqueous base solution.[16]

Bromination of IIIa gave the dibromo derivative VIIa. This compound gave on lactonization the bromolactone VIIIa, characterized by its nmr spectrum[17] and by its reaction with base, that gave the known[18] keto diacid IX. Similarly, the reaction of IIIa with bromine chloride gave a product to which the structure Xa was assigned, since the usual base treatment gave the lactone XIa, characterized by its nmr[17] and ir spectrum. Treatment of IIIb with bromine or bromine chloride gave the esters VIIb and Xb, respectively. It is of interest that no isomers of VII or X were found in the halogenations of III and its esters. It seems that the opening of the bromonium ion, though not the rate-determining step in these reactions,[19-21] is the product determining one. A different isomer in a diaxial reaction could be obtained only when the carboxyls occupy axial positions in the transition state. Such a transition state would develop two diaxial bromine–carboxyl interactions making it of



a, R = H
b, R = CH_3

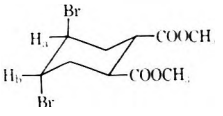
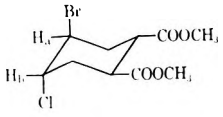
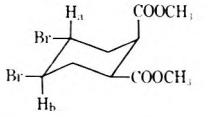
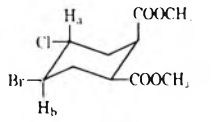
(5) R. Creve, A. Heinke, and Ch. Sommer, *Chem. Ber.*, **89**, 1978 (1956).
(6) Another isomer (*ca.* 5%) was also formed. Our unpublished results.
(7) D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.*, **72**, 1066 (1950).
(8) D. H. R. Barton and W. Rosenfelder, *J. Chem. Soc.*, 1048 (1951).
(9) G. Alt and D. H. R. Barton, *ibid.*, 4284 (1954).
(10) R. L. Eliel and R. S. Haber, *J. Org. Chem.*, **24**, 143 (1959).
(11) D. H. R. Barton, E. Miller, and H. T. Young, *J. Chem. Soc.*, 2598 (1951).
(12) J. G. Ziegler and A. C. Shabica, *J. Amer. Chem. Soc.*, **74**, 4891 (1952).
(13) H. J. Hageman and E. Havinga, *Rec. Trav. Chim. Pays-Bas*, **85**, 1141 (1966).
(14) J. Valls and E. Toromanoff, *Bull. Soc. Chim. Fr.*, 758 (1961).
(15) Our unpublished results.
(16) V. R. Kutcherov, A. L. Shabanov, and A. S. Onishenko, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 844 (1963); A. S. Onishenko, A. L. Shabanov, and V. R. Kucherov, *ibid.*, 852 (1963).
(17) E. Dunkelblum and J. Klein, *Tetrahedron Lett.*, 55 (1968).
(18) P. C. Ayres and R. A. Raphael, *J. Chem. Soc.*, 1779 (1958).
(19) R. E. Buckles, J. L. Miller, and R. J. Thurmaier, *J. Org. Chem.*, **32**, 888 (1967).
(20) R. P. Bell and M. Pring, *J. Chem. Soc. B*, 1119 (1966).
(21) J. H. Rolston and K. Yates, *J. Amer. Chem. Soc.*, **91**, 1483 (1969).

much higher energy relative to that with equatorial carboxyls, although a nonnegligible amount of the conformer with axial carboxyls[22] is present in III.

The reaction of Ia with bromine chloride gave, in good yield, a single diacid contaminated with a small amount of a lactone. Products of similar stereochemistry were obtained in this reaction with the dimethyl ester and anhydride of I, as shown by the interconversion of all these products. Base treatment of the adduct formed from Ia gave, unexpectedly, the chlorolactone XIIa, whose methyl ester XIIb was characterized by nmr.[17] This lactone, *i.e.*, XIIb, was of different stereochemistry from the lactone VIb obtained[16] from the product Va of bromination of Ia. The nmr spectrum in chloroform of the methyl ester of the product of reaction of Ia with bromine chloride was inconclusive but in pyridine and particularly in benzene the hydrogens α to the halogens (Table I) showed coupling constants, proving their diaxial anti conformation[23] and consequently the trans arrangement of the halogens. One of the α protons appeared at 100 MHz in the latter solvent as a septet (degenerate octet) with coupling constants of 12, 8, and 4 Hz (τ 5.84), and the other (τ 6.19) as a more involved multiplet with a width of the band similar to that of the first α proton (Figure 1). The structure of the ester is therefore XIIIb and this ester is present predominantly in one conformation, since the other possible conformation has a diaxial bromine–ester interaction. The esters VIIb and Xb are apparently also predominantly in a conformation with equatorial ester groups.

TABLE I

NMR SPECTRA OF HALO ESTERS AT 60 MHz

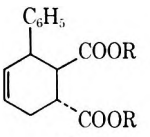
Ester	In pyridine, H_a,H_b	In benzene, H_a,H_b
	τ 5.22 (m), $W_{1/2}{}^a$ = 8 Hz	τ 5.90 (m), $W_{1/2}$ = 8 Hz
	τ 5.40 (m), $W_{1/2}$ = 8 Hz	τ 6.10 (m), $W_{1/2}$ = 8 Hz
	τ 5.45 (t, d), J_1 = 9 Hz, J_2 = 3 Hz	τ 5.75(t,d), J_1 = 8 Hz, J_2 = 3 Hz τ 6.20 (m), $W_{1/2}$ = 18 Hz
	τ 5.65 (m), $W_{1/2}$ = 22 Hz	τ 5.90 (t, d), $S_1{}^b$ = 8 Hz; S_2 = 4 Hz τ 6.25 (t), S = 7 Hz

[a] Half-width of the peak. [b] These are separations between the components of the multiplet.

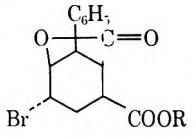
The displacement of the bromine cis to the carboxyls indicates that cyclization to a γ-lactone by the trans chlorine displacement is very difficult in this system and an ionization of the carbon–bromine bond cis to the carboxyl with subsequent cyclization is a preferred process. This ionization is possibly assisted by the neighboring chlorine. Bromine exerts generally a much more powerful neighboring group assistance than chlorine, but effects due to the greater carbon–chlorine than carbon–bromine bond strength might favor the ionization of the carbon–bromine bond in our system. The possibility that the lactonization occurred on a product of displacement of bromine by triethylamine, where the ammonium group was trans to the carboxyls, cannot be excluded.

The stereochemistry of XIII proves the preferential formation in this system of the bromonium ion cis to the carboxyls. The reason for it is not entirely clear, but it can be assumed that this ion is stabilized by the interaction with the π electrons of the axial carboxyl group. This is therefore perhaps a particular case that should not be generalized. Halogenation of the anhydride, the ester, and the acid I proceeds with a similar stereochemistry unlike the epoxidation reaction[2,3] and is possible owing to the lower steric requirements of the halogenating agent relative to the peracid.

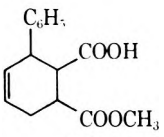
In order to obtain more information on the course of the reaction, we studied the bromination of the phenyl-substituted dicarboxylic acid XIVa in which the position of the axial carboxyl is determined (position 2) by the relative stabilities of the conformers. Bromination of this acid gave directly a bromolactone. The same product was obtained by bromolactonization of the salt of XIVa. Structure XVa was assigned to this compound, since the ester XVb was obtained by bromination of the monoester XVI, formed by treatment of the anhydride of XIVa with methanol. Bromination and a Hunsdiecker reaction of XVI with subsequent dehydrobromination yielded 3-phenylbenzoic acid. The trans disposition of the bromine substituent relative to the lactone ring in XV follows from its nmr spectrum showing the hydrogen α to oxygen at τ 5.17 as a doublet with a coupling constant[17] of 4 Hz.



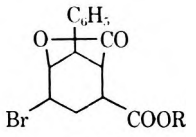
XIV



XV



XVI



XVII

a R = H
b R = CH_3

It is of interest that bromination of the dimethyl ester XIVb gave directly XVb in fair yield (40%). However, bromination of the anhydride of XIVa yielded a mixture from which an isomeric lactone was isolated in low yield (15%) after hydrolysis and lactonization in basic conditions. Structure XVIIa was assigned to this lactone since its ester (XVIIb) showed in the nmr spectrum a singlet at τ 4.99 for the hydrogen α to the oxygen and a doublet of doublets at τ 6.70 for the hy-

(22) Z. Welwart, *Bull. Soc. Chim. Fr.*, 2203 (1964).

(23) The lower than ordinary coupling constants for an anti arrangement of the protons is due to the halogens: E. I. Snyder, *J. Amer. Chem. Soc.*, **88**, 1155 (1966); R. O. C. Norman and C. B. Thomas, *J. Chem. Soc. B*, 598 (1968); C. A. Kingsbury and W. B. Thornton, *J. Org. Chem.*, **31**, 1000 (1966).

drogen α to bromine with coupling constants of 11 and 6 Hz as expected.[17]

It seems, therefore, that the bromonium ion of XIV is formed trans to the carbonyl groups, differently from that of I, where cis bromonium ion formation was inferred. The reason for this effect is the bulk of the phenyl group in XIV which together with the equatorial carboxyl forces the axial carboxyl group in an "unnatural" conformation[24] with the oxygen pointing inside the ring. Such a conformation hinders sterically the formation of a cis bromonium ion and also stabilizes by a neighboring group effect the charge dispersed on the carbon atoms of the trans bromonium ion. The presence of these effects is supported by the unusual direct lactonization during the bromination of the diester XIVb.

Experimental Section

Infrared spectra were determined neat, if not stated otherwise, on a Perkin-Elmer 337 spectrophotometer, and nmr spectra on a Varian A 56/60 instrument in CCl_4 or $CDCl_3$ using tetramethylsilane as an internal standard. Melting points were not corrected.

trans-[25] and *cis*-[25] cyclohex-4-ene-1,2-dicarboxylic acids (IIIa and Ia, respectively), trans[25] and cis anhydrides,[26] and their methyl esters[27] were prepared by known methods.

***cis*-3-Phenylcyclohex-4-ene-*cis*-1,2-dicarboxylic acid (XIVa)** was prepared from the anhydride[28] by dissolution in aqueous sodium hydroxide and subsequent acidification, mp 195–197° (water). Esterification of this acid with diazomethane yielded the dimethyl ester XIVb, mp 61–62° (ethanol), ν_{max} 1740 cm^{-1} (Nujol). *Anal.* Calcd for $C_{16}H_{18}O_4$: C, 70.1; H, 6.6. Found: C, 69.9; H, 6.7.

Methyl *cis*-2-carboxy-*cis*-3-phenylcyclohex-4-enecarboxylate (XVI) was obtained by dissolution of the anhydride[28] of XIVa (20 g) in boiling methanol (150 ml). The precipitate, formed after cooling the solution, was crystallized twice from ethyl acetate giving 11 g melting at 174–175°, ν_{max} 1740 cm^{-1} (Nujol). *Anal.* Calcd for $C_{15}H_{16}O_4$: C, 69.2; H, 6.2. Found: C, 69.0; H, 6.1.

Halogenations.—The substituted cyclohexene (0.05 mol) in dichloromethane (75 ml) was cooled in an ice bath, and an equivalent amount of bromine or bromine chloride, freshly prepared by addition of an equivalent amount of bromine to liquid chlorine[13,29] in dichloromethane (25 ml), was added dropwise with stirring. In the case of the diacids, the reaction was performed on suspensions, due to their low solubility. The solvent was evaporated after the completion of the reaction and the residue was recrystallized.

***trans*-2-Carboxy-*cis*-4-bromo-*trans*-5-chlorocyclohexanecarboxylic acid (Xa)** was obtained from IIIa and bromine chloride in 70% yield, mp 195–196° (water), ν_{max} 1720 cm^{-1}. *Anal.* Calcd for $C_8H_{10}BrClO_4$: C, 33.6; H, 3.5. Found: C, 33.8; H, 3.9.

Dimethyl ester Xb was obtained from IIIb: yield, 90%; mp 72–73° (ethanol); ν_{max} 1740 cm^{-1}. *Anal.* Calcd for $C_{10}H_{14}BrClO_4$: C, 38.2; H, 4.5. Found: C, 38.5; H, 4.5.

***cis*-2-Carboxy-*cis*-4-bromo-*trans*-5-chlorocyclohexanecarboxylic acid (XIIIa)** was obtained in 60% yield from Ia, mp 193–195° (ethyl acetate–hexane), ν_{max} 1720 cm^{-1}. *Anal.* Calcd for $C_8H_{10}BrClO_4$: C, 33.6; H, 3.5. Found: C, 33.8; H, 3.6.

Dimethyl ester XIIIb was prepared from Ib: bp 160–165° (1 mm); yield, 60%; ν_{max} 1740 cm^{-1}. A weak lactone band appears at 1790 cm^{-1}. *Anal.* Calcd for $C_{10}H_{14}BrClO_4$: C, 38.2; H, 4.5. Found: C, 39.4; H, 4.1.

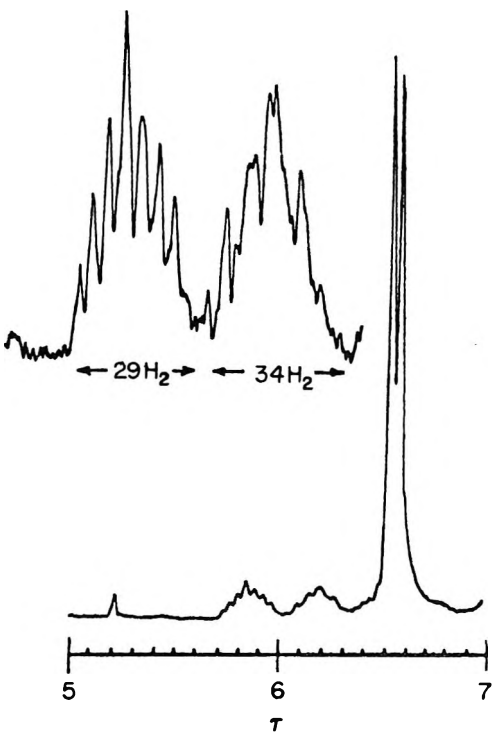


Figure 1.—Nmr spectrum of XIIIb in benzene at 100 MHz.

The anhydride of XIIIa was prepared from the anhydride of Ia in 70% yield: mp 122–123° (benzene–hexane); ν_{max} 1880, 1800, and 1725 cm^{-1}. *Anal.* Calcd for $C_8H_8BrClO_3$: C, 35.9; H, 3.0. Found: C, 35.6; H, 3.2.

***trans*-2-Carboxy-*cis*-4-bromo-*trans*-5-bromocyclohexanecarboxylic acid (VIIa)** was obtained from IIIa and bromine: yield, 85%; mp 184–185° (acetone–water); ν_{max} 1720 cm^{-1}. *Anal.* Calcd for $C_8H_{10}Br_2O_4$: C, 29.1; H, 3.3; Br, 48.5. Found: C, 28.9; H, 3.5; Br, 48.6.

The diester VIIb was obtained in 70% yield from IIIb, mp 75–76° (ethanol), ν_{max} 1740 cm^{-1}. *Anal.* Calcd for $C_{10}H_{14}Br_2O_4$: C, 33.5; H, 3.0. Found: C, 33.5; H, 3.7.

***cis*-2-Carboxy-*cis*-3-phenyl-*cis*-4-hydroxy-*trans*-5-bromocyclohexanecarboxylic acid lactone-(2,4) (XVa)** was obtained in 90% yield by bromination of XIVa, mp 201–202° (ethyl acetate), ν_{max} 1800 and 1725 cm^{-1}. *Anal.* Calcd for $C_{14}H_{13}BrO_4$: C, 51.7; H, 4.0. Found: C, 51.6; H, 4.0.

Esterification of XVa with a diazomethane gave XVb, mp 108–109° (ethanol), ν_{max} 1800 and 1750 cm^{-1}. *Anal.* Calcd for $C_{15}H_{15}BrO_4$: C, 53.1; H, 4.4; Br, 23.6. Found: C, 52.9; H, 4.3; Br, 23.5.

The ester XVb was also obtained in 40% yield from XIVb.

Bromination of the anhydride of XIVa (11 g), subsequent treatment with triethylamine in DME, and evaporation of DME under reduced pressure left a residue that was dissolved in DMSO (50 ml) and methyl iodide (15 ml). The mixture was stirred overnight, poured on water, and extracted with dichloromethane. Chromatography on alumina and elution with benzene–chloroform yielded a product that was crystallized from benzene–cyclohexane (2 g), mp 125–126°, ν_{max} 1790 and 1740 cm^{-1}. *Anal.* Calcd for $C_{15}H_{15}BrO_4$: C, 53.1; H, 4.4; Br, 23.6. Found: C, 52.8; H, 4.3; Br, 23.4.

Bromination of the sodium salts of XVI and XIVa was carried out in aqueous solution; 0.02 mol of XVI or XIVa was dissolved in an aqueous solution of 0.02–0.04 mol of NaOH, respectively. To this cooled solution 3.2 g of Br_2 in 50 ml of water containing 2.4 g KBr was added dropwise. The reaction mixture was acidified and the precipitate collected. The filtrate was extracted with ether. A 90% yield of XVb was obtained from XVI and a similar yield of XVa from XIVa.

Lactonization.—The halogenated acid (3 g) was refluxed for 2 hr in 1,2-dimethoxyethane (50 ml) and 3 ml of Et_3N. The reaction mixture was cooled and filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed rapidly with dilute HCl, and dried and the solvent evaporated.

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trans,trans,trans-2-Carboxy-4-hydroxy-5-bromocyclohexanecarboxylic acid lactone-(2,4) (VIIIa) was obtained in 80% yield from VIIa, mp 129–130° (ethyl acetate), ν_{max} 1790 and 1720 cm^{-1}. Esterification of VIIIa with diazomethane gave VIIIb, mp 89–90° (benzene), ν_{max} 1790–1740 cm^{-1}. *Anal.* Calcd for $C_9H_{11}BrO_4$: C, 41.1; H, 4.2. Found: C, 41.3; H, 4.2.

Methyl *trans,trans,trans*-2-carboxy-4-hydroxy-5-chlorocyclohexanecarboxylate lactone-(2,4) (XIb) was prepared in 40% yield from Xa and subsequent esterification with diazomethane, mp 92° (ethanol), ν_{max} 1800 and 1740 cm^{-1}. *Anal.* Calcd for $C_9H_{11}ClO_4$: C, 49.4; H, 5.0; Cl, 16.2. Found: C, 50.0; H, 5.1; Cl, 16.1.

Methyl *cis*-2-carboxy-*cis*-4-hydroxy-*trans*-5-chlorocyclohexanecarboxylate lactone-(2,4) (XIIb) was obtained from XIIIa and subsequent esterification with diazomethane, bp 150–155° (0.5 mm), ν_{max} 1800 and 1740 cm^{-1}. *Anal.* Calcd for $C_9H_{11}ClO_4$: C, 49.4; H, 5.0; Cl, 16.2. Found: C, 49.4; H, 5.0; Cl, 16.0.

Registry No.—Vb, 26595-97-1; VIIa, 26595-79-9; VIIb, 26595-80-2; VIIIa, 26595-81-3; VIIIb, 19914-90-0; Xa, 26595-83-5; Xb, 26595-84-3; XIb, 26595-85-7; XIIb, 26595-86-8; XIIIa, 26595-87-9; XIIIb, 26595-88-0; XIII anhydride, 26595-89-1; XIVa, 26595-90-4; XIVb, 26595-91-5; XVa, 26595-92-6; XVb, 19914-94-4; XVI, 26595-94-8; XVIIb, 19914-95-5; *trans*-2-carboxy-*cis*-4-chloro-*trans*-5-bromocyclohexanecarboxylic acid dimethyl ester (from Table I), 26595-96-0.

Solvolysis Studies of Cycloalkylcarbinyl Tosylates. Effect of Adjacent Ring Size on the Rates and Products. Ionization Constant Determinations of Cycloalkanecarboxylic Acids

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Received May 6, 1970

First-order titrimetric rate constants, activation parameters, and products were determined for the acetolysis of cycloalkylcarbinyl tosylates of ring size five through twelve. First-order formolysis rate constants were also determined for the series, and trifluoroacetolysis first-order rate constants were determined for cyclohexyl-, cyclononyl-, and cycloundecylcarbinyl tosylates. Ionization constants were measured for the cycloalkanecarboxylic acids of ring size five through twelve. A small rate spread was observed for the series, with the maximum rate being observed for cyclononylcarbinyl tosylate. The observed rate profiles closely parallel the cycloalkane ring strain profile calculated from combustion data. The products (seven- through twelve-membered rings) were mainly 1-methylcycloalkenes, which were shown by deuterium substitution in one case to arise *via* a 1,2-hydride shift. The rate spread was considered to be due to nucleophilic hydrogen participation at the transition state (k_Δ). A smaller contribution of a solvent assisted (k_s) pathway also contributed to the total solvolytic rate. Hydrogen participation is proposed as being directly related to relief of ring strain (six- through twelve-membered rings). Inductive contributions of the adjacent ring are also of importance. Cyclopentylcarbinyl tosylate appears to solvolyze *via* a nonclassical ion (carbon participation) to yield ring expanded products.

In the mechanistic analysis of solvolytic reactions of primary substrates it has been proposed that there are competing pathways for displacement of the leaving group. These routes have been designated as k_Δ (anchimerically assisted ionization) and k_s (anchimerically unassisted ionization) and depend on the solvent and substrate structure.[2,3] The suggestion has been made that the k_s route is the nucleophilic solvent assisted process[4] and we shall adopt this terminology in this manuscript and return to the original definition of Winstein.[3]

These pathways are simultaneous processes and no crossover occurs between them. In solvents of high ionizing power and low nucleophilicity such as trifluoroacetic acid, the k_Δ/k_s ratios for primary substrates are much higher than in formic acid.[2,5] The solvolyses of primary tosylates have also been performed in fluorosulfuric acid[6,7] and sulfuric acid.[8]

The formation of carbonium ions or ion pairs (k_c route) from primary substrates seems highly unlikely as these cations are perhaps far too unstable to exist in solution.[9-12] A strong nucleophilic solvent bond is indicated in the solvolysis of these substrates proceeding through the k_s route. On the basis of rate, solvent, and isotope effects in the solvolysis of ethyl trifluoromethanesulfonate, it was concluded that substantial bonding to a nucleophilic solvent molecule at the transition state was required even with such a good leaving group as the trifluoromethanesulfonate anion.[13]

On the basis of these pathways (k_s and k_Δ) for primary substrate solvolyses, it has been concluded by Schleyer and coworkers[14] that the presence of any rearranged product in the solvolysis of simple primary systems can be taken as *prima facie* evidence for neighboring group participation.

This picture of competing k_Δ and k_s routes, with no interconversion between them, has been successfully utilized in the interpretation of the solvolysis

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rates of 2-arylethyl tosylates.[15-18] In these cases one must include a term for the fraction of phenonium ions which go on to product and do not undergo internal return.

The solvolytic study of a series of cycloalkylcarbinyl tosylates seemed of considerable interest to determine the effect of adjacent ring size on the rates and products. The effect of having a primary reaction center adjacent to a ring could lead to three competitive solvolytic pathways: (a) k_s route, (b) k_Δ route with carbon participation, and (c) k_Δ route with hydrogen participation. It appeared that hydrogen participation (k_Δ) might be the most energetically favorable process in the six- through twelve-membered ring systems since a tertiary cation would be formed while carbon participation would lead to a ring-expanded secondary cation. The magnitude of the k_s route is difficult to estimate. However, if a strong solvent bond occurs at the transition state (k_s route) leading to unrearranged product, then the k_Δ route in order to be competitive may not have a rate considerably greater than the k_s route.[4]

Previous Studies.—The acetolyses of the small ring systems, cyclopropylcarbinyl tosylate[19-21] and cyclobutylcarbinyl tosylate,[22] have been reported and discussed. The acetolysis of cyclopentylcarbinyl *p*-nitrobenzenesulfonate at 80° yields 62% cyclohexene and 18% cyclohexyl acetate.[23] The acetolysis of cyclohexylcarbinyl tosylate at 115° yields less than 2% ring-expanded products[24,25] and cycloheptylcarbinyl brosylate is reported to yield only unrearranged acetate.[26] Acetolysis rates have been reported and discussed for cyclopentylcarbinyl brosylate,[27] cyclohexylcarbinyl brosylate,[27,28] and cycloheptylcarbinyl brosylate.[26,29]

Nitrous acid deaminations of cycloalkylcarbinyl amines have been studied. Cyclopropylcarbinylamine leads to an alcohol mixture containing 47% cyclobutanol[30] and cyclobutylcarbinylamine yields mainly cyclopentanol.[31] In the deaminations of the medium to large size cycloalkylcarbinylamines, significant amounts of ring-expanded products have been obtained.[32-35] The deaminations of isobutylamine and various deuterated analogs have been extensively studied and the mechanisms discussed.[36-38] The pyrolyses of cyclohexylcarbinyl tosylate,[24] cyclohexylcarbinyl mesylate,[39] cyclohexylcarbinyl borate,[40] and cyclobutylcarbinyl borate[40] have been reported. Cyclopentyl- and cyclohexylcarbinyl acetates have also been pyrolyzed and yield the corresponding methylenecycloalkanes.[41-43]

Synthetic Methods.—The cycloalkylcarbinyl tosylates (five- through twelve-membered rings) were prepared from the corresponding alcohols.[44] Cycloheptylcarbinol was prepared by lithium aluminum hydride reduction of cycloheptanecarboxylic acid.[45] Cyclononylcarbinol and cyclodecylcarbinol were prepared from the corresponding 2-carbethoxycycloalkanones by the following sequence: (a) preparation of the ethylene thioketal by reaction with boron trifluoride etherate and 1,2-ethanedithiol; (b) desulfurization of the thioketal with Raney nickel to yield the carbethoxycycloalkane; and (c) lithium aluminum hydride reduction to the carbinol. Cyclodecylcarbinol was also obtained by lithium aluminum hydride reduction of 1-carbomethoxycyclodecene in refluxing 1,2-dimethoxyethane.

Cyclooctylcarbinyl tosylate, deuterated at the ring position holding the tosylate carbon, was prepared from β-*d*-carbethoxycyclooctane by lithium aluminum hydride reduction and subsequent tosylation. Deuteration of the ester was accomplished with ethereal triphenymethyl sodium followed by addition of ethanol-d_1.[46]

Cyclooctane-, cyclononane-, and cyclododecanecarboxylic acids were prepared by hydrolysis of the corresponding esters. Cyclodecane- and cycloundecanecarboxylic acids were prepared by catalytic hydrogenation of the corresponding 1-carboxycycloalkenes. These latter compounds were obtained by a modified Favorskii reaction on cycloundecanone and cyclododecanone, respectively, according to the procedure described by Garbisch.[47]

Kinetic Procedures.—The acetolysis and formolysis titrimetric procedures were similar to those of Winstein and coworkers[48] and Roberts and coworkers.[49] The sealed ampoule technique was utilized for the acetolyses and formolyses run above 50°. The solvolyses were run in buffered media except where noted. The trifluoroacetolysis procedure was essentially that of Peterson and coworkers.[50] The samples were quenched in methanol and the decrease in the ultraviolet absorption maximum at 273 mμ was followed.

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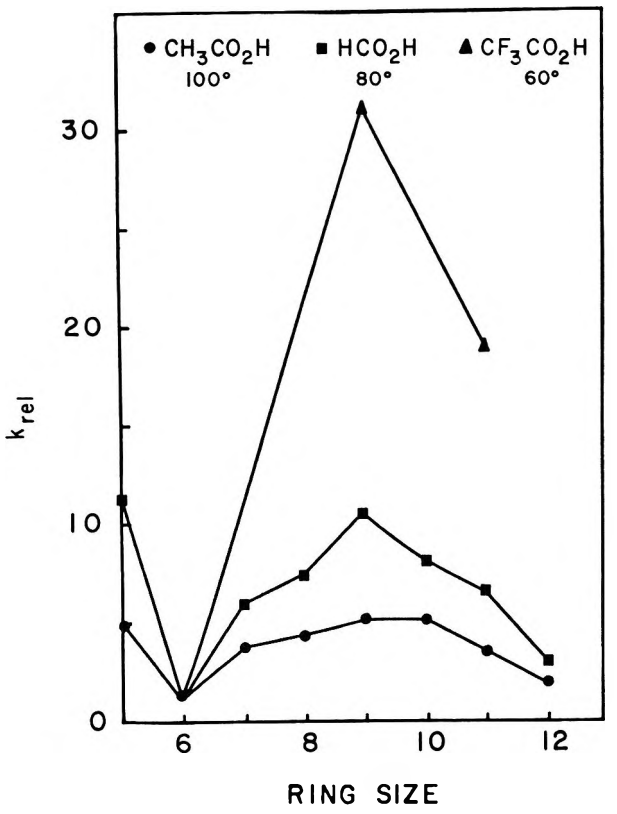

Figure 1.—Variation of the solvolysis rates (k_t) of the cycloalkylcarbinyl tosylates with the ring size.

Solvolysis Products.—The products produced under acetolysis conditions were determined. The cycloalkylcarbinyl tosylates were solvolyzed at about 120°. The analyses were performed by nmr or vpc or a combination of these two procedures. The procedure is described in the Experimental Section.

Ionization Constant Determinations.—As a possible probe into the inductive effect of the adjacent ring, the ionization constants of the five- through twelve-membered cycloalkanecarboxylic acids were determined in 50% aqueous ethanol. The procedure followed was essentially that of Hahn and coworkers with minor modifications.[51]

Results and Discussion

The calculated first-order titrimetric rates constants (k_t) for the acetolyses of the cycloalkylcarbinyl tosylates are tabulated in Table I.

The relative rate data (cyclohexylcarbinyl tosylate as the reference compound) are plotted in Figure 1. One notes a maximum in the acetolysis rates at the nine-membered ring carbinyl system.

Although the ring size effect in the tosylates studied is small, it is consistent for both acetolysis temperatures. The agreement of the rate data with previously published rates is generally good as shown in Table II.

The activation parameters are tabulated in Table III.

It is interesting to compare the general curve shape of Figure 1 with the plot of the ring strain *vs.* ring size data shown in Figure 2. The curve profiles are remarkably similar.

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TABLE I

CYCLOALKYLCARBINYL TOSYLATES. ACETOLYSIS RATE DATA[a]

Ring size	Temp, °C[b]	$k_t \times 10^5$ sec^{-1}[c]
5	100.0	2.54 ± 0.10
	130.0	38.10 ± 0.9
6	100.0	0.534 ± 0.021
	130.0	9.53 ± 0.26
7	100.0	1.92 ± 0.10
	130.0	33.7 ± 0.7
8	100.0	2.37 ± 0.10
	(100.0)	(2.33 ± 0.17)[d]
	130.0	44.7 ± 1.9
9	100.0	2.75 ± 0.13
	130.0	48.3 ± 2.8
10	100.0	2.68 ± 0.21
	(100.0)	(2.44 ± 0.21)[d]
	130.0	39.4 ± 3.2
11	100.0	1.89 ± 0.09
	130.0	31.8 ± 1.4
12	100.0	1.01 ± 0.08
	130.0	19.9 ± 0.7
β-*d*-8	100.0	1.80 ± 0.12

[a] A preliminary report of these data was presented at the First Northeast Regional Meeting of the American Chemical Society, Boston, Mass., Oct 15, 1968, Abstract No. 205. [b] Temperature deviation ±0.10°. [c] Average of two or more kinetic runs; the error is the average standard deviation. [d] Without sodium acetate.

TABLE II

ACETOLYSIS OF CYCLOALKYLCARBINYL TOSYLATES. RATE COMPARISONS WITH PUBLISHED DATA

Ring size	Temp, °C	$k_t \times 10^6$ sec^{-1} This study[a]	$k_t \times 10^6$ sec^{-1} Lit. value	Ref
5	80	3.23	2.99[a,b]	27
5	80	3.23	3.25[a,c]	23
6	80	0.592	0.500[a,b]	27
6	100	5.34	5.06	28
6	100	5.34	3.88	25
7	65	0.360	0.383[a,b]	26

[a] With sodium acetate present. [b] Data published for *p*-bromobenzenesulfonate (OBs) ($k_{OBs} = 3k_{OTs}$). [c] Data published for *p*-nitrobenzenesulfonate (ONs) ($k_{ONs} = 11.1\ k_{OTs}$).

TABLE III

ACETOLYSIS OF CYCLOALKYLCARBINYL TOSYLATES. ACTIVATION PARAMETERS

Ring size	E_a, kcal	ΔS^*, eu
4[a]	25.1	−8.7
5	27.0 ± 0.8	−9.2 ± 2.7
6	28.7 ± 0.9	−7.7 ± 2.7
7	28.5 ± 1.0	−5.8 ± 3.5
8	29.3 ± 0.9	−3.2 ± 3.0
9	28.5 ± 1.1	−5.0 ± 3.9
10	26.6 ± 1.6	−10.1 ± 5.5
11	28.1 ± 0.9	−6.8 ± 3.2
12	29.8 ± 1.6	−3.5 ± 5.6
i-Bu[b]	28.9 ± 0.5	−7.8 ± 1.9

[a] Data from ref 22. [b] S. Winstein and H Marshall, *J. Amer. Chem. Soc.*, **74**, 1120 (1952).

The major acetolysis product (C-7 through C-12) as shown in Table IV is the 1-methylcycloalkene. This product could arise by a 1,2-hydride shift followed by proton loss from the tertiary cation or by elimination to form the methylenecycloalkane followed by rearrangement to the endocyclic olefin. Small amounts of 1-methylcycloalkyl acetates and methylenecyclo-

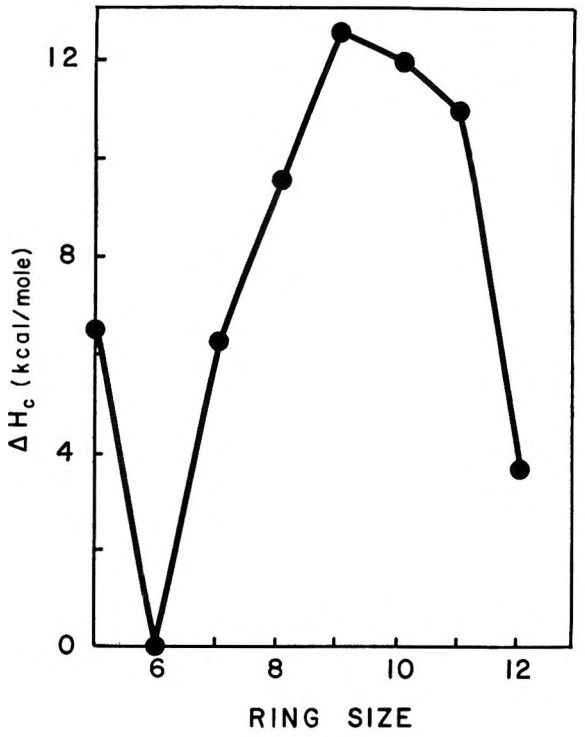


Figure 2.—Correlation of the ring size with the ring strain energy from combustion data.

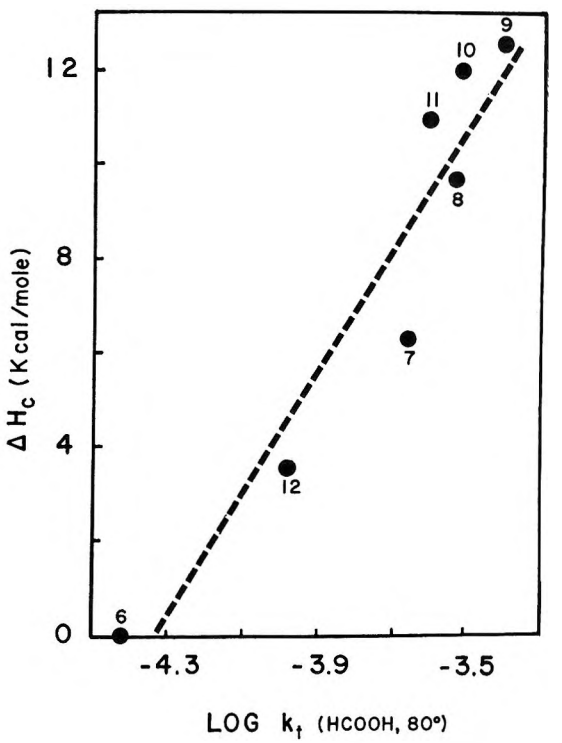
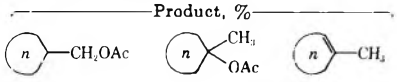


Figure 3.—Correlation of the formolysis rates (log k_t) of the cycloalkylcarbinyl tosylates at 80° with the ring strain energy from combustion data.

TABLE IV

CYCLOALKYLCARBINYL TOSYLATES. ACETOLYSIS DATA

Ring size, n	Product, % 		
4[a]	<1		
5[b]	60.5	1.1	1.6
6	49	5	46
7[c]	12.9	1.2	82.4
8	15.9	1.7	82.4
9	12		88
10	5		95
11	11		89
12	21.9	2.9	75.2
i-Bu[d]	~17		

[a] Also 78% cyclopentyl acetate; data from ref 22. [b] Also 9.2% cyclohexene and 27.6% cyclohexyl acetate. [c] Also 3.5% methylenecycloheptane. [d] Data from ref 2.

alkanes were also found along with unrearranged acetate. No ring expanded products were found except in the cases of cyclopentylcarbinyl tosylate and cyclobutylcarbinyl tosylate. These latter two cases will be discussed separately.

Since the acetolysis data for the cycloalkylcarbinyl tosylates showed a small rate variation among the compounds studied, it was of interest to utilize buffered formic acid as the solvent (less nucleophilic and higher ionizing power). The formolysis rate data (k_t) are tabulated in Table V and show the same rate pattern as the acetolysis (Figure 1) with a rate range of 11. The rate enhancement compared to acetic acid is about 100 (Table VI). The formolysis rates correlate to some extent (excluding cyclopentylcarbinyl tosylate) with ring strain as shown in Figure 3.

Trifluoroacetic acid is a much better ionizing solvent and a poorer nucleophile than acetic or formic acid.[2,5] A rate decrease would be expected for a substrate dependent on nucleophilic solvent participation. On the other hand its greater ionizing power would accentuate any rate enhancement due to hydrogen participation.

The trifluoroacetolysis of the six-, nine-, and eleven-membered ring carbinyl tosylates (Table VII and Figure 1) shows a further rate separation, a factor of 31 be-

TABLE V

CYCLOALKYLCARBINYL TOSYLATES. FORMOLYSIS RATE DATA

Ring size	Temp, °C[a]	$k_t \times 10^4$ sec^{-1}[b]
5	80.0	4.29 ± 0.30
6	80.0	0.388 ± 0.015
	100.0	2.83 ± 0.18
7	80.0	2.23 ± 0.10
8	80.0	2.86 ± 0.15
9	80.0	4.08 ± 0.23
10	80.0	3.11 ± 0.11
11	80.0	2.53 ± 0.08
12	80.0	1.11 ± 0.14[c]

[a] Temperature deviation ±0.10°. [b] Average of two kinetic runs; the error is the average standard deviation. [c] One run only.

TABLE VI

SOLVOLYSIS OF CYCLOALKYCARBINYL TOSYLATES. RATE COMPARISONS

Ring size	$k_{HCO_2H}/k_{CH_3CO_2H}$	$k_{CF_3CO_2H}/k_{CH_3CO_2H}$
5	133	
6	65	419
7	102	
8	114	
9	131	2460
10	88	
11	115	2030
12	109	

TABLE VII
CYCLOALKYLCARBINYL TOSYLATE.
TRIFLUOROACETOLYSIS RATE DATA

Ring size	Temp, °C[a]	$k_t \times 10^5$ sec^{-1}[b]
6	60.0	2.13 ± 0.12
	80.0	14.2 ± 1.3
9	60.0	66.7 ± 6.2
11	60.0	40.2 ± 2.2

[a] Temperature deviation ±0.10°. [b] Average of two kinetic runs; the error is the average standard deviation.

tween the six- and nine-membered ring compounds. The rate increase for trifluoroacetolysis over acetolysis (Table VI) is greater than 2000 for the nine- and eleven-membered rings indicating a possible increase in hydrogen participation for these rings. Cyclohexylcarbinyl tosylate, on the other hand, exhibits a rate increase of only 419 in trifluoroacetic acid compared to the rate in acetic acid.

The activation data for cyclohexylcarbinyl tosylate in the three solvent systems are tabulated in Table VIII. Pritzkow and Schoppler[52] have solvolyzed a

TABLE VIII
SOLVOLYSIS OF CYCLOHEXYLCARBINYL TOSYLATE.
ACTIVATION PARAMETERS[a]

Solvent[b]	$k_1 \times 10^{-9}$ sec^{-1}[a]	E_a, kcal	ΔS^*, eu[a]
CH_3CO_2H	0.309	28.7 ± 0.9	−7.7 ± 2.7
HCO_2H	41.4	26.0 ± 1.6	−7.0 ± 5.6
CF_3CO_2H	406	22.3 ± 2.2	−15.0 ± 7.6

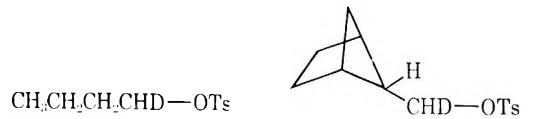
[a] Calculated at 25°. [b] Buffered with the sodium salt of the acid.

number of simple (RCH_2CH_2OTs where R = *n*-alkyl) primary alkyl tosylates in buffered acetic acid and reported second-order kinetics. Cyclohexylcarbinyl tosylate was also reported to show a second-order acetolysis rate in the presence of potassium acetate although no experimental data were given.[28]

As a check on the first-order reaction rates, cyclooctyl- and cyclodecylcarbinyl tosylates were solvolyzed in unbuffered acetic acid. First-order rate constants were obtained (Table I) with only 2 and 9% decreases, respectively, compared to the buffered studies, which are within the range of a normal salt effect.

The solvolysis rates (k_t) of isobutyl tosylate in ethanol, acetic acid, and formic acid have been analyzed in terms of competing k_Δ and k_s routes.[2] The magnitude of k_s was approximated by assigning the yield of unrearranged solvolysis product to this route with the remainder being assigned to k_Δ (hydrogen or methyl participation). In acetic acid (75°), 79% of the reaction proceeds through the k_Δ route. At 100°, 17% of isobutyl acetate is produced in the acetolysis reaction. In the trifluoroacetolysis of isobutyl tosylate no evidence for a second-order reaction was found as k_s was not affected by added sodium trifluoroacetate (second-order rate constants were observed for CH_3OTs, EtOTs, and *n*-PrOTs under these conditions). The k_Δ route predominates in the trifluoroacetolysis of isobutyl tosylate. Wiberg and Hess[22] have previously analyzed the solvolyses of isobutyl tosylate *via* SN1 and SN2 mechanistic routes. The validity of their product dissection must be questioned since no account is taken in this analysis of the route by which rearranged olefin arises.[2]

Streitwieser[53] has solvolyzed chiral 1-*d*-*n*-butyl tosylate (1) in formic acid and obtained inverted 1-*d*-*n*-butyl formate. Wiberg and Hess[22] have prepared and solvolyzed optically active *endo*-bicyclo[2.1.1]-hexane-5-meth-d_1-yl tosylate (2) in unbuffered acetic acid at 108°. The primary alcohol that was isolated after separation and reduction with lithium aluminum



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hydride had undergone complete inversion, thus indicating the k_s origin of the unrearranged acetate.

Product studies were not done on chiral cycloalkylcarbinyl tosylates. However, the above reported cases of inversion in the solvolysis of primary tosylates argue strongly for a k_s route to unrearranged acetate products.

Therefore, the product data were used to separate the titrimetric rate constants (k_t) into k_Δ and k_s paths[2] using the following relationships.

$$k_t = k_\Delta + k_s \qquad \frac{k_\Delta}{k_s} = \frac{P_t\ (\text{rearranged})}{P_s\ (\text{unrearranged})}$$

The data are given in Tables IX and X. The rates

TABLE IX
RATES OF k_Δ AND k_s PATHS FOR THE ACETOLYSIS OF CYCLOALKYLCARBINYL TOSYLATES AT 100°

Ring size	$k \times 10^5$ sec^{-1}	
	k_s	k_Δ
4[a]	0.43	42
5	1.55	0.99
6	0.26	0.27
7	0.25	1.67
8	0.37	1.98
9	0.33	2.42
10	0.13	2.57
11	0.21	1.67
12	0.22	0.78
i-Bu[b]	0.06	0.32

[a] Data from ref 22, k_Δ route with carbon participation. [b] Data from ref 2.

TABLE X
SOLVOLYSIS OF CYCLOALKYLCARBINYL TOSYLATES.
RELATIVE RATES

n	k_t CH_3CO_2H, 100°	k_t CH_3CO_2H, 130°	k_Δ[a] CH_3CO_2H, 100°	HCO_2H,[b] 80°	CF_3CO_2H,[b] 60°
5	4.8	4.0	3.7	11.1	
6	1.0	1.0	1.0	1.0	1.0
7	3.6	3.5	6.2	5.8	
8	4.4	4.7	7.3	7.4	
9	5.2	5.1	9.0	10.5	31.3
10	5.1	4.1	9.5	8.0	
11	3.5	3.3	6.2	6.5	18.9
12	1.9	2.1	2.9	2.9	

[a] Corrected for k_s product. [b] Use of k_t; no products were determined, but k_Δ probably constitutes the major pathway.

(52) W. Pritzkow and H. Schoppler, *Chem. Ber.*, **95**, 834 (1962).

(53) A. Streitwieser, Jr., *J. Amer. Chem. Soc.*, **77**, 1117 (1955).

for the k_s and k_Δ paths shown in Table IX are slightly greater than for isobutyl tosylate, with the exception of cyclopentylcarbinyl tosylate, a special case. A rate spread of about 10 is shown for the k_Δ path.

A note of caution should be introduced here. Schleyer and coworkers[14] have obtained chiral adamantylcarbinyl acetate which showed complete *retention* of configuration from the acetolysis of chiral adamantylcarbinyl tosylate (d_1). The adamantylcarbinyl system cannot be directly compared to the cycloalkylcarbinyl systems. Still, the possibility must be kept in mind that solvent attack on an intermediate hydrogen-bridged ion could also yield the cycloalkylcarbinyl acetates which would have the retained configuration; however, the tertiary product would be strongly favored.

Let us compare the relative rates in the three solvents as shown in Table X. The relative acetolysis rates at the two temperatures are about the same, and correction of the acetolysis rates for the k_s product leads to a relative rate sequence which is virtually identical with that for the formolyses (in formic acid the k_Δ route predominates). The trifluoracetolyses show a further expanded rate range and in the same direction.

Bartlett and coworkers[23] and Kotani and coworkers[24] have subjected, respectively, cyclopentyl- and cyclohexylcarbinyl acetates to acetolysis conditions and found no rearrangement products. Thus the k_s product is not a source of further products. Methylenecyclopentane has been shown to rearrange to 1-methylcyclopentene and 1-methylcyclopentyl acetate under acetolysis conditions.[23] As a further probe into the elimination mechanism, methylenecyclooctane and methylenecyclodecane were subjected to acetolysis conditions and were found to rearrange to the corresponding 1-methylcycloalkenes. The tertiary acetates, 1-methylcyclohexyl acetate and 1-methylcyclododecyl acetate, formed the corresponding 1-methylcycloalkenes under acetolysis conditions.

To distinguish between a mechanism involving a 1,2-hydride shift or an elimination mechanism, β-*d*-cyclooctylcarbinyl tosylate was solvolyzed. The acetolysis product ratios were comparable to those found for the undeuterated compound. The 1-methylcycloalkene contained a deuterium in the methyl group corresponding to 100% 1,2-hydride shift (nmr analysis). The unrearranged acetate still contained the β-deuterium, further substantiating the k_s nature of its origin.

In the acetolysis of β-*d*-cyclooctylcarbinyl tosylate at 100°, an isotope effect of 1.32 (k_H/k_D) was observed. Winstein and Takahashi[54] have reported a k_H/k_D ratio of 2.26 at 25° (1.85 calculated at 100°) for the acetolysis of 3-*d*-3-methyl-2-butyl tosylate. Since the product arises mainly from hydrogen (deuterium) migration, this value may indicate the degree of hydrogen participation at the transition state.

A free-energy plot of k_t (acetolysis rates) of the cycloalkylcarbinyl tosylates *vs.* the observed cycloalkyl tosylate acetolysis rates is shown in Figure 4. The agreement is good considering the different nature of the transition states involved (solvent participation effects) and prompts some conclusion. The dependence of cycloalkyl tosylates rates on relief of ring strain

(54) S. Winstein and J. Takahashi, *Tetrahedron*, **2**, 316 (1958).

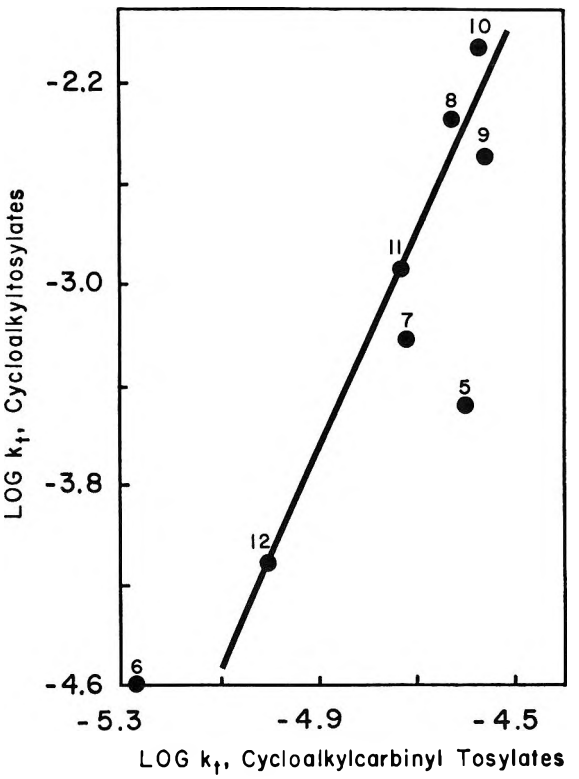


Figure 4.—Correlation of the acetolysis rates (log k_t) of the cycloalkyl tosylates at 50° with the acetolysis rates (log k_t) of the cycloalkylcarbinyl tosylates at 100°.

has been proposed.[55] Linear relationships have been found in the alicyclic series of rings five through ten, *e.g.*, the borohydride reductions of cycloalkanones and the acetolyses of the cycloalkyl tosylates. The correlation of Figure 4 (five ring excluded) might be construed as evidence for hydrogen participation as the major path with resultant partial release of ring strain in the solvolysis of the cycloalkylcarbinyl tosylates. A correlation between rates and expected hydrocarbon strain release has been proposed as evidence for anchimeric assistance in the rearrangement of a series of esters derived from bicyclo[*m.n.*0]alkane-1-methanols.[56]

The mechanistic route for the six- through twelve-membered cycloalkylcarbinyl tosylates appears to be an ionization anchimerically assisted by hydrogen participation (k_Δ) to lead to a tertiary cation along with a competitive pathway with nucleophilic solvent attack at the primary center (k_s) to lead to unrearranged acetate (Scheme I).

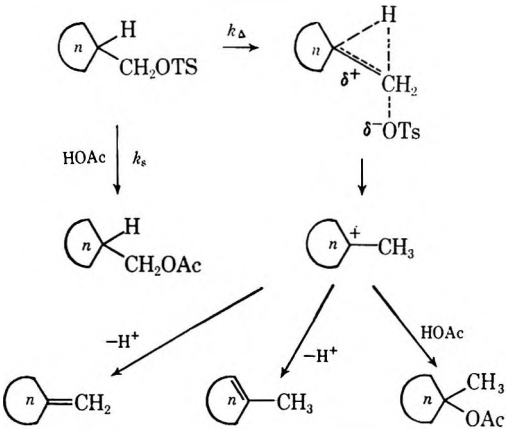
The parallelism of the solvolytic rate profile with the ring size *vs.* ring strain plot suggests that hydrogen bridging is to some extent related to partial release of internal ring strain; *i.e.*, rings of greatest internal strain can release nonbonded repulsions by hydrogen participation at the transition state thus making the ring carbon more sp^2 in character. In solvents of increasingly poorer nucleophilicity, the migrating hydrogen would supply a greater proportion of the nucleophilic driving force ($k_\Delta \gg k_s$).

In the case of cyclohexylcarbinyl derivatives, there is little tendency for a hybridization change of ring carbon from sp^3 to sp^2 since the ring conformation

(55) H. C. Brown and K. Ichikawa, *ibid.*, **1**, 221 (1957).

(56) W. G. Dauben, J. L. Chitwood, and K. V. Scherer, Jr., *J. Amer. Chem. Soc.*, **90**, 1014 (1968).

SCHEME I
ACETOLYSIS OF CYCLOALKYLCARBINYL TOSYLATES. REACTION PATHWAYS

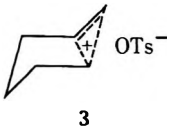


is already strain-free. This is reflected in the slower rate of acetolysis of cyclohexylcarbinyl tosylate and the equality of the k_s and k_Δ contributions to k_t (Table IX).

Cyclopentylcarbinyl and cyclobutylcarbinyl tosylates are special cases. The formolysis and acetolysis rates of these compounds are as high as for cyclononyl- and cyclodecylcarbinyl tosylates. The acetolysis products (Table IV) included 37% ring expanded products, and Bartlett[23] has found 80% ring expansion in the acetolysis of cyclopentylcarbinyl *p*-nitrobenzenesulfonate. Separation of the tosylate rate into k_Δ and k_s paths gives a k_s (Table IX) which is inconsistent with the other values of the k_s reaction for the series. Bartlett obtained only 5% unrearranged acetate, but the difference may be explained on the basis of difference in leaving groups and a much different temperature.

Olah and coworkers[57] have studied the formation of 1-methylcyclopentyl cation from various cyclohexyl and methylcyclopentyl precursors, in the appropriate antimony pentafluoride systems. Although they have found this cation to be the only species present at −60°, equilibrium mixtures at 25° contain 77% cyclohexane derivatives. They favor a protonated cyclopropane intermediate in the reaction mechanism.

Bartlett[23] proposed the nonclassical "stage" **3** as a transition state or intermediate in the acetolysis of cyclopentylcarbinyl *p*-nitrobenzenesulfonate. Judging from the agreement in rates observed, it seems logical



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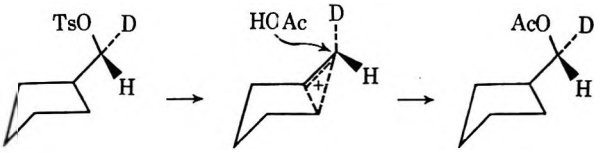
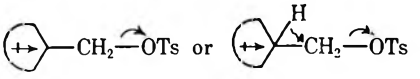
that the tosylate would solvolyze through a similar "stage." One of Bartlett's basic objections to direct initial formation of the classical ion was the difference in cyclohexene–cyclohexyl acetate ratios between the solvolyses of the cyclopentylcarbinyl ester (3.4:1) and the cyclohexyl ester (7.7:1). If the classical ion were formed directly by carbon migration, these ratios should be the same. The "folded" nonclassical ion would be geometrically less favorable for proton elimination than the flatter classical ion.

The existence of this ion also might help to explain the higher apparent k_s rate previously noted. Solvent attack on **3** could yield cyclopentylcarbinyl acetate, as well as ring expanded products. Cyclopentylcarbinyl acetate with retained configuration would be expected.



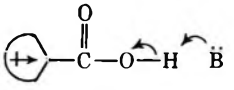
If one compares the ring expanded product fraction with that from the 1,2-hydride shift, a carbon to hydrogen participation ratio of 13.6:1 is obtained for the tosylate and a ratio of 5.3:1 is obtained for the *p*-nitrobenzenesulfonate. It would then appear that as the leaving group becomes better, carbon participation becomes less important. In the extremely energetic deamination of cyclopentylcarbinyl amine,[33] a carbon–hydrogen migration ratio of 4:1 was found which is consistent with this theory. This may be due to an entropy effect which requires more substrate and solvent reorganization for a carbon shift than for hydrogen.

Ionization Constants of Cycloalkanecarboxylic Acids.—Inductive effects of the ring may also play a role in the solvolysis of the cycloalkylcarbinyl tosylates.



Electron donation by the ring would stabilize the species proceeding through the k_s route or the intermediate formed *via* the k_Δ route. In addition, the hydrogen migration (k_Δ) would lead to release of internal nonbonded interactions.

As a probe into the inductive contribution to the solvolysis reaction of the cycloalkylcarbinyl tosylates, it would be desirable to have a model reaction which is dependent only on the inductive effect of the ring. The ionization of cycloalkanecarboxylic acids can perhaps provide such a model.



In the acids, an increase in electron density at the carbonyl carbon would decrease the ease of ionization thus decreasing the acidity. As the ring size is increased, one might expect a progressive decrease in acidity due to the inductive contribution of the methylene groups. This decrease should level off, as the effect of an additional methylene group is attenuated at a greater distance from the carboxyl group. An inverse correlation should be expected between the ionization constants of the cycloalkanecarboxylic acids and the solvolysis rates of the cycloalkylcarbinyl tosylates (if inductive effects only are operative and solvent effects are mutually similar).

The ionization constants of the cycloalkanecarboxylic acids of ring size five through twelve were measured. The data, presented in Table XI and Fig-

(57) G. A. Olah, J. M. Bollinger, C. A. Cupas, and J. Lukas, *J. Amer. Chem. Soc.*, **89**, 2692 (1967).

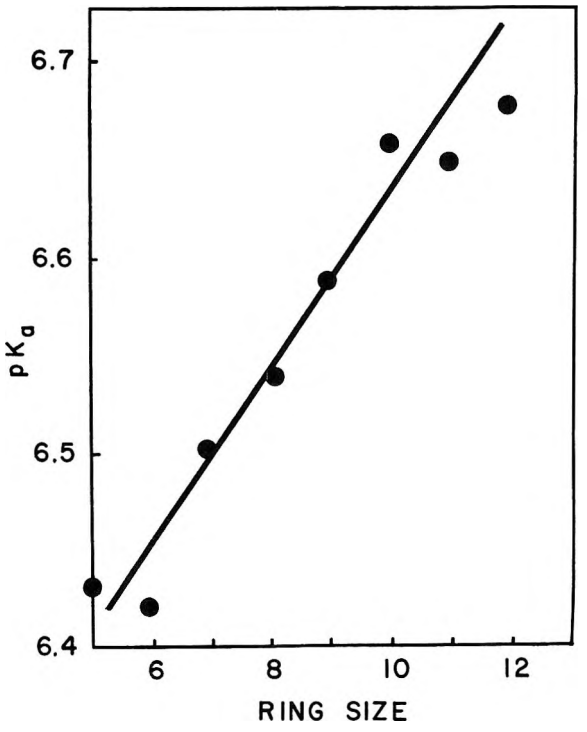


Figure 5.—Plot of the pK_a of the cycloalkanecarboxylic acids *vs.* the ring size.

TABLE XI
IONIZATION CONSTANTS OF CYCLOALKYLCARBOXYLIC ACIDS

Ring size	pK_a	$K_a \times 10^7$
5	6.43 ± 0.01	3.73
6	6.42 ± 0.01	3.79
7	6.50 ± 0.02	3.13
8	6.54 ± 0.01	2.87
9	6.59 ± 0.01	2.55
10	6.66 ± 0.01	2.17
11	6.65 ± 0.01	2.21
12	6.68 ± 0.02	2.08
i-Bu	6.24 ± 0.01	5.68

ure 5, show a steady increase in pK_a up to about the ten-membered ring, leveling off at that point, presumably due to the attenuation of the inductive effect.

Correlation of the pK_a values with the formolysis rates of the cycloalkylcarbinyl tosylates is reasonable for the six- through nine-membered rings, as shown in Figure 6. This lends some support to the idea that the hydrogen participation in these cases may be partially inductive in nature. However, solvation effects are also of importance in the measurement of ionization constants, and the relative magnitude of these effects is impossible to assess. The ionization constants for the cycloalkanecarboxylic acids were measured in 50% aqueous ethanol, while the solvolyses of the cycloalkylcarbinyl tosylates were done in acetic, formic, and trifluoroacetic acids.

Conformational effects also are important, although the carbinyl tosylate group would be expected to be in an equatorial position, well away from the bulk of the ring. The larger, less rigid rings might serve to inhibit solvation of the carbinyl tosylate group, thus offsetting the greater inductive effect. If this occurred, however, the rate decrease should also be reflected in the k_s rates, which is not the case (see Table IX).

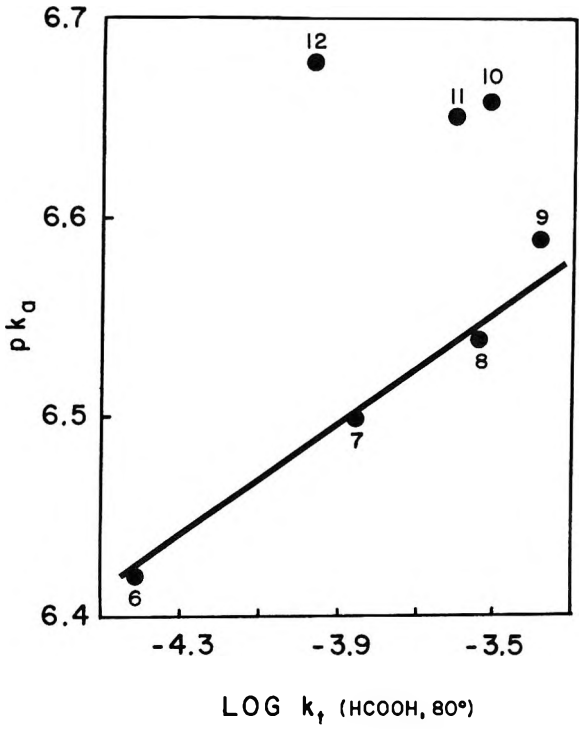


Figure 6.—Correlation of the formolysis rates (log k_t) of the cycloalkylcarbinyl tosylates at 80° with the pK_a values of the cycloalkanecarboxylic acids.

Conclusions

The solvolyses of the cycloalkylcarbinyl tosylates with ring sizes of six through twelve proceed with a rate spread due to nucleophilic hydrogen bridging at the transition state. The intermediate 1-methylcycloalkyl cation produced by the 1,2-hydride shift then yields the 1-methylcycloalkene by loss of a proton or reacts with solvent to form the tertiary ester.

The hydrogen bridging is directly related to the relief of ring strain offered by formation of the sp^2 center in the ring and partially to an inductive effect due to electron release by the ring, which could also stabilize the developing positive center. A direct SN2 displacement by solvent (k_s), which yields the unrearranged ester, is competitive with the hydrogen bridging (k_Δ). The reaction pathways are summarized in Scheme I.

Cyclopentylcarbinyl tosylate appears to solvolyze by way of a nonclassical ion yielding ring-expanded products. The considerably higher "apparent" k_s rate may be evidence to indicate that the nonclassical ion is indeed an intermediate.

Experimental Section

Nuclear magnetic resonance spectra (nmr) were taken on a Varian A-60 spectrometer. The peak positions are reported in ppm from internal tetramethylsilane as the reference and carbon tetrachloride as solvent. Ultraviolet measurements were taken with a Cary 14 spectrophotometer. Vapor phase chromatographic analyses were performed on an Aerograph A-90-P instrument. The microanalyses were performed by the MHW Laboratories, Garden City, Mich. All melting and boiling points are uncorrected.

A. Synthetic Section. General Procedures. Thioketalization. Method A.[58]—The β-keto ester (5 g) was dissolved in 15 ml of 1,2-ethanedithiol, and 1 ml of boron trifluoride etherate

(58) J. F. Tinker, *J. Org. Chem.*, **16**, 1417 (1951).

was added. The reaction mixture was protected by a drying tube, left at room temperature overnight, and then heated at 60° for 2 hr. After cooling, 25 ml of ether was added, and the reaction mixture washed first with several portions of 10% aqueous sodium hydroxide, then with saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The ether was removed on an aspirator, and the residue was distilled at reduced pressure to yield the thioketal ester.

Desulfurization. Method B.[59]—Active Raney nickel (5 teaspoons of 50% slurry in water, Wm. Grace no. 28, ~40 g of Ni) was placed in a 250-ml erlenmeyer flask equipped with a ground glass joint and fitted with a condenser. The slurry was washed with five 50-ml portions of ethanol to remove the water, and 4 g of thioketal dissolved in 50 ml of ethanol was added. The mixture was heated at gentle reflux (bath temperature 80–90°) for 3 days.

The reaction mixture was cooled and filtered, and the nickel residue was washed with methylene chloride. The filtrate was dried over anhydrous magnesium sulfate, the solvent removed on an aspirator, and the residue distilled at reduced pressure to yield the cycloalkyl carboxylic ester.

Lithium Aluminum Hydride Reduction. Method C.[45]—A suspension of 2.5 g of lithium aluminum hydride in 75 ml of dry ether was stirred at room temperature in a flask equipped with a drying tube, condenser, and addition funnel. A solution of ester to be reduced (0.1 mol) in 20 ml of dry ether was added dropwise with stirring. After addition was complete, the reaction mixture was allowed to reflux for 2 hr and cooled. The excess lithium aluminum hydride was destroyed by careful addition of water, and the resulting salts were dissolved with 10% hydrochloric acid. The layers were separated and the aqueous phase was extracted twice with ether. The combined organic phases were washed with saturated sodium chloride and dried over anhydrous magnesium sulfate, and the ether was removed on the aspirator. The residue was distilled at reduced pressure.

Tosylation. Method D.[45]—The alcohol to be tosylated was dissolved in dry pyridine (3 ml/1 g of alcohol) and cooled to 0° in an ice bath. The *p*-toluenesulfonyl chloride (10% molar excess) was dissolved in 3 ml of dry pyridine and also cooled to 0°. The two solutions were mixed, and the tightly stoppered flask was placed in the refrigerator overnight. The reaction mixture was poured into ice water, and the mixture extracted with petroleum ether. The extract was washed with 10% hydrochloric acid, 10% sodium bicarbonate, and water. The organic phase was dried over anhydrous magnesium sulfate and placed in the freezer to crystallize.

Hydrolysis. Method E.[60]—The ester to be hydrolyzed (2 g) was added to 20 ml of 25% sodium hydroxide and refluxed overnight. The reaction mixture was cooled, acidified to congo red with 10% hydrochloric acid, and extracted with ether. The ether extract was washed with saturated sodium chloride and dried over anhydrous magnesium sulfate, and the ether was removed on the aspirator. The residue was distilled at reduced pressure.

Acetylation of the Cycloalkylcarbinols and Cycloalkanols. Method F.[61]—The alcohol to be esterfied (2 g) was dissolved in 20 ml of dry pyridine, and 8 ml of acetic anhydride was added. The mixture, protected with a drying tube, was refluxed for 1 hr and cooled.

The reaction mixture was poured into 75 ml of ice water and then extracted with methylene chloride. The extract was washed with 10% hydrochloric acid, then with water, and dried over anhydrous potassium carbonate, and the solvent was removed on an aspirator. The residue was distilled at reduced pressure.

Preparation of Reference *tert*-Acetates from the Corresponding Ketones. Method G.—Magnesium turnings (0.06 g-atom) were placed in a 100-ml flask fitted with a condenser and an addition funnel and protected with a drying tube. A solution of methyl iodide (4.26 g, 0.03 mol) in 20 ml of dry ether was slowly added with stirring, maintaining a slow reflux rate. The mixture was allowed to reflux an additional 15 min, and a solution of 0.025 mol of the parent ketone in 10 ml of ether was added slowly, with cooling. After addition was complete, the mixture was stirred for 10 min, and then 20 ml of acetic anhydride was added with stirring. The reaction mixture was poured into ice water and extracted with ether. The extract was washed with saturated aqueous sodium bicarbonate and aqueous sodium chloride and dried over anhydrous magnesium sulfate; the ether was removed on an aspirator. The residue was distilled at reduced pressure.

Thioketals.—The thioketals were prepared from the β-keto esters *via* the general procedure A and the physical properties and analytical data are detailed in Table XII.

TABLE XII

THIOKETAL FORMATION USING METHOD A

Thioketal ring size	Registry no.	% yield	Bp (mm), mp, °C
8[a]	26600-30-6	84	124 (0.15)
9[a]	26600-31-7	83	39–41
10[a]	26600-32-8	73	146 (0.1)
12[a]	26600-33-9	89	95–96

[a] Satisfactory combustion analytical data (±0.35) have been obtained on these compounds. Ed.

Carbethoxycycloalkanes.—The general procedure B was utilized to desulfurize the thioketals. The experimental results are tabulated in Table XIII.

TABLE XIII

ESTERS FORMED BY DESULFURIZATION USING METHOD B

Carbethoxycycloalkane ring size	Registry no.	% yield	Bp (mm), °C
8[a]	26600-34-0	87	83 (0.2)
9[a]	26600-35-1	81	75 (0.1)
10[a]	26600-36-2	87	83 (0.2)

[a] Table XII, footnote *a*. Ed.

Cycloalkylcarbinols.—The general procedure C was utilized to convert the esters to the corresponding cycloalkylcarbinols. The results are summarized in Table XIV.

TABLE XIV

CYCLOALKYLCARBINOLS PREPARED BY PROCEDURE C

Cycloalkylcarbinol ring size	Registry no.	% yield	Bp (mm), °C
7[a]		92	45–48 (0.08)[b]
9[c]	26600-37-3	87	79–80 (0.5)
10[c]	3668-38-0	89	86–88 (0.3)

[a] Starting from cycloheptanecarboxylic acid. [b] Reference 45, bp 79–82° (4 mm). [c] Table XII, footnote *a*. Ed.

Cyclodecylcarbinol from Cyclododecanone.—The synthesis of 1-carbomethoxycycloundecene was accomplished from cyclododecanone following the procedure of Garbisch and Wohllebe.[47] This ester was converted to cycloundecanone, and cycloundecanone was converted to 1-carbomethoxycyclodecene. Reduction of the latter compound with lithium aluminum hydride in refluxing 1,2-dimethoxyethane led to cyclodecylcarbinol. This method constitutes an efficient synthesis of this carbinol.

Preparation of the Tosylates.—The general procedure described in method D was followed and the results are listed in Table XV. The nmr data are listed in Table XVI.

β-*d*-Cyclooctylcarbinyl Tosylate. A. β-*d*-Carbethoxycyclooctane.[46]—A solution of triphenylmethylsodium (*ca.* 0.0452 mol) was prepared according to the method of Renfrow and Hauser[62] and transferred under nitrogen pressure to a 1-l. flask equipped with a magnetic stirrer. Carbethoxycyclooctane (2.54 g, 0.0138 mol) was added, and the reaction mixture was stirred at room temperature under nitrogen. After 1 hr, 20 ml (0.334 mol) of ethanol-d_1 was added, and the mixture was stirred for 2 hr. Dilute acetic acid (10%, 200 ml) was added, the mixture was transferred to a separatory funnel, and the aqueous layer was discarded. The ether solution was washed with water and

(59) R. Mozingo, D. E. Wolf, S. A. Harris, and K. Folkers, *J. Amer. Chem. Soc.*, **65**, 1013 (1943).

(60) O. Kamm and J. B. Segur, "Organic Synthesis," Coll. Vol. I, Wiley New York, N. Y., 1941, p 391.

(61) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, N. Y., 1964, p 247.

(62) W. B. Renfrow and C. R. Hauser, "Organic Synthesis," Coll. Vol. II, Wiley, New York, N. Y., 1943, p 607.

TABLE XV

CYCLOALKYLCARBINYL TOSYLATES

Cycloalkylcarbinyl tosylate ring size	Registry no.	% yield	Mp, °C
5[a]	21856-53-1	98	8–11
6	3725-11-9	79	30–31[b]
7[a]	16472-98-3	94	41–42
8[a]	16472-97-2	77	23–24
9[a]	26600-43-1	84	32.5–34
10[a]	26630-78-4	86	22–24
11[a]	26600-44-2	91	18.5–20
12[a]	26600-45-3	64	64–65

[a] Table XII, footnote *a*. Ed. [b] C. F. Wilcox, Jr., and S. S. Chibber, *J. Org. Chem.*, 27, 2332 (1962), mp 32–33°.

TABLE XVI

NMR SPECTRA OF THE CYCLOALKYLCARBINYL TOSYLATES

Cycloalkylcarbinyl tosylate ring size	A_2B_2, q, 4 H aromatic H	d, 2 H, RCH_2OTs	s, 3 H, $-CH_3$	Ring envelope
5	7.49	3.82	2.45	0.9–1.9, 9 H
6	7.51	3.75	2.45	1.0–1.8, 11 H
7	7.50	3.71	2.41	1.0–2.0, 13 H
8	7.51	3.72	2.43	1.49, 15 H (1.71, shoulder)
9	7.50	3.72	2.42	1.45, 17 H
10	7.50	3.72	2.48	1.45, 19 H
11	7.50	3.78	2.42	1.38, 21 H
12	7.51	3.80	2.44	1.29, 23 H

saturated sodium chloride and dried over anhydrous magnesium sulfate; the ether was removed on the aspirator. The residue was distilled at reduced pressure yielding β-*d*-carbethoxycyclooctane in 77% yield (2.08 g), bp 53–56° (0.2 mm), bp 51–53° (0.2 mm), for the undeuterated compound. The nmr spectrum showed absorption at δ 4.05 (q, 2 H, CH_3CH_2O-), 1.58 (envelope, 14 H, ring), and 1.22 (t, 3 H, CH_3CH_2O-). The absorption for the β proton at δ 2.4 in the β-H ester was absent.

B. β-*d*-Cyclooctylcarbinol.—Method C was used to convert 2.00 g (0.17 mol) of the parent ester to β-*d*-cyclodecylcarbinol in 98% yield (1.47 g). The product distilled at 54–56° (0.1 mm). The nmr spectrum showed absorption at δ 5.21 (s, 1 H, $-OH$), 3.28 (s, 2 H, RCH_2OH), and 1.59 (envelope, 14 H, ring).

C. β-*d*-Cyclooctylcarbinyl Tosylate.—Method D was used to convert 1.47 g (0.0102 mol) of the parent alcohol to β-*d*-cyclooctylcarbinyl tosylate in 96% yield (2.82 g). The product was recrystallized from pentane and was an oil at room temperature. The nmr spectrum showed absorption at δ 7.51 (A_2B_2 quartet, 4 H, aromatic protons), 3.73 (s, 2 H, RCH_2OTs), and 1.48 (envelope, 14 H, ring).

Reference Acetates.—The reference primary and secondary acetates were prepared *via* general procedure F. Some of the substances were not obtained analytically pure but structures were unambiguously assigned by nmr spectroscopy. These data are tabulated in Tables XVII and XVIII.

The general procedure G was used to prepare the tertiary acetates listed in Table XIX, which also summarizes the nmr data.

Carboxylic Acids.—Cyclooctane-[63] and cyclononanecarboxylic acids were prepared *via* the hydrolysis following procedure E of the corresponding carbethoxycycloalkanes. The hydrolysis of 1-carbomethoxycyclodecene yielded 1-cyclodecenecarboxylic acid. The 1-cyclodecenecarboxylic acid was catalytically hydrogenated to cyclodecanecarboxylic acid.[63] Cycloundecanecarboxylic acid was prepared *via* catalytic hydrogenation of 1-cycloundecenecarboxylic acid which had been prepared from hydrolysis *via* procedure E of 1-carbomethoxycycloundecene (prepared from cycloundecanone using the procedure of Garbisch and Wohllebe[47]). Cyclododecanecarboxylic acid was prepared *via* hydrolysis of carbethoxycyclododecane. The nmr data for the cycloalkanecarboxylic acids are tabulated in Table XX along with pertinent literature references.

B. Kinetics (Kinetic Procedures).—The procedures described below are well known and closely follow the references cited. The standard acetolysis technique was used below 100° and the sealed ampoule technique for higher temperature acetolyses and for the formolyses.

Acetolysis (Standard Technique).[48,49]—The tosylate to be solvolyzed (0.2–0.7 mmol) was weighed into a 25-ml volumetric flask and dissolved in 10 ml of a 0.1 *N* solution of sodium acetate in acetic acid. The flask was immersed in a constant temperature bath and allowed to come to temperature equilibrium. Aliquots (1-ml portions) were pipetted into 6 ml of 50:50 pentane–acetic acid quench solution contained in a 25-ml erlenmeyer. One drop of 1% crystal violet indicator in acetic acid was added, and the sample was titrated with 0.025 *N* perchloric acid in acetic acid. The first sample was taken as zero time; for each sample, the time, bath temperature, and titrant volume were recorded. The infinity sample was taken after at least 12 half-lives had elapsed. The bath temperature in general varied to the extent of ±0.05°.

Acetolysis (Sealed Ampoule Technique).—The tosylate to be solvolyzed (0.5–0.9 mmol) was weighed into a small flask and dissolved in 10.0 ml of a 0.1 *N* solution of sodium acetate in acetic acid. Nine 1-ml aliquots were removed and sealed in small glass ampoules. The ampoules were placed in a constant temperature bath and allowed to come to temperature equilibrium. The first sample was taken as zero time. Each ampoule was rinsed with ether to remove traces of bath oil, carefully wiped, broken, and placed in a 125-ml erlenmeyer. A quench of 50:50 pentane–acetic acid (6 ml) and two drops of 1% crystal violet in acetic acid were added. The sample was titrated with standard 0.025 *N* perchloric acid in acetic acid. The time, titrant volume, and bath temperature were recorded for each sample; the temperature varied over a ±0.1° range. The infinity sample was allowed to remain in the bath for at least 12 half-lives.

Acetolysis (Unbuffered Technique).—The procedure was the same as for the standard and sealed ampoule techniques, except that the tosylate was dissolved in 10.00 ml of stock acetic acid, and 1 ml of 0.1 *N* sodium acetate in acetic acid was added with the quench solution to neutralize the *p*-toluenesulfonic acid formed during the reaction. The excess sodium acetate was titrated as for the other techniques.

Formolysis.—The formolysis procedure was exactly the same as for the sealed ampoule acetolysis technique, except that sodium formate in formic acid was used in place of sodium acetate in acetic acid.

Trifluoroacetolysis.[50]—The tosylate to be solvolyzed was weighed into a 25-ml flask and dissolved in 10.00 ml of a 0.125 *N* solution of sodium trifluoroacetate in trifluoroacetic acid. Eight aliquots of about 1.2 ml were removed and sealed in small glass ampoules. The ampoules were placed in a constant temperature bath and allowed to come to temperature equilibrium; the first sample was taken as zero time. Each ampoule was removed from the bath, quickly cooled to room temperature, opened, and a 1-ml aliquot was removed. The aliquot was quenched by pipetting directly into about 45 ml of methanol in a 50-ml volumetric flask. The flask was then made up to the mark with methanol, and the ultraviolet absorbance was measured at the 273.0 mμ maximum. The spectrophotometer was zeroed at 280.0 mμ with the actual sample. The time, uv absorbance, and bath temperature were recorded for each sample; the temperature varied over ±0.1°. The infinity sample was allowed to remain in the bath for at least 7 half-lives.

Calculations (Titrimetric Procedures).—The first-order titrimetric rate constants and the activation parameters were calculated according to the standard procedures.[64] The calculations were performed on an IBM computer using an appropriate program. The data treatment was the same for the spectrophotometric monitoring of the trifluoroacetolysis except that absorption data were used in the first-order rate expression.

Error Treatment.—The error in the activation energy was calculated according to the procedure outlined by Wiberg.[65]

(63) J. G. Traynham and J. S. Dehn, *J. Amer. Chem. Soc.*, **89**, 2139 (1967).

(64) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, New York, N. Y., 1964.

(65) K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, p 378.

TABLE XVII

CYCLOALKYLCARBINYL ACETATES FROM PROCEDURE F

Cycloalkylcarbinyl acetate ring size	Registry no.	% yield	Bp (mm), °C	d, 2 H, RCH_2OAc	s, 3 H, $-OCOCH_3$	Ring envelope
5		51	29–31 (1)[a]	3.80	1.95	1.1–1.8, 9 H
6	937-55-3	66	39–40 (0.7)[b]	3.90	1.95	1.0–1.9, 11 H
7	26600-50-0	54	55–56 (0.7)	3.79	1.95	1.6–1.8 13 H
8	26600-51-1	88	110 (11)	3.78	1.98	1.5–1.6, 15 H
9	26630-81-9	83	(Crude)	3.81	1.98	1.51, 17 H
10[c]	26600-52-2	42	(Crude)	3.82	1.95	1.51, 19 H
11	26600-53-3	63	100–101 (0.7)	3.82	1.98	1.46, 21 H
12	26660-54-4	52	116 (0.7)	3.85	1.98	1.38, 23 H

[a] R. C. Schreyer, *J. Amer. Chem. Soc.*, **74**, 3242 (1954), bp 45–50° (5 mm). [b] A. Favorsky and I. Borgmann, *Chem. Ber.*, **40**, 4863 (1907), bp 199–201° (740 mm). [c] Also contaminated with 51% 1-methylcyclodecene and 7% methylenecyclodecane.

TABLE XVIII

NMR SPECTRA OF SECONDARY ACETATES PREPARED *via* PROCEDURE F

Cycloalkyl acetate ring size	Registry no.	% yield	Bp (mm), °C	Broad s, 1 H, R_2CHOAc	s, 3 H, $-OCOCH_3$	Ring envelope
6[a]	622-45-7	67	38 (1)	4.64	1.95	1.2–1.85, 10 H
7[b]	18631-70-4	68	44–45 (1.2)	4.82	1.93	1.57, 12 H
8[c]	772-60-1	86	92 (11)	4.86	1.92	1·60, 16 H
12[d]	6221-92-7	73	97–98 (0.7)	4.91	1.92	1.35, 18 H

[a] L. Brunel, *Ann. Chim.*, 6, 207 (1905), bp 175°. [b] M. Kobelt, P. Barman, V. Prelog, and L. Ruzicka, *Helv. Chim. Acta*, **32**, 256 (1949), bp 95–96° (11 mm). [c] Reference *b*, bp 95–96° (11 mm). [d] Reference *b*, bp 141–142° (11 mm).

TABLE XIX

NMR DATA AND YIELDS OF TERTIARY ACETATES PREPARED *via* PROCEDURE G

1-Methyl-1-cycloalkyl acetate ring size	Registry no.	% yield	Bp (mm), °C	s, 3 H, CH_3OCO-	OAc | $CH_2-C=$ and ring envelope
5[a]	26600-59-9	21	36–38 (6.5)	1.91	1.65–1.5, 11 H
6[b]	16737-30-7	32	32–33 (0.3)	1.91	1.4–1.6, 13 H
7[c]	26600-61-3	15	45–46 (0.3)	2.01	1.4–1.9, 15 H
8	26600-62-4	3	Crude	1.89	1.2–1.7, 17 H
12	26600-63-5	86	41–45	1.89	1.1–1.6, 25 H

[a] A. C. Cope, D. Ambros, E. Ciganek, C. F. Howell, and Z. Jacura, *J. Amer. Chem. Soc.*, **82**, 1750 (1960), bp 66–67° (30 mm). [b] Reference *a*, bp 75–76° (17 mm). [c] Reference *a*, bp 74–74.5° (17 mm).

TABLE XX

LITERATURE AND NMR COMPARISONS OF THE CYCLOALKANECARBOXYLIC ACIDS

Cycloalkanecarboxylic acid ring size	Registry no.	Bp (mm), °C	s, 1 H, $-COOH$	Broad m, 1, $>CHCOOH$	Ring envelope
8[a]	4103-15-5	96–97 (0.3)	12.08	2.50	1.5–2.0, 14 H
9[b]	3667-74-1	94 (0.15)	12.19	2.52	1.3–2.0, 16 H
10[c]	3203-36-9	115 (0.13)	12.09	2.70	1.4–1.9, 18 H
11[d]	831-67-4	107 (0.1)	12.04	2.50	1.3–1.9, 20 H
12[e]	884-36-6	93–95	11.69	2.35	1.1–1.8, 22 H

[a] Reference 63, bp 108° (0.12 mm). [b] Reference 63, bp 118° (0.15 mm). [c] Reference 63, bp 122–123 (0.11 mm). [d] Societe des Usines Chimiques Rhone-Poulenc, French Patent Addn 78253; *Chem. Abstr.*, **57**, 16437*f* (1962), bp 118° (0.06 mm). [e] P. LaFont and Y. Bonnet, French Patent 1,286,709; *Chem. Abstr.*, **57**, 16437*b* (1962), mp 98°.

The error in the entropy of activation was calculated according to the equation also proposed in this reference.

C. Product Studies (General Procedure).—An amount of tosylate sufficient to produce a solution of concentration equivalent to the kinetic runs was dissolved in 50 ml of glacial acetic acid containing 0.41 g of sodium acetate. The solution was refluxed (120°) for at least 12 half-lives, cooled, diluted with 200 ml of water, and extracted with pentane. The combined extracts were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate. The vpc analyses were performed on the crude extract. The nmr analyses were performed on the residue after the pentane had been carefully fractionated off. The vpc ratios were determined by relative peak areas on a 9-ft Apiezon L column. Peaks were generally identified by the enrichment technique for the olefins and acetates. Ring-expanded secondary acetates were eliminated as possible products by the use of the enrichment technique with authentic samples. The product analysis in certain cases was performed by a combination of the nmr and vpc analyses. The product analyses are detailed in Table IV.

Stability Studies.—Under solvolysis conditions, 1-methylcyclohexyl acetate formed mainly 1-methylcyclohexene, 1-methylcyclododecyl acetate yielded 1-methylcyclododecene, cyclodecylcarbinyl acetate showed no change, methylenecyclooctane was converted to 1-methylcyclooctene, and methylenecyclodecane was converted to 1-methylcyclodecene.

D. Ionization Constant Determinations[51] (Apparatus).—The titration apparatus consisted of a jacketed titration vessel of 90-ml capacity, two burets, two electrodes, a nitrogen inlet, and a magnetic stirrer. Water from a constant temperature bath maintained at 25 ± 0.06° was circulated through the jacket.

The burets were of the automatic-zero type with integral reservoirs; they were filled by nitrogen pressure and protected by drying tubes filled with Ascarite. One buret (25 ml) delivered carbon dioxide-free ethanol, and one buret (5 ml) delivered aqueous carbonate-free sodium hydroxide. The electrodes were Fisher No. 13-639-12 (glass) and No. 13-639-52 (calomel); a Beckman Model G pH meter was used for the titrations. The nitrogen was passed through two gas washing bottles filled with 50% aqueous ethanol, and the titration vessel was covered with a sheet of parafilm.

Procedure.—A sample of the acid (about 0.33 mmol) was placed in the titration vessel and dissolved in 25 ml of ethanol, with stirring. Carbon dioxide-free water (25 ml) was pipetted in, and the solution allowed to come to thermal equilibrium (10–15 min). The initial pH reading was taken and a 0.5-ml aliquot of 0.02 *N* sodium hydroxide was added, followed by a 0.5-ml aliquot of ethanol. The mixture was stirred for 30 sec and allowed to stand for 15 sec, and the pH reading was taken. About 30 readings per run were taken in this manner, up to pH 11. Nitrogen flow was maintained throughout the run.

Solutions.—Carbon dioxide-free distilled water was prepared by boiling distilled water for 5 min, stoppering the flask, and allowing it to cool. Carbon dioxide-free ethanol was prepared by bubbling dry nitrogen through absolute ethanol for 20–30 min.

Carbonate-free sodium hydroxide was prepared by dissolving reagent grade sodium hydroxide (4 g) in 4 ml of carbon dioxide-free water and allowing to stand. A 1.1-ml portion of the supernatant 50% solution was diluted to 1 l., which was approximately 0.02 *N*. The solution was standardized against potassium hydrogen phthalate with phenolphthalein indicator.

The pH 4.00 buffer (25°) was prepared by dissolving 10.2114 g (0.05 mol) of potassium hydrogen phthalate in 1 l. of carbon dioxide-free water. The pH 9.18 buffer (25°) was prepared by dissolving 19.0687 g (0.05 mol) of sodium borate decahydrate (borax) in 1 l. of carbon dioxide-free water.

Calculations.[66]—The pK_a values were calculated at each point and corrected for H^+ activity below pH 7 and for OH^- activity above pH 7. The following equations were used.

pH 0–7 $pK_a = pH + [(HA) - (H^+)] - \log [(A^-) + (H^+)]$

pH 7 $pK_a = pH + \log (HA) - \log (A^-)$

pH 7–14 $pK_a = pH + \log [(HA) + (OH^-)] - \log [(A^-) - (OH^-)]$

The activity corrections were assumed to be the same for 50% ethanol as for water; the constant pK_a values obtained support this assumption. It was also assumed that the pH reading was equal to the logarithm of the reciprocal of the hydrogen ion concentration; no correction was made for the liquid-junction potential.

The pK_a values were converted to K_a values, averaged, and reconverted to an average pK_a. The pK_a value with the largest deviation from the average was discarded, and a new average pK_a determined. The process was repeated until the largest deviation was less than 0.03 pH unit. The calculations were performed on an IBM 1130 computer. The values are presented in Table XI.

Registry No.—*β-d*-Carbethoxycyclooctane, 26600-46-4; *β-d*-cyclooctylcarbinol, 26600-47-5; *β-d*-cyclooctylcarbinyl tosylate, 26600-48-6; cycloalkylcarbinyl acetate (5 ring size), 26600-49-7.

Acknowledgment.—The authors wish to thank the National Science Foundation (GP-9248) for financial support.

(66) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962.

The Chemistry of Acylsalicylamides. I. The Base-Catalyzed Decomposition of *O*-Benzyloxycarbonylglycyl-*N*-ethylsalicylamide

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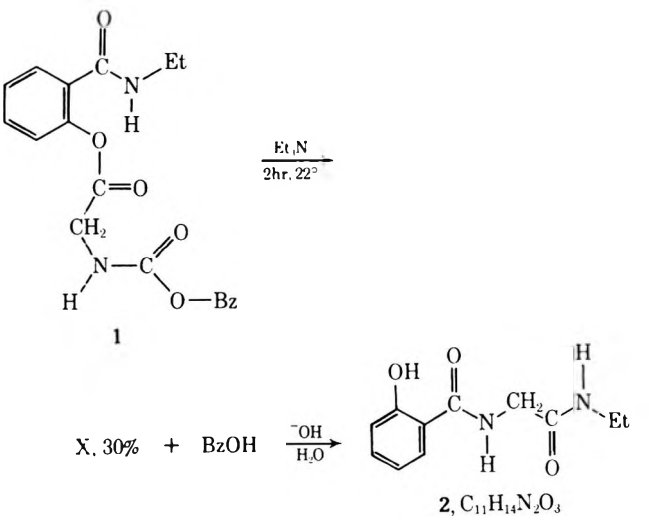
Received June 12, 1970

The structure of the major product obtained when *O*-benzyloxycarbonylglycyl-*N*-ethylsalicylamide (**1**) is treated with triethylamine is shown to be 3-(*N*-ethylacetamido)-1,3-benzoxazine-2,4-dione (**3**). The extensive ring–chain tautomerism potentially open to this substance has been realized under forcing conditions by conversion of **3** upon treatment with dimsyl sodium in DMSO into 1-salicyloyl-3-ethylhydantoin (**8**).

In the course of an investigation of the properties of benzyloxyamino acid esters of *N*-ethylsalicylamide,[1] we noted a ready decomposition of these substances under basic conditions and a formation of benzyl alcohol, along with one of a series of new, highly crystalline, neutral substances. Ring–chain tautomerism of an unusually rich kind was a possible complication for these species, and in this paper we wish to present evidence which establishes the structure of the simplest of these species and which determines the facility with which it equilibrates with its tautomers.

When *O*-benzyloxycarbonylglycyl-*N*-ethylsalicylamide[2] (**1**) is treated in acetonitrile solution with triethylamine, a red, tarry mixture of products is formed from which a highly crystalline substance, X, $C_{12}H_{12}N_2O_4$, is readily isolable. Careful saponification of this



substance results in a nearly quantitative conversion to salicyloylglycine ethylamide (**2**), an observation which establishes an amide insertion reaction of the

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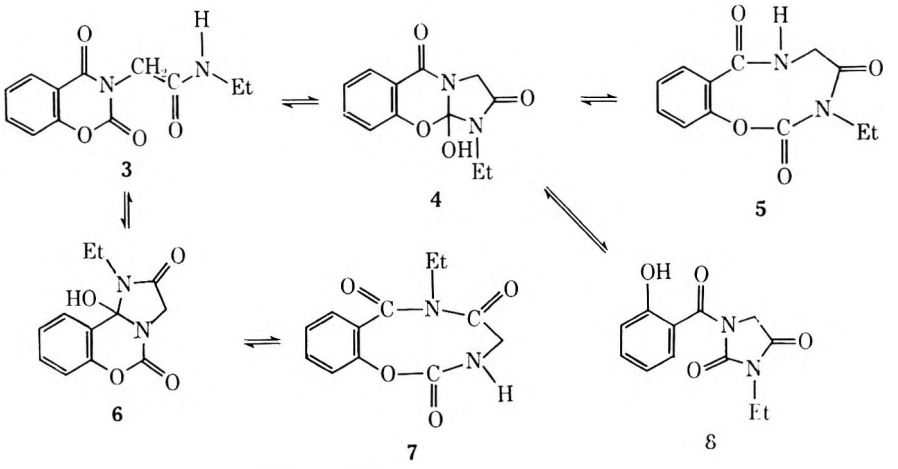
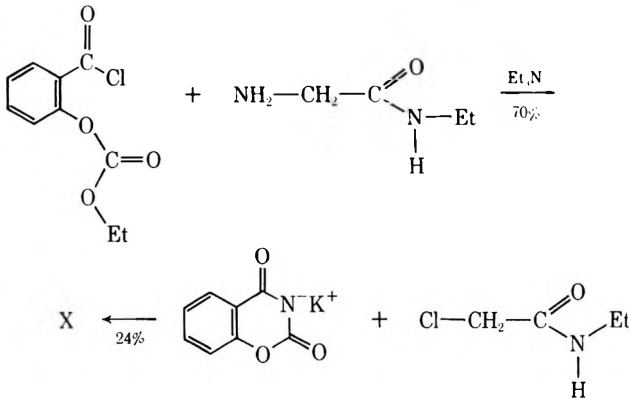
(1) D. S. Kemp and R. B. Woodward, *Tetrahedron*, **21**, 3019 (1965); D. S. Kemp, *ibid.*, **23**, 2001 (1967); D. S. Kemp, Ph.D. Thesis, Harvard University, 1964.

(2) D. S. Kemp, S. W. Wang, G. Busby III, and G. Hugel, *J. Amer. Chem. Soc.*, **92**, 1050 (1970).

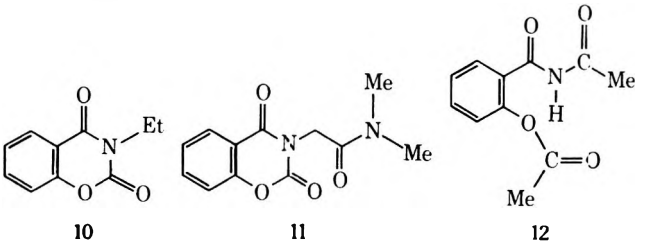


Brenner type[3] to have occurred between **1** and **2**, and which moreover establishes the likely existence of the glycine amide and salicyloyl moieties of **1** as elements of the structure of X. Even with this restriction there remained a problem of selecting one among six structures (**3**–**8**) for X, each of which might be supposed to be in equilibrium with the others *via* a series of internal carbonyl additions.[4,5] Provided these equilibrations could be established as occurring slowly, the observation that X is obtainable in two alternative ways as shown below is very strong support for assignment of structure **3** to X, but in the absence of such information these independent syntheses contribute nothing to



the resolution of the problem beyond further support for the prior conclusion that X contains salicyloyl and glycine amide moieties.

In organic solvents the infrared carbonyl absorption of X shows a characteristic two-band pattern (Figure 1 and Table I) which by comparison with models **10** and **11** appears to rule out structure **6**. The observation that **12**, which may be regarded as a rough



model for the macrocycle **7**, shows a carbonyl absorption pattern nearly identical with that of X indicates that, without further model information, infrared evidence is insufficient to exclude the remaining structures.

Evidence supportive of the cyclol structure **6** was obtained when X was treated with triethyloxonium ion, followed by triethylamine. An ethylated substance, Y, is obtained whose infrared carbonyl absorption is that of X, yet is clearly demonstrated by its nmr spectrum to possess an ethoxy function. Of the tautomers **3**–**8**, only **6** meets the infrared data and possesses an OH function convertible to an ethoxyl group.

$$\underset{C_{12}H_{12}N_2O_4}{X} + Et_3O^+BF_4^- \longrightarrow \underset{C_{14}H_{16}N_2O_4}{Y}$$

On the other hand, nmr data for X itself are only compatible with structure **3**. While initial observations of X, which for solubility reasons were conducted in trifluoroacetic acid, showed the *N*-ethylmethylene resonance as a quartet, other measurements carried out in deuterated DMSO, DMF, or pyridine showed a well-defined quintet for this resonance, a result which requires the ethylamide function to be secondary.

At this juncture the choice lay between assignation of **3** as the structure of the substance which carries with it the conclusion that the secondary amide carbonyl absorption for this substance falls at the anomalously high value of 1735 cm^{-1}, or the view that the molecule

TABLE I

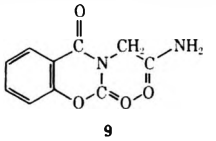
IR ABSORPTION OF X AND MODEL SUBSTANCES IN CH_2Cl_2

Substance	Carbonyl absorption, cm^{-1}
X	1705, 1765
10	1705, 1765
12	1698, 1766
Y	1705, 1765

(3) M. Brenner, *et al.*, *Helv. Chim. Acta*, **40**, 1497 (1957).

(4) For reviews of ring–chain tautomerism, see P. R. Jones, *Chem. Rev.*, **63**, 461 (1963); G. S. Hammond in M. R. Newman, "Steric Effects in Organic Chemistry," Wiley, New York, N. Y., 1966, p 460.

(5) Still more extravagant examples of ring–chain tatutomeric behavior are, in principle, possible in related systems; **9**, for example, is one among ten tautomers. It is important to note that none of the structures **3**–**8**



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are *a priori* excludable on grounds of stability. The presence of but a single saturated atom in **5** and **7** rules out internal nonbonded interaction as a destabilizing feature of these nine-ring species, while the observation of equilibria which favor cyclol isomers for not dissimilar systems[6] requires that **4** and **6** be considered as structural possibilities.

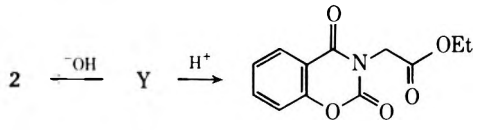
(6) R. G. Griot and A. J. Frey, *Tetrahedron*, **19**, 1661 (1963).

is a veritable Proteus, able to interconvert in a variety of media among the structures **3**–**8**, and that the nmr and ir observations taken in different media in fact correspond to different structures.

The observation that a sample of independently synthesized 3-salicyloyl-1-ethylhydantoin (**8**) is distinct from X and shows no tendency to equilibrate with it under mild conditions implies that ring–chain tautomeric shifts, at least in the series **3**–**4**–**8**, are not facile for these substances.

At the same time, the observation that the solid state infrared spectra (KBr) of X and **11** are identical in the carbonyl region, showing absorption maxima at 1645, 1700, and 1760 cm^{-1}, may be taken to support either the structural assignment of **3** with emphasis on the anomalous solution spectrum of this substance or the notion of limited but facile ring–chain interconvertability.

Further support for the assignment of **3** to X was available from the hydrolysis behavior of Y, which under basic conditions yields **2** and under acetic conditions, the ethyl ester, **13**, independently synthesized from ethyl chloroacetate and the sodium salt of *O*,*N*-carbonylsalicylamide. This latter observation is com-



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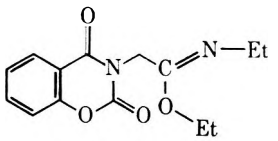
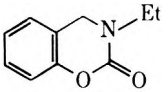
pletely consistent with assignment of the imino ether structure **14** to Y, but quite inconsistent with assignment of a structure such as the ethyl ether of the cyclol **6**. The anomalous infrared absorption of this imino



14 ≡ Y

ether, which lacks the characteristic absorption at *ca.* 1650 cm^{-1},[7] remains unexplained.

Conclusive evidence for the structural assignment of **3** to X is provided by the ultraviolet spectral data summarized in Table II. A crude model for the chromophore of the cyclol **6** is provided by the urethane **15**.[8]



15

The observation of ultraviolet absorption identical in all qualitative features for the 1,3-benzoxazine-2,4-dione derivatives **10**, **11**, and **13**, as well as for X, a finding which holds in dichloromethane as well as in ethanol, firmly establishes **3** as the structure for X in both hydroxylic and nonhydroxylic solvents.[10] The

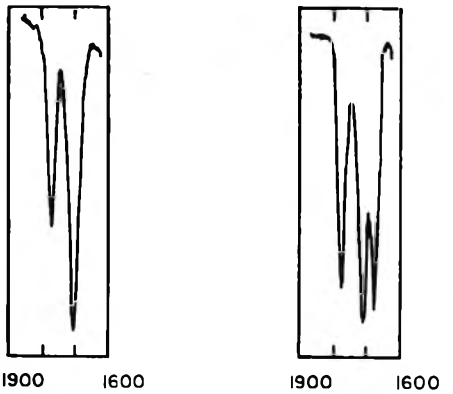


Figure 1.—Infrared carbonyl absorption (dichloromethane): a = X; b = **11**.

TABLE II
ULTRAVIOLET SPECTRAL DATA

Substance	λ_{max}, mμ (EtOH)	ε
10	236	10,300
	238	9,980
	288	2,420
	295	2,030
13	236	11,200
	288	2,400
	297	2,120
14 ≡ Y	238	11,500
	288	2,400
	296	2,120
11	236	11,800
	287	2,500
	295	2,210
3 ≡ X	237	12,600
	288	2,600
	297	2,260
15	225	3,450
	267	904
	275	739
8	238	9,460
	306	4,460
12	sh 240	2,000

conversion of **1** to **3** is best regarded as strictly analogous to a simple Brenner rearrangement,[3] for which likely intermediates are *N*-benzyloxycarbonylglycyl-*N*-ethylsalicylamide and *N*-salicyloyl-*N*-ethoxycarbonylglycylethylamide.

A remaining question was whether the ring–chain tautomerism of **3** to **8** could be observed under any conditions and the availability of **3** to **8** made it possible to examine this point. When either of these substances was allowed to remain overnight in acetonitrile containing triethylamine, only starting materials and hydrolysis products were isolated. Substitution of the stronger base, tetramethylguanidine, resulted in the recovery of starting material and **2** from **3**, and of

(7) *Cf.*, for example, H. Peter, M. Brugger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **46**, 579 (1963).

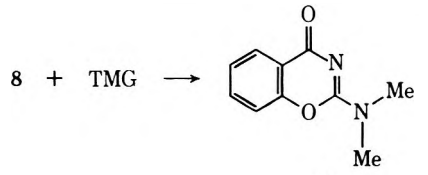
(8) Synthesized by Raney nickel desulfurization of 3-ethyl-1,3-benzoxazine-4-thia-2,4-dione.[9]

(9) D. S. Kemp and R. B. Woodward, *Tetrahedron*, **21**, 3034 (1965).

(10) In the light of the amide absorption in CH_2Cl_2 at 1705 cm^{-1} which **3** exhibits, it is of interest to note that *N*-alkylamides in the vapor phase or in very dilute solutions are reported to lie in the range of 1720–1700 cm^{-1}.[11] Also pertinent is the absorption of phthalimidoglycylethylamide at 1780 (weak), 1720 (strong), and 1680 cm^{-1} (shoulder).

(11) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 209.

3-ethylhydantoin and 2-dimethylamino-1,3-benzoxazin-4-one (**16**), identified by its formula and spectral features, from **8**. On the other hand, treatment of



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3 for 3 hr at 25° with sodium methylsulfinylmethide in DMSO resulted in conversion to **8**, isolable in *ca.* 30% yield along with 17% starting material; longer reaction times resulted in more extensive decomposition. Although other components were present in trace amounts, no attempt was made to identify them. While the presence of small amounts of **4**, **5**, **6**, and **7** cannot be excluded, it may be noted that the anion of **8** would be expected to be favored under the strongly basic reaction conditions. Clearly the conceptual mechanistic scheme which interconverts **3** with its ring–chain tautomers requires excessively severe conditions to realize it in practice.

Experimental Section

All melting points are corrected. Unless otherwise stated, magnesium sulfate was used as a drying agent. Infrared spectra were recorded with a Perkin-Elmer 237 spectrometer, ultraviolet spectra with Cary 11 and 14 spectrometers, and nmr spectra with a Varian A-60 spectrometer, using tetramethylsilane as an internal standard. Microanalyses were performed by Scandinavian Microanalytical Laboratory, Copenhagen, Denmark, and Galbraith Laboratories, Knoxville, Tenn. Unless otherwise stated, solvents and reagents were Spectro or Reagent Grade.

3-(*N*-Ethylacetamido)benzoxazine-2,4-dione (3). 1. From *O*-Benzyloxycarbonylglycyl-*N*-ethylsalicylamide (1).[12]—To a solution of 19 g (0.06 mol) of **1** in 100 ml of dry MeCN was added 4.5 g (0.05 mol) of triethylamine. After 24 hr at 25° the solution was taken to dryness *in vacuo* and the resulting dark red residue combined with 10 ml of CH_2Cl_2 and 10 ml of cyclohexane. The resulting solid was collected and washed with CH_2Cl to yield 4.4 g, 32%, mp 248.0–250.0°. Recrystallization from MeCN yielded a sample: mp 249.5–250.0°; nmr (CF_3CO_2H) δ 1.3 (t, 3, J = 7 Hz), 3.5 (quartet, 2, J = 7 Hz), 5.6 (s, 2), 7.9 (m, 5); nmr (pyridine) δ 1.0 (t, 3, J = 7 Hz), 3.3 (quintet, 2, J = 7 Hz), 4.9 (s, 2), 7.2–8.2 (m, 4), 8.5 (s, broad, 1). *Anal.* Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 57.96; H. 5.02; N, 11.10.

2. From 1,3-Benzoxazine-2,4-dione and *N*-Ethylchloroacetamide.[13]—To a stirred suspension of 8.15 g (50 mmol) of **17** and 1.40 g (58 mmol) of NaH in 100 ml of DMF was added 6.7 g (55 mmol) of *N*-ethylchloroacetamide. After 7 hr at 25° and 80° for 1 hr, the slurry was chilled and filtered, and the filtrate was concentrated *in vacuo*. The residue, 5 g, was recrystallized from methanol to yield 3.0 g of **3**, mp 248–250°, 24%, mmp 248.5–250°.

3. From Glycine Ethylamide and Ethoxycarbonylsalicyloyl Chloride.[14]—Benzyloxycarbonylglycine ethylamide was prepared from ZGlyOH and ethylamine, mp 100.7–101.2°. *Anal.* Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.86; H, 6.94; N, 11.89.

Hydrogenation of this substance followed by treatment with HCl yielded glycine ethylamide hydrochloride, mp 140.5–141.2°. *Anal.* Calcd for $C_4H_{11}N_2OCl$: C, 34.63; H, 8.00; N, 20.21; Cl, 25.58. Found: C, 34.48; H, 8.25; N, 19.21; Cl, 25.48.

To a stirred, ice-cooled solution of 0.3 g (2 mmol) of glycine ethylamide hydrochloride and 0.44 g (4 mmol) of triethylamine in 25 ml of CH_3CN was added dropwise 0.5 g (2 mmol) of ethoxycarbonylsalicyloyl chloride. The solution was stirred for 30 min at 25° and then was concentrated. The residue was dissolved in CH_2Cl_2, and the solution was extracted with two 10-ml portion of 1 N HCl, two 10-ml portions of 5% $NaHCO_3$, and 10 ml of water and then was dried, concentrated, and seeded to yield 0.37 g of solid, mp 249.0–.250.0°, 69%, mmp 250.0–251.0°.

3-(*N*,*N*-Dimethylacetamido)-1,3-benzoxazine-2,4-dione (11).—By the procedure outlined in 2 above, *N*,*N*-dimethylchloroacetamide was combined with the potassium salt of *O*,*N*-carbonylsalicylamide[15] in DMF. After 10 hr at 110°, the mixture was filtered, and the filtrate was evaporated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2, and the solution was filtered to remove starting material. Evaporation, followed by several crystallizations from ethanol, yielded 20% of product, mp 162–163.5°, identical with a sample prepared from glycine dimethylamide and ethoxycarbonylsalicyloyl chloride. *Anal.* Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.01; H, 4.94; N, 11.19.

3-(Acetamido)-1,3-benzoxazine-2,4-dione.—By the procedure outlined in 2, chloroacetamide was combined with the potassium salt of *O*,*N*-carbonylsalicylamide in DMF. After 9 hr of heating, the mixture was cooled and filtered. The filtrate was concentrated *in vacuo* to an oil which was crystallized from ethanol to give 30% of product, 258.5–260° dec (lit.[14] 250° dec). Recrystallization raised the melting point to 264.5–266.5°. *Anal.* Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.30; H, 3.78; N, 12.61.

Reactions of 3-(*N*-Ethylacetamido)-1,3-benzoxazine-2,4-dione (3). 1. Alkaline Hydrolysis. Salicyloylglycine *N*-Ethylamide (2).—A solution of 48 mg of **3** in 3 ml of 1:1 acetone–water was subjected to the slow addition (3 hr) of 1.5 equiv of 0.1 N sodium hydroxide solution. The resulting solution was acidified to pH 1, stripped of acetone *in vacuo*, and extracted with ethyl acetate. Drying and evaporation yielded a residue which was recrystallized from ethyl acetate–cyclohexane to yield 30 mg of solid, mp 161–163°, identical in all respects with samples prepared by Brenner rearrangement of *O*-glycyl-*N*-ethylsalicylamide or by saponification of the product obtained from *O*-acetoxybenzoyl chloride and glycine *N*-ethylamide. Recrystallization yielded a sample: 165.0–165.8°; ir (KBr) 1680 (amide C=O), 1650 cm^{-1} (salicylamide C=O). *Anal.* Calcd for $C_{11}H_{14}N_2O_3$: C, 59.44; H, 6.35; N, 12.61. Found: C, 59.30; H, 6.55; N, 12.53.

2. Alkylation with Triethyloxonium Fluoroborate.—To a solution of 0.27 g (1.4 mmol) of triethyloxonium fluoroborate in 8 ml of dichloromethane was added 0.32 g (1.3 mmol) of **3**, and the resulting suspension was refluxed for 40 min at which point a clear solution was observed. The solution was extracted successively with 0.5 N sodium bicarbonate and water and then was dried and evaporated. The residue was extracted repeatedly with hot cyclohexane. Evaporation and crystallization from cyclohexane yielded 0.18-g plates (50%) of **14**: mp 105–106.5°; ir ($CHCl_3$) 1770, 1705 cm^{-1}; nmr ($CDCl_3$) δ 1.1 (t, 3, J = 7.5 Hz), 1.2 (t, 3, J = 7.5 Hz), 3.35 (quartet, 2, J = 7.5 Hz), 4.0 (quartet, 2, J = 7.5 Hz), 4.8 (s, 2), 7.2–8.2 (m, 4). *Anal.* Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H 5.84 N, 10.10. Found: C, 61.04; H, 5.95; N 10.04.

When 85 mg of the above product was heated to boiling in 7 ml of ethanol and 0.5 ml of 0.1 N hydrochloric acid and then was cooled a yield of 68 mg (91%) of product precipitated, mp 126–127°. This substance was identical in all respects with 3-carbethoxymethyl-1 3-benzoxazine-2,4-dione (**3**), prepared by the alkylation of the potassium salt of *O*,*N*-carbonylsalicylamide with ethyl chloroacetate.[15]

When 48 mg of the above product was dissolved in a minimum volume of ethanol containing a few drops of 2 N sodium hydroxide, and the resulting solution was acidified with hydrochloric acid after 10 min at 25°, filtered, and concentrated, 34 mg (88%) of salicyloylglycine ethylamide (**2**) was obtained, identical in all respects with a sample obtained as described above.

3. Reaction with Bases in Aprotic Solvents.—A solution of sodium methylsulfinylmethide was prepared by dissolving 50 mg (2 mmol) of sodium hydride (washed free of oil with hexane) in 10 ml of dry DMSO. To this was added 250 mg (1 mmol) of **3**, and the resulting solution was stirred at 25° for 3 hr. The orange mixture was neutralized with 1.1 ml of 1 N hydrochloric acid, and the solvents were removed *in vacuo*. The residual oil

(12) D. S. Kemp, S. W. Wang, G. Busby, III, and G. Hugel, *J. Amer. Chem. Soc.*, **92**, 1050 (1970).

(13) W. Jacobs and W. Hiedelberger, *J. Biol. Chem.*, **21**, 145 (1915).

(14) E. Fisher and R. Freundenberg, *Justus Liebigs Ann. Chem.*, **372**, 36 (1910).

(15) A. Einhorn and C. Mettler, *Chem. Ber.*, **35**, 3650 (1902).

was partitioned between water and ethyl acetate, and the organic phase was dried and concentrated. Three crops of starting material totaling 40 mg (17%) were recovered. The aqueous phase, upon evaporation yielded 4 mg (3.4%) of 3-ethylhydantoin. Preparative tlc of the residual organic phase on silica gel using ethyl acetate–chloroform, 1:1 as eluent yielded a main fraction of 66 mg (27%) of 1-salicyloyl-3-ethylhydantoin (**8**), identified by infrared spectrum and melting point which was undepressed upon admixture of an authentic sample.

3-Ethyl-1,3-benzoxazin-2-one (**15**).—Roughly 10 g of Raney nickel was washed with water and dioxane and then added to a solution of 2.0 g of 3-ethyl-4-thio-1,3-benzoxazine-2,4-dione in 25 ml of dioxane. The slurry was stirred at room temperature for 30 min whereupon an additional 5 g of washed Raney nickel was added. After a further 45 min, the liquid was decanted, and the catalyst was washed with three 20-ml portions of dioxane. Concentration yielded an oil which was applied to an alumina column (40 g) and eluted with benzene–ethyl acetate. The product was recrystallized from cyclohexane: yield 30%; mp 57.0–58.0°; ir ($CHCl_3$) 1710 cm^{-1} (carbonate C=O); nmr ($CDCl_3$) δ 1.3 (t, 3, J = 7 Hz), 3.5 (quartet, Z, J = 7 Hz), 4.5 (s, 2), 7.1 (m, 4). *Anal.* Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.96; H, 6.37; N, 7.87.

1-Salicyloyl-3-ethylhydantoin (**8**). **A. O-Benzyloxybenzoyl Chloride.**[16]—A solution of 7.5 g of *O*-benzyloxybenzoic acid in 10 ml of thionyl chloride was allowed to stand for 1 hr and then was heated intermittantly for 30 min until gas evolution ceased. The excess thionyl chloride was removed *in vacuo* and the residual oil was flash distilled in a short-path still equipped with a pressure-equalizing dropping funnel. The pot temperature was maintained at 200–210° and the still head was heated to 160–170° with a heating tape. The substance boils in the range 160–165° (0.1 mm), yield 5.8 g, 68%. If carefully freed of excess oxalyl chloride by evacuation, product prepared by reaction of *O*-benzyloxybenzoic acid with oxalyl chloride in benzene may be used without distillation.

2. 1-(O-Benzyloxybenzoyl)-3-ethylhydantoin (**18**).—*O*-Benzyloxybenzoyl chloride (4.5 g, 18 mmol) was added in small portions, with stirring, to a solution prepared by adding 2.1 g (17 mmol) of 3-ethylhydantoin[17] to 10 ml of dry DMF containing 0.44 g (18 mmol) of washed sodium hydride. After 30 min the solvent was removed *in vacuo* and the residue was triturated with 250 ml of ether. A solid was collected, washed with water, and recrystallized from ethanol to yield 1.4 g (25%) of product, mp 139.5–140.0°. An additional 0.6 g of product could be recovered from the ether filtrate (total yield, 35%). Recrystallization from ethanol raised the melting point to 141.5–142.5°. *Anal.* Calcd for $C_{19}H_{18}N_2O_4$: C, 67.45; H, 5.36; N, 8.28. Found: C, 67.53; H, 5.20; N, 8.14.

3. 1-Salicyloyl-3-ethylhydantoin (**8**).—A solution of 1.9 g (5.7 mmol) of **18** in 15 ml of ethyl acetate and 20 ml of dioxane was treated with 0.2 g of 5% palladium on carbon, purged with nitrogen, and hydrogenated at 1 atm, 25° for 8 hr. The resulting suspension was filtered, the solvent was stripped, and the solid residue was recrystallized from ethyl acetate–cyclohexane to yield 1.3 g (90%) of crude product. Recrystallization yielded material of mp 113.5–115°: ir (CH_2Cl_2) 3350, 1800, 1745, 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.25 (t, 3, J = 7.5 Hz), 3.6 (quartet, 2, J = 7.5 Hz), 4.5 (s, 2), 6.7–7.2 (m, 4), 9.5 (s, 1). *Anal.* Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.30; H, 4.93; N, 11.34.

Reaction of 1-Salicyloyl-3-ethylhydantoin with Tetramethylguanidine. 2-Dimethylamino-1,3-benzoxazin-4-one (**16**).—A solution of 0.25 g (1 mmol) of **8** and 0.13 g of tetramethylguanidine in 10 ml of acetonitrile distilled from P_2O_5 was stirred at room temperature for 24 hr in a flask equipped with drying tube. The mixture was then neutralized with 1.1 ml of 1 *N* hydrochloric acid and evaporated to dryness. Trituration in ethyl acetate followed by filtration resulted in the recovery of 0.8 g of tetramethylguanidine hydrochloride. By repeated evaporation and trituration with ether, a total of 0.07 g of crude **16** was obtained. Recrystallization yielded 31 mg (16%): mp 152–153°; ir (CH_2Cl_2) 1675 cm^{-1} (C=O). *Anal.* Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.01; H, 5.44; N, 14.58.

Registry No.—**1**, 26595-68-6; **2**, 4611-36-3; **3**, 26595-70-0; **8**, 26595-71-1; **11**, 26595-73-3; **14**, 26595-72-2; **15**, 26595-74-4; **16**, 776-70-5; **18**, 26595-76-6; benzoylcarbonylglycine ethylamide, 21855-73-2; glycine ethylamide hydrochloride, 26595-78-8; 3-(acetamido)-1,3-benzoxazine-2,4-dione, 26600-29-3.

Acknowledgment.—Financial support from National Institutes of Health Grant GM-13453 and National Science Foundation Grant GP8329 is gratefully acknowledged.

(16) J. B. Cohen and H. W. Dudley, *J. Chem. Soc.*, 661 (1961).
(17) H. Finkbeiner, *J. Org. Chem.*, **30**, 3418 (1965).

Kinetics and Mechanism of Hydrolysis of *N*-Arylimidic Esters

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Received May 26, 1970

The influence of aryl substituents, pH, temperature, general acid–base catalysts, and solvent polarity on the kinetics of hydrolysis of ethyl *N*-arylformimidates and ethyl *N*-arylacetimidates was studied in aqueous and aqueous dioxane solutions. The data indicate that hydrolysis of these imidates involves rate-limiting reaction of the conjugate acids of the imidates with water in acidic solutions, and with hydroxide ion in alkaline solutions. Although alkoxyanilinocarbinols are probably intermediates in alkaline solutions, they may not be intermediates in acidic solutions. Hydrolysis at low pH may be a concerted process involving simultaneous C–O bond formation and C–N bond cleavage. The falloff in hydrolysis rate in strongly acidic solutions may be due to the diminished water activity of the solvent, rather than to a change in the rate-limiting step. The two sets of products formed in alkaline imidate hydrolyses may arise from competing reactions of a single intermediate, rather than from reactions of two different intermediates in acid–base equilibrium.

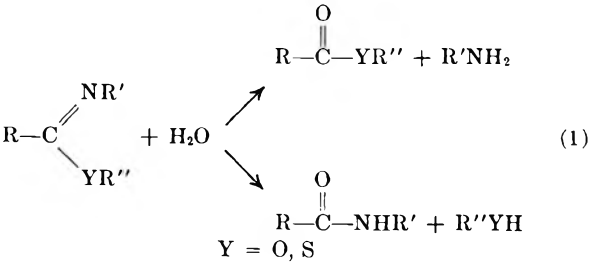
The mechanisms of hydrolysis reactions of imidic esters and related compounds have stimulated much research in the past decade. These reactions are interesting because their kinetics provide direct evidence for the existence of tetrahedral intermediates in nucleophilic displacement reactions at acyl carbon. Moreover, the same tetrahedral intermediates presumably are involved in imidate hydrolysis and ester aminolysis. Information on the mechanisms of formation and breakdown of the tetrahedral intermediates involved in imidate hydrolysis is therefore pertinent to the mechanisms of an important group of acyl transfer reactions.

Reactions whose kinetics have been studied include hydrolyses of alkyl benzimidates,[1-3] alkyl *N*-substituted acetimidates,[4,5] and phenyl *N*-alkylacetimidates.[6,7] Hydrolysis reactions of heterocyclic imidic esters and alkoxyiminium cations such as *N*-(methoxymethylene)morpholinium ion,[8] 2-(*N*-phenylimino)tetrahydrofuran,[9-11] and 2-methyloxazoline[12-14] have also been studied.

Hydrolysis reactions of thioimidates and related compounds, which are mechanistically similar to those of imidates, have also received attention. Reactions studied include hydrolyses of alkyl N-substituted thioimidates,[15,16] alkylthiomidium cations,[15-17] 2-substituted thiazolines,[13,18-20] 2,3-disubstituted thiazolinium ions,[13,19] and 2-methyl-5,6-dihydro-4*H*-1,3-thiazine.[19]

pH rate profiles have been determined for hydrolyses of a number of imidates and thioimidates. The most frequently observed profiles are "bell-shaped," with rate falloffs on either side of a plateau extending from pH 1 or 2 to a pH near that corresponding to the pK_a of the imidate, with a secomd plateau at high pH. Hydrolyses of ethyl *N*-phenylacetimidate,[4] phenyl *N*-methylacetimidate,[6] trifluorethyl *N*-methylacetimidate,[5] 2-(*N*-phenylimino)tetrahydrofuran,[9] Δ^2-oxazolines,[12,14] ethyl *N*-phenylthiobutyrimidate,[15] and Δ^2-thiazolines[18-20] exhibit this type of pH dependence. A few imidate hydrolyses have pH profiles with intermediate pH plateaus which are lower than the high pH plateaus. Examples are hydrolyses of alkyl *N*-alkylacetimidates,[4,5] methyl *N*-ethylthioacetimidate,[16] and 2-methyl-Δ^2-dihydrothiazine.[19] Alkyl thioimidates exhibit bell-shaped pH profiles with a rapidly rising rate at high pH, due to nitrile formation by elimination of thiols.[15] Alkoxyimidium, alkylthioimidium, and related heterocyclic cations, such as alkyl N,N-disubstituted thioimidium cations,[15-17] *N*-(methoxymethylene)morpholinium ion,[8] and 2,3-dimethyl-Δ^2-thiazolinium ion,[19] hydrolyze at rates which are independent of pH at low pH, but which increase with increasing pH at high pH. Several imidate hydrolyses were shown to be subject to general acid–base catalysis.[1,4,6,9,13,15,17]

The products as well as rates of imidate hydrolyses are pH dependent. Typically, an ester and an amine (or an amino ester, in the case of heterocyclic imidates) are the products at low pH, while an amide and an alcohol (or a hydroxyamide) are the products at high pH (eq 1). Usually the pH range at which the reaction



(1)

products change differs from that at which reaction rate changes.[4-9,16] Product composition is also influenced by the presence of bifunctional catalysts such as phosphate, bicarbonate, and carboxylate ions, which catalyze the formation of esters and amines.[4,8,10,15]

In acidic solutions, ethyl *m*-toluimidate[3] and 2-methyl-Δ^2-oxazoline[13] hydrolyze about twice as fast in H_2O as in D_2O.

Effects of structure on rate and mechanism of imidate hydrolysis have received less attention than the effects

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of pH and buffer catalysis. In 0.12 *N* HCl, ethyl benzimidate hydrolysis exhibits a Hammett ρ value of +1.4.[3] Hydrolysis of 2-aryl-Δ^2-thiazolines has a ρ value of +2.1 at pH 0.5, and a ρ value of approximately zero at pH 4. At pH 2.5, the Hammett plot for this reaction was nonlinear.[20] As is usually observed for reactions involving nucleophilic addition to acyl carbon, a formic acid derivative (Δ^2-thiazoline) is considerably more reactive than the analogous acetic acid derivative (2-methyl-Δ^2-thiazoline).[20] Electron-withdrawing alkoxy substituents accelerate the hydrolysis of *N*-methylacetimidates in acidic solutions but are rate retarding in alkaline solutions.[5] The influence of N substituents on hydrolytic reactivity of a series of structurally related imidic esters has not been studied, although it appears that alkyl *N*-alkylacetimidates are less reactive than alkyl *N*-phenylacetimidates at low pH but more reactive at high pH.[4]

The only nonheterocyclic *N*-arylimidic ester whose hydrolysis has been studied in detail is ethyl *N*-phenylacetimidate.[4] In aqueous 10% acetonitrile at 30°, this substance hydrolyzes with a first-order rate constant of about 7×10^{-3} sec^{-1} in the pH range 1–5. Above pH 8 the rate is constant at about 7×10^{-6} sec^{-1}. The inflection point of the sigmoid curve connecting the two rate plateaus is at about pH 6.3. The hydrolysis products also depend on pH. Below pH 6, aniline and ethyl acetate are essentially the only products. Above pH 10, formanilide and ethanol are the products (eq 1, R = CH_3; R′ = C_6H_5; Y = O; and R″ = C_2H_5). At intermediate values of pH, aniline and formanilide are both produced. The inflection point of the sigmoid product composition–pH curve falls at pH 7.7. At constant pH, low concentrations of bifunctional catalysts such as phosphate and bicarbonate cause major increases in aniline yield, while monofunctional catalysts have little effect.

More than one mechanism can account for the kinetic and product composition data for imidate hydrolysis.[21] The mechanism proposed by Chaturvedi and Schmir for hydrolysis of ethyl *N*-phenylacetimidate is outlined in Scheme I.[4]

If acid-catalyzed dehydration of the uncharged alkoxyanilinocarbinol II occurs at low pH, this mechanism leads[9] to rate eq 2. The simpler rate equation (3) re-

$$k_{obsd} = \frac{[H^+](k_2 + k_{-5}[OH^-])(k_4/k_{-2})}{([H^+] + K_1)([H^+] + k_4/k_{-2})} \quad (2)$$

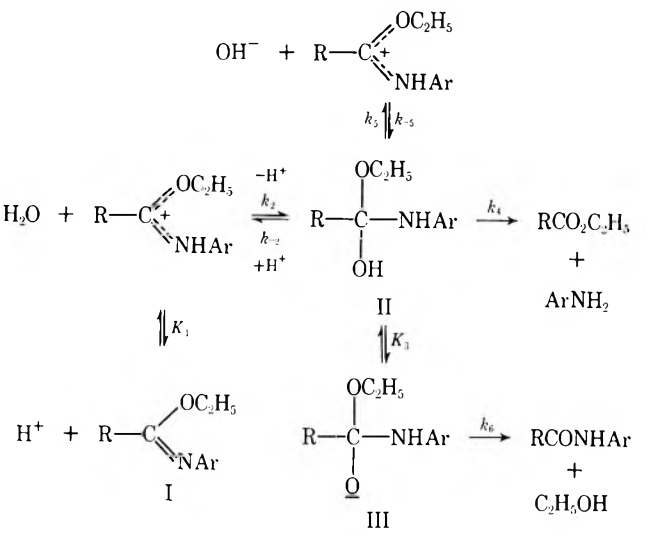
sults if it is assumed that dehydration of II is negligibly slow, *i.e.*, that $k_4 \gg k_{-2}\,[H^+]$. If the reaction follows eq 3, formation of II by reaction of the conjugate acid

$$k_{obsd} = \frac{[H^+](k_2 + k_{-5}[OH^-])}{[H^+] + K_1} \quad (3)$$

of the imidic ester with water or hydroxide ion is rate limiting over the entire pH range. In the absence of buffer catalysis, the composition of the reaction products depends on the values of K_3, k_4, and k_6, which do not appear in the rate equation.

The principal objective of the work described below was to determine the effect of *N*-aryl substituents on the hydrolytic reactivity of ethyl *N*-arylformimidates and ethyl *N*-arylacetimidates in solutions of low, intermediate, and high pH, and to investigate the effects of solvent polarity, temperature, and solvent acidity on these reactions. The results obtained suggest that the mechanism of Scheme I may require modification.

SCHEME I



Experimental Section

Materials.—The dioxane used in the reaction solutions was purified by the procedure of Fieser,[22] and was distilled from molten sodium shortly before use. Reagent grade chemicals were used in preparing all of the kinetic solutions.

The ethyl *N*-arylformimidates were prepared from triethyl orthoformate and aromatic primary amines by the procedure of Roberts[23,24] and are known compounds.[23-26] The ethyl *N*-arylacetimidates were prepared similarly from triethyl orthoacetate and aromatic primary amines.[27]

Buffer Solutions.—Acetic acid–sodium acetate buffers used in the kinetic experiments had the concentrations, ionic strengths, and buffer ratios shown in Table I.

TABLE I
ACETATE BUFFERS USED IN KINETIC EXPERIMENTS

Buffer	[HOAc]	[HOAc]/[NaOAc]	[NaCl]
A-1	0.00860	0.500	0.0344
A-2	0.01718	0.500	0.0172
A-3	0.0258	0.500	0.00
B-1	0.00860	1.00	0.0430
B-2	0.01718	1.00	0.0344
B-3	0.0258	1.00	0.0258
C-1	0.00860	1.50	0.0458
C-2	0.01718	1.50	0.0402
C-3	0.0258	1.50	0.0344

Rate Measurements.—The hydrolysis reactions, which are first order under the conditions used, were followed spectrophotometrically with a Cary Model 14 recording spectrophotometer equipped with a thermostated cell holder. Reaction solutions were prepared by thoroughly mixing appropriate volumes of the desired aqueous solutions and a very dilute dioxane solution of the imidic ester. Reaction solutions were allowed to come to thermal equilibrium with the cell holder before starting the recorder. Nominally aqueous reaction solutions were prepared by adding 10 λ of a dioxane solution of the imidic ester to 3.00 ml of the aqueous solution in the absorption cell.

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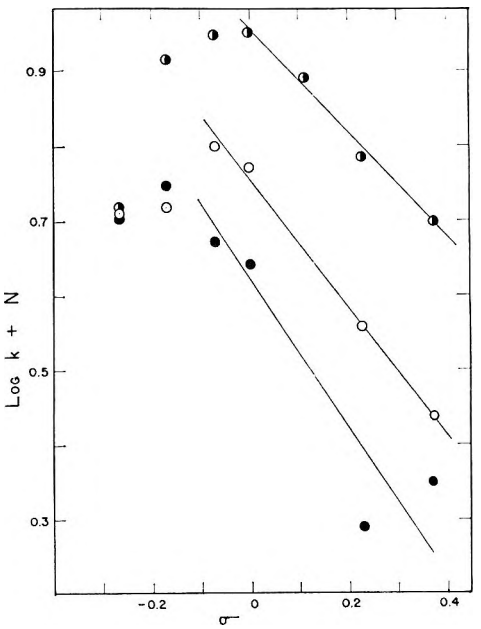

Figure 1.—Hammett plots for hydrolysis of ethyl *N*-arylformimidates: ◑, log k_{H+} in aqueous 60% dioxane–acetate buffers at 30° ($N = -4$); ○, log k_{HA} in aqueous 60% dioxane–acetate buffers at 30° ($N = +2$); ; ●, log k_0 in alkaline aqueous 20% dioxane at 45° ($N = +4$).

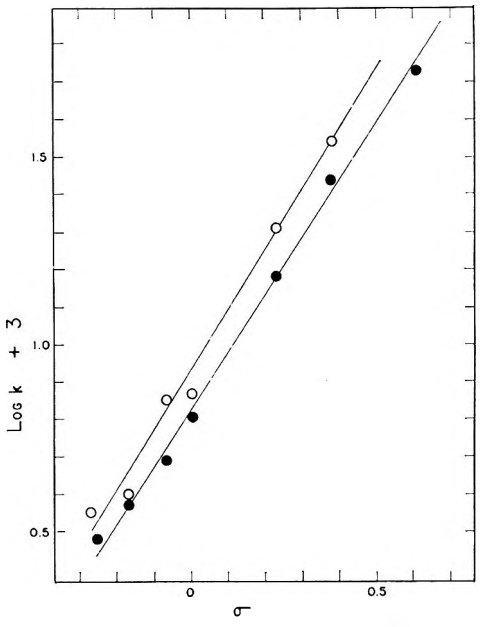

Figure 2.—Hammett plots for hydroxide ion catalyzed hydrolysis of ethyl *N*-arylformimidates in alkaline aqueous 20% dioxane at 45°, ○; for hydrolysis of ethyl *N*-arylacetimidates in aqueous 0.12 *N* HCl at 30°, ●.

Identification of Reaction Products.—Since the arylamines and anilides produced by the hydrolysis reactions have quite different ultraviolet absorption spectra, hydrolysis products were identified spectrophotometrically.

Calculations.—First-order rate constants were calculated graphically from plots of log $(A_\infty - A_t)$ *vs.* t, or by the method of Guggenheim,[28] and are expressed in reciprocal seconds. All rate constants listed in the tables are averages of two or more runs, with agreement between runs usually being within 3%. Energies of activation were calculated from the Arrhenius equation by the least-squares method. Entropies of activation were calculated for 25° as described by Bunnett, using the Arrhenius activation energies and preexponential factors.[29]

Results

The rates of hydrolysis of a series of ethyl *N*-arylformimidates were measured at several temperatures in aqueous dioxane–acetic acid–sodium acetate buffers of three dioxane concentrations. The kinetic data are summarized in Table II. These reactions exhibit buffer catalysis in solutions containing 20, 40, and 60% dioxane, although in 20% dioxane the fraction of the total hydrolysis rate due to buffer catalysis is small. Ultraviolet absorption spectra of the reaction solutions after complete hydrolysis were indistinguishable from those of the primary aromatic amines from which the imidic esters were formed; so it is inferred that ethyl formate and anilines are the products under the conditions used.

Kinetic data for reactions studied in buffers of three different buffer ratios are accurately described by the rate law of eq 4, where k_{obsd} is the experimental first-

$$k_{obsd} = k_{H^+}K_i([HOAc]/[OAc^-]) + k_{HA}[HOAc] \quad (4)$$

order rate constant, K_i is the dissociation constant for acetic acid, and k_{H^+} and k_{HA} are the apparent catalytic coefficients of hydronium ion and acetic acid. There was no detectable spontaneous (uncatalyzed) reaction, and hydrogen ion catalytic coefficients for hydrolysis reactions studied in buffers were calculated by assuming spontaneous rates of zero. Hydrolysis rate is not markedly affected by changing the salt used to maintain constant ionic strength of the buffers from sodium chloride to sodium nitrate.

Catalytic coefficients of hydronium ion and acetic acid for the various ethyl *N*-arylformimidate hydrolyses, derived from the data of Table II, are collected in Table III. Hammett plots of log k_{H^+} or log k_{HA} *vs.* the substituent constants of the *N*-aryl substituents[30] for reactions in the 60% dioxane buffers are nonlinear, and exhibit downward curvature (Figure 1). Both electron-withdrawing and electron-releasing aryl substituents diminish reactivity in aqueous dioxane–acetate buffers.

Table III also lists Arrhenius activation energies and entropies of activation for the acetic acid catalyzed and hydronium ion catalyzed hydrolysis of ethyl *N*-arylformimidates in aqueous dioxane–acetate buffers. The energies of activation are quite low and are offset by large negative entropies of activation. There is no clear correlation between the nature of the aryl substituents and the values of the activation parameters for either the hydronium ion or the acetic acid catalyzed reactions.

The catalytic coefficients of acetic acid for hydrolysis of ethyl *N*-phenylformimidate in aqueous dioxane buffers at 12° decrease rapidly with increasing dioxane concentration, while the catalytic coefficient of hydronium ion is relatively insensitive to solvent composition.

Ethyl *N*-arylformimidates hydrolyze less than a hundredth as fast in alkaline 20% dioxane solutions as in acetate buffers of the same dioxane concentration. The products of alkaline hydrolysis are formanilides and

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TABLE II

HYDROLYSIS OF X—C_6H_4N=$CHOC_2H_5$ IN AQUEOUS DIOXANE–ACETATE BUFFERS

X	Registry no.	Buffer[a]	10^3k_{obsd} at temp, °C		
		60% Dioxane			
			14.8°	30.0°	45.0°
p-CH_3O	26419-17-0	B-1	0.719	1.48	2.86
		B-2	1.00	1.91	3.56
		B-3	1.16	2.36	4.36
p-CH_3	15296-47-6	B-1	1.06	2.08	4.03
		B-2	1.34	2.62	4.83
		B-3	1.54	2.97	5.71
m-CH_3	15296-46-5	B-1	1.21	2.39	4.04
		B-2	1.47	2.89	5.10
		B-3	1.54	2.97	5.71
			11.8°	30.0°	45.0°
H	6780-49-0	A-1	0.656	1.44	2.67
		A-2	0.875	1.95	3.54
		A-3	1.09	2.32	4.50
		B-1	1.07	2.19	4.23
		B-2	1.33	2.73	5.23
		B-3	1.52	3.52	6.15
		C-1	1.60	3.20	6.27
		C-2	1.80	3.78	7.20
		C-3	2.07	4.23	8.04
		C-1[b]		3.49	
			14.8°	30.0°	45.0°
		C-2[b]		4.03	
		C-3[b]		4.43	
p-Cl	13506-16-6	B-1	0.790	1.52	2.75
		B-2	0.955	1.86	3.40
		B-3	1.12	2.14	3.95
m-Cl	15296-49-8	A-1		0.778	
		A-2		1.01	
		A-3		1.26	
		B-1	0.652	1.28	2.32
		B-2	0.770	1.47	2.81
		B-3	0.895	1.72	3.28
		C-1		1.90	
		C-2		2.22	
		C-3		2.38	

X	Registry no.	Buffer[a]	10^3k_{obsd} at temp, °C		
		60% Dioxane			
			30.0°	45.0°	60.0°
o-Cl	13506-15-5	B-1	0.326	0.627	1.13
		B-2	0.377	0.736	1.36
		B-3	0.428	0.825	1.5
			45.0°	60.0°	75.0°
o-CH_3	4943-59-3	B-1	0.946	1.71	2.84
		B-2	1.18	2.12	3.58
		B-3	1.44	2.51	4.22
		40% Dioxane			
			12.2°	30.0°	45.0°
H		A-1	8.16	16.2	27.0
		A-2	9.28	18.6	31.5
		A-3	10.8	20.9	36.5
		B-1		30.8	
		B-2		32.6	
		B-3		35.3	
		C-1		43.0	
		C-2		46.3	
		C-3		48.0	
		20% Dioxane			
			−3.8°	12.2°	
H		A-1	20.2	42.5	
		A-2	20.5	45.3	
		A-3	21.0	49.2	
p-CH_3O		A-2		21.4	
p-CH_3		A-2		35.8	
m-CH_3		A-2		48.6	
p-Cl		A-2		33.2	
m-Cl		A-2		31.0	

[a] See Table I for compositions of buffer solutions. [b] $NaNO_3$ was used to maintain constant ionic strength, rather than NaCl.

ethanol. In alkaline dioxane solutions the reaction follows the rate law of eq 5, where k_0 is the rate of the

$$k_{obsd} = k_0 + k_{OH}[OH^-] \quad (5)$$

pH independent reaction, and k_{OH} is the catalytic coefficient of hydroxide ion. Kinetic data for hydrolysis of ethyl *N*-arylformimidates in alkaline 20% dioxane are collected in Table IV, and catalytic coefficients and activation parameters derived from them appear in Table V. Electron-withdrawing aryl substituents diminish the ratio of uncatalyzed to hydroxide ion catalyzed hydrolysis. The uncatalyzed reaction is retarded by electron-withdrawing aryl substituents ($\rho \cong -0.7$), while the hydroxide ion catalyzed reaction is accelerated by such substituents ($\rho = +1.7$) (see Figures 1 and 2). For the hydroxide ion catalyzed reaction, energies of activation are independent of the nature of the aryl substituent, while both entropies and energies of activation are structure dependent for the uncatalyzed reaction.

The effect of aryl substituents on hydrolytic reactivity of *N*-arylimidic esters at low pH was studied by hydrolyzing a series of ethyl *N*-arylacetimidates in aqueous 0.12 *N* hydrochloric acid. In the vicinity of pH 1 the imidates are essentially completely protonated, and reaction rate is almost independent of acid concentration. Kinetic data and activation parameters for acid hydrolysis of several ethyl *N*-arylacetimidates and ethyl *N*-phenylpropionimidate appear in Table VI.

In acidic solutions log k_{obsd} correlates well with σ, leading to $\rho = +1.5$ for this reaction (see Figure 2). An *o*-chloro substituent increases reactivity, while *o*-methyl and *o*-ethoxy substituents decrease it. Ethyl *N*-phenylpropionimidate hydrolyzes about twice as fast as the corresponding acetimidate.

The effect of solvent acidity and water activity on rates of hydrolysis of three imidates was investigated. Rates of hydrolysis of ethyl *N*-phenylformimidate, ethyl *N*-phenylacetimidate, and ethyl *N*-*m*-chlorophenylacetimidate were measured at 25° in a series of dilute to moderately concentrated aqueous perchloric acid solutions. The hydrolysis of ethyl *N*-*m*-chlorophenylacetimidate was also studied in aqueous hydrochloric acid solutions. The experimental data are tabulated in Tables VII and VIII.

Bunnett plots[31] of log k_{obsd} *vs.* log a_w (a_w is the activity of water in the reaction solution) are curved in the region of low acid concentration, with tangents at log $a_w = 0$ larger than 10, but are nearly linear in the region

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Table III

Catalytic Coefficients and Acivation Parameters for Hydrolysis of X—C_6H_4N=$CHOC_2H_5$ in Aqueous Dioxane–Acetate Buffers

X	Temp, °C	10^3k_{HA}[a]	$10^{-4}k_{H^+}$[b]	$10^3E_{a_{HA}}$[c]	$\Delta S^{\ddagger}_{HA}$[d]	$10^3E_{a_{H^+}}$[c]	$\Delta S^{\ddagger}_{H^+}$[d]
			60% Dioxane				
p-CH_3O	14.8	2.56	2.6				
	30.0	5.12	5.2	7.4	−42	8.6	−10
	45.0	8.7	12				
p-CH_3	14.8	2.79	4.2				
	30.0	5.2	8.4	7.2	−43	8.8	−9
	45.0	9.8	18				
m-CH_3	14.8	2.50	5.0				
	30.0	6.3	8.9	9.6	−34	7.4	−13
	45.0	12.3	17				
H	11.8	2.6	4.5				
	30.0	5.9	9.0	7.7	−41	8.1	−11
	45.0	10.9	20				
p-Cl	14.8	1.92	3.1				
	30.0	3.60	6.1	7.8	−41	8.2	−12
	45.0	7.0	12.3				
m-Cl	14.8	1.41	2.6				
	30.0	2.81	5.0	8.3	−40	8.2	−12
	45.0	5.6	10				
o-Cl	30.0	0.59	1.4				
	45.0	1.27	2.6	10	−38	8.3	−14
	60.0	2.61	5.1				
o-CH_3	45.0	2.87	3.5				
	60.0	4.65	6.5	7.6	−44	10.7	−6
	75.0	8.0	15				
			40% Dioxane				
H	12.2	15.3	1.7				
	30.0	27.3	3.5	7.0	−40	6.6	−20
	45.0	55.1	5.5				
			20% Dioxane				
H	−3.8		0.9			6.4	−20
	12.2	39	1.9				

[a] Catalytic coefficients of acetic acid. [b] Catalytic coefficients of hydronium ion, calculated from kinetic data and ionization constants of acetic acid in aqueous dioxane from ref 38. [c] Cal/mol. [d] Cal/(mol degree).

Table IV

Hydrolysis of X—C_6H_4N=$CHOC_2H_5$ in Alkaline 20% Dioxane Solutions

X	[NaOH]	10^4k_{obsd} at temp, °C 30.0	45.0	60.0
p-CH_3O	0.0172	1.63	5.65	16.8
	0.0344	1.77	6.31	18.6
	0.0566	2.08	6.88	20.2
p-CH_3	0.0172		6.30	
	0.0344		6.89	
	0.0566		7.68	
m-CH_3	0.0172		5.86	
	0.0344		7.30	
	0.0566		8.30	
H	0.0172	1.90	5.69	15.1
	0.0344	2.46	6.95	20.4
	0.0566	2.96	8.23	24.1
p-Cl	0.0172		5.57	
	0.0344		8.80	
	0.0566		12.6	
m-Cl	0.0172	2.56	8.09	20.2
	0.0344	4.53	14.5	37.3
	0.0566	6.40	20.1	49.3

corresponding to water activities below 0.7. The slopes of the linear portions are about 5. Graphs of log k_{obsd} *vs.* (H_0 + log [H^+]) are nearly linear for all four reactions. The slopes of these lines [the Bunnett–Olsen ϕ values for the reactions[32] have values ranging from 1.07 to 1.2 (Figure 3).

(32) J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, **44**, 1917 (1966).

Table V

Catalytic Coefficients and Activation Parameters for Hydrolysis of X—C_6H_4N=$CHOC_2H_5$ in Alkaline 20% Dioxane

X	10^4k_0 (45°)	10^3k_{OH} (45°)	$10^3E_{a_0}$[a]	$\Delta S_0^{\ddagger}$[b]	$10^3E_{a_{OH}}$[a]	$\Delta S_{OH}^{\ddagger}$[b]
p-CH_3O	5.05	3.58	16.0	−25	13.5	−29
p-CH_3	5.58	4.01				
m-CH_3	4.70	7.12				
H	4.42	7.38	14.2	−31	13.6	−27
p-Cl	1.96	20.4				
m-Cl	2.24	34.9	15.2	−30	13.6	−25

[a] Cal/mol. [b] Cal/(mol degree).

These data also show that in acidic solutions ethyl *N*-phenylformimidate hydrolyzes about 550 times as fast as ethyl *N*-phenylacetimidate, and that ethyl *N*-*m*-chlorophenylacetimidate hydrolyzes about 4–5 times as fast in moderately concentrated hydrochloric acid solutions as it does in perchloric acid solutions of the same water activity.

Discussion

The pH hydrolysis rate profiles for typical imidic esters exhibit two regions in which rate is independent of pH. It is generally assumed that these rate plateaus correspond to rate-limiting formation of alkoxyaminocarbinol intermediates by reaction of the conjugate acid of the imidate with water and with hydroxide ion. This assumption accounts for the shape of the pH rate pro-

TABLE VI

HYDROLYSIS OF X—C_6H_4N=CR—OC_2H_5 IN AQUEOUS 0.120 *N* HCl

R	Registry no.	X	Temp, °C	10^4k_{obsd}	10^4E_a[a]	$\Delta S^{\pm}$[b]
CH_3	26431-30-1	*p*-C_2H_5O	14.2	6.37		
			30.0	30.5	16.7	−17
			45.2	111		
CH_3	26431-31-2	*p*-CH_3	14.2	8.03		
			30.0	37.1	16.6	−17
			45.2	136		
CH_3	26431-32-3	*m*-CH_3	14.2	11.2		
			30.0	49.6	16.4	−17
			45.2	184		
CH_3	19655-72-2	H	14.2	14.1		
			30.0	64.8	16.4	−16
			45.2	233		
CH_3	26431-34-5	*p*-Cl	4.6	12.1		
			14.2	34.4	16.6	−14
			30.0	152		
CH_3	26431-35-6	*m*-Cl	4.6	22.9		
			14.2	64.0	15.8	−16
			30.0	255		
CH_3	26431-36-7	3,4-Cl_2	4.6	54.1		
			14.2	149	14.9	−17
			30.0	540		
CH_3	26431-37-8	*o*-Cl	4.6	19.1		
			14.2	49	15.9	−15
			30.0	214		
CH_3	26431-38-9	*o*-CH_3	14.2	2.74		
			30.0	13.4	17.0	−18
			45.2	50		
CH_3	26431-39-0	*o*-C_2H_5O	14.2	9.23		
			30.0	39.6	15.8	−19
			45.2	137		
C_2H_5	24433-70-3	H	14.2	27.9		
			30.0	122	16.6	−14
			45.2	480		

[a] Cal/mol. [b] Cal/(mol degree).

TABLE VII

HYDROLYSIS OF X—C_6H_4N=CR—OC_2H_5 IN AQUEOUS PERCHLORIC ACID AT 25°

$[HClO_4]$	Log a_w[a]	10^4k_{obsd} R = X = H	R = CH_3; X = H	R = CH_3; X = *m*-Cl
0.824	−0.015		174	681
1.648	−0.033		82.9	356
2.472	−0.060		42.7	162
3.296	−0.097		18.2	77.5
4.120	−0.142	4260	7.45	33.8
4.944	−0.210	1610	3.13	
5.768	−0.302	515	0.942	3.92
6.592	−0.418	141	0.26	1.11

[a] a_w = water activity. Values obtained by interpolation of data from ref 31.

files and provides an explanation for the fact that rate and product composition are different functions of pH.

Most discussions of the detailed mechanism of imidate hydrolysis assume that carboxylate ester and amine are formed by breakdown of an uncharged alkoxyaminocarbinol (II of Scheme I), or a zwitterion in equilibrium with it, while amide and alcohol are produced from the conjugate base of the alkoxyaminocarbinol (III of Scheme I). As Schmir and Cunningham point out, however, the kinetic and product data can be accounted for by other reaction schemes (ref 9, footnote 24).

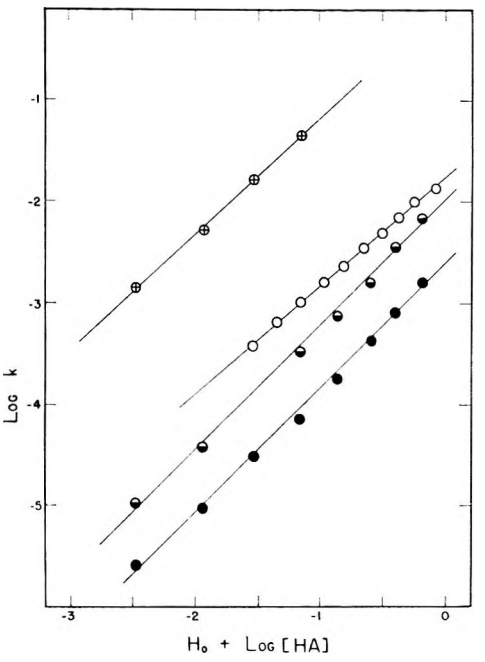


Figure 3.—Bunnett–Olsen plots for hydrolysis of ethyl *N*-arylimidates in moderately concentrated aqueous acid solutions at 25°: ⊕, ethyl *N*-phenylformimidate, perchloric acid; ○, ethyl *N*-*m*-chlorophenylacetimidate, hydrochloric acid; ⊖, ethyl *N*-*m*-chlorophenylacetimidate, perchloric acid; and ●, ethyl *N*-phenylacetimidate, perchloric acid.

TABLE VIII

HYDROLYSIS OF *m*-ClC_6H_4N=$C(CH_3)OC_2H_5$ IN AQUEOUS HYDROCHLORIC ACID AT 25°

[HCl]	Log a_w[a]	10^4k_{obsd}
0.669	−0.011	137
1.338	−0.023	96.8
2.007	−0.040	72.3
2.676	−0.058	48.6
3.345	−0.082	35.2
4.014	−0.107	22.9
4.683	−0.140	16.3
5.352	−0.164	10.2
6.021	−0.215	6.46
6.690	−0.259	3.90

[a] a_w = water activity. Values obtained by interpolation of data from ref 31.

Alkoxyaminocarbinols are amide hemiacetals, and their hydrolysis reactions may have some features in common with those of amide acetals. Amide acetals hydrolyze in both acidic and alkaline solutions. Due in part to their extremely high reactivity, amide acetals are difficult subjects for kinetic studies. No published kinetic data on hydrolysis of simple amide acetals exist. *N*,*N*-Dimethylbenzamide diethyl acetal hydrolysis is general acid catalyzed in aqueous dioxane buffers and is independent of pH in alkaline solutions.[33] Amide acetals hydrolyze to esters and amines under acidic conditions but yield mostly amides and alcohols under alkaline conditions.[33-35] In other words, the products of amide acetal hydrolysis vary with pH in a manner similar to that observed for imidate hydrolysis, even though the amide acetals cannot be in equilibrium

(33) W. Doo, M. A. Thesis, University of California, Santa Barbara, Sept 1969.

(34) H. Meerwein, W. Florian, N. Schon, and G. Stopp, *Justus Liebigs Ann. Chem.*, **641**, 1 (1961).

(35) T. Taguchi and Y. Kawazoe, *J. Org. Chem.*, **26**, 2699 (1961).

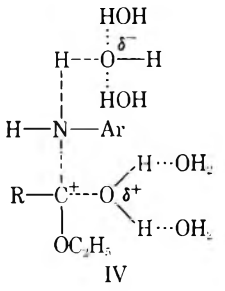
with conjugate bases analogous to III of Scheme I. This, together with the extremely high reactivity of amide acetals under acidic conditions, raises several questions concerning the mechanism of imidic ester hydrolysis. These include the following. Are amide hemiacetals too reactive to be intermediates in imidate hydrolyses in acidic solutions? Is amide hemiacetal dehydration the only plausible explanation for the fall-off of imidate hydrolysis rate with increasing acidity in strongly acidic solutions? And finally, is an acid–base equilibrium between two intermediates necessary to account for the pH dependence of imidate hydrolysis product composition?

Hydrolysis of *N*-Arylimidic Esters in Acidic Solutions.—A considerable body of kinetic evidence supports the conclusion that the rate-limiting step of imidate hydrolysis in the region of the low pH plateau involves reaction of water with the conjugate acid of the imidic ester. In addition, substituent effects on rates of hydrolysis of ethyl *N*-arylacetimidic esters in acidic solutions are readily accounted for if the rate-limiting step of the reaction involves attack by water on the acyl carbon of the conjugate acid of the imidic ester. Imidic ester conjugate acids are alkoxyaminocarbonium ions: substituents which stablize carbonium ions should diminish their reactivity with nucleophiles, and *vice versa*. Alkyl groups on the acyl carbon should stabilize the imidate conjugate acids, and a methyl group, with three α hydrogens, should stabilize the conjugate acid of an acetimidate somewhat more effectively than the ethyl group of the conjugate acid of a propionimidate, which has only two α hydrogens. This would account for the fact that ethyl *N*-phenylpropionimidate hydrolyzes about twice as fast as ethyl *N*-phenylacetimidate in dilute hydrochloric acid solutions (Table VI). It would also provide at least a partial explanation for the fact that ethyl *N*-phenylformimidate hydrolyzes more than 500 times as fast as the corresponding acetimidate in acidic solutions, although steric and hydration effects probably also play a role in this case.

Similarly, electron-attracting substituents in the *N*-aryl group should destabilize the conjugate acids of ethyl *N*-arylimidic esters and render them more susceptible to attack by water. This also is supported by the data of Table VI: hydrolysis rates of ethyl *N*-arylacetimidates in dilute hydrochloric acid solutions correlate well with Hammett's σ constants, with a ρ of +1.5 (Figure 2). Ortho substituents on the *N*-aryl group appear to influence reactivity primarily by their electronic rather than their steric properties. In ethyl *N*-arylacetimidate hydrolysis, *o*-methyl and *o*-ethoxy substituents decrease reactivity; *o*-chloro increases it.

The observation that differences in hydrolytic reactivity of a series of meta- and para-substituted ethyl *N*-arylacetimidates in dilute hydrochloric acid are due largely to differences in activation energy rather than differences in entropy of activation is also reasonable, if the principal influence of substituents is on the strength of the developing acyl carbon–water oxygen bond in the rate-limiting transition state.

Alkoxyaminocarbinols are usually assumed to be products of the rate-limiting reaction of water with imidate conjugate acids. However, it seems likely that these tetrahedral species have no finite existence in acidic solutions. The large negative entropies of activation for imidate hydrolysis in acidic solutions suggest that assembly of the rate-limiting transition state requires considerable ordering of the solvent. This view is supported by the Bunnett–Olsen ϕ values of 1.1–1.2 for hydrolysis of *N*-arylformimidates and *N*-arylacetimidates in aqueous hydrochloric and perchloric acid solutions (Figure 3), which suggest that the rate-limiting transition state contains about five more water molecules than the species from which it is formed.[32] Such a high degree of hydration can be accounted for by assuming that the rate-limiting step involves concerted general acid–base catalyzed conversion of the imidate conjugate acid to aniline plus the conjugate acid of a carboxylate ester. The transition state structure may resemble IV, in which C–O bond formation is further advanced than C–N bond cleavage.



IV

The treatment of Bunton and Shiner[36] leads to an estimated solvent deuterium isotope effect of $k_{H_2O}/k_{D_2O} \cong 2$ for a transition state having structure IV, in agreement with experimental observation.[3,13]

pH rate profiles for hydrolyses of imidates, thioimidates, oxazolines, and thiazolines exhibit rate decreases at low pH (usually below pH 2). These rate decreases have been attributed to acid-catalyzed dehydration of alkoxyaminocarbinol II, although it has been recognized that a strong dependence of hydrolysis rate on water activity would lead to a similar rate falloff at moderately high acidities.

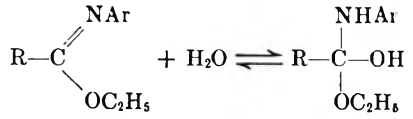
If, as argued above, the alkoxycarbinolamine is best thought of as a transition state rather than as an intermediate in *N*-arylimidic ester hydrolysis, it follows that the decrease in hydrolysis rate with increasing acidity in moderately concentrated solutions of hydrochloric or perchloric acid (Tables VII and VIII) is a water activity effect. This conclusion is strengthened by the fact that excellent straight lines are obtained in Bunnett–Olsen plots[32] of log k_{exp} *vs.* $(H_0 + \log HX)$ (Figure 3). It should be pointed out, however, that eq 2, derived on the assumption of reversible alkoxycarbinolamine formation, also predicts a strong rate decrease with increasing acid concentration, provided that hydrogen ion activities are substituted for hydrogen ion concentrations.

Hydrolysis of *N*-Arylformimidic Esters in Aqueous Dioxane–Acetate Buffers.—In aqueous dioxane–acetate buffers, ethyl *N*-arylformimidate hydrolyses follow the rate law of eq 4 (Tables II and III). Both the acetic acid and the hydronium ion catalyzed reactions exhibit very low Arrhenius activation energies and large negative entropies of activation. Plots of both k_{H^+} and k_{HA} *vs.* σ are nonlinear, exhibiting downward curvature (Figure 1). Downward curvature in Hammett plots

(36) C. A. Bunton and V. J. Shiner, *J. Amer. Chem. Soc.*, **83**, 42, 3207, 3214 (1961).

may be due to a change in the rate-limiting step of the reaction. In the present instance, however, another cause seems more probable.

The low activation energies of these reactions (6–9 kcal/mol) suggest that the rate-limiting step is preceded by a preequilibrium with a negative temperature coefficient. Preequilibria which might be involved are hydration of the imidate conjugate acid, dissociation of acetic acid, and protonation of the imidate, whose equilibrium constants are designated by K_{hyd}, K_{HA}, and H_b, respectively. Imidate hydration (eq 6) is estimated to



(6)

be endothermic, so that K_{hyd} should increase with increasing temperature. The dissociation constant of acetic acid in aqueous dioxane is relatively insensitive to temperature in the temperature region used in the kinetic measurements.[37] The temperature dependence of K_b for imidates is not known, but K_b for amines has a negative temperature coefficient,[38,39] and it is reasonable to assume that K_b for other nitrogen bases also decreases with increasing temperature.

If K_b appears in the rate equation, preequilibrium imidate hydration is excluded, since the rate equation for rate-limiting general acid catalyzed hydrolysis of the alkoxyanilinocarbinol is given by eq 7. However, if imidate hydration is rate limiting in acetate buffers, as it appears to be in mineral acid solutions, the rate equation is given by eq 8, where the first term repre-

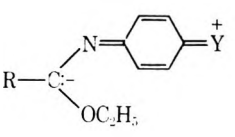
$$k_{exp} = kK_{hyd}K_{HA}[HOAc]/[OAc^-] + k'K_{hyd}[HOAc] \quad (7)$$

$$k_{exp} = kK_bK_{HA}[HOAc]/[OAC^-] + k'K_bK_{HA}[HOAc] \quad (8)$$

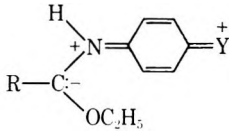
sents water-catalyzed hydration of the alkoxyanilinocarbonium ion, and the second term represents its general acid catalyzed hydration. The first term on the right side of eq 8 corresponds to hydrolysis of the imidate by the same mechanism which operates at low pH in solutions of strong acids. The second term may describe acetate ion catalyzed reaction of water with the acyl carbon of the protonated imidate, or may correspond to proton transfer from acetic acid to imidate nitrogen, concerted with C–N bond fission and water-catalyzed nucleophilic attack by water on the acyl carbon of the imidate. The second process, in which charge is developed on carboxyl oxygen of acetic acid and on oxygen of the water molecule which is functioning as a general base catalyst, seems more likely than the first, in which charge is reduced on both anilino nitrogen and acetate oxygen. Otherwise, it is difficult to account for the fact that the catalytic coefficient of acetic acid increases as the dioxane concentration of the reaction solution decreases (see Table III).

If the points for the *N*-*p*-tolyl- and *N*-*p*-anisylformimidates are excluded, Hammett plots of log k_{H^+} and log k_{HA} for ethyl *N*-arylformimidate hydrolysis in aqueous 60% dioxane–acetate buffers have slopes of approximately −0.6 and −0.9, respectively (Figure 1). The negative ρ values require that the negative ρ for protonation of the imidates (K_b) has a larger magnitude than the positive ρ for reaction of the conjugate acids with water (k and k' of eq 8).

It is unlikely that the negative deviations of the points for the *N*-*p*-anisyl- and *N*-*p*-tolylformimidates from the Hammett plots defined by the other imidates are due to stabilization of the alkoxyanilinocarbonium ion conjugate acids of these compounds by the electron-donating para substituents, for if this were the case a similar deviation should have been observed for hydrolysis of *N*-arylacetimidates in dilute hydrochloric acid (Figure 2). The negative deviations of the points for these two compounds suggest that *p*-alkoxy and *p*-methyl substituents may stabilize the imidates relative to their conjugate acids. Canonical structures such as V may make larger contributions to the resonance hybrid of the imidate than structures such as VI make to its conjugate acid, owing to the close proximity of positive charges in the latter.



V



VI

Hydrolysis of *N*-Arylformimidic Esters in Alkaline Solutions.—The fact that hydrolysis rate and product composition are independent functions of pH in alkaline solution leads to the conclusion that alkaline hydrolysis of ethyl *N*-arylimidic esters does not involve a preequilibrium between the imidic ester and alkoxyanilinocarbinol II. Chaturvedi and Schmir[4] found that the high pH plateau of the pH rate profile for ethyl *N*-phenylacetimidate hydrolysis begins at about pH 8, at which the hydrolysis products consist of about 40% aniline and 60% acetanilide. Above pH 10, however, acetanilide is essentially the only product. If the tetrahedral hydrate II is in equilibrium with the imidic ester, the experimental results require that the rate-limiting step involve conversion of II to another intermediate, which yields products *via* two fast processes of different pH dependence. Such a reaction scheme seems unnecessarily complex.

Hydrolysis of ethyl *N*-arylformimidates in dilute 20% dioxane–sodium hydroxide solutions follows the rate law of eq 5. Previously, hydroxide ion catalysis of imidate hydrolysis has been observed only for substrates which exist in cationic form in alkaline solution due to the presence of quaternary nitrogen atoms.[8,15–17] A hydrolytic pathway which is first order in hydroxide ion is not accommodated by the generally accepted mechanisms of *N*-substituted imidic ester hydrolysis (Scheme I, $k_2 \gg k_{-2}$, $k_5 \ll k_{-5}$). Scheme I could be modified to include a hydroxide dependent pathway by assuming that hydroxide ion may react with the unprotonated imidate to form an anilide ion [HC(OC$_2$H$_5$)(OH)(NAr)$^-$] which is in equilibrium with III.

While alkoxyanilinocarbinols (II) may not be intermediates when *N*-arylimidic esters hydrolyze in acidic solutions (see above), they probably are discrete intermediates in the alkaline hydrolysis of these compounds.

Otherwise, it would be difficult to account for the fact that the product forming steps follow the rate-limiting step in alkaline solutions. The pH-indepen-

(37) H. S. Harned and L. D. Fallon, *J. Amer. Chem. Soc.*, **61**, 2374 (1939).
(38) L. L. Schalager and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 14 (1963).
(39) E. J. King, "Acid-Base Equilibria," Pergamon Press, Macmillan, New York, N. Y., 1965, p 187.

dent process which produces II in alkaline solutions presumably involves reaction of hydroxide ion with the conjugate acid of the imidate.

The usual explanation for the dependence of imidate hydrolysis product composition on pH assumes that amine and ester are formed from a more highly protonated intermediate than that which yields amide and alcohol. A scheme involving an equilibrium between intermediates II and III satisfactorily accounts for the experimental observations (see Scheme I). Alternatively, alkaline imidate hydrolysis may resemble alkaline hydrolysis of amide acetals, in which two sets of products are formed by competing reactions of the amide acetal. The alkoxyanilinocarbinol II may form aniline and carboxylate ester by an Se2 reaction with hydronium ion, and form anilide and alcohol by dissociation to alcohol and an anilinohydroxycarbonium ion, which is converted to the anilide by loss of a proton. Amide acetals exhibit measurable electrical conductivity in polar aprotic solvents,[34,40] presumably owing to dissociation to alkoxyaminocarbonium and alkoxide ions, and a similar dissociation of alkoxyanilinocarbinol II in water seems reasonable. If this dissociation occurs, both sets of products may be formed from II. The mechanism of the product forming step in alkaline hydrolysis of imidic esters remains open.

If the uncatalyzed alkaline hydrolysis of *N*-arylimidic esters involves rate-limiting reaction of hydroxide ion with the imidate conjugate acid, it will follow the rate law of eq 9, where K_b is the basicity constant

$$k_o = kK_bK_w \quad (9)$$

of the imidate and K_w is the autoprotolysis constant of water. The observed activation parameters (Table V) for this reaction are thus complex quantities. From the known enthalpy and entropy of dissociation of water[41] and enthalpies and entropies of protonation of imidates estimated from those of amines (ref 36, p 14), I estimate the enthalpy of activation for the reaction of hydroxide ion with ethyl *N*-phenylformimidium ion to be about 10 kcal/mol and the entropy of activation to be about −25 eu. These values are reasonable for a bimolecular reaction of this charge type.

k_0 values for alkaline *N*-arylformimidate hydrolysis were obtained from intercepts of k_{exp} *vs.* $[OH^-]$ plots, and are of low precision in the case of imidates having electron-withdrawing aryl substituents. Making allowance for this, the Hammett ρ value obtained for the imidates except the *p*-methoxy- and *p*-methyl-substituted compounds (Figure 1) is *ca.* −0.7 for the uncatalyzed reaction. The negative deviation of the points for the *p*-anisyl and *p*-tolyl compounds can be rationalized by the same argument used above for the hydrolysis reactions in acetate buffers.

The rate-limiting step of the hydroxide-catalyzed hydrolysis reaction probably involves attack by hydroxide ion on the acyl carbon of the *N*-arylformimidate. This bimolecular process, which is analogous to that involved in alkaline hydrolysis of amides and esters, should have a substantial negative entropy of activation, as is observed. The Hammett ρ value of +1.7 (Figure 2) for this reaction is of the expected sign and of reasonable magnitude for a nucleophilic addition to a carbon–nitrogen double bond.

(40) G. Simchen, H. Hofmann, and H. Bredereck, *Chem. Ber.*, **101**, 42 (1968).

(41) E. A. Moelwyn-Hughes, "Physical Chemistry," 2nd ed, Macmillan, New York, N. Y., 1961, p 877.

Mechanism of the Base-Catalyzed Synthesis of Azobenzenes

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Received August 22, 1969

The base-catalyzed reaction between aniline and nitrosobenzene to form azobenzene has been investigated kinetically under homogeneous reaction conditions. Energy of activation, entropy of activation, and Hammett ρ values are calculated. The mechanism is postulated as nucleophilic attack of the negatively charged nitrogen atom of aniline on the nitrogen atom of nitrosobenzene. This is the reverse of the mechanism proposed for the same reaction in acid solution.

The base-catalyzed reaction between aniline and nitrosobenzene to form azobenzene was first utilized by Campbell[1] and coworkers. Hot concentrated sodium hydroxide was used with toluene as the solvent with the result that the reaction took place at the interface of a two-phase system. Azoxy compounds are also a minor product of this reaction. In order to investigate the kinetics and to elucidate the mechanism of this reaction, homogeneous reaction conditions are desirable. It was found that a homogeneous reaction mixture could be obtained by using tetramethylammonium hydroxide in a 80% pyridine–20% water, by volume, solution. It was then possible to follow the kinetics of the reaction spectrophotometrically.

* To whom correspondence should be addressed.

(1) N. Campbell, A. W. Henderson, and D. Taylor, *J. Chem. Soc.*, 1281 (1953).

Results

In 0.10 *M* tetramethylammonium hydroxide solutions (80% pyridine–20% water by volume) with the initial concentration of aniline 0.025–0.250 *M* and that of nitrosobenzene 0.050–0.300 *M*, the rate of the reaction was found to be proportional to the product of the stoichiometric concentrations of aniline and nitrosobenzene. The pseudo-second-order rate constants, *k*, were calculated by means of a FORTRAN IV G program on an IBM 360/50 computer. The constants were satisfactory as shown in Table I.

In 80% pyridine–20% water, under the experimental conditions used, the pseudo-second-order rate constant for the formation of azobenzene is linearly related to the tetramethylammonium hydroxide concentration. The linear equation is

$$k = (0.29 + 70.4s) \times 10^{-4} \text{ l. mol}^{-1} \text{ sec}^{-1}$$

TABLE I
PSEUDO-SECOND-ORDER RATE CONSTANTS OF AZOBENZENE FORMATION IN 80% PYRIDINE–20% WATER SOLUTION (TETRAMETHYLAMMONIUM HYDROXIDE CONCENTRATION 0.10 *M* AT 30°)

Initial concentration, *M*		$k \times 10^4$
Aniline	Nitrosobenzene	l. mol^{-1} sec^{-1}
0.02	0.10	7.62
0.05	0.10	7.39
0.07	0.10	7.06
0.10	0.10	7.33
0.15	0.10	7.42
0.25	0.10	7.31
0.10	0.05	7.52
0.10	0.15	7.01
0.10	0.20	7.35
0.10	0.30	7.56
	Average	7.36

where s is the stoichiometric concentration of tetramethylammonium hydroxide in moles. As is apparent in the equation, the k value at neutrality is a small positive value (Figure 1 and Table II). All of the

TABLE II
PSEUDO-SECOND-ORDER RATE CONSTANTS *vs.* TETRAMETHYLAMMONIUM HYDROXIDE CONCENTRATION[a]

$k \times 10^4$	[$(CH_3)_4NOH$] in mol/l.
7.33	1.10
5.51	0.075
3.90	0.050
2.05	0.025

[a] See Figure 1.

apparent activation parameters were calculated from the apparent second-order rate constants at a temperature of 40°. A computer program using the slope of the plot of ln k *vs.* $1/T$ calculated the apparent activation energy (E_a), apparent activation free energy ($\Delta G^{\ddagger}_{40}$), apparent activation enthalpy ($\Delta H^{\ddagger}_{40}$), and and apparent activation entropy ($\Delta S^{\ddagger}_{40}$) for the formation of azobenzene. They were found to be 16.0, 22.4, and 15.4 kcal mol^{-1} and −22.2 cal deg^{-1} mol, respectively.

The rates of the reactions of aniline with substituted nitrosobenzenes and those of substituted anilines with nitrosobenzene were measured in 80% pyridine–20% water (3.10 *M* tetramethylammonium hydroxide). The results listed in Tables III–VI show that electron-attracting groups (*e.g.*, *p*-nitro) in anilines increase the rate of the reaction, while electron-releasing groups (*e.g.*, *p*-methyl) decrease the rate of the reaction. The effect is reversed for substituents of nitrosobenzene. In both cases, the relative rates of the reaction satisfy the Hammett equation. The values of ρ were calculated to be about −2.1 for the condensations of aniline with substituted nitrosobenzenes. Although the scatter is large in this case, the trend is there. The value of ρ is +2.0 for the condensations of substituted anilines with nitrosobenzene (see Figure 2 and Table VII).

Discussion

Since a linear relationship exists between the tetramethylammonium hydroxide concentration and the pseudo-second-order rate constant, the hydroxide ion is presumed to be involved in the transition state.

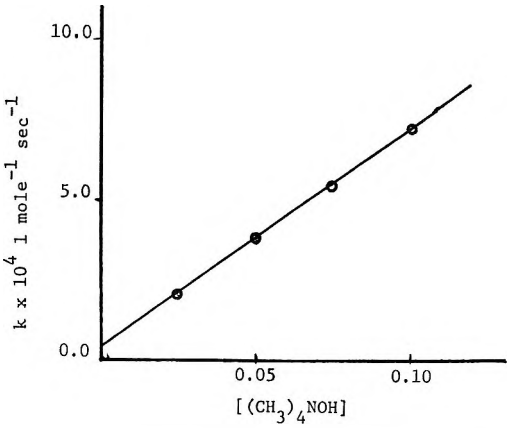

Figure 1.—Plot of pseudo-second-order rate constants *vs.* tetramethylammonium hydroxide concentration: 80% pyridine–20% water at 30° (azobenzene formation).

TABLE III
APPARENT SECOND-ORDER RATE CONSTANTS FOR THE CONDENSATION OF ANILINE WITH SUBSTITUTED NITROSOBENZENES IN 0.10 *M* TETRAMETHYLAMMONIUM HYDROXIDE, 20% WATER–80% PYRIDINE SOLUTIONS

Substituent	Temp, °C	$k \times 10^3$ l. mol^{-1} sec^{-1}
4-CH_3	30.0	1.4
	40.0	3.3
	50.0	5.4
3-CH_3	30.0	1.0
	40.0	1.9
	50.0	4.7
H	30.0	0.77
	40.0	1.6
	50.0	4.1
4-Cl	30.0	0.36
	40.0	0.50
	50.0	0.96
3-Cl	30.0	0.10
	40.0	0.19
	50.0	0.48
4-Br	30.0	0.20
	40.0	0.47
	50.0	0.99
3-Br	30.0	0.11
	40.0	0.21
	50.0	0.48
4-CH_3O	30.0	1.8
	40.0	1.9
	50.0	4.1
3-CH_3O	30.0	3.7
	40.0	7.0
	50.0	45

A probable reaction mechanism (eq 1–4) is shown for this relationship. A small contribution to the overall

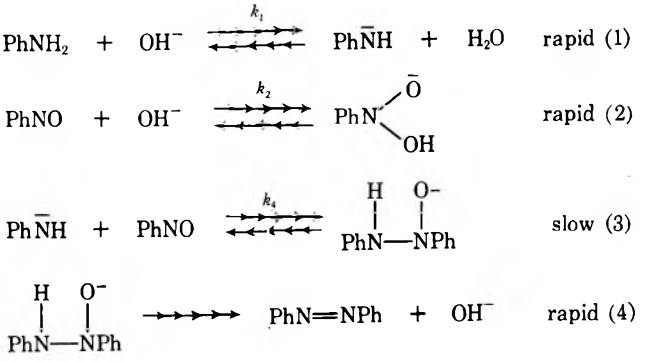

TABLE IV

ACTIVATION PARAMETERS AND MEASURES OF RELIABILITY FOR THE CONDENSATION OF ANILINE WITH SUBSTITUTED NITROSOBENZENES IN 0.10 *M* TETRAMETHYLAMMONIUM HYDROXIDE, 20% WATER–80% PYRIDINE SOLUTIONS

Substituent	E_a, kcal/mol	$\Delta G^{\ddagger}_{40}$, kcal/mol	$\Delta H^{\ddagger}_{40}$, kcal/mol	$\Delta S^{\ddagger}_{40}$, eu/mol	Coefficient of variation[a]	Standard deviation[a]
4-CH_3	13.03	21.92	12.41	−30.37	1.40	0.081
3-CH_3	14.98	22.25	14.35	−25.20	1.21	0.074
H	16.03	22.36	15.41	−22.21	1.32	0.084
4-Cl	9.61	23.10	8.99	−45.05	1.39	0.104
3-Cl	15.12	23.69	14.50	−29.35	1.20	0.101
4-Br	15.42	23.14	14.80	−26.62	0.13	0.010
3-Br	14.40	23.63	13.78	−31.45	0.63	0.053
4-CH_3O	8.10	22.26	7.48	−47.22	3.49	0.210
3-CH_3O	24.05	21.45	23.43	6.32	8.25	0.376

[a] Measures the variability between the experimental points plotted (ln k) and the least-squares value as calculated for a line drawn through these points.

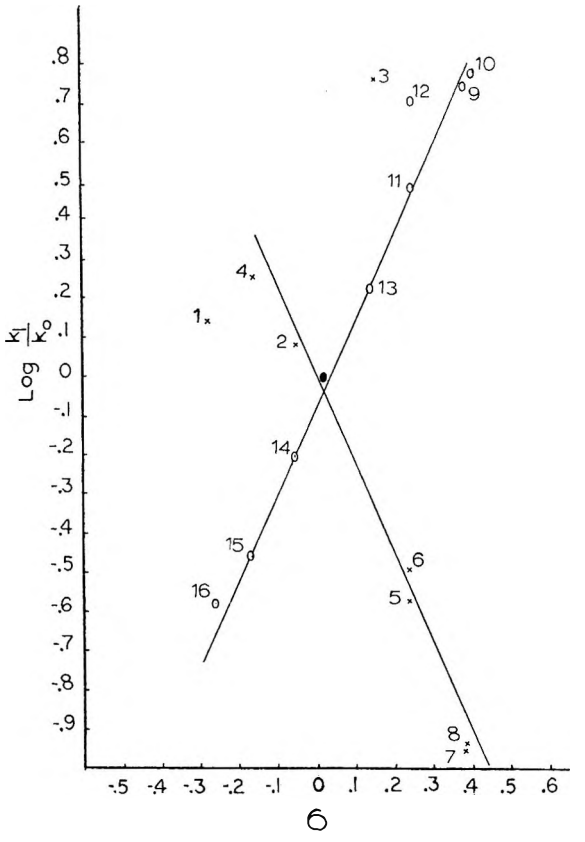

Figure 2.—Plot of log (k/k_0) *vs.* σ, [$(CH_3)_4NOH$] = 0.10 *M* (80% pyridine–20% water at 40°): ●, unsubstituted; ×, aniline with substituted nitrosobenzenes; ○, substituted anilines with nitrosobenzenes; 1, 1-CH_3; 2, 3-CH_3; 3, 3-CH_3O; 4, 4-CH_3; 5, 4-Br; 6, 4-Cl; 7, 3-Cl; 8, 3-Br; 9, 3-Cl; 10, 3-Br; 11, 4-Cl; 12, 4-Br; 13, 3-CH_3O; 14, 3-CH_3; 15, 4-CH_4; 16, 4-CH_3O.

TABLE V

APPARENT SECOND-ORDER RATE CONSTANTS FOR THE CONDENSATION OF SUBSTITUTED ANILINES WITH NITROSOBENZENE IN 0.10 *M* TETRAMETHYLAMMONIUM HYDROXIDE, 20% WATER–80% PYRIDINE SOLUTIONS

Substituent	Temp, °C	$k \times 10^3$, l. mol^{-1} sec^{-1}
4-CH_3	30.0	0.29
	40.0	0.62
	50.0	1.4
3-CH_3	30.0	0.57
	40.0	1.0
	50.0	2.4
4-CH_3O	30.0	0.21
	40.0	0.40
	50.0	1.0
3-CH_3O	30.0	1.4
	40.0	2.6
	50.0	6.0
H	30.0	0.80
	40.0	1.6
	50.0	4.1
4-Cl	30.0	3.2
	40.0	4.4
	50.0	9.9
4-Br	30.0	3.3
	40.0	9.8
	50.0	16
3-Br	30.0	4.9
	40.0	7.8
	50.0	24
4-NO_2	30.0	110
3-NO_2	40.0	54
3-Cl	30.0	4.3
	40.0	8.5
	50.0	20

k is conceivable from the reaction between neutral molecules in the presence of the solvent, aqueous pyridine, as was shown in the relation between k and acidity. Equation 1 shows how electron withdrawal from aniline increases the rate of condensation, and eq 2 shows how electron donation to nitrosobenzene increases the rate of condensation.

The substituent effects on nitrosobenzene (ρ = −2.1) and the effect on aniline (ρ = +2.0) are consistent with the above mechanism of a nucleophilic attack of the negatively charged nitrogen atom of aniline on the nitrogen atom of nitrosobenzene. This is just the reverse substituent effect as seen in the mechanism for the acid-catalyzed condensation of anilines with nitrosobenzenes. This was found to be an electrophilic attack of the nitrogen atom of activated nitrosobenzene on the nitrogen atom of aniline.[2]

Experimental Section

Commercial aniline, 3- and 4-chloroanilines, 3- and 4-methylanilines, and 3- and 4-methoxyanilines were purified by vacuum distillation. Commercial 3- and 4-nitroaniline were recrystallized from water and commercial 4-bromoaniline was recrystallized from ethanol. The following boiling and melting points were obtained: aniline, bp 85–85.5° (25 mm); 3-chloroaniline, bp 99–100° (10 mm); 4-chloroaniline, bp 104–105° (11 mm);

(2) Y. Ogata and Y. Takagi, *J. Amer. Chem. Soc.*, **60**, 3591 (1958).

TABLE VI

ACTIVATION PARAMETERS AND MEASURES OF RELIABILITY FOR THE CONDENSATION OF SUBSTITUTED ANILINES WITH NITROSOBENZENE IN 0.10 *M* TETRAMETHYLAMMONIUM HYDROXIDE, 20% WATER–80% PYRIDINE SOLUTIONS

Substituent	E_a, kcal/mol	$\Delta G^{\ddagger}_{40}$, kcal/mol	$\Delta H^{\ddagger}_{40}$, kcal/mol	$\Delta S^{\ddagger}_{40}$, eu/mol	Coefficient of variation[a]	Standard deviation
4-CH_3	15.11	22.96	14.49	−27.04	0.21	0.016
3-CH_3	13.93	22.66	13.31	−29.87	1.51	0.103
4-CH_3O	15.36	23.23	14.73	−27.11	1.09	0.085
3-CH_3O	14.47	22.08	13.85	−26.27	1.28	0.075
H	16.03	22.36	15.41	−22.21	1.32	0.084
4-Cl	10.85	12.74	10.23	−36.74	2.94	0.154
4-Br	15.50	21.24	14.88	−20.32	3.11	0.150
3-Br	15.53	12.38	14.91	−20.67	4.52	0.209
4-NO_2						
3-NO_2						
3-Cl	14.86	21.33	14.24	−22.64	1.21	0.057

[a] Measures the variability between the experimental points plotted (ln k) and the least squares value as calculated for a line drawn through these points.

TABLE VII

VALUES OF LOG k_{40}/k_{040} *vs.* σ IN 0.10 *M* TETRAMETHYLAMMONIUM HYDROXIDE 20% WATER–80% PYRIDINE SOLUTIONS[a]

Substituent	Registry no.	σ, ρ, or m	$\log \frac{k_{40}}{k_{040}}$
Condensation of Aniline with Substituted Nitrosobenzenes			
4-CH_3	623-11-0	−0.17	0.23
3-CH_3	620-26-8	−0.07	0.07
H	586-96-9		0.00
4-Cl	932-98-9	+0.23	−0.50
3-Cl	932-78-5	+0.37	−0.92
4-Br	3623-23-2	+0.23	−0.58
3-Br	13125-68-3	+0.39	−0.89
4-CH_3O	1516-22-8	−0.27	0.13
3-CH_3O	26595-63-1	+0.12	0.79
Condensation of Substituted Anilines with Nitrosobenzenes			
4-CH_3	106-49-0	−0.17	−0.45
3-CH_3	108-44-1	−0.07	−0.20
4-CH_3O	104-94-9	−0.27	−0.60
3-CH_3O	536-90-3	+0.12	0.20
H	62-53-3		0.00
4-Cl	106-47-8	+0.23	0.47
4-Br	106-40-1	+0.23	0.67
3-Br	591-19-5	+0.39	0.75
3-Cl	108-42-9	+0.37	0.71

[a] See Figure 2.

3-methylaniline, bp 99–99.5° (24 mm); 4-methylaniline, bp 115–116° (13 mm); 3-nitroaniline, mp 112–113°; 4-nitroaniline, mp 147–148°; nitrosobenzene mp 68°. 3-Methylnitrosobenzene,[2] mp 53°, was prepared by the ferric chloride oxidation of 3-methylphenylhydroxylamine which was obtained by the reduction of 3-nitrotoluene with zinc. The crude product was steam distilled and the distillate recrystallized from ethanol. 4-Methylnitrosobenzene,[3] 3- and 4-chloronitrosobenzene,[4] 3-[5] and 4-bromonitrosobenzene,[6] and 3-[7] and 4-methoxynitrosobenzenes[8] were prepared by similar procedures. The following melting points were obtained: 4-methylnitrosobenzene, mp 48°; 3-chloronitrosobenzene, mp 72°; 4-chloronitrosobenzene, mp 90°; 3-bromonitrosobenzene, mp 78°; 4-bromonitrosobenzene, mp 92°; 3-methoxynitrosobenzene, mp 48°; 4-methoxynitrosobenzene, mp 35°. 3-Bromoaniline was prepared by catalytic hydrogenation of 3-bromonitrobenzene and was purified by vacuum distillation, bp 122–124° (10 mm).

ACS analyzed pyridine, bp 115.5°, and distilled reagent grade toluene, bp 110.5°, were used in the kinetic runs. All melting and boiling points agree with those in the literature.

Reaction Products.—A mixture of nitrosobenzene (0.53 g), aniline (0.47 g), and tetramethylammonium hydroxide (0.9 g) was dissolved in a mixture of 40 ml of pyridine and 10 ml of distilled water and the solution was allowed to stand at room temperature for 4 hr. The solution was then extracted with toluene, the toluene was removed under vacuum, and a reddish orange precipitate of azobenzene was obtained. The yield was 0.82 g (90%). On recrystallization from ethanol, orange crystals were obtained melting at 68° (lit.[9] mp 68°). 3- and 4-chloroazobenzenes, 3- and 4-methylazobenzenes, 3- and 4-methoxyazobenzenes, and 3- and 4-nitroazobenzenes were prepared by similar procedures. The following melting points were obtained: 3-chloroazobenzene, mp 67.5° (lit.[10] mp 89°); 3-bromoazobenzene, mp 69° (lit.[10] mp 69°); 4-bromoazobenzene, mp 91° (lit.[10] mp 90–91°); 3-methylazobenzene, mp 18° (lit.[11] mp 18°); 4-methylazobenzene, mp 71–72°) (lit.[12] mp 72°); 3-methoxyazobenzene, mp 33° (lit.[13] mp 32.5–33.5°); 4-methoxyazobenzene, mp 64° (lit.[14] mp 64°); 3-nitroazobenzene, mp 95–96° (lit.[15] mp 96°); 4-nitroazobenzene, mp 134–136° (lit.[15] mp 134–135°).

A Typical Procedure for the Rate Measurement.—To 25 ml of a 0.2 *M* solution of aniline (20 ml of pyridine–5 ml of water) thermostated at 30° was added 25 ml of a 0.2 *M* solution of nitrosobenzene (20 ml of pyridine–5 ml of water) similarly thermostated. The 0.1 *M* tetramethylammonium hydroxide pentahydrate was added to initiate the reaction and stirring was begun. At 5-min intervals a 1-ml aliquot was removed and extracted with four 10-ml portions of toluene. The toluene extracts were then diluted to exactly 50 ml. The absorbance at the wavelength of maximum absorption in the visible region (442 mμ) of the azobenzene product was measured with a Cary 15 spectrophotometer. The rate constants were calculated from the variation of the concentration estimated from the absorption.

It was determined that (1) Beer's law was satisfied over the measured range of concentration, (2) nitrosobenzene and the anilines showed no absorption at this wavelength, and (3) the reaction was better than 95% complete after long reaction times.

Registry No.—4-Nitroaniline, 100-01-6; 3-nitroaniline, 99-09-2.

(3) E. Bamberger and A. Rising, *Justus Liebigs Ann. Chem.*, **316**, 282 (1901).
(4) R. E. Lutz and M. R. Lytton, *J. Org. Chem.*, **2**, 68 (1937).
(5) R. D. Haworth and A. Sapworth, *J. Chem. Soc.*, **119**, 768 (1921).
(6) E. Bamberger, *Ber.*, **28**, 1218 (1895).
(7) O. Baudisch and R. Furst, *ibid.*, **48**, 1665 (1915).
(8) A. Rising, *ibid.*, **37**, 43 (1904).
(9) P. Griess, *ibid.*, **9**, 134 (1876).
(10) E. Bamberger, *ibid.*, **29**, 103 (1896).
(11) P. Jacobson and A. W. Nanniga, *ibid.*, **28**, 2548 (1895).
(12) C. Mills, *J. Chem. Soc.*, **67**, 925 (1895).
(13) P. Jacobson and F. Honigsberger, *Ber.*, **36**, 4093 (1904).
(14) C. Smith, *J. Chem. Soc.*, **93**, 842 (1908).
(15) E. Bamberger and R. Hubner, *Ber.*, **36**, 3803 (1904).

Organic Peroxides. IX.[1] Kinetics of the Thermal Decomposition of Bis(5-hexenoyl) Peroxide in Toluene. General Solution of the First-plus-x-Order Rate Expression[2]

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Received January 19, 1970

Results of iodometric kinetics experiments are reported for decompositions of 5-hexenoyl peroxide in toluene and benzene at temperatures between 60 and 85°. The kinetic behavior in 0.03 M toluene solutions is such as to suggest that the peroxide undergoes a relatively simple homolytic decomposition at low concentrations. Kinetics data on a 0.2 M solution in toluene are used to estimate the importance of radical induced decomposition in that solvent, using the general solution for the first-plus-x-order rate expression, $\ln([P]^{1-x} + \alpha) = (x - 1)k_d t + \ln([P]_0^{1-x} + \alpha)$, in which $\alpha = k_i/k_d$. Data for the 0.2 M toluene solution fit this equation with any number of x,α combinations, when $1 < x < 2$. Products of the decomposition in toluene are those which are typical of diacyl peroxide decompositions. There is a more pronounced decrease in the yields of C-5 olefins in the presence of DPPH than there is in the yields of other products, which indicates that the main product derived from free 4-pentenyl radicals in toluene is 1-pentene. The failure of the 4-pentenyl radical to cyclize in solution is in agreement with some observations published by others.

This paper is a continuation of a series of papers dealing with unsaturated diacyl peroxides.[5]

Results

The results of some iodometric kinetics experiments on 5-hexenoyl peroxide in dilute toluene solutions at several temperatures between 60 and 85°, and one experiment on the decomposition of n-hexanoyl peroxide in toluene at 77°, are reported in Table I.

For the most part, the kinetics data were obtained on 0.03 M toluene solutions. These data were found to fit the first-order rate law to a high degree of precision throughout a substantial per cent decomposition. Therefore, the rate constants for the kinetics experiments at 0.03 and 0.036 M are apparent k_d values derived from the first-order rate law.

However, a plot of ln [P] *vs.* time for the kinetics experiment at 0.22 M 5-hexenoyl peroxide concentration in toluene showed definite curvature,[6-8] such as to suggest that the correct form of the rate law is

$$-d[P]/dt = k_d[P] + k_i[P]^x \quad (1)$$

in which the exponent $x > 1$. The integral of eq 1, when $x \neq 1$, is eq 2, in which $\alpha = k_i/k_d$.

$$\ln([P]^{1-x} + \alpha) = (x - 1)k_d t + \ln([P]_0^{1-x} + \alpha) \quad (2)$$

Equation 2 correctly reduces to the first-order rate law at $\alpha = 0$. It shows no dependence upon peroxide concentration at $x = 1$, under which condition the first-order rate law with slope equal to the sum of rate constants ($k_d + k_i$) applies. Equation 2 behaves most poorly when x is near unity and α is large with respect to $[P]^{1-x}$.

When the [P],t data for the 0.22 M run are plotted according to the first-order law, a decrease in rate at long times is observed. Therefore, the correct value of x in eq 2 lies in the range 1–2.

Computer programs were devised for the determination of the optimum values of x, α, k_d, and the intercept. If the residual is defined as the difference between the two sides of eq 2, the least-squares values of x and α are 1.91 and 1.85, respectively. The corresponding least-squares value for k_d is presented in Table I, and plotted in Figure 1. While the least-squares value of x is in fair agreement with the mechanism we subsequently propose, one must be most circumspect in deciding upon the correct values of x and α from [P],t data in which [P] is determined by iodometric titration.

The equation is quite insensitive, and when x is assigned any fractional value between 1.1 and 2.0, a corresponding α can be computed which will accommodate [P],t data for the 0.22 M run quite well. Thus, the average per cent error in peroxide concentration, *i.e.*, $100[\Sigma([P]_{obsd} - [P]_{calcd})^2/n]^{1/2}/[\bar{P}]$, lies between 0.51 and 0.61% for $x = 1.91$, $\alpha = 1.85$ (the least-square values); for $x = 2.0$, $\alpha = 2.1$; for $x = 1.5$, $\alpha = 1.8$;[9] and even for $x = 1.3$, $\alpha = 2.7$.[9] Likewise, values for the per cent error in k_d, *i.e.*, 100σ (in k_d)/k_d, lie in the range 0.45–0.50% for all the x,α pairs mentioned, and for many additional x,α pairs.

Ideally, the value of k_d deduced from eq 2 using data from the 0.22 M run should be *lower* than the apparent value of k_d deduced from the first-order law using the data from the 0.036 M run. While the least-squares values of x and α do not yield an equation which meets this condition, Figure 1 shows that the k_d obtained from eq 2 (with $x = 1.91$, $\alpha = 1.85$) lies very near the value predicted by the $1/T$ line defined by the k_d's determined

(1) A complete list of previous papers is given in paper VIII in this series: R. C. Lamb and J. R. Sanderson, *J. Amer. Chem. Soc.*, **91**, 5034 (1969).

(2) Presented at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 7–12, 1969. Supported, at East Carolina University, by a grant from the National Science Foundation (NSF-GP-7393). Preliminary work at the University of Georgia was supported by a grant from the Air Force Office of Scientific Research (AF-AFOSR-543-64). *Cf.* "12th Annual Chemistry Program Review," AFOSR-66-1854, Fiscal Year 1966, pp 134–138.

(3) To whom correspondence should be addressed: East Carolina University.

(4) This paper was taken in part from the thesis of W. E. McNew, Jr., presented in partial fulfillment of the requirements for the M.S. degree, University of Georgia, June 1965.

(5) (a) R. C. Lamb, F. F. Rogers, Jr., G. C. Dean, Jr., and F. W. Voigt, Jr., *J. Amer. Chem. Soc.*, **84**, 2635 (1962); (b) R. C. Lamb, P. W. Ayers, and M. K. Toney, *ibid.*, **85**, 3483 (1963); (c) R. C. Lamb, J. G. Pacifici, and P. W. Ayers, *J. Org. Chem.*, **30**, 3099 (1965); (d) R. C. Lamb, J. G. Pacifici, and L. P. Spadafino, *ibid.*, **30**, 3102 (1965); (e) R. C. Lamb, L. P. Spadafino, R. G. Webb, E. B. Smith, W. E. McNew, and J. G. Pacifici, *ibid.*, **31**, 147 (1966). References 5a–e constitute a partial list of previous papers.

(6) C. G. Swain, W. H. Stockmayer, and J. T. Clarke, *J. Amer. Chem. Soc.*, **72**, 5426 (1950).

(7) P. D. Bartlett and K. Nozaki, *ibid.*, **69**, 2299 (1947); *ibid.*, **68**, 1686 (1946); *ibid.*, **68**, 1495 (1946).

(8) W. E. Cass, *ibid.*, **68**, 1976 (1946).

(9) The last two x,α pairs give $k_d = 7.31 \times 10^{-5}$ and 4.90×10^{-5} sec^{-1}, respectively, which are considerably lower than the value of k_d observed for 0.036 M run.

TABLE I
DECOMPOSITION RATES OF 5-HEXENOYL AND HEXANOYL PEROXIDE

Medium	$[P]_0$[a]	No. of samples	Temp, °C	$10^5(k_d \pm \sigma)$, sec^{-1}	Half-life, min	Per cent reaction
			5-Hexenoyl Peroxide			
Toluene	0.030	6	60.1	1.06 ± 0.02	1089	44
Toluene	0.030	7	70.4	4.15 ± 0.03	278.3	77
Toluene	0.036	7	76.4	8.59 ± 0.05	134.5	72
Toluene	0.218	9	76.4	9.30 ± 0.04[b]	124.2[d]	81
Toluene	0.218	9	76.4	9.43 ± 0.04[c]	122.5[d]	81
Toluene	0.030	7	77.0	10.08 ± 0.08	144.7	76
Toluene	0.030	5	85.0	26.68 ± 0.17	43.3	57
			Hexanoyl Peroxide			
Toluene	0.030	7	77.0	11.86 ± 0.08	97.4	78

[a] Initial molar peroxide concentration. [b] Calculated by adjustment of data to eq 2, with $x = 1.91$ and $\alpha = 1.85$. [c] Same data as used in previous entry, adjusted to eq 2, with $x = 2$ and $\alpha = 2.1$. [d] These values were calculated from $(\ln 2)/k_d$, in which k_d was obtained from eq 2. The measured half-life was actually near 90 min.

at other temperatures. (Obviously, the apparent k_d value obtained with the 0.036 M solution at 76.4° is low.)

It is instructive to consider the average fraction of the peroxide which undergoes induced decomposition within a given run. The *instantaneous* fraction (f) of the peroxide which undergoes induced decomposition is given by eq 3.

$$f = \frac{k_i[P]^x}{k_d[P] + k_i[P]^x} = 1 - [1/(1 + \alpha[P]^{x-1})] \quad (3)$$

The *average* fraction ($\bar{f}$) may then be defined by eq 4.

$$\bar{f} = \frac{\int_0^{[P]_0} [1 - (1/1 + \alpha[P]^{x-1})]d[P]}{\int_0^{[P]_0} d[P]} = 1 - (1/[P]_0) \int_0^{[P]_0} \frac{d[P]}{1 + \alpha[P]^{x-1}} \quad (4)$$

The necessary integral cannot be obtained in closed form except for $x = 1.5$ or 2. Since the latter value is very near our least-squares value of x, *we* may approximate $\bar{f}$ using eq 5.

$$\bar{f} = 1 - (1/\alpha[P]_0) \ln (1 + \alpha[P]_0) \quad (5)$$

With the x,α pair 2, 2.1, the following values of $\bar{f}$ may be calculated: 0.18 at $[P]_0 = 0.22$ M; 0.10 at 0.11 M; 0.037 at 0.036 M; and 0.031 at 0.030 M. Inasmuch as the latter calculation shows that only 3% of the peroxide decomposes by induced decomposition at $[P]_0 = 0.03$ M (at 76.4°), we have not attempted to adjust data from the 0.030 M runs to eq 2.

If the small amount of induced decomposition in the 0.030 M runs is ignored, and all the "k_d" values for 0.03 M toluene solutions listed in Table I are treated as first-order rate constants, and adjusted by least-squares to a log (k_d/T) *vs.* $(1/T)$ function, one obtains the following parameters: $\Delta H^* = 30.2 \pm 0.4$ kcal and $\Delta S^* = +9.2$ eu.

The products of the decomposition were determined by glpc and are presented in Table II. For the decompositions in toluene solutions, the product analysis accounts for 87% of the C-5 hydrocarbon groups which were present in the original peroxide samples. Yields of the same products were also measured for decompositions in toluene containing excess DPPH.

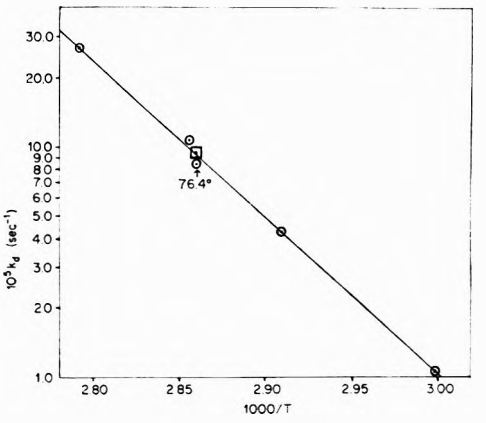


Figure 1.—Plot of log (10^5k_d) *vs.* $1000/T$ for decompositions of bis(5-hexenoyl) peroxide in toluene. ⊙, observed first-order rate constants obtained on 0.030 or 0.036 M solutions. ⊡, k_d's obtained by adjustment of data from 0.22 M run to eq 2.

TABLE II
DECOMPOSITION PRODUCTS OF 5-HEXENOYL PEROXIDE[a]

Products	Peroxide, M: 0.11–0.22 (toluene)[b,c]	0.11 (toluene, 0.1 M DPPH)	0.22 (toluene, 0.22 M DPPH)
1-Pentene and 1,4-pentadiene	0.80	0.11	0.02
1,9-Decadiene	0.16	0.15	0.10
4-Pentenyl 5-hexenoate	0.16	0.08	0.06
5-Hexenoic acid	0.11	n.d.	n.d.
6-Phenyl-1-hexene[d]	0.22	0	0
Bibenzyl	0.16–0.11	0	0

[a] Yields are based on glpc data, and are given in mole per mole of peroxide; n.d. = not determined. [b] Data in this column are averaged for four decompositions at $[P]_0 = 0.11$, 0.13, 0.15, and 0.22 M. Only bibenzyl yield showed $[P]_0$ dependence. The yields obtained were 0.16, 0.15, 0.12, and 0.11 mol/mol peroxide, respectively. [c] The C-5 alkenes were not separated. In addition to the products listed, a trace of benzyl 5-hexenoate was observed. [d] The isomeric ring-substitution product, 5-(*p*-tolyl)-1-pentene, could not be detected in the reaction mixtures.

Discussion

The weight of evidence indicates that, in 0.03 M solution in toluene, 5-hexenoyl peroxide decomposes predominantly by a relatively simple homolytic process. These points of evidence are as follows. (a) The kinetics data for 0.03 M toluene solutions follow the first-order law through two or more half-lives to a high degree of precision. (b) Careful analysis of kinetics of a 0.22 M solution indicates that approximately 3% of the peroxide decomposes by radical induced decomposition at 0.03 M concentration. (c) The value obtained

for E_a (30.9 kcal) is not significantly lower than those for propionyl (31.1 kcal) and *n*-butyryl (31.2 kcal)[10] peroxides in toluene. (d) The observed rate of decomposition of 5-hexenoyl peroxide is 20% less than that of its saturated analog, hexanoyl peroxide, at 77°. (e) The activation entropy, ΔS^*, is significantly positive, which is to be expected for homolysis, but not for rearrangement reactions in which cyclic or highly polar transition states are involved.

The kinetics data will not support a postulate of neighboring group effect of the double bond, such as has been postulated for decompositions of some 5-phenyl-4-pentenoyl peroxides,[5a,e] and for other peroxides of similar structure.[11] This observation is in keeping with previous evidence which we have reported for decompositions of 6-heptenoyl[5b] and 4-pentenoyl[5e] peroxides.

Therefore, the mechanism of decomposition of bis(5-hexenoyl) peroxide in toluene at 0.03 *M* is, predominantly, a first-order homolysis of the type that is usual for saturated aliphatic diacyl peroxides.

Inasmuch as induced decomposition constitutes no more than 20% of the reaction even at $[P]_0 = 0.22$ *M*, the delineation of the exact mechanism of induced decomposition is more difficult. Nevertheless, we do feel that the information which has been collected on the decompositions of bis(5-hexenoyl) peroxide suggests the following tentative mechanism, in which the terminology used is that of Swain, Stockmayer, and Clark.

$$P \longrightarrow 2eR\cdot \quad (e = \text{free radical efficiency}) \qquad (1)$$

$$R\cdot + SH \longrightarrow RH + S\cdot \qquad (2)$$

$$R\cdot + P \longrightarrow R{-}\overset{\overset{O}{\|}}{C}{-}OR + R\cdot \qquad (3)$$

$$R\cdot + R\cdot \longrightarrow RR \text{ (or disproportionation products)} \qquad (5)$$

$$R\cdot + S\cdot \longrightarrow RS \text{ (or disproportionation products)} \qquad (6)$$

$$S\cdot + S\cdot \longrightarrow SS \qquad (7)$$

R— or R· = 4-pentenyl group or free radical

S— or S· = benzyl group or free radical

None of the three possible termination steps can be rigorously denied by our product studies, for the products contain 1,9-decadiene (RR), 6-phenyl-1-hexene (RS), and bibenzyl (SS). To be sure, the latter two compounds are not formed in the presence of DPPH, while the yield of 1,9-decadiene is only slightly affected by DPPH. While this is good evidence that 1,9-decadiene is, for the most part, a cage recombination product, there is no way of determining from our data that the C-5 olefins are not formed in part from disproportionation of the 4-pentenyl radical.

In this regard, we undertook some experiments on the decompositions of bis(5-hexenoyl) peroxide in toluene containing BDPA[1,12] with the view of determining the efficiency (e) of radical production by the peroxide. Although BDPA undergoes considerable spontaneous fading in toluene at 76.4°,[5e] the efficiency appears to be in the range 0.45–0.53. The point to be made here is that, although the two termination products, 6-phenyl-1-hexene and bibenzyl, constitute the major portion of termination, these products apparently cannot account for all of the termination required by the efficiency experiments. Therefore, we cannot totally exclude R· + R· (reaction 5) as a termination reaction.

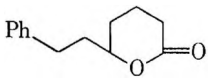
The yield of ester, 4-pentenyl 5-hexenoate, is decreased significantly in the presence of 0.1 *M* DPPH, and, although a substantial portion of the ester must be formed in cage reactions or as a rearrangement product of the peroxide, the evidence seems to indicate that a free radical is involved in the formation of a portion of it. It is for this reason that we have suggested that 4-pentenyl 5-hexenoate is a possible product of induced decomposition.

Given R· + P as the induced decomposition step, and all three termination steps, and making the assumption that $k_6 = 2(k_5k_7)^{1/2}$, one can deduce the following steady-state solution for R·.

$$(R\cdot)_{SS} = \frac{[2k_1fP]}{k_2[SH] + 2(k_1k_5f[P])^{1/2}} \approx (2k_1f/k_2[SH])[P]$$

The approximation results from the fact that $k_2[SH]$ is very likely at least an order of magnitude greater than $2(k_1k_5f[P])^{1/2}$. The approximate solution for $(R\cdot)_{SS}$ leads to a rate expression of the form of eq 1 in which $x = 2$, which is very near our least-squares value of 1.93.

Early in this work, it was anticipated that the double bond would be involved in the induced decomposition, *via* a mechanism similar to that described by Hart and Cloupek.[13] This line of reasoning led us to synthesize 7-phenyl-5-heptanolactone (**1**) which could conceivably



1

have been formed by the reaction of benzyl radicals with bis(5-hexenoyl) peroxide. However, we were unable to detect this lactone in the decomposition products of the peroxide in 0.22 *M* toluene solution.

The product studies indicate that the 4-pentenyl radical is a major initial product of the homolysis of 5-hexenoyl peroxide in toluene, inasmuch as the presence of excess DPPH reduces the yield of C-5 olefins (1-pentene and 1,4-pentadiene) by a factor of eight. Neither cyclopentane, cyclopentene, nor methylcyclobutane was observed in the products; therefore, the 4-pentenyl radical does not cyclize in toluene. This result is in agreement with observations of Walling and Pearson,[14] who generated the 4-pentenyl radical by reacting 4-pentene-1-thiol with triethyl phosphite; by Walling, Cooley, Ponaras, and Racah,[15] who generated the radical by the reaction of tri-*n*-butyltin hydride with 5-bromo-1-pentene; and by Kaplan,[16] who reported a "trace" of cyclopentyl benzoate in the decomposition of benzoyl peroxide in the presence of 5-iodo-1-pentene at 115°.

Finally, we wish to reemphasize the fact that the same set of [P],*t* data can be described accurately by eq 2

(10) J. Smid, A. Rembaum, and M. Szwarc, *J. Amer. Chem. Soc.*, **78**, 3315 (1956).

(11) T. W. Koenig and J. C. Martin, *J. Org. Chem.*, **29**, 1520 (1964).

(12) (a) C. F. Koelsch, *J. Amer. Chem. Soc.*, **79**, 4439 (1957); (b) S. L. Solar and R. M. Lindquist, *ibid.*, **82**, 4285 (1960); (c) R. Kuhn and F. A. Neugebauer, *Monatsh. Chem.*, **95**, 3 (1964).

(13) H. Hart and F. J. Cloupek, *J. Amer. Chem. Soc.*, **85**, 1155 (1963). See also ref 5b.

(14) C. Walling and M. A. Pearson, *ibid.*, **86**, 2262 (1964).

(15) C. Walling, J. H. Cooley, A. A. Ponaras, and E. J. Racah, *ibid.*, **88**, 5361 (1966).

(16) L. Kaplan, *J. Org. Chem.*, **32**, 4059 (1967).

with a variety of x,α pairs, particularly when the fraction of peroxide which undergoes induced decomposition (f) is small.

Experimental Section[17]

5-Hexenoic Acid.—The procedure described by De La Mare, Kochi, and Rust[18] was used, except that the quantities of reagents were tripled, and the procedure for the isolation of the product was altered.

The chloroform layer was extracted with saturated sodium bicarbonate solution which was subsequently acidified and extracted with ether. The ether extract was dried and the ether was removed. The crude acid remaining was distilled at reduced pressure three or four times in order to render the acid colorless and of high purity.

A typical synthesis produced about a 25% yield of the acid, bp 55.5–58° (0.4 mm) and n^{25}D 1.43244 (lit.[19] n^{20}D 1.4343). The ir spectrum showed the C=O band at 1715, the C=C band at 1645, and RCH=CH_2 bands at 990 and 913 cm^{-1}. The acid chloride was prepared by treatment of the acid with phosphorus trichloride. The infrared spectrum showed the C=O band at 1832, the C=C band at 1645, and RCH=CH_2 bands at 990 and 917 cm^{-1}.

5-Hexenoyl peroxide was prepared by treatment of the acid chloride with an excess of sodium peroxide in ether at 0°, following the procedure described by Hart and Wyman[20] for the preparation of cyclopropaneformyl peroxide.

The peroxide could not be made to crystallize. The purity of the liquids was determined by iodometric titration with standardized 0.01 N sodium thiosulfate. The peroxide was discarded if the purity was less than about 95%. Infrared spectra showed the carbonyl doublet at 1923 and 1783 cm^{-1}, and RCH=CH_2 bands at 991 and 917 cm^{-1}. Hexanoyl peroxide was prepared by a similar procedure.

4-Pentenyl 5-Hexenoate.—This ester was prepared by the reaction of 4-penten-1-ol with an equivalent quantity of acid chloride.

After washing the organic layer with sodium bicarbonate solution and drying, distillation was performed on an 18-in. spinning-band column at a constant pressure of 1 mm. A small fraction having a characteristic ester odor was collected, bp 69.0–70.0° and n^{25}D 1.44072, and used in preparing a standard solution for use in gas–liquid chromatography analyses. The ir spectrum showed a C=O band at 1724, a CO band at 1157, a C=C band at 1631, and RCH=CH_2 bands at 990 and 906 cm^{-1}. *Anal.* Calcd for $C_{11}H_{18}O_2$: C, 72.45; H, 9.96. Found:[21] C, 72.56; H, 9.85.

1,9-Decadiene was prepared by a Grignard coupling method described by von Braun, *et al.*[22] 6-Phenyl-1-hexene was similarly prepared by coupling 3-phenylpropylmagnesium chloride with allyl bromide.[23]

7-Phenyl-5-heptanolactone (1).—This lactone was prepared by subjecting 2-(2-phenylethyl)cyclopentanone to the Baeyer–Villiger reaction, using the peroxytrifluoroacetic acid method according to a procedure described by Smissman, Muren, and Dahle.[24] The starting ketone was synthesized by a method described by Adkins and Hager,[25] mp (of its 2,4-dinitrophenylhydrazone) 90–92°. The ir spectrum of the lactone showed strong peaks at 1757, 1250, 1053, and 704 cm^{-1}. Its nmr spectrum showed aliphatic and aromatic absorptions in a 11:5 ratio required of the expected lactone. The aliphatic protons appeared as a group of overlapping multiplets at 1.3–3.05 and as a multiplet centered at δ 4.15 in a 10:1 ratio. The latter absorption may be ascribed to the methine proton deshielded by the ether oxygen. The presence of a second multiplet centered at δ 3.6 could be ascribed to the corresponding methylene proton absorption of the possible isomeric lactone. The relative intensity of the multiplet at δ 3.6 and 4.15 suggested the presence of less than 15% of the isomeric lactone.

Kinetics Runs.—The solvents used were of reagent grade, and were redistilled before use. Approximately 4-ml portions of a peroxide solution were transferred into previously weighed kinetic vials using a 5-ml syringe equipped with a long, slim hypodermic needle. The vials were then stoppered, weighed, and placed in a Dry Ice–acetone bath. The vials were degassed and sealed under vacuum. The bath used was thermostated to ±0.02°. After its heating period, the contents of each vial were analyzed by iodometric titration, using isopropyl alcohol as the assay solvent.

Product Studies.—The product-study runs were carried out with vials similar to those used for kinetics runs. The product yields were obtained by comparing glpc peak areas with those of authentic standards.

Registry No.—5-Hexenoyl peroxide, 26384-97-4; hexanoyl peroxide, 2400-59-1; 4-pentenyl 5-hexenoate, 26384-99-6.

Acknowledgment.—We are indebted to the grant agencies which made this work possible,[1] and to Mr. Floyd E. Woodard for the synthesis of **1** and for his considerable help with the computer work.

(17) Perkin-Elmer Models 421, 137, and Beckman IR-12 infrared spectrophotometers were used in this work. Beckman GC-2 and Perkin-Elmer Mod 1900 gas chromatographs were used in the products study. A Hitachi PE Model R-20 nmr spectrometer was used to record the nmr spectra; tetramethylsilane was the internal standard. Boiling points are uncorrected.

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(21) Analysis performed by Midwest Microlab, Inc., Indianapolis, Ind.

(22) J. von Braun, H. Deutsch, and A. Schmatlock, *Ber.*, **45**, 1246 (1912).

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(25) H. Adkins and G. F. Hager, *J. Amer. Chem. Soc.*, **71**, 2965 (1949).

The Total Synthesis of (±)-Isonootkatone. Stereochemical Studies of the Robinson Annelation Reaction with 3-Penten-2-one

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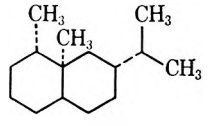
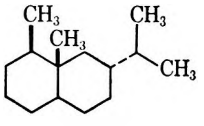
Received June 24, 1970

The total synthesis of (±)-isonootkatone (α-vetivone) is described. The key step involves annelation of 4-isopropylidene-2-carbomethoxycyclohexanone with *trans*-3-penten-2-one to give the bicyclic enone with cis-related CH_3 and CO_2CH_3 substituents. A study on the stereochemistry of this reaction using 2-carbomethoxycyclohexanone as the keto ester component showed that the cis isomer was favored in *tert*-butyl and *tert*-amyl alcohol at low temperature. Completion of the isonootkatone synthesis involved reduction (to CH_3) of the CO_2CH_3 grouping in the ketal derivative of the aforementioned annelation product and, finally, ketal hydrolysis. The reduction was effected most efficiently *via* the sequence $CO_2CH_3 \rightarrow CH_2OH \rightarrow CHO \rightarrow CH_3$.

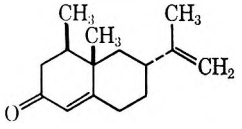
One of the more interesting aspects of the eremophilane–valencane sesquiterpenes from a synthetic point of view is the cis-related vicinal methyl substituents on the hydronaphthalene framework. Over the past decade a number of efforts, some successful, have been made to devise general solutions to this problem.[1] Our initial interest in this area arose from the finding that α-vetivone, long regarded as a hydroazulene, was in fact a double bond isomer of nootkatone.[2]



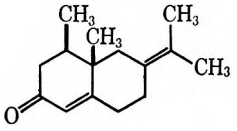
eremophilane



valencane

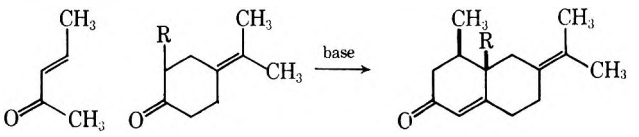


nootkatone

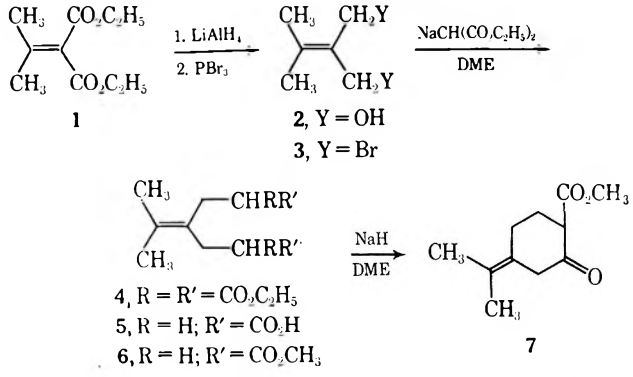


isonootkatone (α-vetivone)

In considering potential synthetic routes to isonootkatone, we were intrigued by the possibility of a direct approach involving simultaneous introduction of the vicinal methyl groupings, or their equivalents, and the conjugated ketone functionality *via* basic condensation of 3-penten-2-one with a 4-isopropylidenecyclohexanone. An *a priori* analysis of the probable stereochemical outcome of such a condensation reaction suggested that the desired cis isomer might predominate if the cyclohexanone moiety possessed an activating group such as carbomethoxyl at the 2 position.[3] This requirement detracted only slightly from the directness of our proposed scheme since such a grouping could presumably be readily converted to the desired angular methyl substituent. Accordingly, we undertook a synthesis of the requisite cyclohexanone **7** (Scheme I).



SCHEME I



Diethyl isopropylidenemalonate (**1**)[4] upon reduction with lithium aluminum hydride afforded the corresponding diol **2**. This reaction also gave a considerable amount of 2-isopropyl-2-propen-1-ol, the product of 1,4-hydride addition to malonate **1** followed by reduction–elimination of the resulting enolate.[5] Various attempts to diminish this side reaction were to no avail. Nonetheless, since the desired diol **2** could be readily separated from the allylic alcohol by-product, and in view of the ready availability of the malonic ester **1**, alternative routes to diol **2** were not explored.

* To whom correspondence should be addressed.

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(2) J. A. Marshall and N. H. Andersen, *Tetrahedron Lett.*, 1011, (1967); K. Endo and P. de Mayo, *Chem. Commun.*, 89, (1967).

(3) For a preliminary report, see J. A. Marshall, H. Faubl, and T. M. Warne, Jr., *ibid.*, 753 (1967).

(4) A. C. Cope and E. M. Hancock, *J. Amer. Chem. Soc.*, **60**, 2644 (1938).

(5) For a mechanistic analysis of this reaction, see J. A. Marshall, N. H. Andersen, and A. R. Hochstetler, *J. Org. Chem.*, **32**, 113 (1967).

TABLE I

CONVERSION OF 2-CARBOMETHOXYCYCLOHEXANONE (8) TO METHYL *cis*- AND *trans*-4-METHYL-1(9)-OCTAL-2-ONE-10-CARBOXYLATE (9a AND 9b)

Entry	Base[a]	Base/keto ester ratio	Solvent	Temp, °C	Yield, %	cis (9a)/ trans (9b)[b]
1	KO-*tert*-Am	0.064	*tert*-AmOH	−15	65	3.08
2	KO-*tert*-Bu	0.068	*tert*-BuOH	0	77	2.32
3	KO-*tert*-Bu	0.116	*tert*-BuOH	0	55	2.2
4	KO-*tert*-Bu	0.043	*tert*-BuOH	30	68	1.45
5	KO-*tert*-Bu	0.180	*tert*-BuOH	27	69	1.39
6	KO-*tert*-Bu	0.298	*tert*-BuOH	30	78	1.25
7	LiO-*tert*-Bu	0.197	*tert*-BuOH	25	62	0.84
8	KOMe	0.113	MeOH	0	39	1.12
9	NaOMe	0.113	MeOH	−15	62	1.07
10	NaOMe	0.109	MeOH	−10	72	0.93
11	NaOMe	0.133	MeOH	40	58	0.98
12	NaOMe	0.180	DMSO	29	72	0.61
13	NaOMe	0.200	THF	22	75	0.75
14	NaH	0.091[c]	THF	0	63	1.07
15	NaH	0.050	Et_2O	0	38	0.52
16	LiH	0.200	Et_2O	30	50	1.00

[a] Conversion to the enone products was effected with 2 *M* NaOMe. [b] Analysis of the enol ether derivatives. [c] 4-Chloro-2-pentanone was employed in this experiment and an additional equivalent of base was initially present to effect dehydrochlorination.

Treatment of diol **2** with phosphorous tribromide afforded the dibromide **3**. Alkylation of this dibromide with diethyl sodiomalonate in DME followed by hydrolysis, decarboxylation, and esterification produced the diester **6**. This substance readily cyclized upon treatment with sodium hydride in DME to give the keto ester **7** in 60% overall yield based on diol **2**.

Before proceeding further with our projected isonootkatone synthesis, we decided to examine the stereochemistry of the proposed condensation step using 2-carbomethoxycyclohexanone (**8**) as the keto ester component. The choice of this keto ester was based upon its availability and the expectation that the reaction products could be readily converted to compounds of known stereochemistry.

The results of this study are summarized in Table I. The conditions described therein led mainly to the diketo ester Michael adducts. Cyclization of these adducts was effected with methanolic sodium methoxide and the product analysis was carried out on the enones **9a** and **9b**. Since the ratios of these cyclized products varied markedly with the Michael reaction conditions, and were reproducible for a given set of conditions, the possibility of stereochemical equilibration *via* reverse Michael condensation in the cyclization step appears unlikely. After considerable searching for a direct method of analyzing enones **9a** and **9b**, we discovered that the enol ether derivatives **11a** and **11b** could be prepared in nearly quantitative yield and were readily separated by vapor phase chromatography. The stereochemistry of these enones was ultimately ascertained through their conversions to the methyl octalones **20a** and **20b** of known structure. We defer discussion of this correlation to a later point in this paper.

The data shown in Table I indicate the range of isomer ratios obtainable through changes in conditions for the Michael addition of keto ester **8** to *trans*-3-penten-2-one. We could not examine all the conceivable variables and the postulates which follow therefore must be considered tentative. However, they do suggest directions for further study and are set forth in this context.

In methanol, temperature changes appeared to exert little influence on product stereochemistry. Increasing the reaction temperature from −15 to 40° decreased the isomer ratio from 52:48 to 50:50 (entries 9–11). Although this change is in the direction of lower specificity, it is well within the range of experimental error, and we do not regard the variation as significant. Attempts to extend the range of the temperature study were thwarted by the low solubility of the keto ester and its enolate below −20°.

In *tert*-butyl alcohol the percentage of cis isomer **9a** increased from 58–59% to 70–75% upon lowering the reaction temperature from 30 to 0° (entries 2–6). Thus, low temperature appears to enhance the selectivity of the reaction in this solvent. Unfortunately, lower reaction temperatures could not be examined owing to solidification of the *tert*-butyl alcohol. The product formed in *tert*-amyl alcohol at −15° contained over 75% of the cis isomer **9a**. This change could be attributed to the lower reaction temperature, although the greater bulk of *tert*-amyl alcohol relative to *tert*-butyl alcohol may also be a contributing factor (see below).

The basicity of the reaction medium determines the relative concentration of keto ester anion and may also influence the reaction by altering the ionic strength (a salt effect). Studies on this point were made using potassium *tert*-butoxide in *tert*-butyl alcohol (entries 2 *vs.* 3 and 4 *vs.* 6). In each case, lower concentrations of base led to increased proportions of the cis isomer **9a**. In entry 14, 4-chloro-2-pentanone was used as a 3-penten-2-one equivalent. Here, an equimolar amount of sodium hydride, in addition to the catalytic amount required for the Michael addition, was added to effect dehydrochlorination during the reaction.

Inasmuch as all the bases employed are capable of converting keto ester **8** into its conjugate base, we reasoned that the basic anion should have little influence on the course of the reaction. The cation on the other hand, can affect the enolate in two ways: (1) it can change the steric bulk of the transition state by its size and degree of solvation; (2) it can alter the reactivity of the enolate by the degree of covalency or ionic char-

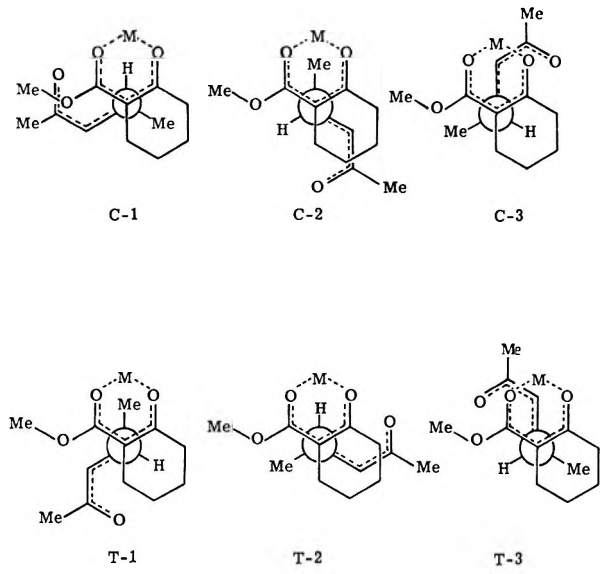
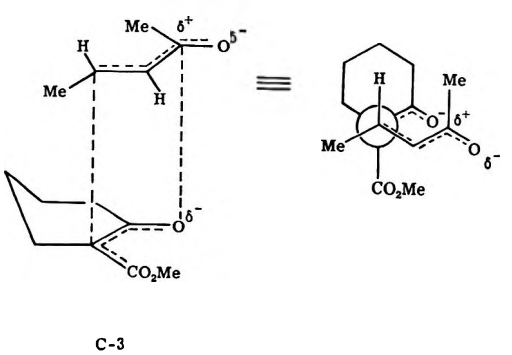


Figure 1.—Transition states for the Michael addition of 2-carbomethoxycyclohexanone to *trans*-3-penten-2-one.

acter associated with the cation–enolate pair. Potassium and sodium enolates gave essentially identical results (entry 8 *vs.* 9) whereas lithium enolates tended to give lower proportions of the cis isomer **9a** (entry 6 *vs.* 7). The magnitude of the variation between lithium and potassium enolates was not great enough to encourage exhaustive searches in that direction. Attempts to utilize magnesium enolates were unsuccessful, possibly owing to the apparent insolubility of these enolates and the requisite alkoxide bases.

Table I clearly shows that the reaction solvent exerts a marked influence upon product stereochemistry. This effect may arise from polar interactions in the transition state and from dissociative interactions with the cation–enolate ion pair. It could also simply stem from steric factors through solvated ions and polar portions of the reacting molecules. In methanol little stereoselectivity was observed, whereas in bulkier alcohol solvents increased amounts of the cis product **9a** were formed. Aprotic solvents generally favored the trans isomer **9b** regardless of solvent polarity.

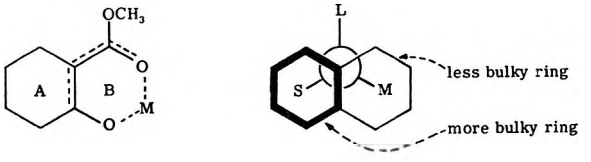
In proposing a mechanism to account for these observations, we considered explanations based upon both electronic and steric factors. Our original hypothesis assumed that the preferred transition state would be one in which steric interactions between the enone and enolate were minimized, and in which there existed a stabilizing electronic interaction between the enolate anion and the electropositive carbon of the enone carbonyl.[3] Such a transition state would resemble C-3 shown below and would lead to octalone **9a**. This simple hypothesis had to be modified since it provided no role for the metal cation or the solvent and could not adequately account for observed variations in the ratio of cis to trans isomers (Table I).



Before going further into the question of stereochemistry, we must consider the conformations available to the reactant molecules. Noack and Jones[6] have shown by infrared and Raman measurements that both the s-cis and s-trans conformations of trans-3-penten-2-one are appreciably populated. We assume that the carbomethoxy portion of keto ester **8** adopts an antiperiplanar conformation analogous to that of methyl acetate.[7,8]

Our proposal assumes that Michael addition of keto ester **8** anion to *trans*-3-penten-2-one involves perpendicular approach to the U form of the keto ester enolate.[9,10] Newman projection formulas which show the various staggered group arrangements along the axis of the developing C–C bond are diagrammed in Figure 1. Conformations C-1 through C-3 would lead to the cis isomer **9a**, whereas the trans isomer **9b** could arise *via* the conformers T-1 through T-3. The s-cis and s-trans conformations of the pentenone appear to have similar steric and electronic requirements, and therefore only the former are shown.

In light of the foregoing considerations our findings seem best explained on steric grounds. The chelated anion of β-keto ester **8** may be regarded as a bicyclo[4.4.0]decane substituted with heteroatoms (I). In this system, the most favored steric arrangement in the Michael addition transition state is illustrated below (II).



II

S = H, M = CH_3,

L = CH_3COCH

The actual steric interactions between rings A and B and the incoming vinyl ketone undoubtedly depend on the nature of cation M^+ and upon the solvent. For potassium and sodium enolates in alcohol, the metal–enolate bond should be highly solvated and thus dissociated. When the alcohol is bulky, as is the case with *tert*-butyl and *tert*-amyl alcohol, the solvated ring B (see above) offers greater steric hinderance than ring A. The lower energy transition state then resembles C-1, and the principal product is the cis isomer **9a**.

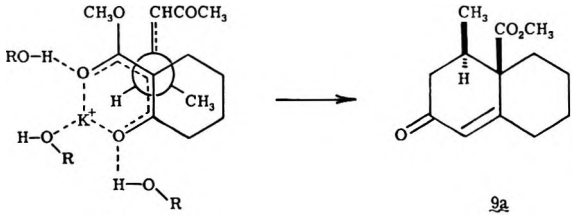
(6) K. Noack and R. N. Jones, *Can. J. Chem.*, **39**, 2225 (1961).

(7) J. K. Wilmburst, *J. Mol. Spectrsc.*, **1**, 201 (1957); T. Mizazawa, *Bull. Chem. Soc. Jap.*, **34**, 691 (1961).

(8) W. Klyne and V. Prelog, *Experientia*, **16**, 521 (1960).

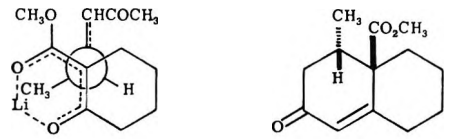
(9) *Cf.* A. Brandstrom, *Ark. Kemi*, **6**, 155 (1953); S. J. Rhoads and A. W. Decora, *Tetrahedron*, **19**, 1645 (1963); S. J. Rhoads and R. W. Hasbrouch, *ibid.*, **22**, 3557 (1966); S. J. Rhoads and R. W. Holder, *ibid.*, **26**, 5443 (1969); H. E. Zaugg and A. D. Schaefer, *J. Amer. Chem. Soc.*, **87**, 1857 (1965).

(10) *Cf.* E. Wenkert, A. Afonso, J. B. Bredenbert, C. Kaneka, and A. Tahara, *ibid.*, **86**, 2038 (1964); T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968); M. E. Kuehne and J. A. Nelson, *ibid.*, **35**, 616 (1970).



C-1 9a

In aprotic solvents, and with lithium enolates, the metal–oxygen bond has considerable covalent character, and there are fewer tightly bound solvent molecules. Under these conditions, ring A (see above) is the more sterically demanding ring, and the favored transition state T-1 leads to the trans isomer **9b**.



T-1 9b

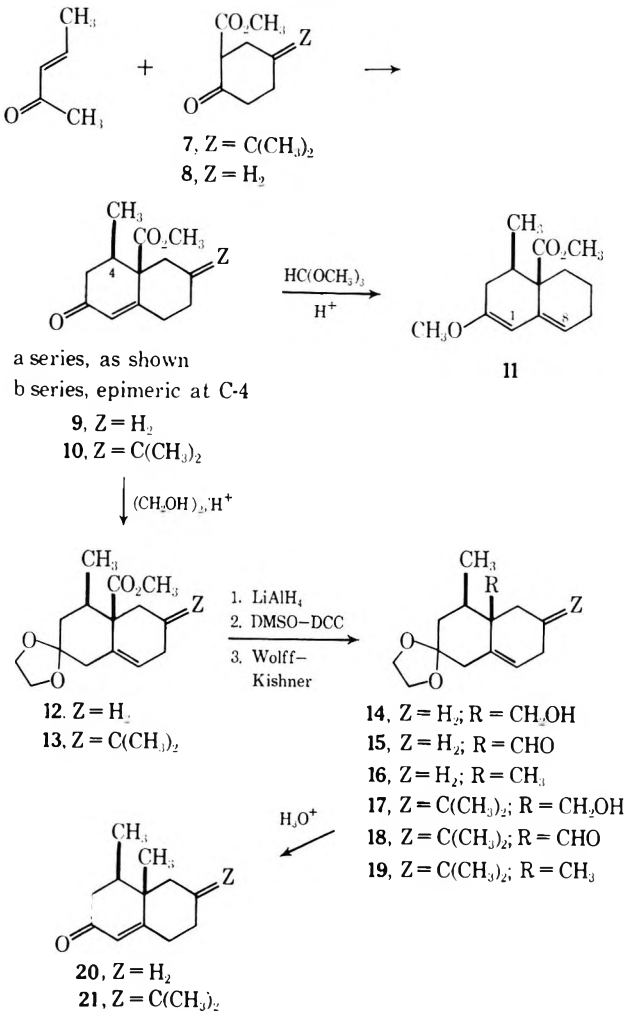
Having discovered conditions for obtaining the desired stereochemical results in the model studies, we could now test the applicability of this discovery to our proposed isonootkatone synthesis. We were gratified to find that the annelation of keto ester **7** with 3-penten-2-one in *tert*-amyl alcohol–potassium *tert*-amylate followed by treatment with methanolic sodium methoxide to effect aldol cyclization proceeded smoothly and gave the desired keto ester **10a** as a crystalline readily purifiable substance.

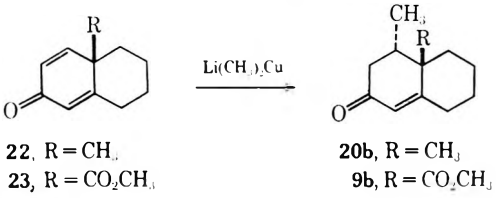
In our initial studies on the further conversion of keto ester **7** to isonootkatone, we effected reduction of the methanesulfonate derivative of ketal alcohol **17a** with lithium in ammonia.[3] This reaction led mainly to recovered alcohol *via* S–O cleavage; the desired hydrogenolysis product **19a** (C–O cleavage) was formed in low yield. Our attempts to improve the ratio of C–O to S–O cleavage in this reaction showed little promise and we therefore sought other means for the $CO_2CH_3 \rightarrow CH_3$ conversion.

After an unfruitful survey[11] of methods based upon the sequence $CO_2CH_3 \rightarrow CH_2OH \rightarrow CH_2X \rightarrow CH_3$, we examined the alternative sequence $CO_2CH_3 \rightarrow CH_2OH \rightarrow CHO \rightarrow CH_3$. This route proved highly satisfactory when the alcohol oxidation step was effected with Moffatt's dimethyl sulfoxide–dicyclohexylcarbodiimide reagent (Scheme II).[12] Other oxidation methods gave poor results apparently owing to competing oxidation involving the double bond of ketal alcohol **14**. Reduction of the aldehyde **15** *via* a modified Wolff–Kishner procedure afforded the desired methyl compound in high yield.

Application of this sequence to mixtures of the keto esters **9a** and **9b**, secured through annelation of keto ester **8**, led to the corresponding mixtures of ketones **20a** and **20b**. The identity of these two isomers was confirmed as follows. Addition of lithium dimethylcopper[13] to dienone **22** afforded a 91:5 mixture of enones **20a** and **20b**. Mechanistic considerations[14] and analogy[1e,15] support the assignment of structure **20b** as the major conjugate addition product. The identity of enones **20a** and **20b** was further substantiated through spectral comparison with authentic samples.[16] An enriched specimen of the trans CH_3/CO_2CH_3 enone **9b** was obtained through conjugate addition of lithium dimethylcopper to the dienone ester **23**. The above-mentioned considerations also apply to this conjugate methylation reaction and support the indicated stereochemistry for the major product.

SCHEME II





(11) T. M. Warne, Jr., "The Total Synthesis of (±)-Isonootkatone," Ph.D. Thesis, Northwestern University, June 1970, pp 67–72.

(12) K. E. Pitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5670 (1965).

(13) H. O. House, W. L. Respess, and G. M. Witesides, *J. Org. Chem.*, **31**, 3128 (1966).

(14) J. A. Marshall and N. H. Andersen, *ibid.*, **31**, 667 (1966).

(15) R. Weichert, U. Kerb, and K. K. Kieslish, *Chem. Ber.*, **96**, 2765 (1963); W. J. Wechter, *J. Org. Chem.*, **29**, 163 (1964); H. Mori, *Chem. Pharm. Bull.*, **10**, 386 (1962); W. J. Wechter, G. Slomp, F. A. MacKellar, R. Weichert, and U. Kerb, *Tetrahedron*, **21**, 1625 (1965).

(16) (a) R. M. Coates and J. E. Shaw, *Chem. Commun.*, 47 (1968). (b) R. L. Hale and L. H. Zalkow, *ibid.*, 1249 (1968). (c) Private communication with J. J. Sims. We are indebted to Professor Sims for providing an infrared spectrum of the trans-fused decalone related to enone **20a**.

With a reliable method in hand for the $CO_2CH_3 \rightarrow CH_3$ conversion the completion of our isonootkatone synthesis posed no problems. Keto ester **10a** was converted to the ketal derivative **13a** and this material was subjected to the aforementioned sequence to give the ketal **19a**. Acidic hydrolysis then afforded racemic isonootkatone (**21a**) identified through spectral and chromatographic comparison with the natural material isolated from vetiver oil.

Experimental Section[17]

2-Isopropylidene-1,3-propanediol (2).—To a stirred mixture of 89 g (2.35 mol) of lithium aluminum hydride in 3.8 l. of ether[17a] was added 385.2 g (1.93 mol) of diethyl isopropylidene malonate[4] at a rate to maintain reflux. The mixture was stirred for 100 hr, and treated in turn with 89 ml of water, 89 ml of 15% aqueous NaOH, and 267 ml of water.[18] Stirring was continued until the salts had coagulated, solid sodium sulfate was added, and the mixture was filtered and concentrated under reduced pressure to give the crude alcohol mixture.

The inorganic salt cake was stirred overnight with 3 l. of refluxing ethyl acetate to give, after filtration and concentration under reduced pressure, 40.4 g of the acetate of diol **2**. Saponification with aqueous methanolic KOH afforded 21 g of crude diol **2** which was combined with the above described alcohol mixture. Distillation afforded two major fractions: (1) **2-isopropenyl-2-propen-1-ol** [60.5 g (31%); bp 34–52° (10 mm); n^{28}D 1.432; $\delta_{TMS}^{CCl_4}$ 4.97, 4.80 (doublets, $J \sim 1.5$ Hz, C=CH_2), 4.02 (-CH_2O-), and 1.05 ppm (doublet, $J = 7$ Hz, isopropyl CH_3)]; (2) diol **2** [64.5 g (29%); bp 74–78° (0.1 mm); n^{25}D 1.483; $\delta_{TMS}^{CCl_4}$ 4.45 (OH), 4.12 (-CH_2O-), and 1.85 ppm (CH_3)].

The benzylidene derivative was prepared by treatment of diol **2** with benzaldehyde in refluxing benzene containing a small amount of *p*-toluenesulfonic acid. The analytical sample, mp 55.5–56°, was secured by recrystallization from hexane.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.7; H, 7.8.

2-Isopropylidene-1,3-dibromopropane (3).—Following the procedure of Hwa and Sims,[19] 5.78 g (50 mmol) of diol **2** was added with efficient stirring over 90 min to 4.00 ml (42 mmol) of phosphorous tribromide containing a drop of 48% HBr and maintained at 0°.[17a] The mixture was stirred an additional 1 hr, whereupon the product separated as a dark oil. After standing overnight the upper product layer was removed by pipet and isolated *via* ether extraction at low temperature[17b] affording 9.86 g (82%) of dibromide **3**: bp 50° (0.01 mm); mp *ca.* 10°; $\delta_{TMS}^{CCl_4}$ 4.12 (CH_2-Br) and 1.85 ppm (CH_3).

This highly lachrymatory substance deteriorated rapidly, even when stored at −20° and it was therefore used immediately after *distillation*.

Diethyl 2,6-Di(ethoxycarbonyl)-4-isopropylideneheptanedioate (4).—A solution of 176 g (1.1 mol) of diethyl malonate in 350 ml of DME was added slowly to a suspension of NaH (1.0 mol, secured from 48.0 g of 50% mineral oil dispersion through hexane washing) in 300 ml of DME.[17a] A solution of 14.48 g (0.060 mol) of dibromide **3** was added over a 2–3 hr period and the mixture was stirred for an additional 20 hr. Ethereal acetic acid was added to neutralize the excess sodiomalonate and the product was isolated with ether[17b] and distilled, affording 22.84 g (95%) of the tetraester **4**, bp 180° (0.007 mm). The analytical sample was secured by two additional short-path distillations.

Anal. Calcd for $C_{20}H_{32}O_8$: C, 59.98; H, 8.06. Found: C, 60.2; H, 8.1.

4-Isopropylideneheptanedioic Acid (5).—A solution of 15.05 g (37.5 mmol) of tetraester **4** and 10.0 g of KOH in 200 ml of ethylene glycol was heated at reflux for 12 hr.[17a] The cooled mixture was poured into water and extracted with ether to remove neutral by-products. The aqueous solution was acidified with concentrated HCl and the product was isolated with ether[17b] affording 6.89 g (97%) of solid diacid **5**. Recrystallization from ethyl acetate–hexane afforded needles, mp 96°. The analytical sample, mp 99°, was obtained *via* sublimation [95° (0.01 mm)].

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 60.1; H, 8.1.

Dimethyl 4-Isopropylideneheptanedioate (6).—According to the esterification procedure of Clinton and Laskowski,[20] 7.28 g (37.4 mmol) of diacid **5** in 160 ml of 1,2-dichloroethane, 18 ml of methanol, and 0.3 ml of concentrated sulfuric acid was stirred at reflux for 3 hr.[17a] The product was isolated with 1,2-dichloroethane[17b] and distilled affording 7.23 g (87%) of diester **6**, bp 85–95° (0.01 mm).

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.1; H, 8.9.

Methyl 4-Isopropylidene-2-oxocyclohexanecarboxylate (7).—A solution of 16.30 g (67.0 mmol) of diester **6** in 50 ml of DME was added to a suspension of NaH (230 mmol secured from 9.68 g of 51% mineral oil dispersion through hexane washing) in 1.15 l. of DME.[17a] The mixture was stirred at reflux for 6.5 hr, allowed to cool, and acidified with ethereal acetic acid. The product was isolated with ether[17b] and distilled, affording 11.75 g (90%) of keto ester **7**, bp 103–105° (0.50 mm).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.3; H, 8.2.

Annelation of Keto Ester 8 with *trans*-3-Penten-2-one.—The following procedure is representative of the reactions described in Table I. To a solution of 4.71 g (30 mmol) of keto ester **8** in 14 ml of 1.4 *M* KO-*tert*-Am (1.9 mmol) in *tert*-AmOH at −10 to −15° was added 3.20 g (38 mmol) of *trans*-3-penten-2-one over 8.5 hr.[17a] The solution was maintained at 0° for 15 hr and the product was isolated with ether[17b] affording 5.94 g of crude Michael adduct. This material was cyclized by treatment with 15 ml of 2 *M* NaOMe in MeOH at room temperature for 22 hr.[17a] Isolation with ether[17b] and distillation afforded 4.30 g (65%) of keto ester mixture **9a** and **9b**: bp 128–132° (0.01 mm); $\delta_{TMS}^{CCl_4}$ 5.76 (vinyl H), 3.70 (CO_2CH_3), 0.95 (axial CH_3 doublet, $J = 6.3$ Hz), and 0.91 ppm (equatorial CH_3 doublet, $J = 5.9$ Hz).

Recrystallization of the above sample from pentane afforded material, mp 75–76°, whose spectral properties coincided with those of the cis isomer **9a**. Vpc analysis of the enol ether derivative of this material showed it to be an 88:12 mixture of the epimers **11b** and **11a**.

Methyl 4*t*-Methyl-1(9)-octal-2-one-10*r*-carboxylate (9b).—Lithium dimethylcopper was prepared according to House, *et al.*,[13] from 4.67 ml of 1.6 *M* ethereal MeLi and 0.743 g (3.90 mmol) of CuI in 10 ml of ether at 0°.[17a] To this stirred solution was added 0.400 g (1.90 mmol) of dienone **22** in 25 ml of ether.[17a] After one hr at 0° the mixture was poured into aqueous ammonium chloride–ammonium hydroxide and the product was isolated with ether[17b] affording 0.414 g of enone **9b**, bp 121° (0.01 mm), mp 70.5–72°, after recrystallization from pentane. The spectral data for this compound coincided with that of the trans component **9b** of the annelation product. Vpc analysis of the enol ether derivative of this material showed it to be an 87:13 mixture of the epimers **11b** and **11a**.

Conversion of Keto Esters 9 to the Enol Ethers 11.—A solution of 200 mg (0.90 mmol) of a keto ester **9** mixture and 70 mg of *p*-toluenesulfonic acid monohydrate in 5.0 ml of trimethyl orthoformate was stirred at room temperature for 1.5–2 hr.[17a] The initially colorless solution became green and a precipitate could be observed after 1 or 2 min. The reaction was quenched with aqueous sodium bicarbonate and the product was isolated[17b] and distilled affording 205 mg (97%): bp 100–110° (0.01 mm); $\delta_{TMS}^{CCl_4}$ 5.43 (H-8 triplet of **11a**, $J \sim 4$ Hz), 5.29 (H-8 triplet of **11b**, $J \sim 4$ Hz), 5.15 (H-1), 3.50 and 3.57 (CH_3O), 0.99 (CH_3 doublet of **11a**, $J = 5.5$ Hz), and 0.83 ppm (CH_3 doublet of **11b**, $J = 6.4$ Hz). The two epimers were cleanly separated *via* gas chromatography on both Carbowax 20M and FFAP columns.

Conversion of Keto Ester 9 to Enone 20.—A mixture of 300 mg (1.35 mmol) of keto esters **9a** and **9b** (Table I, entry 10), 10 ml of ethylene glycol, and 52 mg of *p*-toluenesulfonic acid in 25 ml of benzene was stirred at reflux with azeotropic water removal *via* a Dean–Stark trap for 23 hr.[17a] The cooled mixture

(17) (a) The apparatus described by W. S. Johnson and W. P. Schneider ("Organic Syntheses," Coll. Vol. IV, Wiley, New York, N. Y., 1963, p 132) was used to maintain a nitrogen atmosphere. (b) The isolation procedure consisted of thorough extractions with the specified solvent, washing the combined extracts with saturated brine solution, and drying the extracts over anhydrous magnesium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator. (c) Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(18) *Cf.* L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 584.

(19) J. C. Hwa and H. Sims, *Org. Syn.*, **41**, 49 (1961).

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

was poured into aqueous sodium bicarbonate and the product was isolated with ether[17b] affording 329 mg (92%) of ketal **12**.

A solution of this ketal in 25 ml of ether was heated with 76 mg (2.0 mmol) of lithium aluminum hydride at reflux for 5 hr. Water, 15% NaOH, and sodium sulfate were added (see above)[18] and the mixture was filtered to give, after removal of solvent under reduced pressure, 270 mg (92%) of the hydroxy ketal **14**.

A 490-mg (2.05 mmol) sample of alcohol **14** comparable to that described above was stirred overnight with a solution of 1.27 g (6.15 mmol) of dicyclohexylcarbodiimide, 0.08 ml of trifluoroacetic acid, 0.16 ml of pyridine, and 4.0 ml of dimethyl sulfoxide[12] in 4.0 ml of benzene.[17a] The mixture was poured into 25 ml of EtOAc and 540 mg of oxalic acid in 5 ml of MeOH was added. After 0.5 hr the product was isolated with EtOAc[17b] and distilled affording 439 mg (90%) of aldehyde **15**: bp 105° (0.02 mm); λ_{max}^{film} 3.69 and 5.80 μm (CHO).

A 220-mg (0.93 mmol) sample of the above aldehyde in solution with 2.5 ml of 64% aqueous hydrazine and 6 ml of ethylene glycol was heated at 110° for 1 hr[17a] A 1-g portion of KOH was added and the temperature was increased to 200° for 2 hr. The solution as allowed to cool and the product was isolated with hexane.[17b]

A 475-mg sample of material comparable in quality to that described above was heated at reflux with a solution of 45 ml of methanol and 15 ml of 10% aqueous HCl for 5 hr.[17a] The product was isolated with methylene chloride[17b] and distilled affording 312 mg (82%) of enone **20**, bp 80–95° (0.01 mm). Analysis by vpc indicated a 50:41 mixture of **20a** and **20b**. The identity of these isomers was confirmed by peak enhancement with authentic samples.[16]

The above sequence was carried out on a sample of the keto ester 9 secured *via* addition of lithium dimethylcopper to dienone ester **23**, affording a 78:18 mixture (vpc analysis) of enones **20b** and **20a**.

4*t*,10*r*-Dimethyl-1(9)-octal-2-one (20b).—Lithium dimethylcopper was prepared from 3.6 ml of 1.6 *M* ethereal MeLi and 0.571 g (3.0 mmol) of CuI in 20 ml of ether at 0°.[13] A solution of 0.244 g (1.5 mmol) of dienone **22** in 8 ml of ether was added,[17a] and the mixture was stirred for 1 hr and poured into aqueous ammonium chloride–ammonium hydroxide. The product was isolated with ether[17b] and distilled, affording 0.247 g (92%) of enone **20** (a 91:5 mixture of **20b** and **20a** according to vpc analysis), bp 85–95° (0.10 mm).

Methyl 4*c*-Methyl-6-isopropylidene-1(9)-octal-2-one-10*r*-carboxylate (10a).—The Michael–aldol sequence was carried out on 7.26 g (37.0 mmol) of keto ester **7** according to the procedure described above affording 6.47 g (67%) of solid keto ester **10**. Recrystallization from hexane afforded 2.45 g of white needles: mp 70–71°; λ_{max}^{KBr} 5.75, 5.95, and 6.13 μm; $\delta_{TMS}^{CCl_4}$ 5.83 (H-1), 3.67 (CH_3O), 1.68 (vinyl CH_3), and 1.02 ppm (CH_3 doublet, J = 6 Hz). The analytical sample was obtained by sublimation at 55–60° (0.01 mm).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.46. Found: C, 73.5; H, 8.5.

Methyl 2,2-Ethylenedioxy-4*c*-methyl-6-isopropylidene-10*r*-carboxylate (13a).—A 0.726-g (2.77 mmol) sample of keto ester **10a** was stirred at reflux with 24 mg of *p*-toluenesulfonic acid and 5 ml of ethylene glycol in 32 ml of benzene with water removal *via* a Dean–Stark trap.[17a] The product was isolated with ether[17b] and distilled affording 0.813 g (96%) of ketal **13a**: bp 120–125° (0.02 mm); $\delta_{TMS}^{CDCl_3}$ 5.58 (H-8), 3.92 ($-OCH_2CH_2O-$), 3.60 (CH_3O), 1.72, 1.60 (vinyl CH_3s), and 1.00 ppm (CH_3 doublet, $J \sim 5$ Hz).

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.6; H, 8.6.

2,2-Ethylenedioxy-4*c*-methyl-6-isopropylidene-1(9)-octalin-10*r*-carboxaldehyde (18a).—Ketal ester **13a** (0.93 g, 3.26 mmol) was reduced with lithium aluminum hydride according to the procedure described above for ester **12** affording the alcohol **17a**. This material was oxidized using 6.4 ml of DMSO, 0.254 ml of pyridine, 0.127 ml of trifluoroacetic acid, and 2.035 g (9.9 mmol) of DCC in 6.40 ml of benzene as described above to give the aldehyde **18a** (0.89 g, 98%): bp 119–125° (0.01 mm); λ_{max}^{film} 3.67 and 5.80 μm; $\delta_{TMS}^{CDCl_3}$ 9.48 (aldehyde H), 5.68 (H-1), 3.90 ($-OCH_2-CH_2O-$), 1.71 1.64 (vinyl CH_3s), and 1.05 ppm (CH_3 doublet, J = 5 Hz).

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.7; H, 8.7.

(±)-Isonootkatone (21a).—The reduction procedure described above for ketal aldehyde **15** was employed using 0.520 g (1.88 mmol) of aldehyde **18a** affording 0.399 g (81%) of ketal **19a**: bp 108–113° (0.01 mm); $\delta_{TMS}^{CDCl_3}$ 5.30 (H-1), 3.92 ($-OCH_2CH_2O-$), 1.70 (vinyl CH_3), 0.93 (CH_3 doublet, J = 5.5 Hz), and 0.84 ppm (CH_3).

The above sample of ketal **19** in 12 ml of acetone, 1 ml of water, and 0.25 ml of concentrated HCl was stirred at reflux for 0.5 hr.[17a] Solid sodium bicarbonate was added and the product was isolated with pentane[17b] and distilled affording 0.316 g (95%) of impure isonootkatone (**21a**), bp 110° (0.015 mm). This material was purified *via* chromatography on silica gel and distillation [85–95° (0.01 mm)]. The material thereby obtained (166 mg) solidified. The spectral properties of this substance matched those of natural isonootkatone.[2]

Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.5; H, 10.1.

Methyl 1(9),3-Hexal-2-one-10-carboxylate (23).—A solution of 3.28 g (15.7 mmol) of methyl 1(9)-octal-2-one-10-carboxylate and 3.97 g (17.5 mmol) of 2,3-dichloro-5,6-dicyanobenzoquinone in 130 ml of benzene and 6.8 ml of acetic acid was stirred at reflux for 40 hr.[17a] The mixture was filtered and the filtrate was washed with 10% aqueous NaOH, saturated aqueous sodium bicarbonate, and dried to give, after removal of solvent under reduced pressure, 2.66 g (82%) of yellow solid. Recrystallization from hexane afforded 1.98 g of dienone ester **23**: mp 115–117°; λ_{max}^{KBr} 5.78, 6.01, 6.12, and 6.22 μm; $\delta_{TMS}^{CCl_4}$ 6.68 (H-4 doublet, J = 10 Hz), 6.18 (H-3, 4 lines, $J_{3,4}$ = 10 Hz, $J_{3,1}$ = 1.5 Hz), 6.11 (H-1 doublet, J = 1.5 Hz), and 3.72 ppm (CH_3O). The analytical sample, mp 118.5–119°, was obtained by sublimation [65° (0.01 mm)].

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.9; H, 6.8.

Registry No.—**2**, 2035-85-0; **2** benzylidene derivative, 26419-14-7; **3**, 26430-96-6; **4**, 26430-97-7; **5**, 26430-98-8; **6**, 16981-92-3; **7**, 26431-00-5; **9a**, 26431-01-6; **9b**, 26419-15-8; **10a**, 26431-02-7; **11a**, 26431-03-8; **11b**, 26431-04-9; **13a**, 26431-05-0; **15a**, 26431-06-1; **15b**, 26431-14-1; **18a**, 26431-07-2; **19a**, 26431-08-3; **20a**, 26431-09-4; **20b**, 26431-10-7; **21a**, 16981-90-1; **23**, 26431-12-9; 2-isopropenyl-2-propen-1-ol, 26431-13-0.

Acknowledgment.—We are indebted to the National Institutes of Health for their support of this work through a research grant (5 RO1 CA11089).

Comparative Mobility of Halogens in Reactions of Dihalobenzenes with Potassium Amide in Ammonia

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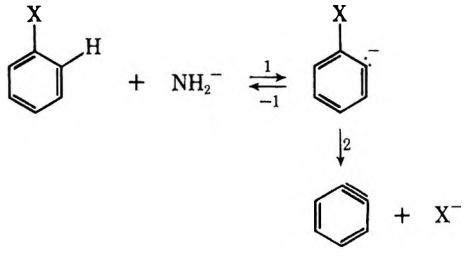
Received June 22, 1970

Dihalobenzenes in which the two halogens are unlike release two different halide ions, generally in unequal amounts, on reaction with KNH_2. From *m*-dihalobenzenes, the relative yields of halide ion are in the order I > Br > Cl, but *o*- and *p*-dihalobenzenes give more complex patterns because either of two steps in the aryne-forming reaction may be rate limiting. Under reaction conditions, haloanilines furnish little halide ion. When potassium anilide is the base, the heavier halogen is in all cases released preferentially.

Reactions of potassium amide
With halobenzenes in ammonia
Via benzyne intermediates occur.[3,4]
Bergstrom and associates[5] did report,
Based on two-component competition runs,
Bromobenzene the fastest to react,
By iodobenzene closely followed,
The chloro compound lagging far behind,
And fluorobenzene to be quite inert
At reflux (−33°).
Reactions with *para*-dihalobenzenes,
In which the halogens were not the same,
The same order of mobility revealed,
But differences in reactivity
Were somewhat less in magnitude.

The irregular mobility rank
Explanation finds in the mechanism
Whereby arynes are formed.[3,4] There are two steps:
Abstraction of the ortho proton
And then expulsion of the halogen
From the anion intermediate.
In Scheme I the mechanism is set forth.

SCHEME I



Here proton removal is favored, in rate
And in respect to equilibrium,
By high electronegativity
Of halogen.[6] But the expulsion step
Is faster in the opposite order.
According to the evidence, for both
Iodine and bromine step 1 limits rate.[3]
But on the other hand, the setting free
Of halogen determines total rate
For chlorine and fluorine atoms on the ring.

We have repeated the experiments
With dihalobenzenes of Bergstrom's group.
They are extended to the isomers
Meta and ortho, and to the action
Of potassium anilide reagent.
Throughout, halide ions have been determined
By potentiometric titration
In which end points for diverse halide ions
Are discrete, and easy to recognize.
Nitrogenous products were not assayed.

Results

Data for reactions of all nine mixed
Dihalobenzenes (excluding fluorine)
With four equivalents of amide base
Are set forth in Table I. Reactions
With the same base in deficiency
Appear, for six substrates, in Table II.
In Table I, more than one halide ion
Is set free from each dihalobenzene
Molecule. This suggests the possibility
That maybe haloanilines too react
With potassium amide. In Table III

TABLE I

REACTIONS OF DIHALOBENZENES WITH EXCESS POTASSIUM AMIDE IN AMMONIA[a]

Halogens present	Orientation	Registry no.	Halide ion yields, %[b] I⁻	Br⁻	Cl⁻	Total	Ratio[c]
Cl, Br	ortho	694-80-4		98.5	1	109.5[d]	90/10
	meta	108-37-2		101	7.5	108.5[d]	93/7
	para	106-39-8		95.5	8.0	103.5[e]	92/8
				97.5	8.0	105.5[d]	92/8
Br, I	ortho	583-55-1	71	83		154	46/54
			64	73.5		137.5	47/53
	meta	591-18-4	96	17.5		113.5	85/15
	para	589-87-7	50.5	70		120.5	42/58
Cl, I	ortho	615-41-8	93.5		42.5	136	69/31
			93.5		32.5	126	74/26
	meta	625-99-0	95.5		6.5	102	93/7
	para	637-87-6	96		14	110	87/13

[a] Reaction conditions: 0.02 mol of dihalobenzene with 0.08 mol of KNH_2; time 10 min, unless otherwise noted. [b] Reckoned on the basis of one halide ion per molecule of dihalobenzene; thus, the first experiment afforded 0.0197 mol of Br^- and 0.0022 mol of Cl^-. [c] Ratio of heavier halide ion to lighter halide ion. [d] 15 min. [e] 20 min.

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(2) NOTE FROM EDITOR.—Although we are open to new styles and formats for scientific publication, we must admit to surprise upon receiving this paper. However, we find the paper to be novel in its chemistry, and readable in its verse. Because of the somewhat increased space requirements and possible difficulty to some of our nonpoetically inclined readers, manuscripts in this format face an uncertain future in this office. However, we take this opportunity to encourage readers and authors to examine carefully a new format represented by the articles on pages 3591–3646 and the *Editor's Notice* in the November 1970 issue of this journal.

(3) J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., and L. A. Carlsmith, *J. Amer. Chem. Soc.*, **78**, 601 (1956).

(4) J. F. Bunnett, *J. Chem. Educ.*, **38**, 278 (1961).

(5) F. W. Bergstrom, R. E. Wright, C. Chandler, and W. A. Gilkey, *J. Org. Chem.*, **1**, 170 (1936).

(6) J. Hine and P. B. Langford, *ibid.*, **27**, 4149 (1962).

TABLE II

REACTIONS OF DIHALOBENZENES WITH A DEFICIENCY OF POTASSIUM AMIDE IN AMMONIA[a]

Halogens present	Orientation	Halide ion yields, %[b] I⁻	Br⁻, Cl⁻	Total	Ratio[c]
Cl, Br	para		56.5	56.5	100/0[d]
Br, I	ortho	37	38	75	49/51
	meta	68	8	76	89/11
	para	23.5	37	60.5	39/61[e]
		26.5	41.5	68	39/61[e]
Cl, I	meta	63.5		63.5	100/0
2-Bromo-4-iodotoluene		46.5	27.5	74	63/37

[a] Reaction conditions: 0.02 mol of dihalobenzene or dihalotoluene with 0.03 mol of KNH_2, for 10 min. [b] Reckoned on the same basis as in Table I; yields based on KNH_2 (the limiting reagent) are 1.33 times greater than listed. [c] Ratio of heavier halide ion to lighter halide ion. [d] Bergstrom, *et al.*,[5] reported 89/11 and 85/15. [e] Bergstrom, *et al.*,[5] reported 32/68.

TABLE III

REACTIONS OF HALOANILINES WITH EXCESS POTASSIUM AMIDE IN AMMONIA[a]

Substituent	Halide ion yield, %	Substituent	Halide ion yield, %
m-Chloro	0.6	*p*-Bromo	3.0
p-Chloro[b]	0.6	*m*-Iodo	5.7
m-Bromo	2.6	*p*-Iodo	1.6

[a] Reaction conditions: 0.02 mol of haloaniline with 0.10 mol of KNH_2; time 10 min, unless otherwise noted. [b] 30 min.

TABLE IV

REACTIONS OF DIHALOBENZENES WITH EXCESS POTASSIUM ANILIDE IN AMMONIA[a]

Halogens present	Orientation	Halide ion yields, %[b] I⁻	Br⁻, Cl⁻	Total	Ratio[c]
Cl, Br	para		11.5	11.5	100/0
Br, I	ortho	3.2	2.6	5.8	54/46
	meta	89	15	104	86/14
	para	36	5.5	41.5	87/13
Cl, I	meta	90.5		90.5	100/0

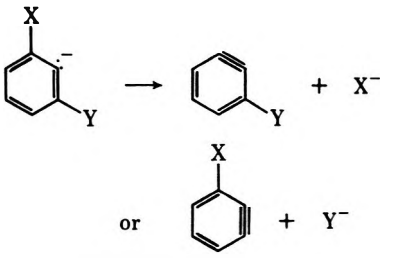
[a] Reaction conditions: 0.02 mol of dihalobenzene with 0.08 mol of potassium anilide and a slight excess (0.01 mol) of aniline; for 30 min. [b] Reckoned on the basis of one halide ion per molecule of dihalobenzene. [c] Ratio of heavier halide ion to lighter halide ion.

Are shown experiments which demonstrate
That haloanilines react but to
A slight degree under conditions such as used.
Tribromobenzene isomerizations
Are well catalyzed by potassium
Anilide in liquid ammonia.[7]
It was therefore of interest to see
The effect of this base on mobility.
Results are assembled in Table IV.

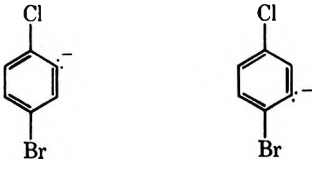
Discussion

In meta isomers, the hydrogen between
Two ortho halogens is more acidic than
The other hydrogens.[6] In consequence,
Halide expulsion to form arynes
Occurs predominantly from those anions
That are doubly ortho substituted.[8,9]

Therefore either halide ion doth derive
From the very same anion, and which
Is preferentially expelled depends
Upon the intrinsic labilities
Of the two covalent bonds to halogen.



In Table I, data pertaining to
The meta isomers show clearly that
Carbon–iodine bonds more readily break
Than carbon–bromine bonds, and furthermore
That carbon–chlorine bonds are even more
Resistant. This is, of course, a familiar
Order of reactivity. Somewhat puzzling
Is that the heavier–lighter halide ratio
From *meta*-iodochlorobenzene
Is just the same as from *meta*-bromo-
Chlorobenzene. One would have expected
Almost exclusive iodine release
From the former compound. In Table II,
And likewise in examples found in Table IV,
The anticipated insignificance
Of chlorine release is however manifest.
Ortho and para isomers behave
Almost identically in Table I.
From the two bromoiodobenzenes,
Bromide release predominates in slight degree.
Clearly, the proton abstraction step (Scheme I)
Is for the most part rate determining.
From *ortho*- and *para*-bromochloro-
Benzenes, bromide ion is liberated
Some ten times faster than is chloride ion.
The two anions concerned are **1** and **2**.



1 **2**

Doubtless **1** is formed more rapidly
But mostly to the parent molecule reverts.[8]
Anion **2** is not so quickly formed
But decomposes to a large extent[10]
With liberation of a bromide ion.
Remarkably, the *ortho*- and *para*-
Iodochlorobenzenes are less prone
Than corresponding bromochlorobenzenes
The heavier halogen to set free.
The reason surely is that iodine

3 **4**

(7) C. E. Moyer, Jr., and J. F. Bunnett, *J. Amer. Chem. Soc.*, **85**, 1891 (1963); J. F. Bunnett and G. Scorrano, *ibid.*, in press.
(8) J. A. Zoltewicz and J. F. Bunnett, *ibid.*, **87**, 2640 (1965).
(9) J. K. Kim, unpublished observations.
(10) M. Aufrere, unpublished observations.

But weakly aids formation of ion **4**;
Release of chlorine then from ion **3**,
Preferred over **4** in its free energy,
Creeps close to that of iodine less firmly bound.
para-Bromoiodobenzene demonstrates
An inversion of mobility
As the proton-seeking reagent is changed
From amide ion (in Table I or II)
To anilide (in Table IV). Release
Of iodine is preferred with anilide.
The same effect has three times been observed
With oligohalobenzenes, although
Interpretation is obscured somewhat
By disproportionations which occur
In several cases.[7,11] Isomerizations
Are improbable with the present substrate.
In the anilide–aniline milieu,
ortho-halophenyl anions revert
To parent molecules more frequently
Than they do with the amide base. Therefore,
Release of halide ion is determined
Relatively more by the lability
Of the carbon–halogen bonds concerned
Than by rates of abstraction of protons.
The haloanilines do not react
Extensively with excess amide ion,
As shown in Table III. In harmony
Appears the fact that yields of halide ion
With surplus amide ion slightly exceed
One ion from each dihalobenzene molecule
(Table I). However, *ortho*-iodo
Substrates afford much more halide ion
Than can be attributed to subsequent
Attack on the haloanilines that form.
An unexpected pathway of reaction,
Unclear in its details, is thus revealed.
This complication, our thanks to him,
Is under study by Jhong Kook Kim.

(11) J. F. Bunnett and C. E. Moyer, Jr., *J. Amer. Chem. Soc.*, in press.

Experimental Section

Materials.—All dihalobenzenes were used as supplied by Eastman Kodak Co., except *m*-bromoiodobenzene which was distilled [bp 72.5–73.5° (1 Torr)] to remove a colored impurity. *p*-Bromo- and *p*-chloroanilines (from Eastman Kodak) and *m*-chloro-, *m*-iodo-, and *p*-iodoanilines (from Aldrich Chemical Co.) were used without further purification. 2-Bromo-4-iodotoluene, bp 96.5–97.0° (1 Torr), was synthesized by standard methods from a sample of 3-bromo-4-methylacetanilide which had been prepared by Dr. T. Okamoto.

Reaction Procedure.—Reactions were carried out substantially as described by Bunnett and Moyer.[11] In all cases, 500 ml of liquid ammonia was used, the dihalobenzene or halobenzene was added in solution in diethyl ether, and the addition funnel was rinsed with ether, the total volume of ether used being 70 ml. Reaction mixtures were usually dark red-brown in color. After the times listed in the tables, an excess of crushed ammonium nitrate was added, the ammonia was allowed to evaporate, and the residue was transferred to a separatory funnel with alternate washings of water and ether. The (alkaline) water layer was separated, and the ether layer was washed with water. The combined aqueous layers were adjusted to pH 3–4 by addition of dilute nitric acid, warmed briefly to expel dissolved ether, and diluted to the mark in a volumetric flask. Aliquots were titrated potentiometrically with silver nitrate, a radiometer titrator–titrigraph being used.

For reactions with dihalobenzenes in excess (Table II), the apparatus and procedure of Bunnett and Hrutfiord[12] were used without modification.

Registry No.—2-Bromo-4-iodotoluene, 26670-89-3; potassium amide, 17242-52-3.

(12) J. F. Bunnett and B. F. Hrutfiord, *ibid.*, **83**, 1691 (1961).

The Reactions of *in situ* *n*-Propylmagnesium, -cadmium, and -zinc Reagents with 4-*tert*-Butylcyclohexanone. Addition *vs.* Reduction and the Stereochemistry of Each

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Received September 8, 1969

The stereochemistry of both addition and reduction products of 4-*tert*-butylcyclohexanone with *n*-propylmagnesium, -cadmium, and -zinc reagents has been determined. Reactivity among Cd and Zn reagents varies over a wide range with a change in metal and halide ion, factors which also affect addition–reduction and the stereochemistry of both reactions. Cd reagents exhibit the greatest preference for addition over reduction. The Zn reagent leads to the nonthermodynamic reduction product (axial alcohol) in two instances.

In view of the striking tendency of methylcadmium and methylzinc reagents to add to 4-*tert*-butylcyclohexanone (**1**) from the axial side,[2] we undertook an investigation of the addition of *n*-propyl organometallics to the same ketone. The reaction of *n*-PrM (M = Mg, Cd, Zn) with **1** offered the opportunity to determine both the relative importance of addition and reduction with the various reagents as well as the stereochemistry of both processes (Scheme I).

After our experiments had been completed, preliminary results by Abenhaim[3] were published, including some experiments on the addition and reduction, with the stereochemistry of addition (only) reported for these same propyl reagents with 4-*tert*-butylcyclohexanone. Although no experimental details were described, the organometallic reagents employed by Abenhaim were presumably those containing bromide ion exclusively. His results are somewhat misleading inasmuch as he reported neither the yield of alcohol products nor the stereochemistry of reduction.

We should like to report our detailed study of the

* To whom correspondence should be addressed.

(1) (a) National Science Foundation Trainee, 1966–1969; (b) National Defense Education Act Fellow, 1966–1969.

(2) P. R. Jones, E. J. Goller, and W. J. Kauffman, *J. Org. Chem.*, **34**, 3566 (1968).

(3) M. Abenhaim, *C. R. Acad. Sci., Ser. C*, **267**, 1426 (1968).

TABLE I
REACTION OF *n*-PROPYL ORGANOMETALLIC REAGENTS WITH 4-*tert*-BUTYLCYCLOHEXANONE[a]

Reagent[b] (*M*)	% unchanged ketone[c]	% addition[d]	Ratio, addn/redn	% 2[e]	% 5[f]
PrMgBr (0.8)	1	66	1.9 (2.3)[h]	68	95
PrMgBr (0.1)	1	57	1.3	69[g]	95
PrMgI (0.8)	4	66	1.9	67	87
Pr_2Cd (I, I, 0.4)	11	86	6.1	52[g]	72
Pr_2Cd (I, Cl, 0.4)	19	91	10	61	70
Pr_2Cd (I, Br, 0.4)	22	91	10	55	72[j]
Pr_2Cd (Br, Br, 0.4)	63	89	8.1 (4.66)[h]	75 (80)[h]	74
Pr_2Zn (I, I, 0.3)	77	65	1.9	54	74[i]
Pr_2Zn (I, Br, 0.3)	77	54	1.2	57	48[i,j]
Pr_2Zn (Br, Br, 0.3)	87	28	0.39 (0.89)[h]	69 (75)[h]	19[i]

[a] Values are averages of at least two experiments with deviation of ±2% unless otherwise stated. For each experiment the value was the average of at least three glpc injections, for which deviation was ±2%. Corrections have been made for differences in response ratios (see Experimental Section). [b] Mg and Zn reactions were run with 4 molar equiv/equiv of ketone; Cd reactions were run with 2 molar equiv. Halogens in parenthesis indicate, respectively, the propyl halide and metal halide used. [c] Reproducible within ±5% in separate reaction runs. % = [area (ketone)/area (ketone) + Σ area (alcohols)] × 100. [d] Normalized yields: % addition + % reduction = 100%. [e] Normalized yields: % **2** + % **3** = 100%. [f] Normalized yields: % **4** + % **5** = 100%. [g] Single reaction run. [h] Reference 3. [i] Deviation of ±3% in separate reaction runs. [j] In the Zn reaction, **4** underwent 5% equilibration to **5** after 3 hr; no equilibration was noted with Cd.

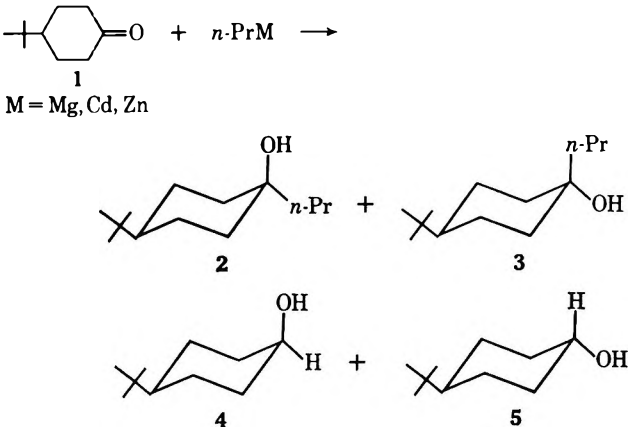
reactions of a variety of *n*-propyl reagents of Mg, Cd, and Zn, containing various halides, from the point of view of addition *vs.* reduction as well as the stereochemistry of *both* the addition and reduction process.

Some striking contrasts among Mg, Cd, and Zn reagents and between the methyl[2] and *n*-propyl reagents are evident from Table I. The nature of the metal and halide ions present exerts marked effects on reactivity, addition *vs.* reduction, and stereochemistry. A rough measure of reactivity, based on the amount of unchanged ketone under standard reaction conditions, indicates the superior reactivity of Mg and the very low reactivity of Zn reagents, in particular, the propylzinc (Br, Br) reagent employed by Abenhaim.[3] The propyl reagents of Cd and Zn are less reactive than the methyl[2] compounds, as well.

With regard to competition between addition and reduction, the cadmium reagents show the least tendency to effect reduction, the zinc reagents the greatest. Only in the latter case does the nature of the halide ion have any significant effect on addition–reduction although one would predict that the behavior of Grignard and cadmium reagents would be sensitive to halide, too, on the basis of currently accepted mechanisms for the additions[4] and reductions[5] with RMgX.

With all of the propyl reagents there is more equatorial addition than from the corresponding methyl compounds. This reflects the greater steric interference to axial attack with the larger propyl group, in accord with the transition state model recently proposed by Cherest and Felkin.[6] It should be noted that the cadmium and zinc reagents containing only bromide ion act as the "bulkiest," affording the least amount of axial attack. In the four-center transition state postulated for addition of cadmium and zinc reagents,[2] a tightening of the transition state (by a change from I to Br, for example) may well increase steric interactions between the β- and γ-propyl carbons and the 3,5-diaxial hydrogens, and thus the formation of **3** by axial attack would be impaired.

SCHEME I



The stereochemistry of reduction shows a striking contrast. Whereas both Mg and Cd reagents give preferentially axial reduction (the former being more stereoselective), the Zn reagents in two cases gave the nonthermodynamic isomer **4** as the major product. Because **4** was shown to undergo some equilibration to **5** (see Table I, footnote *j*), the stereoselectivity of the propylzinc reductions is in fact higher than that indicated in Table I. This serves as still further evidence[7] against product-development control in reactions of cyclohexanones. The fact that only zinc reagents show a change in stereochemistry of reductions with halide is surprising because reductions with all those reagents presumably involve six-center transition states. It would have been expected that the stereochemistry of all reductions would be insensitive to halide, as is the case for asymmetric reduction of methyl *tert*-butyl ketone with Grignard reagents from (+)-1-halo-2-methylbutane.[5b]

These many variations in behavior may represent a delicate balance between steric and electronic effects, which depend, among other things, on the dimensions of four- and six-center transition states, size and electronegativity of halide, and the differences in length and strength of carbon–metal bonds.

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Experimental Section

The experimental conditions, modeled closely after those with methyl reagents,[2] are typified by the following representative procedures.

Reaction of *n*-Propylmagnesium Bromide and Iodide with 4-*tert*-Butylcyclohexanone (1).—To a reaction flask containing 7 ml of anhydrous ether was added an ethereal solution of 11.2 ml of 2.32 *M* *n*-propylmagnesium bromide (26 mmol). The contents were cooled to 0° by means of an ice bath prior to the addition of a solution of 1.0 g (6.5 mmol) of **1** in 15 ml of ether. The temperature remained below 5° during addition. After a total of 15 min at ice-bath temperature, the bath was removed and stirring continued at ambient temperature for 2.75 hr. The Grignard concentration was initially 0.8 *M*, and the reaction was carried out under an atmosphere of dry nitrogen. Hydrolysis of the mixture was carried out at 0–10° with 25 ml of saturated sodium bicarbonate. The ether layer was separated, the aqueous layer was extracted once with 20 ml of ether, and the organic layers were combined and dried over magnesium sulfate. The ether was removed at room temperature on a rotary evaporator to yield 1.1–1.2 g of crude product.

Reaction of Di-*n*-propylcadmium with 1.—An ethereal solution of 11.5 ml of 2.32 *M* *n*-propylmagnesium bromide (26.6 mmol) was added to a stirred mixture of 4.87 g of CdI_2 (13.3 mmol) and 22 ml of anhydrous ether, which was cooled in an ice bath. This addition was carried out such that no ebullition occurred. The ice bath was removed, and the Gilman test was negative after 15 min.

After the di-*n*-propylcadmium reagent had been cooled in an ice bath to an internal temperature of 0–5°, 1 g of **1** (6.5 mmol) dissolved in ether or benzene was added such that the internal temperature did not exceed 5° (addition time approximately 5 min). The mixture was stirred an additional 15 min at ice-bath temperature and then for 105 min (165 min for Zn reagents) at ambient temperature. The solution was cooled in an ice bath to an internal temperature of 0° and hydrolyzed with 30 ml of saturated $NaHCO_3$ solution such that the internal temperature did not exceed 10°. The bath was then removed and the mixture stirred for an additional 5 min. Residual cadmium or zinc salts could be removed by preferential solution of the organic material in benzene, and washing of the solution with ammonia.[8] Unless this purification step was carried out, dehydration products (retention times 2.1 and 6.0 min) appeared in the chromatogram. After work-up and removal of salts, the crude product weighed 1.0–1.2 g.

***cis*- and *trans*-4-*tert*-Butylcyclohexanols (4 and 5).**—Reduction products **4** and **5** were synthesized from **1** by reduction with trimethylamine borane–BF_3[9] and separated on a neutral alumina column by elution with 10% ether–pentane (98 and 90% purity, respectively, by glpc).

***trans*- and *cis*-1-*n*-Propyl-4-*tert*-butylcyclohexanols (2 and 3).**—Identification of the addition products **2** and **3** was based on the previous report[3] that the major isomer from propyl Grignard addition is that of equatorial attack (**2**). Confirmation of this was achieved by isolation of the two epimers from a neutral alumina column by elution with 10% ether–pentane, the axial alcohol **2** being eluted first with mp 73.0–74.5°. *Anal.* Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 79.06; H, 13.45.

3 gave mp 87.0–87.5°. Found: C, 78.80; H, 13.39. The infrared spectra (CS_2) of **2** and **3** bear close analogies in the fingerprint regions with axial and equatorial isomeric pairs previously described by Cross and Whitham:[10] **2** [942, 987, 1188 cm^{-1} (all strong)]; **3** [985, 1022, 1139 cm^{-1} (all strong)]. Further support for the structural assignment comes from Cd or Zn salt-catalyzed dehydration experiments with **2** and **3** during glpc analysis. The epimer with equatorial –OH underwent dehydration preferentially, as shown by the relative decrease in area of the peak assigned to **3**. The analgous behavior has already been reported for the methyl analogs of **2** and **3**.[2]

Equilibration Experiments with 4 and 5.—The following is typical of control experiments to determine whether any equilibration of **4** and **5** occurred during the reactions with Cd or Zn reagents.

A mixture of 0.6 g of 4-*tert*-butylcyclohexanone and 0.4 g of 4-*tert*-butylcyclohexanol (98% **4**) was dissolved in 10 ml of anhydrous ether and added to *in situ* di-*n*-propylcadmium (I, Br) under the same reaction conditions as previously described for this reagent with 4-*tert*-butylcyclohexanone. Aliquots were taken at 3, 8, 12, and 23 hr and hydrolyzed as previously described. Normalized per cent of **4** was found by glpc to be 90% (3 hr) and 88% (23 hr). The calculated value based on ratios shown in Table I is 90%. Similar experiments were carried out with **5** and Cd or Zn reagents. Only in the case of the control experiment of di-*n*-propylzinc (I, Br) with **4** was any equilibration noted [Normalized % of **4**. Calcd: 93 (3 hr); 88 (24 hr). Found: 89 (3 hr); 73 (24 hr).].

Analysis of Reaction Products.—Glpc analyses (STAP, 10% deposited on Chromosorb W, 140°, helium flow rate of 100 ml/min) were performed on crude, isolated products (see above) with no correction for mass balance. The nmr spectrum of a mixture from *n*-propyl Grignard reagent contained no peaks attributable to any materials other than **1**, **2**, **3**, **4**, and **5**. The retention times for **1**, **2**, **3**, **4**, and **5**, respectively, were 12.9, 24.1, 26.3, 15.0, and 17.9 min. In no case could higher boiling components be detected by glpc. Response ratios, as determined from weighed mixtures of two-component pairs, is as follows: **1**:**2**, 0.82 ± 0.01; **1**:**3**, 0.90 ± 0.02; **1**:**4**, 1.02 ± 0.03; **1**:**5**, 1.01 ± 0.05.

Registry No.—*n*-Propylmagnesium bromide, 927-77-5; *n*-propylmagnesium iodide, 10557-57-0; di-*n*-propylcadmium, 5905-48-6; di-*n*-propylzinc, 628-91-1; **1**, 98-53-3.

Acknowledgment.—We thank the Central University Research Fund (University of New Hampshire) for partial support.

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Mechanisms of Hydrogen Cyanide Formation from the Pyrolysis of Amino Acids and Related Compounds[1]

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Received May 11, 1970

Amino acids were pyrolyzed in a helium atmosphere at temperatures from 700 to 1000°. Under these conditions, HCN was a major pyrolysis product. For straight chain and branched acids, HCN production varied in the order $\gamma \gg \beta > \alpha$. The cyclic acids, proline and 4-hydroxyproline, gave the largest yields of all amino acids studied. Extensions of the study to pyrolysis intermediates such as pyrrolidine and 2-pyrrolidone led to observations of high yields of HCN. Unsaturation of the ring containing the nitrogen atom was shown to cause a decrease in yield, as did methyl substitution on nitrogen. Compounds which contain nitrogen as a part of an aliphatic ring which can produce methylenimine—or can furnish such rings as intermediates—were shown to give relatively high amounts of HCN. At 1000° maximum yield was obtained with five-membered-ring compounds. All of these observations support the general hypothesis that HCN formation is favored in those instances in which the pyrolyzed compound either is itself an aliphatic nitrogen containing ring or is formed into such a ring as a reaction intermediate. Under ideal circumstances almost 100% of amino nitrogen is converted to HCN.

Heyns and Pavel[2] showed that thermal treatment of amino acids produces small quantities of hydrogen cyanide. They exposed glycine, alanine, leucine, phenylalanine, tyrosine, and gelatin to temperatures between 310 and 340° and showed HCN to be formed from glycine, alanine, and gelatin.

Winter and Albro[3] pyrolyzed amino acids at 300° and gas chromatographed the resulting C_1 to C_5 amines as a means of characterizing the acid. Each amino acid was shown to give a unique amine profile. Merritt and Robertson[4] also pyrolyzed 17 amino acids under conditions which led to a characteristic pyrolysis product for each acid. Recently, Bryan and Olafsson[5] carried out differential enthalpic analysis of aromatic and heteroaromatic amino acids and obtained thermograms which are characteristic of specific amino acids. In all these investigations, the possible formation of HCN was not mentioned. Patterson, *et al.*,[6] pyrolyzed lysine, leucine, and tryptophan at 850°. HCN was mentioned as a pyrolysis product of lysine hydrochloride, but no quantitative data was given.

It was the purpose of this work to study the pyrolysis of amino acids under conditions such that the factors responsible for HCN formation could be studied. Experiments were chosen so that the molecular structural features favoring HCN formation could be determined and mechanisms for the conversions elucidated.

Experimental Section

Chemicals.—Amino acids were purchased from Nutritional Biochemicals Co. These acids which are homogeneous by paper chromatography, can be assumed to be better than 99.5% pure. Amines and other liquids were obtained from various sources and purified by distillation. 1,4-Diaminobutane dihydrochloride and other solids were used as received from various suppliers.

Pyrolysis.—A modification of an apparatus described by Honaker and Horton[7] was used. This consisted of a 9.53-mm-o.d. Vycor tube enclosed in a 89-mm-long oven. This tube was joined through a toggle valve to a stainless steel "T" which was connected to the injection port of a F & M Model 720 gas chromatograph. An in-line sintered Cambridge filter pad was used to protect the chromatographic column from high-molecular-weight materials. All connections to the injection port were wrapped with a heating tape which was maintained at 150°. Pyrolysis of solids was accomplished by magnetically pushing a porcelain boat containing the sample into the equilibrated hot zone and retracting the magnet. Temperatures, which were monitored at the wall of the pyrolysis tube by a pyrometer, dropped 10° on sample introduction. Liquid samples were pyrolyzed by direct injection into the pyrolysis zone. In all cases, 10^{-5} mol of compound was pyrolyzed. Helium was used as the carrier gas at a flow rate of 80 ml/min. After 1 min the pyrolysis unit was cut off from the chromatograph by closing the toggle valve. Chromatography was continued using helium furnished by a line which bypassed the pyrolysis apparatus and fed into the injection port *via* the "T" assembly.

Chromatography.—The separation of HCN was accomplished by using a 3.05 m × 6.35 mm stainless steel column packed with 80–100 mesh Porapak S. The flow rate of 80 ml/min was not changed. The column was kept at room temperature for 5 min and then temperature programmed to 130° at 20°/min. After 10 min at this temperature, programming was resumed at 5°/min. Programming was continued until 250° was reached. All connections between the pyrolysis zone and the injection port of the chromatography were maintained at 150° by using heating tapes. Under these conditions, HCN eluted sharply and cleanly at 18.5 min. The detector was operated at a temperature of 280° and a filament current of 140 mA. Calibration of recorder response with known samples of HCN assayed on a mass spectrometer permitted quantitative determination of HCN. Overall reproducibility in experiments by this procedure was ±5% for moderate quantities of HCN and ±10% for extremely high amounts. Acetonitrile was eluted at 28.0 min.

Ammonia was separated by the method of Burks.[8] Triethanolamine (5%) was coated onto 40 mesh firebrick. A 2 m × 6.35 mm stainless steel column was used at room temperature with helium flow of 80 ml/min. Ammonia was eluted in 1.5 min.

Results and Discussion

Pyrolysis of α-Amino Acids.—The results of the pyrolysis of some α-amino acids at 1000° are given in Table I. HCN yields can be seen to vary from 8 to 45%. If we consider these results in terms of glycine, we will note that the substitution of hydrogen with alkyl groups lowered HCN yields from 32 to 8%. However, substitution with hydroxymethyl or benzyl groups, raised yields from 32 to 45%.

Of the thermal reactions that glycine might be expected to undergo such as deamination, decarboxylation, and 2,5-piperazinedione formation, the first two reactions should be rather independent of alkyl sub-

* To whom correspondence should be addressed.

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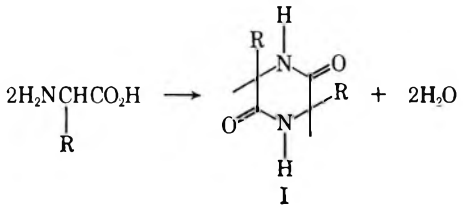
TABLE I

HCN YIELDS FROM α-AMINO ACIDS

Amino acid	Mol of HCN per mol of N (× 100), 1000°
Glycine	32
Alanine	12
Leucine	8
Isoleucine	8
Serine	45
Phenylalanine	43

stitution since functional groups are not thereby affected, while the last-mentioned reaction might be strongly affected if we can assume that bulky substituents might interfere with cyclization. If we can assume further



I

that the formation of these cyclic compounds represents the preferred route to HCN formation then two factors will be pertinent: (1) the tendency for ring formation to occur, and (2) the tendency, once formed, to give HCN. The observed order of HCN formation (glycine > alanine > leucine = isoleucine) would suggest that both factors are relevant. First, we suggest that, for this series, cyclization is easiest when R = H. Once formed, primary scission of I (R = H) will yield methylenimine (CH_2 = NH) or its diradical ($\dot{C}H_2\dot{N}H$). Dehydrogenation of either would afford HCN. In the cases where R = alkyl, similar cleavage of the ring would divert the reaction to alkyl cyanides which would require additional reaction in order that HCN be formed.

We were unable to put forth a reason for the high yields of HCN obtained from serine and phenylalanine. We feel, however, that these compounds deserve further study.

The suggestion that HCN formation was determined by the cyclic intermediates formed during the pyrolysis of the simple amino acids caused us to investigate various nitrogen heterocycles including the cyclic amino acids, proline and 4-hydroxyproline. Heterocycles were chosen so that structural requirements for HCN formation could be ascertained.

HCN Yields from Nitrogen Heterocycles.—The results of the pyrolysis of compounds containing ring nitrogen, including the amino acids proline and 4-hydroxyproline, at 700–1000° are given in Tables II and III. For all substances, HCN yields increased with increasing temperature. At all temperatures, pyrrolidine gave the highest yields of HCN, approaching 100% conversion at 1000°.

Structural influences upon HCN formation can be defined if we interpret the data in terms of pyrrolidine. In light of this compound we might note effects on yield of ring size, ring unsaturation, substitution on the ring nitrogen, and substitution adjacent to the ring nitrogen.

The influence of ring size can be gleaned by noting that the yields from 2-pyrrolidone, 2,5-piperazinedione,

TABLE II

HCN YIELDS FROM NITROGEN HETEROCYCLES

Compd	Mol of HCN per mol of N (× 100) 700°	800°	1000°
Proline			86
4-Hydroxyproline			90
2-Pyrrolidone		67	90
Pyrrolidine	46	77	95
Piperidine	33	47	62
3-Pyrroline	...[a]	26	72
Pyrrole	...[a]	22	87
Piperazine	34	69	80
2,5-Piperazinedione	38	50	81
2-Oxohexamethylenimine			71
N-Methylpyrrole			40
N-Methylpyrrolidine			35

[a] Not measurable.

TABLE III

NITRILE YIELDS AT 800°[c]

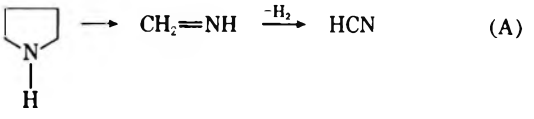
Compd	Mol of HCN per mol of N (× 100)	Relative yields of acetonitrile
Pyrrolidine	77	1
Succinimide	6	0.81
Succinamide	6	≪1
Piperidine	47	1
2,6-Dimethylpiperidine	18	8.1
Other compounds listed in Tables I–VII		None > 2

and 2-oxohexamethylenimine were 90, 81, and 71%, respectively. This evidence along with high yields obtained from pyrrolidine indicate that the five-membered ring is favored with respect to HCN formation.

Further inspection of Table II gives an interesting picture of the role of ring stability in influencing the course of pyrolysis. Comparing pyrrolidine, 3-pyrroline, and pyrrole, it can be seen that unsaturation in the ring inhibits cleavage to HCN. Though this inhibition from the increased stability of the ring is somewhat overcome at 1000°, one can conclude that aromaticity of the ring containing nitrogen will be a factor which decreases HCN yields. Though no data are given here, this observation is in agreement with some we made previously concerning the pyrolysis of pyridine and chlorophyll, yields at 1000° being lower than those obtained at the same temperature in this study.

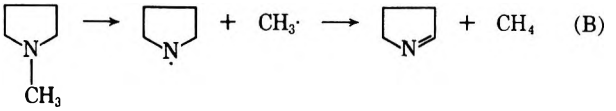
The substitution of methyl for the hydrogen attached to *nitrogen* is shown to greatly reduce HCN yield, cutting it by more than half of the value observed for the unsubstituted compounds (Table II).

This halving of the yields can be rationalized by considering the cleavage necessary to give HCN (eq A).



(A)

Applied to the *N*-methyl derivative, preferential cleavage of the NCH_3 bond would divert the reaction to other



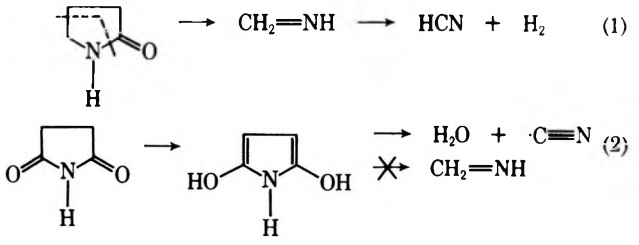
(B)

products (eq B). The relative strength of the NH bond would make cleavage according to eq B less likely.

Effects from substitution on carbon adjacent to the ring nitrogen are summarized in Table III.

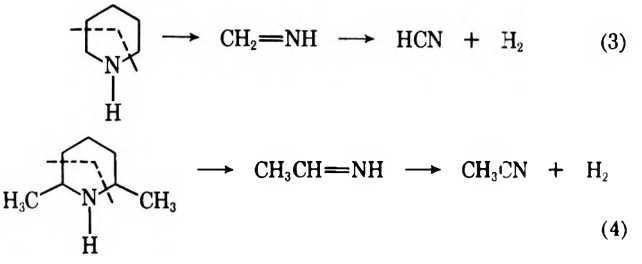
The presence of a single carbonyl group adjacent to the ring nitrogen seems to be of minor or no influence. Incidentally, the yields of HCN obtained from 2,5-piperazinedione are sufficiently high to support the contention that this species is responsible for HCN formation from glycine.

However, two adjacent carbonyls have a profound effect. Thus succinimide was found to give less HCN than any cyclic compound studied (Table III). It gave a yield similar to that observed for succinamide which can be expected to cyclize to succinimide with loss of ammonia. In any event, prevention of facile formation of methylenimine as an intermediate apparently caused more than a tenfold drop in yield. Reac-



tion 2 would require the breaking of a double bond to give a cyanide radical, a process not favored compared to reaction 1.

Diversion of the pyrolysis to another nitrile is illustrated by methyl substitution in the 2,6 positions of piperidine (Table III). The substituted piperidine yielded eight times the amount of acetonitrile as did piperidine. Thermal rupture according to the equations below would rationalize these data. Reaction 4



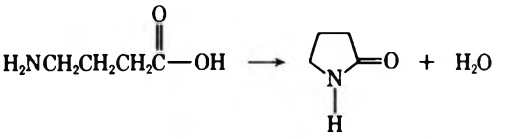
is consistent with the lower yields of HCN from alanine and leucine as opposed to glycine.

Pyrolysis of Isomeric Aminobutyric Acids.—Isomeric aminobutyric acids were pyrolyzed in order to ascertain the effects that amino group position might have an HCN formation and to determine whether this formation would follow the expected tendencies for cyclization to take place. The results are given in Table IV.

TABLE IV
HCN YIELDS FROM ISOMERIC AMINOBUTYRIC ACIDS

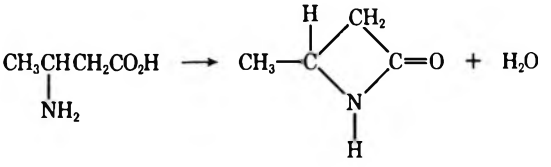
	Mol of HCN per mol of N (× 100)		
Amino acid	700°	800°	1000°
α-Aminobutyric acid	2	4	7
β-Aminobutyric acid	2	8	19
γ-Aminobutyric acid	30	67	77
α-Aminoisobutyric acid			7

The most striking features of these data are the high yields of HCN obtained from the γ acid. Notable, also, are the differences between the β and α acids. The unusually high yield from the γ acid can be attributed to the fact that a suitable pyrolysis intermediate (2-pyrrolidone) can be formed by intramolecular cycliza-



tion. The ability of the γ acid to cyclize by intramolecular reaction means that the necessary intermediate is generated easier than in the case of the α acid because the latter requires a bimolecular reaction. The competing reaction of deamination would then decrease the amount of nitrogen available for HCN formation.

The higher yield of the β as opposed to the α acid is suggestive of the idea that the β acid can react to some extent *via* a cyclic intermediate formed by an intramolecular reaction. Similarly, a 16% conversion to HCN



was obtained for β-alanine at 1000°, which is consistent with the 19% conversion obtained for β-aminobutyric acid (Table IV). To further check these points ammonia determinations were carried out. Table V gives

TABLE V
AMMONIA YIELDS FROM AMINOBUTYRIC ACIDS

Acid	Ammonia yields (peak heights), 1000°
α-Aminobutyric acid	1488
β-Aminobutyric acid	1280
γ-Aminobutyric acid	704

ammonia yields in terms of comparative peak heights. The order observed, namely $\alpha > \beta \gg \gamma$ is the inverse of that observed for HCN formation. The reactions proposed as being controlling in this study are consistent with the ammonia data.

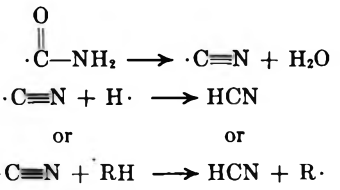
HCN Yields from Dicarboxylic Acids and Derivatives.—Further support of the idea of cyclization being a route favoring HCN production can be obtained from Table VI. The yield of HCN from aspartic

TABLE VI
HCN YIELDS FROM DICARBOXYLIC ACIDS AND DERIVATIVES

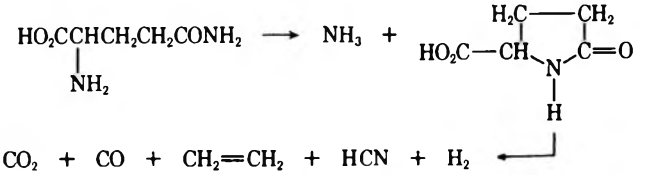
	Mol of HCN per mol of N (× 100)	
Amino acid	700°	1000°
Aspartic acid	0.7	35
Glutamic acid	14	71
Asparagine	2	21
Glutamine	10	46

acid at 1000° is closer to that observed for β-aminobutyric acid than it is to the value obtained from the α acid. Glutamic acid, on the other hand, pyrolyzes as if it were a γ acid. The substitution of a carboxyl group

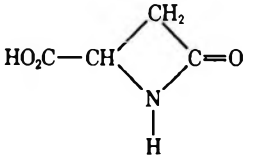
for a hydrogen on the amino bearing carbon had little effect on HCN formation. The substitution of an amide group for carboxyl in asparagine and glutamine is instructive also. If HCN were formed in appreciable quantities from



the yields obtained from these two amides should be similar. However, glutamine yields are significantly higher, 5:1 at 700°, and more than 2:1 at 1000°. The 46% conversion to HCN of glutamine at 1000° is indicative of a process in which more than 90% of the nitrogen in the pyrrolidone carboxylic acid intermediate is converted to HCN. Asparagine would require, of course,



a four-membered ring to give similar yields. Further-



more, considering yields from both asparagine and glutamine, it is clearly shown that HCN attributable to the amide group is produced in less quantities than that obtained from amino nitrogen. Once again, the overriding factor in HCN formation appears to be breakdown of a cyclic structure.

Pyrolysis of Amines.—The pyrolysis of C-4 amines at 800° proved to be instructive (Table VII). The order of HCN production observed for these amines was 1,4-diaminobutane > *n*-butylamine > *sec*-butylamine. The threefold increases in HCN yield of 1,4-diaminobutane over *n*-butylamine and its sixfold increase over *sec*-butylamine is consistent with the fact that the diamine, especially the dihydrochloride, can easily form pyrrolidine whereas the monoamines cannot. At 700°, 1,4-diaminobutane as the free base apparently did not cyclize with the efficiency of the hydrochloride (Table VII). The larger value observed for *n*-butylamine as opposed to the secondary amine is consistent with the expected greater ease of ammonia formation from the secondary amine. These observations are consistent with those made for amino acids.

TABLE VII

HCN YIELDS FROM AMINES

Amine	Mol of HCN per mol of N (× 100) 700°	800°
1,4-Diaminobutane dihydrochloride	20	46
1,4-Diaminobutane	10	42
n-Butylamine	10	14
sec-Butylamine	5	7

Registry No.—Glycine, 56-40-6; alanine, 56-41-7; leucine, 61-90-5; isoleucine, 73-32-5; serine, 56-45-1; phenylalanine, 63-91-2; proline, 147-85-3; 4-hydroxyproline, 51-35-4; 2-pyrrolidone, 616-45-5; pyrrolidine, 123-75-1; piperidine, 110-89-4; 3-pyrroline, 109-96-6; pyrrole, 109-97-7; piperazine, 110-85-0; 2,5-piperazinedione, 106-57-0; 2-oxohexamethylenimine, 105-60-2; *N*-methylpyrrole, 96-54-8; *N*-methylpyrrolidine, 120-94-5; succinimide, 123-56-8; succinamide, 110-14-5; 2,6-dimethylpiperidine, 504-03-0; α-aminobutyric acid, 80-60-4; β-aminobutyric acid, 541-48-0; γ-aminobutyric acid, 56-12-2; α-aminoisobutyric acid, 62-57-7; aspartic acid, 56-84-8; glutamic acid, 56-86-0; asparagine, 70-47-3; glutamine, 56-85-9; 1,4-diaminobutane dihydrochloride, 333-93-7; 1,4-diaminobutane, 110-60-1; *n*-butylamine, 109-73-9; *sec*-butylamine, 13952-84-6; HCN, 74-90-8.

The Effect of Pressure on the Allylation of Hindered Phenoxides[1]

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Received April 22, 1970

The allylations of all 4, 2,6, and 3,5 methyl-, ethyl-, isopropyl-, and *tert*-butyl-substituted phenols have been carried out in alkaline aqueous medium. The 4-alkylphenols give rise to 2-allylphenols and the allyl phenyl ethers as well as products resulting from further allylation. The 2,6-dialkylphenoxide ions yield allyl ethers, 4-allylphenols, and *o*-dienones as well as products containing more than one allyl group, and similar results were obtained with the 3,5-dialkylphenols. Some of these products are sensitive to thermal rearrangements. The product distributions have been measured over a pressure range of 1 atm to several kilobars, and the difference in partial molal volume of the isomeric transition states has been calculated in each reaction. In all cases, the transition states leading to ether formation are larger than those on the way to the ortho-substituted products, which in turn are larger than the transition states leading to the *p*-allylphenols; thus, massive support is provided for the contention that solvation of the O atom in hydroxylic media is of crucial importance in determining the allylation ratios. No systematic correlation with steric hindrance was found, however; the postulate, so well documented in the case of the Menshutkin reaction, that crowded transition states become favored at high pressure is not borne out in this reaction, so that its general validity must be questioned.

If the effect of pressure on a rate constant is known, the activation volume of the reaction can be calculated by means of the expression

$$\left(\frac{\partial \ln k}{\partial p}\right)_T = -\frac{\Delta V^*}{RT}$$

where k is expressed in concentration units at 1 atm. ΔV^*_o can be predicted for most mechanisms with fair accuracy on the basis of (a) comparisons with pressure data for reactions of well-known mechanisms, (b) volume changes in equilibria, and (c) densities and parachor data of stable substances. This ability allows one to use the pressure coefficient of a rate constant as a mechanistic criterion in many cases. Several features make important contributions to ΔV^*_o. Paramount among these are bond formation and cleavage, and charge separation and neutralization. Displacements in which there is no net change in the number of charges have small negative volumes of activation (~ -5 to -10 cm^3/mol), suggesting that bond formation is more advanced in the transition state than the concurrent bond fission.[3]

A factor of great potential interest is that of steric hindrance. Crowded compounds usually have somewhat greater densities than their unhindered isomers, and it would seem reasonable to suppose that hindered transition states would similarly have smaller volume requirements than the unhindered substrates from which they are formed. If this is so, hindered reactions should be accelerated to a greater degree than their unhindered analogs, clearly a possibility of much interest. Evidence for it has been reported by several groups. The first such claim was made by Perrin and Williams[4] in 1937 and quite recently Gonikberg[5] concluded that "the more sterically hindered a chemical reaction, the greater the degree to which it should be accelerated with increasing pressure."

In spite of the evidence,[6] it is probably still too early for such a generalization. Almost all of the examples that have been found are Menshutkin reactions, and even in that reaction the evidence is sometimes more apparent than real since one is often forced to compare data gathered in different solvents, at different temperatures and over different pressure ranges. Also, while it is true that crowded compounds are more dense than their unhindered isomers, the differences in molar volume seem rarely to be more than a cm^3 or two; but the $\Delta\Delta V^*$ values reported are often much larger than that. The potential of this phenomenon, a selective increase of the rate of sterically hindered reactions, appeared to us great enough to warrent a systematic investigation. We report here our results for the alkylation of substituted phenoxide ions in aqueous medium.

Discussion

Allyl chloride was chosen as the alkylating agent and water as the solvent because it is known[7] that, at least with phenoxide ion itself, initially three products form in reasonable amounts under such conditions: allyl phenyl ether, and *o*- and *p*-allylphenol. Since those mixtures can be readily analyzed, it appeared that the effect of pressure on the competition of those three reactions, already known in the case of phenoxide itself, might provide us with a well-documented example of the relation between that effect and steric hindrance in a displacement reaction.

In its execution, the problem was complicated somewhat by the possibilities of further alkylation of the phenolic products, and of rearrangements. Secondary alkylation (see Scheme I) was not found to present serious analytic difficulties in any case; thus, any allyl *o*-allylphenyl ether formed is simply considered *o*-allylphenol, since it must have arisen from that phenol. Any *o*- or *p*-diallylphenol was considered to be formed from both allylphenols; the ratio of the contributions was crudely calculated on the assumption that the rates of allylation at these positions are not affected by the presence of the *m*-allyl group already there. In nearly

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(1) (a) Presented in part at the Second International High Pressure Conference at Schloss Elmau, Germany, May 1968; (b) paper XXII in the series, "Chemical Reactions Under High Pressure."

(2) (a) On leave from Mitsui Toatsu Chemicals, Inc., Yokohama, Japan, 1967–1969; (b) on leave from the Indian Institute of Technology, Kharagpur, India, 1967–1968; (c) on leave from the Sumitomo Chemical Company, Osaka, Japan, 1967–1969.

(3) W. J. le Noble *Progr. Phys. Org. Chem.*, **5**, 207 (1967); *Cf.* also the several excellent reviews and books referred to in the opening paragraph of that paper.

(4) M. W. Perrin and E. G. Williams, *Proc. Roy. Soc., Ser. A*, **159**, 162 (1937).

(5) M. G. Gonikberg, *Russ. J. Phys. Chem.*, **37**, 248 (1963).

(6) Summarized by W. J. le Noble and Y. Ogo, *Tetrahedron*, **26**, 4119 (1970).

(7) N. Kornblum, P. J. Berrigan, and W. J. le Noble, *J. Amer. Chem. Soc.*, **82**, 1257 (1960).

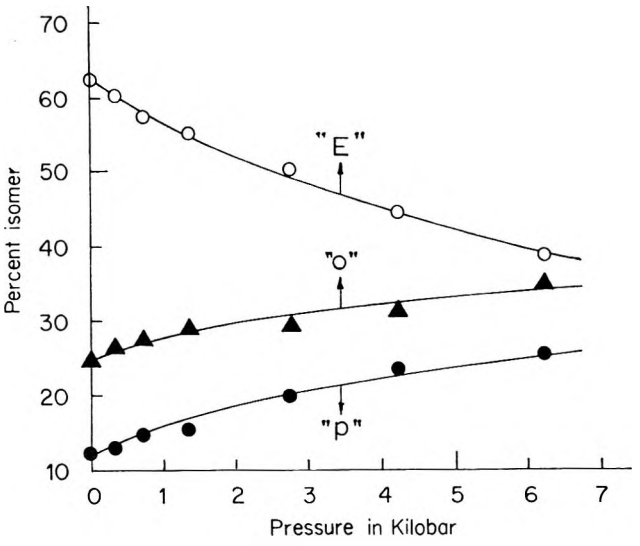
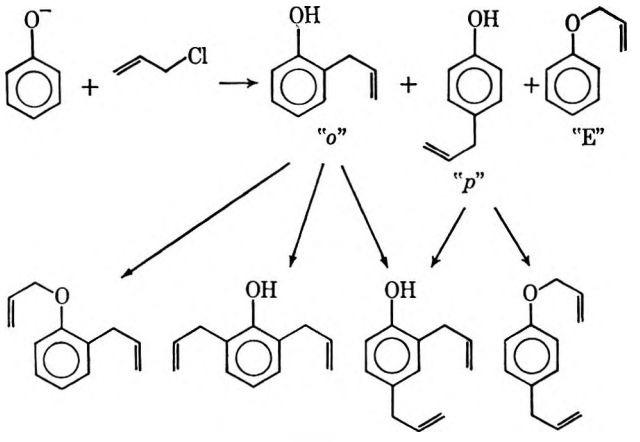


Figure 1.—Primary product distribution in the allylation of 3,5-diisopropylphenoxide ion in water at 25° as a function of pressure.

SCHEME I

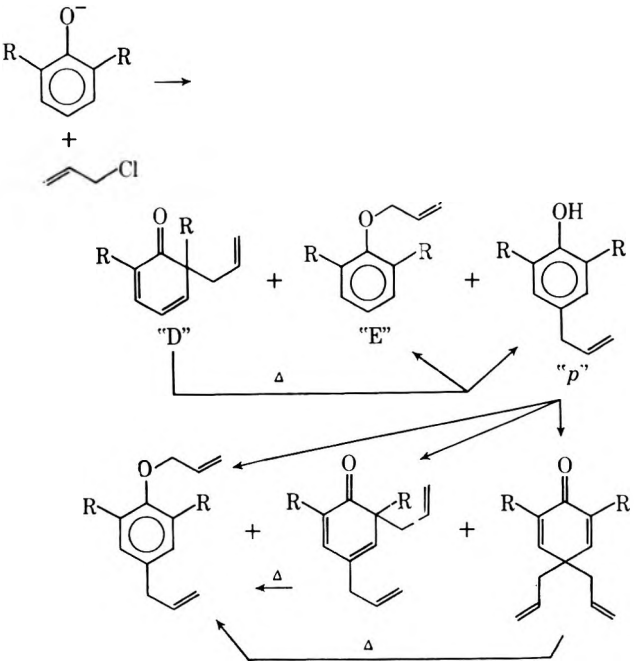


all cases, however, it was possible by means of some preliminary experiments to choose conditions under which this side reaction constituted only a very minor nuisance.

More serious is the problem of rearrangement. The best known of these is of course the Claisen rearrangement; fortunately, the room temperature conditions of our experiments preclude this rearrangement. The allyl 2,6-dialkylphenyl ethers did in some instances rearrange to phenols to a minor extent during injection into the vpc apparatus; however, this occurred in a highly reproducible way, and a correction could be made for it. The 2,6-dialkylphenoxides also gave rise to fair amounts of the cyclohexadienones, which readily rearrange to mixtures of the isomeric allyl phenyl ethers and *p*-allylphenols, as was first described by Curtin.[8] The neutral dienones and ether products could be separated from the phenols by means of extractions with Claisen's alkali. A study of the neutral products showed the dienones to be stable under the conditions of their generation, their separation from the phenols and subsequent concentration to small volume, but during vpc analysis they rearranged quantitatively and reproducibly as shown in Scheme II. This permitted their assay by monitoring of the 4-allylphenols formed in the

(8) D. Y. Curtin, R. J. Crawford, and M. Wilhelm, *J. Amer. Chem. Soc.*, **80**, 1391 (1958).

SCHEME II



neutral fraction. *p*-Dienones were observed only in the allylation of the 2,6-disubstituted *p*-allylphenols and not in the allylation of *p*-alkylphenols (one example of the latter reaction is known[9]).

After the appropriate corrections had been applied for dialkylation, Claisen rearrangement, and dienone rearrangement, the ratios r of the three main products were calculated. Allowance is made for the fact that two ortho positions are available. The slopes of ln r *vs.* p permitted $\Delta\Delta V^*_o$ to be computed. Table I shows the results, considered to have a precision of better than 1 cm³/mol. The individual data are too numerous for a complete recording here; however, Table I shows the product distribution at 1 atm as well as the $\Delta\Delta V^*_o$ values and Figure 1 shows the effect of pressure in the case of 3,5-diisopropylphenoxide ion as a typical example.

Results

The most obvious result is that V^*_E is always larger than V^*_o or V^*_D and that V^*_o, with one minor exception, is always larger than V^*_p. This was first observed with phenoxide itself, and it may be considered to be the result of desolvation; whereas alkylation of the oxygen atom requires substantial desolvation, reaction at the ortho sites requires this to a much smaller degree, and attack at the para carbon atom not at all.[7,10]

As far as steric hindrance is concerned, the $\Delta\Delta V^*$ values are remarkably insensitive to it. Large alkyl groups in the 2 and 6 positions cause a decrease in $V^*_E - V^*_p$, but the effect is small, and in the wrong direction when the individual alkyl groups are considered. Since the substituent effect on the product distribution itself is fairly small and irregular, one might question

(9) R. Barner, A. Boller, J. Borgulya, E. G. Herzog, W. von Philipsborn, C. von Planta, A. Fürst, and H. Schmid, *Helv. Chim. Acta*, **48**, 94 (1965).

(10) (a) W. J. le Noble, *J. Amer. Chem. Soc.*, **85**, 1470 (1963); (b) K. R. Brower, R. L. Ernst, and J. S. Chen, *J. Phys. Chem.*, **68**, 3814 (1964). The solvation (or desolvation) volume itself does not appear to be very sensitive to steric bulk; we have been unable, for instance, to find such an effect in the Menshutkin reaction,[5] and it is known that the ionization volumes of many week acids and bases are virtually independent of their structures.[3]

TABLE I

PRODUCT DISTRIBUTIONS AND THE DIFFERENCES IN ACTIVATION VOLUME IN CM³/MOL FOR THE AQUEOUS ALLYLATION OF THE THREE POSITIONS IN VARIOUS PHENOXIDE IONS[a]

R_2	R_3	R_4	R_5	R_6	*o*	*p*	E	$V^*_E - V^*_{o(D)}$	$V^*_E - V^*_p$
H	H	H	H	H[b]	17	21	62	2.2	7.6
H	H	Me	H	H	41	0	59	3.5	
H	H	Et	H	H	43	0	57	3.3	
H	H	*i*-Pr	H	H	33	0	67	2.5	
H	H	*tert*-Bu	H	H	28	0	72	2.2	
H	Me	H	Me	H	37	45	18	2.0	3.6
H	Et	H	Et	H	34	37	29	5.7	7.6
H	*i*-Pr	H	*i*-Pr	H	25	12	63	3.5	7.5
H	*tert*-Bu	H	*tert*-Bu	H	22	0	78	6.2	
Me	H	H	H	Me	19	61	20	3.0	2.4
Et	H	H	H	Et	27	62	11	2.0	3.0
i-Pr	H	H	H	*i*-Pr	16	66	18	1.9	4.9
tert-Bu	H	H	H	*tert*-Bu	0	100	0		

[a] The temperatures were between 25 and 45°, as detailed in the Experimental Section. [b] See ref 10a.

how severely hindered O-allylation is. With 3,5 substitution, the product distributions give a clear indication of steric hindrance but again any trends in $(V^*_E - V^*_o)$ and in $(V^*_E - V^*_p)$ are small and irregular at best. The reasons for the difference in pressure sensitivity between hindered Menshutkin reactions and phenoxide allylations are not yet clear, and we can only conclude that claims of the generality of a correlation between hindrance and ΔV^* must be regarded with reservation at present.

Experimental Section

Where possible, the commercial parent phenols were employed after suitable purification. All of the new compounds mentioned below (*i.e.*, where no literature reference is given) except those referred to as trace products were subjected to elemental analysis and found to have a C and H per cent within 0.4% of the calculated values. Identification was carried out by nmr in all cases, and the analysis of mixtures was done by vpc. At least four samples were injected in every case, and the areas of the vpc peaks obtained were related to the composition by means of curves constructed by the use of synthetic mixtures.

p-**Cresol.**—2-Allyl-4-cresol[11] and allyl *p*-cresyl ether[12] were prepared at 45° by allylation, separated by means of Claisen alkali,[13] and isolated by fractional vacuum distillation; small samples were further purified by means of vpc. The small scale analytical experiments were carried out at 40° for 48 hr in syringes;[10a] 4.3 mmol of cresol, 0.5 cm³ of 5 *N* sodium hydroxide, and 19 ml of water saturated at room temperature with allyl chloride were used. The excess phenol served to suppress the formation of dialkylated products. After the reaction the contents of the syringe were transferred with 30 ml of benzene to a separatory funnel containing 3 g of sodium chloride and 1 ml of concentrated hydrochloric acid. After the extraction the aqueous part was treated with two more portions of benzene. The combined organic layers were distilled through a 30-cm Vigreux column until 1–3 cm³ remained. This residue was analyzed by means of vpc. A 2-m Chromosorb W column impregnated with Carbowax 20M was used at 167° for all *p*-allylphenol product mixtures.

p-**Ethylphenol.**—The large scale alkylation was carried out as above to give allyl *p*-ethylphenyl ether[12] and 2-allyl-4-ethylphenol.[12] The small scale reactions were also carried out as those with *p*-cresol.

p-**Isopropylphenol.**—The large scale reaction was carried out with 0.15 mmol of the phenol, 0.24 mol of sodium hydroxide, and 0.25 mol of allyl chloride in 150 ml of water at 60° for 80 hr. The products obtained were allyl *p*-isopropylphenyl ether (n^{25}D 1.5074), 2-allyl-4-isopropylphenol (n^{25}D 1.5250), and traces of allyl 2-allyl-4-isopropylphenyl ether and 2,6-diallyl-4-isopropylphenol. The small scale reactions were carried out at 50° for 48 hr; an excess of 0.5 cm³ allyl chloride was used to compensate for evaporation during assembly.

p-tert-**Butylphenol.**—Both the large and small scale reactions were done as with *p*-isopropylphenol to give allyl *p-tert*-butylphenyl ether,[14] 2-allyl-4-*tert*-butylphenol,[14] and a trace of allyl 2-allyl-4-*tert*-butylphenyl ether.

2,6-Dimethylphenol.—The bulk reaction was carried out at 25° with 0.050 mol of the phenol, 0.2 mol of sodium hydroxide, and 25 ml of allyl chloride. The resulting mixture was neutralized at 20° with 10% hydrochloric acid saturated with sodium chloride and extracted three times with 100 ml of benzene. The combined benzene solutions were extracted four times with 50 ml of cold Claisen alkali. The combined Claisen extracts were cooled, neutralized with concentrated hydrochloric acid, and extracted four times with 50 ml of benzene; these extracts were combined, dried, and reduced to a small volume (phenolic residue); the original benzene layer was washed with water, briefly dried over anhydrous magnesium sulfate, and flash evaporated at room temperature (neutral residue). The phenolic part was shown by both nmr and vpc to consist entirely of unreacted starting material and 4-allyl-2,6-dimethylphenol:[15] vpc was carried out for all of the 2,6-dialkylphenol experiments by means of a 4-m column charged with 40% Carbowax 20M absorbed on Chromosorb W (HMDS treated) at 185°. Vpc of the neutral fraction gave rise to allyl 2,6-dimethylphenyl ether,[15] allyl 4-allyl-2,6-dimethylphenyl ether,[16] and 4-allyl-2,6-dimethylphenol[15] (formed by rearrangement of dienone, see below). Ir and nmr spectra of the neutral fraction prior to vpc showed that 2,6-dimethylphenol and 4-allyl-2,6-dimethylphenol were absent (both have a strong band at 2.75 μ) and that the dienone was present, ir 6.05 μ (s); for nmr see below. The neutral fraction could be enriched in the dienone by means of either high vacuum distillation (0.06 mm, temperature below 43°), which gave a mixture of 64% dienone and 36% allyl ether as estimated by means of nmr or tlc. Allyl 2,6-dimethylphenyl ether, allyl 4-allyl-2,6-dimethylphenyl ether, and the dienone have R_f values of 0.94, 0.16, and 0.40, respectively, when a mixture of benzene and petroleum ether (2:1) is used to develop samples of the neutral mixture on an Eastman Chromagram Sheet No. 6060; preparative separation was achieved with a 2-mm layer of silica gel PF 254 (Merck). Samples of the dienone so enriched showed the vpc peaks of its two isomers and of allyl 4-allyl-2,6-dimethylphenyl ether; the latter arises from contamination of the dienone by dialkyldienones (see below). These enriched mixtures allow the following nmr assignments to be made for the monoallyldienone: τ 8.88 (s, 3, quaternary CH_3), 8.21 (s, 3, $=CCH_3$), 7.04–7.90 (m, 2, quaternary CH_2), 4.10–5.25 (m, 3, $CH=CH_2$), 3.14–3.95 ppm (m, 3, $=CH-CH=CH-$). It was confirmed[16] by means of these enriched mixtures that the dienone under the conditions of our vpc separations was completely converted into a mixture of the isomeric ether and phenol in the ratio of 23:77; it was also shown that allyl 2,6-dimethylphenyl ether itself rearranged to the phenolic isomer to the extent of 9% during vpc.

(11) N. Kornblum, P. J. Berrigan, and W. J. le Noble, *J. Amer. Chem. Soc.*, **85**, 1141 (1963).

(12) H. L. Goering and R. R. Jacobson, *ibid.*, **80**, 3277 (1958).

(13) L. Claisen, *Justus Liebigs Ann. Chem.*, **418**, 69 (1919); see p 96.

(14) A. B. Sen and R. P. Rastogi, *J. Indian Chem. Soc.*, **30**, 355 (1953).

(15) D. S. Tarbell and J. F. Kincaid, *J. Amer. Chem. Soc.*, **62**, 728 (1940).

(16) D. Y. Curtin and R. J. Crawford, *ibid.*, **79**, 3156 (1957).

These rearrangements did not affect the retention times or sharpness of the peaks and hence apparently occurred at the hot inlet port (280°). Both the dienone and ether were shown to be stable under the conditions of their formation (at all pressures used here) and work-up prior to vpc injection. When 4-allyl-2,6-dimethylphenol is further allylated, a neutral fraction can be isolated containing the allyl ether and a substantial amount of a 4:3 mixture of 4,6-diallyl-2,6-dimethylcyclohexa-2,4-dienone and 4,4-diallyl-2,6-dimethylcyclohexa-2,5-dienone (the nmr spectrum of the mixture contained methyl signals at τ 8.8 and 8.2 in a 2:5 ratio). Both compounds quantitatively rearranged to the ether during vpc. The analytical experiments were carried out for 48 hr at 25° with 0.0043 mol of 2,6-dimethylphenol, 0.017 mol of sodium hydroxide, 19 ml of water saturated with allyl chloride, and 0.8 ml of additional allyl chloride. The syringes were then emptied with the use of 10 ml of toluene into a separatory funnel containing 3 g of sodium chloride and 2 ml of concentrated hydrochloric acid. The mixture was extracted with three 30-ml portions of toluene, and the combined extracts were dried briefly over anhydrous magnesium sulfate. Diphenyl ether (0.060 g) was added as an internal standard; half of the resulting solution was concentrated by flash evaporation at room temperature and analyzed by means of vpc as described in the bulk reactions. Beside the two phenols and the two ether products, the diphenyl ether was observed in the chromatogram. The other half was treated with Claisen's alkali (four 10-ml portions), dried, concentrated by flash evaporation, and then analyzed by vpc; the starting phenol was absent from this mixture. The entire composition could then be related to the areas of the various peaks in the two chromatograms by means of the data obtained above for the rearrangements of the neutral products.

2,6-Diethylphenol.—A solution of 35 g of sodium nitrite in 100 ml of water is added to a cold, rapidly stirred solution of 75 g of 2,6-diethylaniline in 265 ml of 50% aqueous sulfuric acid during a 10-min period. This slurry is added to a hot mixture of 250 ml of water and 325 ml of 96% sulfuric acid in 30 min. After cooling to 100°, the oily layer is decanted on ice, which leads to the formation of a dark brown solid. Decolorization with carbon black and crystallization from 15% aqueous hydrochloric acid affords a 60–70% yield of 2,6-diethylphenol, mp 36–36.5° (lit.[17] 36–36.5°). The bulk allylation was carried out under the same conditions as those used for the dimethylphenol. Allyl 2,6-diethylphenyl ether (n^{25}D 1.5040), allyl 4-allyl-2,6-diethylphenyl ether (n^{25}D 1.5113), and 4-allyl-2,6-diethylphenol (n^{25}D 1.5268), were obtained. The mono- and diallylated ethers and 6-allyl-2,6-diethylcyclohexa-2,4-dienone could be separated on Chromagram sheets. Small samples of the latter compound (contaminated with 13% of diallylated dienones as shown by the presence of that much diallylated ether in vpc recordings) allowed its identification by nmr as before. During vpc the dienone decomposed completely into an 18–82 mixture of allyl 2,6-diethylphenyl ether and 4-allyl-2,6-diethylphenol. It was also found that pure monoallyl ether during vpc rearranged to the isomeric phenol to the extent of 10.5%, and that all products were stable to the conditions of their formation and subsequent work-up except vpc. The analytical experiments were entirely similar to those carried out with the dimethyl homolog; diphenyl ether was again used as an internal standard.

2,6-Diisopropylphenol.—The bulk reaction, similar to that of the dimethyl homolog, gave rise to allyl 2,6-diisopropylphenyl ether (n^{25}D 1.4970), allyl 4-allyl-2,6-diisopropylphenyl ether (n^{25}D 1.5068), and 4-allyl-2,6-diisopropylphenol (n^{25}D 1.5168). The mono- and diallylated ethers and 6-allyl-2,6-diisopropylcyclohexa-2,4-dienone were again separated on Chromagram sheets; small samples of the latter compound (contaminated with 3% diallyldienones as judged by the amount of the diallylated ether in the vpc recordings) were used for identification by nmr. During vpc the dienone decomposed quantitatively into a 17:83 mixture of allyl 2,6-diisopropylphenyl ether and 4-allyl-2,6-diisopropylphenol. The ether furthermore rearranges to the isomeric phenol to the extent of 15% during vpc; otherwise, all products proved to be stable to preparation and work-up. The analytical experiments were completely similar to those carried out with the dimethyl analog; diphenyl ether was again used as an internal standard.

2,6-Di-*tert*-butylphenol.—Exploratory alkylation experiments were carried out with 50:50 aqueous methanol at 25° and at 1 as well as at 5000 atm for 72 hr; these indicated the formation of three products, the first of which was present in such small traces that it could not be further identified. Also obtained in about a 100:1 ratio were 4-allyl-2,6-di-*tert*-butylphenol (n^{25}D 1.5118), and 2,4-diallyl-6-*tert*-butylphenol, mp 32.5–33°.

3,5-Dimethylphenol.—Bulk allylation at 45° for 25 hr followed by a work-up based on Claisen's alkali and vpc afforded allyl 3,5-dimethylphenyl ether,[18] 2-allyl-3,5-dimethylphenol, mp 43–44°, 4-allyl-3,5-dimethylphenol, mp 63.5–64.5°, and traces of 2,4- and 2,6-diallyl-3,5-dimethylphenols. In the analytical experiments which lasted 24 hr, the temperature was 25°. Vpc was carried out at 200° with the same column as described above for the 2,6-dialkylphenol experiments.

3,5-Diethylphenol.—This material was prepared from commercially available 2,6-diethylaniline by successive *p*-bromination in glacial acetic acid at 15°, diazotation and reduction[19] to 3,5-diethylbromobenzene,[20] and oxidation in 26% yield of the Grignard reagent.[21] It was crystallized from ligroin, mp 75° (lit.[22] 77°). The bulk allylation was carried out for 80 hr as in the preceding case; the analytical experiments were carried out as before at 25°, but for 14 hr; the same vpc conditions were applied. The products are allyl 3,5-diethylphenyl ether (n^{25}D 1.5087), 2-allyl-3,5-diethylphenol (n^{25}D 1.5292), 4-allyl-3,5-diethylphenol (n^{25}D 1.5324), and traces of the 2,4- and 2,6-diallylphenols.

3,5-Diisopropylphenol.—This compound was prepared from *m*-diisopropylbenzene *via* nitration[23] in 95% yield to a mixture of 2- and 4-nitro-1,3-diisopropylbenzene, reduction of the crude mixture for 1 hr at 100° by tin and hydrochloric acid to the anilines (94%), bromination of these anilines as described in the preceding case in 94% yield, and deamination[19] of the mixture in 87% to give 3,5-diisopropylbromobenzene, bp 72.5–74° (1 mm), n^{25}D 1.5250. Oxidation of the Grignard reagent[21] gave a 61% yield of the phenol, which was purified by sublimation, mp 52–53° (lit.[24] 52°). The allylation was allowed to proceed at 25°, 2 days for the bulk reaction, and 3 hr for the analytical work. The products were allyl 3,5-diisopropylphenyl ether (n^{25}D 1.5006), 2-allyl-3,5-diisopropylphenol (mp 50–51°), and 4-allyl-3,5-diisopropylphenol (mp 82.5–83.5°).

3,5-Di-*tert*-butylphenol.—Allylation of this material gave only two products under all conditions, allyl 3,5-di-*tert*-butylphenyl ether (n^{25}D 1.4959), and 2-allyl-3,5-di-*tert*-butylphenol (mp 65–66°).

Registry No.—*p*-Cresol, 106-44-5; *p*-ethylphenol, 123-07-9; *p*-isopropylphenol, 99-89-8; *p*-*tert*-butylphenol, 98-54-4; 2,6-dimethylphenol, 576-26-1; 2,6-diethylphenol, 1006-59-3; 2,6-diisopropylphenol, 2078-54-8; 2,6-di-*tert*-butylphenol, 128-39-2; 3,5-dimethylphenol, 108-68-9; 3,5-diethylphenol, 1197-34-8; 3,5-diisopropylphenol, 26886-05-5; 3,5-di-*tert*-butylphenol, 1138-52-9.

Acknowledgment.—We are pleased to acknowledge generous support for this work by the National Science Foundation.

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Concerning the Stereoselectivity of Lithium Tri-*tert*-butoxyaluminum Hydride

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Received June 17, 1970

The preparation[1-4] and reactions[5-11] of lithium alkoxyaluminum hydrides have been extensively studied in recent years. Considerable useful synthetic information has been obtained, but the mechanisms of such reductions are not well understood. Empirical rules have been developed for such reactions, but exceptions to these rules exist.

The selectivity of a complex metal hydride as a reducing agent depends largely on its steric bulk; a larger hydride molecule is expected to give a higher yield of products resulting from attack at the least hindered side of an asymmetric molecule. As expected from this, lithium trimethoxyaluminum hydride is more selective than lithium aluminum hydride. However, this presumably less bulky methoxy compound is also more selective than the corresponding *tert*-butoxy hydride in a wide range of systems.[5,10] The results obtained by Brown and Deck,[10] and by Haubenstock and Eliel,[5] are summarized in Table I.

The failure of lithium tri-*tert*-butoxyaluminum hydride (I) to follow the usual pattern has been attributed to a change in reaction mechanism. It has been suggested[6,10] that di-*tert*-butoxyaluminum hydride (II) is involved as the actual reducing species, as in the following eq 1 and 2.

$$\underset{\text{I}}{\text{LiAlH(O-}tert\text{-Bu)}_3} \rightleftharpoons \underset{\text{II}}{\text{HAl(O-}tert\text{-Bu)}_2} + \text{LiO-}tert\text{-Bu} \quad (1)$$

$$\text{HAl(O-}tert\text{-Bu)}_2 + \text{ketone} \longrightarrow \text{products} \quad (2)$$

The infrared spectra in solution and the reducing characteristics of independently prepared I and II were compared, and evidence was obtained which is incompatible with this hypothesis. The infrared spectra of the two hydrides, at a concentration of 0.3 *M* in THF solution, were obtained and compared. It was found that the aluminum–hydrogen stretching band of II appeared at 1860 cm^{-1}; the same band in I appeared at 1760 cm^{-1}, and no shoulder or weak band was visible at 1860 cm^{-1}. This experiment indicates that the equilibrium concentration of II in I is less than 1%.

This experiment does not rule out the possibility that II, while present in very low concentration, reacts with ketones so much faster than I that it is the primary reacting species. To test this hypothesis, it was decided to compare the stereoselectivity of I and II in the reduction of cyclic and bicyclic ketones. The ketones chosen for this purpose were 2-methylcyclohexanone, 3,3,5-trimethylcyclohexanone, norcamphor, and camphor.

Reductions were carried out at 0° in THF solution. The samples were hydrolyzed after 2 hr of reaction, and the yields of alcohols and recoveries of starting material were determined by vpc. These data are given in Table II. It can be seen that the stereoselectivity differs significantly in several cases. Since all the reductions were carried out under the same conditions, the recoveries of starting material and yields of total alcohol may be used as rough kinetic data; these show that the two hydrides reduce ketones at similar rates.

Table I
Reaction of Cyclic and Bicyclic Ketones

Ketone reduced	Reducing agent	% less stable alcohol in product	Note
3,3,5-Trimethylcyclohexanone	$LiAlH_4$	52	*a,c*
	$LiAlH(OMe)_3$	75	*a,c*
	$LiAlH(OEt)_3$	83	*a,c*
	$LiAlH(O\text{-}i\text{-}Pr)_3$	54	*a,c*
	$LiAlH(O\text{-}tert\text{-}Bu)_3$	73	*a,c*
Norcamphor	$LiAlH_4$	89	*b,d*
	$LiAlH(OMe)_3$	98	*b,d*
	$LiAlH(OEt)_3$	85	*b,d*
	$LiAlH(O\text{-}tert\text{-}Bu)_3$	93	*b,d*
Camphor	$LiAlH_4$	92	*b,e*
	$LiAlH(OMe)_3$	99	*b,e*
	$LiAlH(O\text{-}tert\text{-}Bu)_3$	93	*b,e*
Isopinocamphone	$LiAlH_4$	89	*b,e*
	$LiAlH(OMe)_3$	98	*b,e*
	$LiAlH(O\text{-}tert\text{-}Bu)_3$	84	*b,e*
2-Methylcyclopentanone	$LiAlH_4$	24	*b,f*
	$LiAlH(OMe)_3$	44	*b,f*
	$LiAlH(OEt)_3$	23	*b,f*
	$LiAlH(O\text{-}tert\text{-}Bu)_3$	28	*b,f*
2-Methylcyclohexanone	$LiAlH_4$	24	*b,f*
	$LiAlH(OMe)_3$	69	*b,f*
	$LiAlH(OEt)_3$	26	*b,f*
	$LiAlH(O\text{-}tert\text{-}Bu)_3$	30	*b,f*
2-*tert*-Butylcyclohexanone	$LiAlH_4$	58	*b,f*
	$LiAlH(OMe)_3$	64	*b,f*
	$LiAlH(O\text{-}tert\text{-}Bu)_3$	54	*b,f*

[a] Reference 5, ether solvent. [b] Reference 10, THF solvent. [c] Unstable alcohol is trans. [d] Unstable alcohol is exo. [e] Unstable alcohol is endo. [f] Unstable alcohol is cis.

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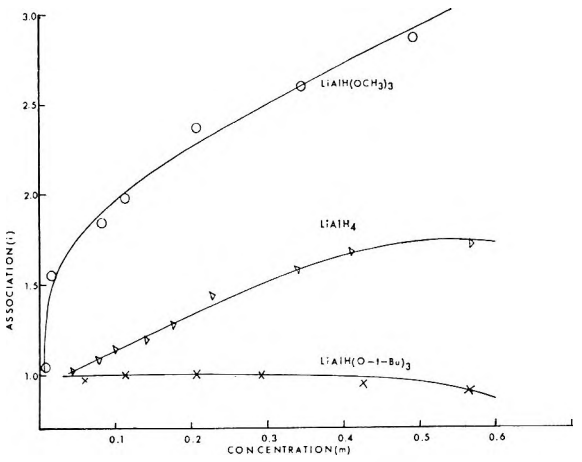

Figure 1.—Association of lithium trialkoxyaluminum hydrides in tetrahydrofuran.

TABLE II

SELECTIVE REDUCTION OF KETONES USING LiAlH(O-*tert*-Bu)$_3$ AND AlH(O-*tert*-Bu)$_2$

	Hydride	% total alcohol yield using I	% total alcohol yield using II	% starting material recovered using I	% starting material recovered using II	% unstable isomer using I	% unstable isomer using II
2-Methylcyclohexanone	*a*	45	52	55	35	36	56
	b	98	71	0	0	38	54
3,3,5-Trimethylcyclohexanone	*a*	94	45	1	40	93	74
	b	88	93	0	0	95	80
Norcamphor	*a*	47	40	48	59	94	90
	b	94	89	0	4	95	93
Camphor	*a*	15	11	81	89	94	75
	b	33	41	58	60	94	80

[a] 1.5:1 molar excess of hydride used. [b] 4.5:1 molar excess of hydride used.

If the concentration of II is less than 1% of that of I, the rate of reduction by II must exceed that of I by at least a factor of 100 for II to be the major reducing species. It may therefore be concluded that the disproportionation reaction proposed[6,10] is not responsible for the lesser stereoselectivity of I.

An alternative explanation for the order of selectivity of the lithium trialkoxyaluminum hydrides is suggested by the association data obtained for these compounds in THF solution. These data are shown in Figure 1. It was found that lithium trimethoxyaluminum hydride displays an increasing degree of association with increasing concentration, while I is monomeric over the same concentration range. The parent compound, lithium aluminum hydride, displays intermediate characteristics. All other factors being equal, a *tert*-butoxy compound is expected to be bulkier than a methoxy compound, but dimerization and higher polymerization of the methoxy compound may produce a reducing agent bulkier than the monomeric LiAl(O-*tert*-Bu)$_3$H.

In order to test this conclusion further, the stereoselectivity of LiAl(OMe)$_3$H and LiAl(O-*tert*-Bu)$_3$H toward 2-methylcyclohexanone was evaluated as a function of concentration. Since LiAl(O-*tert*-Bu)$_3$H appears to be monomeric over a wide concentration range (Figure 1), the ratio of alcohols produced on reduction of 2-methylcyclohexanone should not vary with concentration of the hydride reagent. On the other hand, if association of the reagent is important, a significant change in the ratio of alcohols should be observed as a function of concentration with LiAl(OMe)$_3$H, since the association of this hydride does change with concentration. The data in Table III

TABLE III

EFFECT OF HYDRIDE CONCENTRATION ON THE REDUCTION OF 2-METHYLCYCLOHEXANONE

Molal concn	% less stable isomer LiAl(O-*tert*-Bu)$_3$H	% less stable isomer LiAl(OMe)$_3$H
0.01	23	28
0.10	25	61
0.30	25	62
0.50	26	63

show clearly that the formation of the less stable alcohol remains essentially constant over a 50-fold change in concentration when LiAl(O-*tert*-Bu)$_3$H is used whereas the formation of the less stable alcohol changes significantly in the concentration range where the association of LiAl(OMe)$_3$H changes the most (0.01–0.1 *M*).

The results of these studies indicate clearly that the steric requirement of a hydride cannot be judged by its empirical formula, but rather molecular association studies are required in order to determine its molecular aggregation in solution at the concentration at which it is being employed as a reducing agent.

Experimental Section

Materials.—Tetrahydrofuran was purified by distillation from sodium aluminum hydride under a nitrogen atmosphere. Methanol was purified by distillation from magnesium turnings under a nitrogen atmosphere. *tert*-Butyl alcohol was purified by fractional crystallization. The liquid ketones, 2-methylcyclohexanone and 3,3,5-trimethylcyclohexanone, were purified by vacuum distillation; the solids, norcamphor and camphor, were purified by sublimation under vacuum.

Lithium aluminum hydride solutions in THF were prepared by stirring slurries for 2 days, followed by removal of solids by filtration. Sulfuric acid (100%) was prepared from water and fuming sulfuric acid. Aluminum hydride was prepared by the addition of 100% sulfuric acid to the lithium aluminum hydride solution, followed by removal of the precipitated lithium sulfate.[11] Lithium trimethoxyaluminum hydride and lithium tri-*tert*-butoxyaluminum hydride were prepared by the slow addition of the respective alcohols to the lithium aluminum hydride solution.[4] Di-*tert*-butoxyaluminum hydride was prepared by the slow addition of *tert*-butyl alcohol to the aluminum hydride solution.[12]

Aluminum was determined by complexation with EDTA and back titration with zinc acetate. Active hydride was determined with a Toepler pump by measuring evolved hydrogen after hydrolysis.

Reduction Procedure.—A 25-ml flask, containing a magnetic stirring bar and fitted with a septum stopper and two syringe needles as nitrogen inlet and outlet, was flamed out to remove residual oxygen and water. In the comparison of LiAl(O-*tert*-Bu)$_3$H and Al(O-*tert*-Bu)$_2$H, 5 ml of a 0.213 *M* solution of the ketone in THF was added. The flask was cooled to 0°, and a sufficient amount of the hydride solution was then added by syringe to provide the desired excess. In the comparison of relative yield *vs.* molal concentration, a solution of the desired molality was added to the reaction flask and cooled to 0°. A small sample of 2-methylcyclohexanone was then added by syringe, with vigorous stirring. The volume of ketone was in all cases less than 3% of that of the hydride solution. After 2 hr, the reaction mixture was hydrolyzed using 5 ml of saturated aqueous ammonium chloride solution. The internal standard for vpc analysis was then added and analyses were carried out.

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A diglycerol column at 90° was used to separate the products of the 2-methylcyclohexanone reduction, and a Carbowax 20M column at 125° was used to separate the products in the cases of 3,3,5-trimethylcyclohexanone, norcamphor, and camphor.

Association.—The determination of the association of air- and moisture-sensitive compounds by ebullioscopic techniques is described elsewhere.[13,14] The association studies were carried out in tetrahydrofuran at a pressure of 740.0 mm.

Registry No.—I, 17476-04-9; II, 15649-65-7; $LiAl(OMe)_3H$, 12076-93-6; 2-methylcyclohexanone, 583-60-8.

Acknowledgment.—We wish to acknowledge the support of this work by the Petroleum Research Fund (Grant No. 3211-A3, 4) and the Quality Improvement Funds of the Georgia Institute of Technology.

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Structure and Synthesis of Kahweofuran, a Constituent of Coffee Aroma

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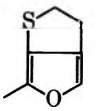
Received August 7, 1970

In the course of detailed analyses of coffee concentrates, a substance with the empirical formula C_7H_8OS, but of unknown constitution, was isolated.[1] In the present paper we outline work on the structure and synthesis of this aroma constituent which we have named kahweofuran (Arab. qahweh, coffee).

The infrared spectrum shows no absorptions which could be ascribed to hydroxyl, mercapto, or carbonyl functions, and it was concluded that both oxygen and sulfur atoms are part of heterocyclic rings. The much more revealing nuclear magnetic resonance spectrum exhibits a one-proton signal at δ 6.91 ascribable to a proton attached to either α or β position of a thiophene ring or to the α position of a furan ring.[2] No other aromatic protons are discernible and the unknown consequently is a trisubstituted furan or thiophene. One of these substituents is a methyl group and the chemical shift of the three-proton singlet (δ 2.17) agrees best with the presence of a 2-methylfuran or a 3-methylthiophene.[3] The remaining two substituents are part of a five-membered ring containing two carbon and one heteroatom. Resonances caused by protons attached to these two carbon atoms appear as a A_2B_2 pattern and comparison of the low-field signals centered at δ 3.57 with those present in the spectra of tetrahydrofuran and tetrahydrothiophene strongly suggest the presence of the latter part structure.[4] Structure **1** tentatively generated by these arguments receives further support from the fact that the furan proton in **1** couples to the high-



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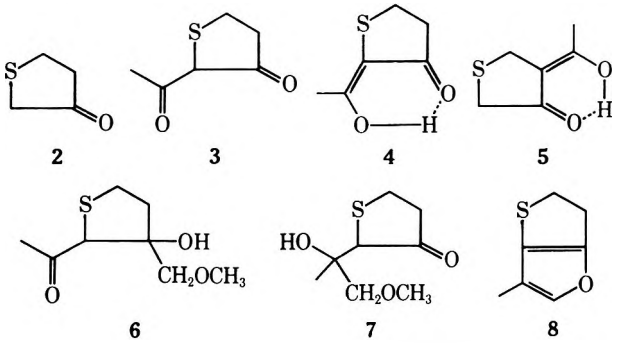
field methylene protons with J = 1.5 Hz in full agreement with the situation encountered previously in 3-methylfuran where benzylic coupling to H_2 is 1.2 Hz, while coupling to H_4 is only 0.5 Hz.[5]

More definitive evidence in favor of structure **1** for kahweofuran was provided by synthesis. Condensation of 3-ketotetrahydrothiophene (**2**)[6] with ethyl acetate in the presence of sodium hydride gave a mixture of β diketones, containing 85% 2-acetyl-3-keto-tetrahydrothiophene (**3** and **4**) and 15% isomer **5**. The ultraviolet absorption maximum (286 mμ) of the minor isomer **5** is strikingly similar to that of 2-acetylcyclohexanone[7] in both neutral and basic solution, while that of the desired isomers **3** and **4** is shifted to 353 mμ and shows no bathochromic displacement on addition of base. Nuclear magnetic resonance spectra in carbon tetrachloride solutions revealed isomer **5** to be completely enolic, while the desired intermediate is a mixture containing 80% enol **4** (or its tautomer) and 20% diketone **3**.



2 **3** **4** **5**

6 **7** **8**

Before proceeding with a discussion of the synthesis, it should be pointed out that the preferential formation of the 2-acetyltetrahydrothiophenes **3** and **4** was anticipated because the intermediate carbanion leading to 2 substitution is stabilized by the 3d orbitals of the neighboring sulfur atoms[8,9] as well as by the carbonyl group. In analogy to the essentially quantitative alkali-catalyzed hydrolysis of 2-acetylcyclopentanone to δ-acetylvaleric acid,[10] we anticipated an organometallic reagent to preferentially add to the cyclic carbonyl function in **3**–**4**. In fact, the addition of methoxymethyl magnesium chloride[11] yielded a mixture of adducts containing two parts of the diastereomeric hydroxy ketones

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6 and one part of what we tentatively believe to be their isomers 7. Separation of these unstable compounds was not possible, and the only evidence in favor of structure 7 is the presence of C-methyl signals in the nmr spectrum of the crude reaction mixture. Steam distillation in the presence of dilute sulfuric acid gave a single product in 15% yield whose infrared, ultraviolet, and mass and nuclear magnetic resonance spectra were indistinguishable from those of "natural" kahweofuran (1). The question as to whether the isomeric furan 8 derived from the minor Grignard adduct 7 was not formed or destroyed under the conditions used remains unanswered. In any event, the possibility that the synthesis described has actually given the furan 8 rather than 1 is excluded by the nmr evidence already discussed. Kahweofuran (1) in the pure state has a violent sulfury odor, but in high dilution it develops a pleasant roasted and smoky note.

Experimental Section

Microanalyses were performed in the laboratory of Dr. E. Palluy, Firmenich et Cie, Geneva. Boiling points are uncorrected. Vapor phase chromatographic (vpc) analyses were performed on a F & M 720 instrument, using a Carbowax 20M column. The following spectrometers were used: nuclear magnetic resonance (nmr), Varian A-60 (TMS as internal standard); infrared (ir), Perkin-Elmer Model 237; ultraviolet (uv), Cary Model 14. Silicic acid Mallinckrodt 100 mesh and silica gel Merck 70–325 mesh were used for column chromatography.

2-Acetyl-3-ketotetrahydrothiophene (3 and 4).—Sodium hydride (1.31 g, 33 mmol, washed free of mineral oil) and 20 ml of dry 1,2-dimethoxyethane were placed in a three-necked flask fitted with a stirrer and a gas inlet tube. A slow stream of nitrogen was passed through the apparatus. The flask was immersed in an ice bath and 3.06 g (30 mmol) of 3-ketotetrahydrothiophene[6] was added to the stirred mixture over a period of 15 min. After hydrogen evolution had ceased (5–10 min), dry ethyl acetate (10 ml) was added over 5 min. Stirring was continued for 60 min at 5° and 60 min at room temperature. The mixture was decomposed with ice and 20 ml of 2*N* H_2SO_4 and extracted with ether. The organic layers were washed with saturated salt solution, dried (Na_2SO_4), and evaporated. Distillation of the residue yielded 865 mg (20%) of the yellow diketone, bp 43–47° (0.2 mm), containing 15–16% 4-acetyl-3-ketotetrahydrothiophene (5). Further purification was achieved by vpc collection: uv max (EtOH) 219 mμ (ε 7000), 353 (5200); uv max (EtOH + NaOH) 219 mμ (ε 7530), 353 (6830); ir ($CHCl_3$) 1740 (w), 1640 (s), 1600 cm^{-1} (s); nmr (CCl_4) enol form, δ 1.95 (s, 3 H), 2.71 (m, 2 H), 3.06 (m, 2 H), 12.6 (s, broad, 1 H) (disappears on exchange with D_2O); nmr (CCl_4) diketone form, δ 2.27 (s, 3 H), 2.71 (m, 2 H), 3.06 (m, 2 H), 3.96 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 144 (89.8), 126 (23.2), 102 (50.2), 88 (100), 43 (81.6).

Anal. Calcd for $C_6H_8O_2S$: C, 49.98; H, 5.60. Found: C, 49.93; H, 5.66.

4-Acetyl-3-ketotetrahydrothiophene (5).—This substance was also obtained by collection: uv max (EtOH) 286 mμ (ε 6500); uv max (EtOH + NaOH) 306 mμ (ε 17,000); ir ($CHCl_3$) 1710 (w), 1640 (s), 1600 cm^{-1} (s); nmr (CCl_4) δ 2.07 (s, 3 H), 3.58 (m, 2 H), 3.69 (s, 2 H), 14.2 (s, broad, 1 H) (disappears on exchange with D_2O); mass spectrum (70 eV) *m/e* (rel intensity) 144 (93.4), 102 (31.4), 70 (50.4), 55 (39.8), 43 (100).

Grignard Adducts 6 and 7.—Magnesium (2.58 g, 0.106 g-atom) was placed in a three-necked flask and activated by heating with a trace of iodine. A slow stream of nitrogen was passed through the apparatus, and 20 ml of freshly distilled methylal and some crystals of mercuric chloride were added. Several minutes after the addition of a few drops of 8.75 g (0.106 mol) of freshly distilled chloromethyl methyl ether, an exothermic reaction commenced, the flask was then immersed in a Dry Ice–acetone bath and the rest of the chloromethyl methyl ether was slowly added at −5° (60 min) with vigorous stirrring. The mixture was stirred for a further 60 min at −5°. A solution of 3.8 g (26.4 mmol) of diketone 3 and 4 in 35 ml of dry methylal was added dropwise at such a rate that the temperature remained between −40 and −50° (30 min). Stirring was continued for 2 hr while the temperature was allowed to rise to room temperature. The reaction product was then poured into cold saturated NH_4Cl solution and extracted with ether twice, washed with saturated salt solution, dried (Na_2SO_4), and evaporated. Distillation gave a yellow oil (3.6 g), bp 80–100° (0.05–0.07 mm), which was chromatographed on 100 g of silicic acid. Elution with chloroform–ethanol (98:2) followed by distillation gave a colorless oil (3.0 g, 60%), bp 64–66° (0.03 mm). Nmr spectroscopy indicated that this material was a 2:1 mixture of the epimers of 2-acetyl-3-hydroxy-3-methoxymethyltetrahydrothiophene (6) and 2-(1-hydroxy-1-methoxymethyl)ethyl-3-ketotetrahydrothiophene (7), respectively. The spectrum (CCl_4) had bands at δ 1.15 (s), 1.25 (s), 2.15 (s), 2.25 (s), 3.3–3.4 (four-overlapping singlets); ir ($CHCl_3$) 3530 (broad), 1710, 1110 cm^{-1}.

Anal. Calcd for $C_8H_{14}O_3S$: C, 50.52; H, 7.42. Found: C, 50.70; H, 7.24.

Kahweofuran (1) (2-Methyl-3-oxa-8-thiabicyclo[3.3.0]-1,4-octadiene).—The mixture of carbinols 6 and 7 (1.5 g) was added dropwise during 30 min to 50 ml of 1 *N* H_2SO_4 while steam distilling. After 1 hr, the distillate (150 ml) was extracted twice with ether, washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated. The remaining orange oil was chromatographed on 20 g of silica gel using hexane–ethyl acetate (9:1) as eluent. Distillation gave kahweofuran as a colorless oil (177 mg, 15%): bp 105–107° (20 mm); uv max (EtOH) 245 mμ (ε 3100); ir ($CHCl_3$) 1630, 1575, 1100, 1075, 920 cm^{-1}; nmr (CCl_4) δ 2.17 (s, 3 H), 2.81 (t, 2 H, *J* = 7 Hz with fine splitting of 1.5 Hz), 3.57 (t, 2 H, *J* = 7 Hz with small fine splitting), 6.91 (t, 1 H, *J* = 1.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 140 (100), 139 (28.4), 111 (37.9), 97 (29.2). The mass spectrum, ir, nmr, and uv spectra of synthetic kahweofuran were indistinguishable from those of the natural product.

Anal. Calcd for C_7H_8OS: C, 60.00; H, 5.75. Found: C, 60.32; H, 5.96.

Registry No.—**1**, 26693-24-3; **3**, 26693-25-4; **4**, 26693-26-5; **5**, 26693-27-6; **6**, 26693-28-7; **7**, 26693-29-8.

Acknowledgment.—We (G. B. and P. D.) are indebted to Firmenich et Cie., Geneva, for generous financial support.

The Effect of Pressure on Acetal Equilibria[1]

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Received March 19, 1970

The influence of pressure upon the rates of chemical reactions in solution continue to be widely investigated.[4-6] Far less interest has been generated for studies concerned with the influence of pressure on chemical equilibria in the solution.[4,6] This general lack of research interest is surprising because (1) pressure remains as a physical variable which can be changed

(1) We gratefully acknowledge support for this work under Grant No. AM-11244 from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

(2) Author to whom correspondence should be addressed.

(3) Undergraduate Research Participant, summer 1969. We wish to acknowledge help given by Mr. Thomas S. Davis with the experimental work.

(4) W. J. le Noble, "Progress in Physical Organic Chemistry," Vol. 5, A. Streitwieser, Jr., and R. W. Taft, Eds., Interscience, New York, N. Y., 1967.

(5) E. Whalley, "Advances in Physical Organic Chemistry," Vol. 2, V. Gold, Ed., Academic Press, New York, N. Y., 1964.

(6) M. G. Gonikberg, "Chemical Equilibria and Reaction Rates at High Pressures," 2nd ed, Izd. AN Bademie SSR, Moscow 1960. Translations of the book have been prepared for the National Science Foundation, Washington, D. C. (NASA TT F-95), by the Israel Program for Scientific Translations, Israel.

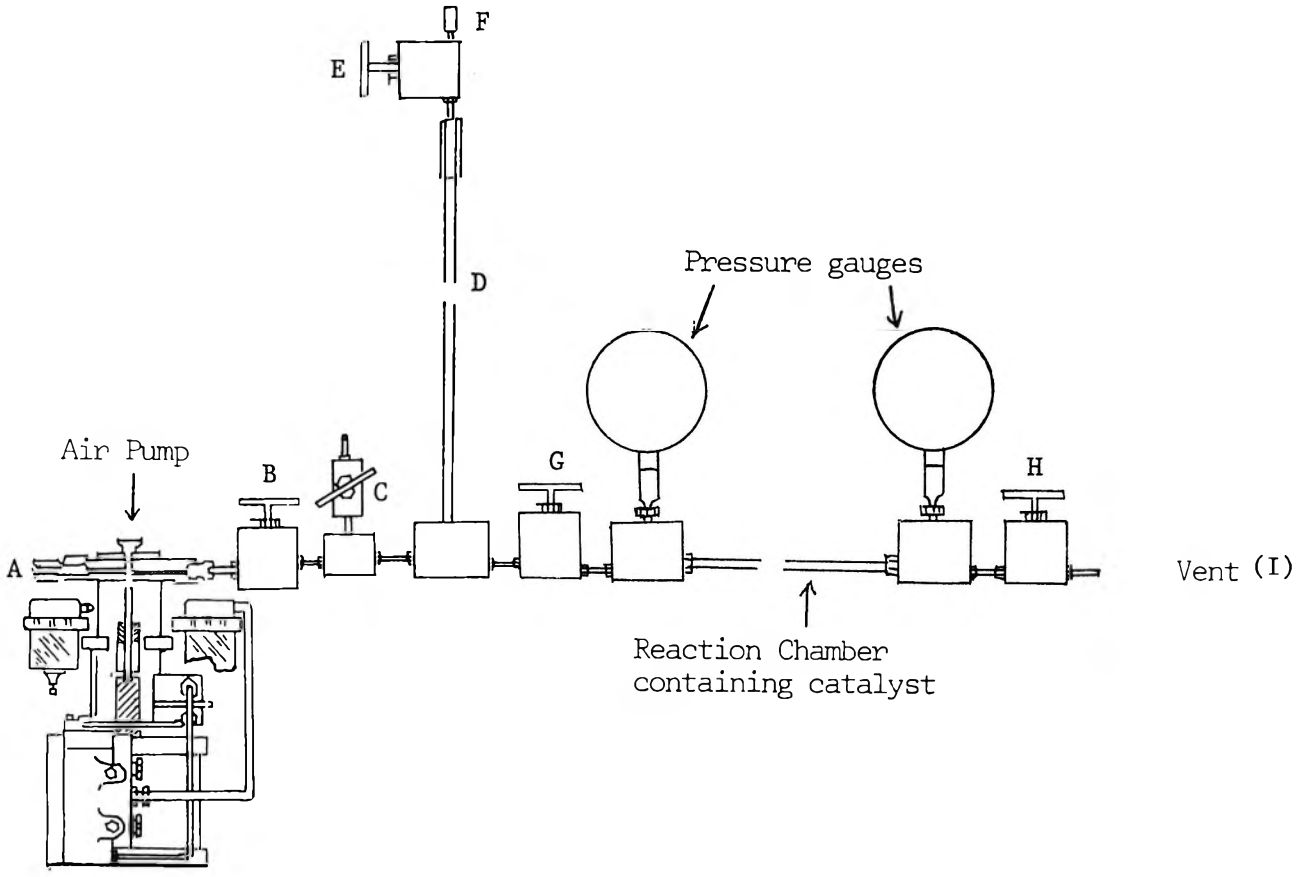

Figure 1.—High pressure reactor.

nearly without limit, (2) remarkable accomplishments have been made with high pressure on an industrial basis (*e.g.*, the polymerization of ethylene and the synthesis of diamonds), and (3) sophisticated components for high pressure studies are available commercially.[7]

For a general chemical system, $aA + bB \rightleftharpoons cC + dD$, beginning with the reactants A and B, one expects the most beneficial effect of pressure upon equilibria when $\Delta n < 0$. Even for cases for which $\Delta n \geq 0$, the use of an appropriate solvent may alter molar volumes such as to provide negative volumes of reaction. Consideration of the equilibria for the conversion of an aldehyde to an acetal, for which $\Delta n = -1$, suggested that the acetal equilibria might be a good choice to evaluate pressure effects on chemical equilibria in solution. Calculation of volumes of reaction based upon densities of reactants and of products for a large number of combinations of aldehydes or ketones with various alcohols gave negative volumes of reaction (values varied from -5 to -20 ml/mol) in each case. Calculation of volumes of reaction based on densities for the esterification of various acids with alcohols ($\Delta n = 0$) gave values near zero in every case (for twenty calculations, Δv varied from $+1.2$ ml/mol to -3.3 ml/mol).

We report our preliminary pressure studies for the reactions of propionaldehyde, benzaldehyde, and cyclohexanone with methanol to form the corresponding dimethyl acetals. Mole ratios of 5:1 of alcohol to the carbonyl compound were used in each case. The reactions were conducted at 25° in a continuous flow reactor while varying the pressure from 1 to 2040 atm. Dowex-50 ion exchange resin was used as the catalyst. This choice of catalyst obviated problems of neutralization of homogeneous acid catalysts under pressure or of having to analyze the mixtures under pressure because once the reactants passed the catalyst zone, the equilibrium was "frozen" and could be vented to atmospheric pressure for analysis.

The results of our studies are summarized in Table I. The volumes of reaction were calculated by plotting

TABLE I

Propionaldehyde and methanol		Cyclohexanone and methanol		Benzaldehyde and methanol	
Pressure, atm	K_x[a]	Pressure, atm	K_x[a]	Pressure, atm	K_x[a]
2040	4.30	2040	0.51	2040	0.93
1700	4.04	1700	0.42	1360	0.64
1360	4.01	1360	0.36	680	0.40
1020	3.58	1020	0.32	272	0.28
680	3.43	680	0.26	1	0.24
1	3.10	1	0.17		
	-4.6[b]		-12.5[b]		-17.5[b]

[a] Mole fraction equilibrium constants. [b] Volume, ml/mol.

log K_x (mole fraction equilibrium constant) against the pressure and determining the slopes.[8] Straight line plots were obtained in each case.

It is apparent from these data that the acetal equilibrium is shifted significantly by an increase in pressure. Because of the simplicity of the operation and the marked improvement in yields, such devices may become more useful in laboratory synthetic work. Further obvious improvements for the systems studied can be realized by (1) using higher mole ratios of alcohol

(7) Reference 4, p 208.

(8) $\Delta V = -2.3RT \frac{\Delta \log K_x}{\Delta P}$.

to the carbonyl moiety and recycling unreacted alcohol, (2) using low temperatures since the heat of reactions is negative,[9] and (3) using significantly higher pressures.

The particular apparatus used in this work is limited to an upper pressure of about 2500 atm. As an example of the value of using much higher pressures we extrapolated the results for cyclohexanone and methanol to 10,000 atm. The extrapolated value of K_x was in excess of 10, which is over a 50-fold increase in K_x compared to the value at atmospheric pressure (0.17).

A brief evaluation also was made of the reaction of benzaldehyde and ethylene glycol and of acetic acid and methanol. The glycol solution "froze" above 270 atm which prevented further pumping. The reaction of acetic acid and methanol was found to be aided by pressure with a volume of reaction being about −5 ml/mol.

Experimental Section

High Pressure Apparatus.—The schematic of the high pressure apparatus is shown in Figure 1. All components of the apparatus were purchased from the American Instrument Co., Silver Spring, Md. The air pump is driven by 80 psi air pressure input to a 6-in. piston with a 0.25-in. output piston, with a maximum discharge pressure of 40,000 psi (2720 atm). The gauges are 6 in., 0–40,000 psi Bourdon-type gauges. The tubing is 304 stainless steel superpressure tubing of $^9/_{16}$, in. o.d., $^3/_{16}$ in i.d. The fittings (connectors, sleeves, couplings, etc.) are all rated at 0–100,000 psi with the bodies constructed of 316 stainless steel and the nuts and sleeves of 416 stainless steel. The valves are rated at 30,000 psi with the bodies constructed of 316 stainless steel and the nuts and sleeves of 416 stainless steel.

The catalyst (75–100 ml of Dowex-50) was contained in the superpressure tubing between the two valve blocks and was retained in the tube by means of a sintered stainless steel filter disk of medium porosity. To the bottom of the left gauge block there was connected a steel tube supporting a 32,000 psi rupture disk.

Operational Procedure.—With all valves open except E, the reaction mixture was fed from a separatory funnel to the system at A and pumped until a free flow was obtained at the vent I. Valve E was then opened and valve H closed to pump solution into the ballast tube D until liquid vented at F. Pumping was suspended and, with all valves closed except E and G, nitrogen was introduced at F under 100 psi. Valve C was opened until 50 ml of liquid (one-half the volume of tube D) vented while maintaining the nitrogen pressure. Valves E and C were closed; pumping was resumed until the desired reaction pressure was reached. Valve H was opened to give a slight flow through vent I at the desired reaction pressure by adjusting the inlet pump pressure and the opening of valve H. The reaction mixture was pumped sufficiently long to establish homogeniety (usually 1 l. or more of mixture). The flow rate had to be sufficiently low to ensure the establishment of equilibrium. With the volume of catalyst used, a flow rate of about 3 ml/min was sufficient for all three acetal systems studied. About 25–30 ml of mixture was collected for analysis, the pressure and flow rate were readjusted, and, after discharging about 250 ml of mixture, another sample was collected for analysis. Upon completion of a run, the system was flushed throughly with anhydrous methanol.

Purification of Reagents and Analyses.—Methanol was purified in 5-l. batches by the method of Lund and Bjerrum.[10] The distillation column (32 × 700 mm) was adiabatic with reflux control and packed with glass helices. Water content, determined for each batch by the Karl Fischer method, was always less than 0.01%.

The Dowex-50, X8 ion exchange resin (H form, strong acid, 20–50 mesh) was washed with water until the water tested neutral to acid test paper. The water was removed by repeated washing of the resin with small amounts of anhydrous methanol and the catalyst was air-dried.

Propionaldehyde was distilled (24 × 450 mm glass column) at atmospheric pressure. The material which boiled from 48–49° was collected. Solutions containing 5 mol of methanol to 1 mol of propionaldehyde were prepared, flushed with nitrogen, and permitted to cool (heat of hemiacetal formation) back to room temperature. The solutions were always used the same day they were prepared to diminish air oxidation of the aldehyde.

The propionaldehyde content of the reaction mixtures was determined by the hydroxylamine–pyridine method.[11] The equilibrium mole fractions were calculated by means of the final propionaldehyde content, the initial amount of reagents, and the stoichiometry. From these values, the mole fraction equilibrium constants were calculated.

Benzaldehyde and cyclohexanone were purified in a standard manner[12] and analyzed for carbonyl content on a Perkin–Elmer 202 spectrophotometer. Extinction coefficients (λ_{max} = 281 mμ for benzaldehyde and λ_{max} = 288 mμ for cyclohexanone) were determined with freshly prepared methanol solutions.

Registry No.—Methanol, 67-56-1; propionaldehyde, 123-38-6; cyclohexanone, 108-94-1; benzaldehyde, 100-52-7.

(9) A useful technique used with ion exchange resins as acetal catalysts developed by N. B. Lorette, W. L. Howard, and J. H. Brown, *J. Org. Chem.*, **24**, 1731 (1959).

(10) H. Lund, and J. Bjerrum, *Ber.*, **64**, 210 (1931).

(11) S. Siggia, "Quantitative Organic Analysis via Functional Groups," 2nd ed, Wiley, New York, N. Y., 1957.

(12) J. M. Bell, D. G. Kubler, P. Sartwell, and R. G. Zepp, *J. Org. Chem.*, **30**, 4285 (1965).

The Relative Ease of 1,2-Proton Shifts. The Origin of the Formyl Proton of Salicylaldehyde Obtained by the Reimer–Tiemann Reaction

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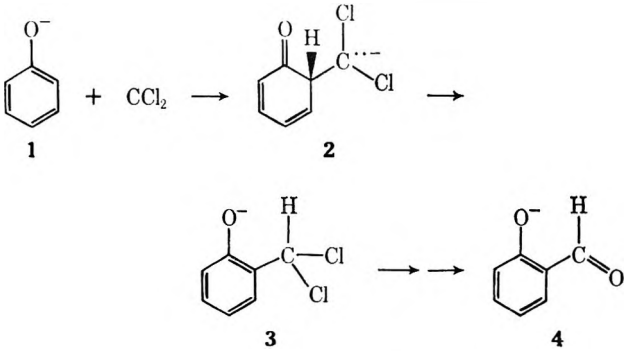
Received June 12, 1970

As a result of Hine's demonstration[1] in 1959 of the intermediacy of dichlorocarbene, the Reimer–Tiemann reaction has been widely accepted as proceeding by the following path, although evidence for the intermediates **2** and **3** has been entirely inferential. The



transformation **2** → **3** is an interesting one in that it can be envisaged as occurring *via* a 1,2-proton transfer. Either on the basis of simple Hückel theory[2] or from orbital symmetry considerations,[3] such transfers are expected to occur with difficulty; yet one can regard **2** → **3**

(1) J. Hine and J. M. van der Veen, *J. Amer. Chem. Soc.*, **81**, 6447 (1959).

(2) See, for example, J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, New York, N. Y., 1965, p 399.

(3) R. B. Woodward and R. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, **8**, 781 (1969).

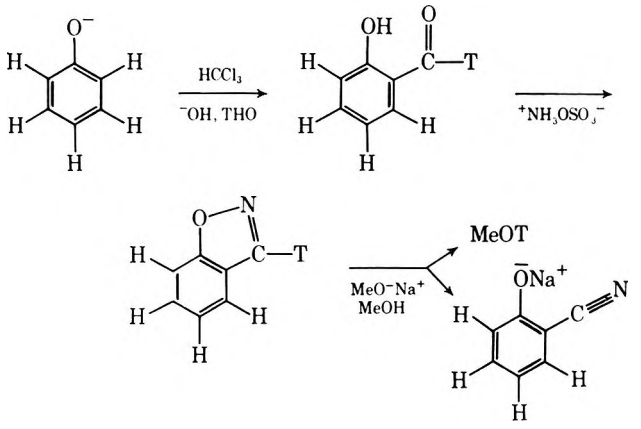
as posing a limiting extreme for either of these analyses in that **2** may be estimated as 40–60 kcal/mol less stable than **3**. Specifically, can the symmetry required of these analyses apply in a situation which is energetically so unsymmetrical?

Some years ago we made the relevant observation that when carried out in D_2O, the Reimer–Tiemann synthesis yields salicylaldehyde bearing >97% deuterium in its formyl grouping and insignificant deuterium in its ring positions.[4] In the present paper I wish to describe results which define this result mechanistically and which explore its scope by means of the more sensitive tool of tritium labeling.

When *O*-acetoxybenzal chloride (**5**) was hydrolyzed under conditions (40% NaOD in D_2O, 70°) exactly the same as those used in the Reimer–Tiemann reaction, a 54% yield of salicylaldehyde was obtained which contained less than 5% of deuterium in its formyl hydrogen position. Since **5** must linger longer as a neutral molecule in this medium it must be more susceptible to exchange than **3**, and this finding therefore requires that deuterium be introduced in the Reimer–Tiemann sequence prior to the appearance of **3**.

As a more compelling probe of the exchange results, the Reimer–Tiemann synthesis of salicylaldehyde was carried out in THO, and the isolated aldehyde was subjected to the indicated degradation scheme (Scheme I).

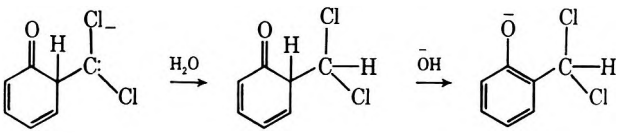
SCHEME I



Salicylaldehyde was obtained which contained 99.6% of its tritium in its formyl group and less than 0.4% in its ring positions. This result establishes the possibility of a very sensitive distinction between protons derived from the ring pool and those derived from the solvent.

Phenol bearing tritium in either the 2 or the 4 position was synthesized by acid-catalyzed exchange with THO and was shown by conversion to 2,4,6-tribromophenol to contain no more than 0.03% of its tritium in the 3 position. When a Reimer–Tiemann synthesis of salicylaldehyde was carried out using this phenol at 0.4% concentration, less than 0.06% of the total molecular tritium of the product was found in the formyl position, a quantity which is within experimental error of the expected value for tritium lost to and reincorporated from solvent during the synthesis. Unfortunately, technical difficulties prohibited carrying out the synthesis under conditions involving greater dilutions of starting material.

These results may be taken to imply that the conversion of **2** → **3** is the actual path for the reaction and that it cannot occur by a single 1,2-proton shift but most probably by a pair of intermolecular proton transfers. The selectivity favoring the latter process must be much greater than a 1000-fold.



2 **3**

The anion **2** might be expected to react at diffusion-controlled rates with water molecules, and one must be able to assess the concentration of free water in these reaction media in order to set numerical limits on a rate constant for the hydride shift. Yagil and Anbar[5] have observed that in such solutions one may anticipate less than an order of magnitude decrease in free water concentration over that of pure water. Thus, while the present findings demonstrate remarkable discrimination against a thermodynamically favorable intramolecular process, the disfavored hydride shift could still conceivably be occurring with a rate constant of *ca.* 10^8 sec^{-1} and not contribute significantly to formation of the observed product.

Experimental Section

7-^2H-Salicylaldehyde.[6]—Into a 1-l. three-necked flask equipped with stirrer, condenser, thermometer, and nitrogen inlet was placed 260 g (13 mol) of 99.5% deuterium oxide; the flask and contents were cooled to 5° during the cautious addition of 100 g (4.4 g-atoms) of clean Na metal. Toward the end of the addition (40 min) the ice bath was removed and the mixture vigorously stirred to promote reaction; 27 g of phenol (0.29 mol) was added; and the slurry was warmed to 80° and stirred until the phenoxide dissolved. The temperature was maintained at 70–80° during the hour required to add 67 g (0.56 mol) of chloroform. The mixture was warmed at 65° for 90 min and then allowed to stand overnight and acidified to pH 1 with cold 5 *N* sulfuric acid. Steam was introduced and distillation allowed to proceed until only clear distillate collected. The distillate was saturated with sodium chloride and extracted with six 10-ml portions of dichloromethane which were pooled, dried, and evaporated to yield 19 g of crude product. The aldehyde was purified through its copper chelate[7] and then was distilled through a spinning-band column, bp 78.5–79.0° (14 mm), 11.1 g, 31%. Mass spectral and nmr data indicated the sample to bear greater than 97% deuterium in its formyl grouping, ir (CCl_4) 2100 cm^{-1} (C–D stretch).

***O*-Acetoxybenzal Chloride.**—Distilled *O*-acetoxybenzaldehyde, 8.1 g (48 mmol), was dissolved in 20 ml of dichloromethane and treated at 20° with 10.1 g (50 mmol) of phosphorus pentachloride. When solid had disappeared, the solvent was stripped, and the residue was distilled, bp 91–96° (3 mm), 9.1 g, 86%. Crystallization from cyclohexane gave solid: mp 48.0–48.8°; nmr (CCl_4) δ 2.2 (s, 3), 7.0 (s, 1), 7.1–8.0 (m, 4); ir (CCl_4) 1770 cm^{-1} (ester C=O). *Anal.* Calcd for $C_9H_8Cl_2O_2$: C, 49.34; H, 3.68; Cl, 32.37. Found: C, 49.26; H, 3.76; Cl, 32.45.

2- and 4-^3H-Phenol.—Phenol, 20 g, was added to 10 ml of 10% sulfuric acid containing 0.245 mCi of tritium. After 4 days of heating to reflux, the mixture was cooled and extracted with ether. The pooled extracts were extracted with fifteen 20-ml portions

(4) D. S. Kemp and R. B. Woodward, unpublished observations.

(5) G. Yagil and M. Anbar, *J. Amer. Chem. Soc.*, **85**, 2376 (1963).

(6) Nmr spectra were taken with a Varian A-60 spectrometer using tetramethylsilane as internal standard. Counting was performed with a Packard 3375 liquid scintillation spectrometer; samples were standardized externally and internally. Microanalysis was performed by Scandinavian Microanalytical Laboratory, Copenhagen, Denmark.

(7) "Organic Syntheses," Coll. Vol. III, Wiley, New York, N. Y., 1955, p 166.

of water, dried ($MgSO_4$), and concentrated. The residue was distilled to yield 8.7 g of phenol, specific activity 0.336 μCi/mmol (calcd: 0.37 μCi/mmol for completed exchange of 2, 4, and 6 protons). Bromination of a sample of this phenol in water containing hydrobromic acid yielded 2,4,6-tribromophenol, mp 188.5–191.0°, specific activity $\leq 1 \times 10^{-4}$ μCi/mmol.

Reimer–Tiemann Synthesis with ^3H-Phenol.—The Reimer–Tiemann procedure given above was repeated by adding 0.81 g of the above phenol and 0.10 g of unlabled salicylaldehyde to a solution of 100.5 g (2.63 mol) of sodium hydroxide in 115 ml of water and treating the solution with 40 g of chloroform. After acidification and steam distillation, the distillate was extracted with fifteen 3-ml portions of dichloromethane which were pooled, dried, and evaporated. The resulting 0.4 g of crude salicylaldehyde was converted directly to benzisoxazole by treatment with 1 g of hydroxylammonium *O*-sulfonate in 2 ml of water, followed by extraction with dichloromethane to remove neutral impurities. The aqueous layer was brought to pH 7 with sodium bicarbonate and extracted with three 5-ml portions of dichloromethane, which were pooled and evaporated. The residue was distilled in a bulb-to-bulb apparatus at 1 mm to yield 0.12 g of benzisoxazole, identified by its infrared spectrum, specific activity 0.134 μCi/mmol. When 97.85 mg of this sample was treated with excess sodium methoxide in methanol and the methanol was recovered quantitatively by lyophilization, it was found to show 71.1 dpm/0.822 mmol or 3.9×10^{-5} μCi/mmol; *o*-cyanophenol recovered by acidification of the lyophilization residue was found to possess 99% of the activity of the benzisoxazole.

Registry No.—Salicyladehyde, 90-02-8; *O*-acetoxybenzal choride, 26693-22-1.

Electronegativity, Acids, and Bases. IV. Concerning the Inductive Effect of Alkyl Groups

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Received May 28, 1970

Although the inductive effects of alkyl groups have long been appreciated, there has been some confusion concerning the electron donating or withdrawing ability of alkyl groups relative to each other and to the hydrogen atom. Thus, there has been some uncertainty concerning the basicity of alkylamines based upon pK_b's in aqueous solution, but Condon[1] has shown clearly that, if hydration effects are accounted for, the basicity order is $R_3N > R_2NH > RNH_2 > NH_3$, in accord with increasing electron density on the nitrogen with increasing substitution. Furthermore, $(CH_3)_3C > (CH_3)_2CH > CH_3CH_2 > CH_3 > H$ in *electron donating* ability toward N, O, C_6H_5, etc. These results have been confirmed in gas phase studies by Munson[2] and by Brauman and Blair.[3]

Recently, Brauman and Blair[3] have measured gas-phase acidities of various aliphatic alcohols and have shown that acidity increases in the order $H_2O < CH_3OH < CH_3CH_2OH < (CH_3)_2CHOH < (CH_3)_3COH < (CH_3)_3CCH_2OH$ and $CH_3CH_2OH < CH_3CH_2CH_2OH < CH_3CH_2CH_2CH_2OH < CH_3CH_2CH_2CH_2CH_2OH < (CH)_3COH$. This indicates that in the alkoxide ions, $R'O^-$, *electron withdrawing* ability also decreases $R_3C > R_2CH > RCH_2 > CH_3 > H$. In terms of any concept of fixed electronegativity[4] the apparent reversal of electronegativity seems paradoxical. Recent molecular orbital calculations by the MINDO[5] and CNDO/2[6] methods have rationalized the experimental results of Brauman and Blair. Some of these "predictions" would have been more useful had they not appeared *a posteriori*. It is the purpose of this note to call attention to earlier, though neglected, work in this area and to interpret these results in terms of simple model.

Though the inductive effects of alkyl groups have been discussed almost exclusively in terms of electron donation, Ingold[7] pointed out that this common behavior was a result of the fact that these groups are generally attached to *more electronegative substituents*. More recently, Schubert and coworkers[8] have cogently argued the same point, alkyl groups can donate *or* accept electron density depending upon the nature of the substrate. Furthermore, the latter workers made an extremely important observation; larger alkyl groups tend to be better electron donors because they are more polarizable. Therefore, they should also *be better electron acceptors when bonded to less electronegative substrates*. Two parameters are thus involved in charge transfer: inherent electronegativity and capacity (polarizability).

In a previous paper,[9] the group electronegativities of alkyl groups were calculated using the principle of electronegativity equalization,[10,11] and it was shown that the inherent or neutral electronegativities of alkyl groups are (1) slightly higher than hydrogen, (2) very similar to each other, ranging from 2.27 to 2.29,[12] and (3) not sufficient to differentiate among the groups. It was also shown that the principal differences among them lie in their varying *charge coefficient*, *b*, the rate at which the electronegativity changes with gain or loss of electron density. The increased electron donor ability of more highly substituted groups (toward electronegative substrates such as N, O, C_6H_5, etc.) results from their relatively low values of *b*, where the electronegativity is expressed as

$$\chi = a + b\delta \qquad (1)$$

Simply stated, other things being equal, the more atoms in a group, the more readily the group can donate electron density since the resulting charge can be spread over more atoms.

In the previous paper[9] it was suggested that the same effect should be operative in allowing a group to *absorb* electron density. At that time, no good examples were known to the author for alkyl groups since the most obvious compounds to consider, the metal alkyls, $M^{\delta+}—R^{\delta-}$, are polymeric and not amenable to treatment. It was pointed out, however, that the electron withdrawing ability of perfluoroalkyls should increase with increasing size and that for transfers of charge density greater than *ca.* 0.1 they will be better acceptors

(1) F. E. Condon, *J. Amer. Chem. Soc.*, **87**, 4481, 4485, 4491, 4494 (1965).
(2) M. S. B. Munson, *ibid.*, **87**, 2332 (1965).
(3) J. I. Brauman and L. K. Blair, *ibid.*, **90**, 6561 (1968); **92**, 5986 (1970).
(4) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960.
(5) N. C. Baird, *Can. J. Chem.*, **47**, 2306 (1969).
(6) T. P. Lewis, *Tetrahedron*, **25**, 4117 (1969).
(7) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953 p 70.
(8) W. M. Schubert, R. B. Murphy, and J. Robins, *Tetrahedron*, **17**, 199 (1962).
(9) J. E. Huheey, *J. Phys. Chem.*, **69**, 3284 (1965)
(10) R. T. Sanderson, *J. Chem. Educ.*, **31**, 2 (1954); "Chemical Periodicity," Reinhold, New York, N. Y., 1969.
(11) J. Hinze and H. H. Jaffé, *J. Amer. Chem. Soc.*, **84**, 540 (1962); J. Hinze, M. A. Whitehead, and H. H. Jaffé, *ibid.*, **85**, 148 (1963).
(12) Based on electronegativities from ref 11: $C_{te} = 2.46$; $H_s = 2.21$; $F_p = 3.90$.

TABLE I
CALCULATED CHARGES IN ALKOXIDE IONS

Anion, RO⁻ [a]	Present work δO	Present work δR	Present work δC	Present work δH	MINDO,[b] δO	CNDO/2,[c] δO
OH^-	−0.658	−0.342		−0.342	−1.08	
CH_3O^-	−0.526	−0.474	−0.161	−0.104	−0.91	−0.68
$C_2H_5O^-$	−0.492	−0.508	−0.114	−0.056	−0.85	−0.67
$C_3H_7O^-$	−0.477	−0.523	−0.093	−0.034	−0.81	−0.66
$C_4H_9O^-$	−0.469	−0.531	−0.081	−0.023		−0.66
$C_5H_{11}O^-$	−0.464	−0.536	−0.074	−0.015		−0.66

[a] The oxygen is assumed to be hybridized with 20% s character in the hydroxide ion and 26.4% s character in the alkoxides. These values are from the 104.5° bond angle in H_2O and the somewhat greater angle (~110°) in alcohols. Under the relaxed steric conditions of the anion, the s character probably changes somewhat. Small changes in s character do not change the results significantly. [b] Reference 5. [c] Reference 6.

than the fluorine atom itself. The results confirmed the earlier arguments of Schubert, *et al.*[8,13]

The experimental work of Brauman and Blair[3] provides striking confirmation of the expectation expressed above. In the negatively charged alkoxide anion (the conjugate base of the acidic alcohol), the negative charge resides predominantly on the oxygen but the ion will be stabilized (*i.e.*, its basicity will be reduced) to the extent that this charge can be delocalized[14] onto the alkyl groups. In this case the electronegativities of the alkyl groups (2.27–2.29) are all *greater* than that of an oxygen atom with a unit negative charge ($\chi_o \leq 0$)[15] and hence absorb electron density from the latter and the larger groups are capable of absorbing a greater amount before becoming saturated. This interpretation is thus essentially the same as that suggested earlier by Schubert, *et al.*,[8] the larger groups are more polarizable and can absorb charge more readily, but may be expressed in terms of electronegativity parameters derived from fundamental *atomic* properties rather than intuitive arguments. The results are given in Table I. It should be noted that these results were obtained using the simplifying assumption of electronegativity equalization.[9-11] The problems and errors inherent in this simplification have been discussed elsewhere[9,16] and attempts have been made to improve the calculations by various means,[17] but it may be said that the *qualitative* trends shown in Table I will not be altered by such attempts to improve the quantitative calculations with the possible exception of the very large groups (*n*-butyl, *tert*-butyl, *n*-pentyl). While the present values can hardly be interpreted as accurate estimates of the real charges, they are internally self-consistent and at least as reasonable as the estimates obtained by more elaborate methods. The very high values of the MINDO estimates (−0.8 to −1.0 on oxygen)[5] and CNDO/2 estimates (−0.67 on oxygen with almost no dependence upon the nature of R)[6,17a] result from the neglect of the effect of forcing large electron densities on a small oxygen atom.[18]

It is apparent that when discussing the inductive effect of groups it will be necessary to consider both inherent electronegativity and relative charge capacity. In some ways, this result is akin to Pearson's suggestions[19] that a hardness–softness factor (the HSAB principle) be considered in addition to inherent strength in acids and bases. However, even here the possibility of confusion can exist. Pearson and Songstad[20] have claimed that the *tert*-butyl group is "harder" than the methyl group and that it is a poorer electron donor (toward electronegative substrates) despite general opinion to the contrary. As can be seen from the above discussion, the *tert*-butyl group is both a better donor and a better acceptor (in appropriate situations) than methyl or hydrogen. If experimental criteria and applications of the HSAB rule indicate that *tert*-butyl is "harder" than methyl, it is apparent that factors other than polarizability must be responsible for "softness." This conclusion has been reached on the basis of other evidence elsewhere.[17,21]

Registry No. —OH^-, 14280-30-9; CH_3O^-, 3315-60-4; $C_2H_5O^-$, 16331-64-9; $C_3H_7O^-$, 26232-83-7; $C_4H_9O^-$, 26232-84-8; $C_5H_{11}O^-$, 26675-02-5.

Acknowledgment.—I should like to thank Professor W. M. Schubert for helpful criticism of this article.

(13) Unfortunately, ref 8 was unknown to the author in 1965. Although derived independently, Figure 1 of ref 9 provides a quantification of Figure 2 of ref 8 for the electron donating and withdrawing properties of alkyl groups with respect to the hydrogen atom.

(14) The term delocalization is used here to mean simply that all the atoms in the alkoxide ion acquire a negative charge through the inductive effect with no implications of conjugation or hyperconjugation.

(15) A *negative* electronegativity, like a negative pH, is an extremely unlikely, though possible situation. The meaning of this value is that oxygen *cannot* contain a total unit negative charge while coexisting in a covalent bond with *any* other atom or group of atoms.

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(20) R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967).

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Preparation of Bridgehead Alkyl Derivatives by Grignard Coupling

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Received April 28, 1970

We have developed a simple, high yield way to convert adamantane-type bridgehead bromides to the cor-

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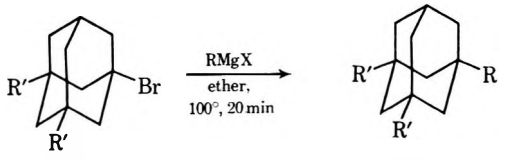
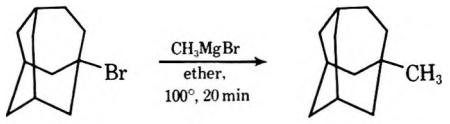
responding methyl (or other alkyl) derivatives. Diamondoid hydrocarbons can often be prepared by rearrangement[1-3] and functional groups added subsequently.[2] One of the most useful methods is ionic bromination, which exhibits a strong preference for bridgehead substitution.[2,4] However, conversion of, *e.g.*, 1-bromoadamantane to 1-methyladamantane according to literature procedures, was a cumbersome, four-step process involving preparation and then reduction of the corresponding carboxylic acid.[5] Direct quaternization of tertiary carbons is not generally very satisfactory. For example, Wurtz coupling reactions have been used to prepare 1-ethyl- and 1-propyladamantane, but the yields were very poor.[6] Grignard reagents are known to react with *tert*-halides, but low yields of alkanes are expected.[7]

Nevertheless, when 1-adamantyl bromide (Ia) was heated in an aerosol pressure bottle with excess CH_3MgBr in ether for only 20 min at 100°, 1-methyladamantane (IIa) was obtained in 83% yield. (More conventional reaction conditions using higher boiling solvents gave unsatisfactory results.) As Table I reveals, this is quite a useful, general procedure for bridgehead methylation. We have applied the reaction not only in the adamantane series, but also to the synthesis of two new compounds, 3-methylhomoadamantane (IV) and 1-methyldiamantane (VI).[8]

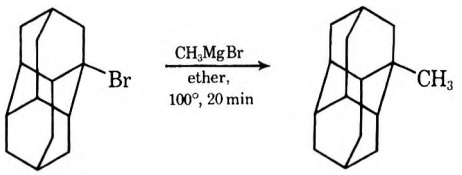


Ia, R' = H
b, R' = CH_3

IIa, R = CH_3; R' = H
b, R = R' = CH_3
c, R = C_2H_5; R' = H
d, R = *tert*-C_4H_9; R' = H
e, R = $CH_2C_6H_5$; R' = H



III IV



V VI

The utility of the procedure was further illustrated by the preparation of 1-methyladamantane (IIa) labeled in the methyl group with ^{13}C and separately with ^{14}C. In these cases it was not possible to use the optimum conditions (large excess of Grignard reagent), but the yields were still satisfactory (64%). It was demonstrated in both instances that no rearrangement occurred; the isotopic labels were found to be exclusively in the methyl groups. The Kuhn–Roth oxidation[9] of 1-methyladamantane-methyl-^{14}C (specific activity 0.34 nCi/mg C) yielded acetic acid isolated as the thallous salt[10] (specific activity 1.83 nCi/mg C). This corresponds to 97.1% of the activity in the starting 1-methyladamantane. The Schmidt degradation of the TlOAc gave inactive CO_2 and methylamine with all of the activity. The mass spectrum of 1-methyladamantane-methyl-^{13}C exhibited the same (M + 1)/M ratio 136/135 (corresponding to adamantyl-^{13}C/adamantyl) as unlabeled 1-methyladamantane. This confirms the suggestion that alkyladamantanes cleave preferentially by loss of the alkyl substituents.[11]

The methylation yields with the bridgehead bromides, Ia, Ib, III, and V, are much better than those reported in the literature for other *tert*-alkyl halides.[7] This provides another instance where the chemistry at the bridgehead of polycyclic bridged ring systems is much cleaner due to the inhibition of competing reactions.[2,17] Ordinary *tert*-halides give elimination byproducts with Grignard reagents;[7] elimination is not possible with adamantane and the other bridged ring systems studied; and yields of coupling products are enhanced as the result.

Other alkyl groups besides methyl may also be introduced, but the yields are not so good (Table I).[12-16] With the higher Grignard reagents, the coupling reaction must compete with Grignard reduction, and considerable adamantane is formed as by-product. When Ia was treated with *tert*-butylmagnesium bromide, only adamantane (the reduction product) was formed (84% yield). However, reasonable yields of 1-ethyladamantane (IIc) and 1-benzyladamantane (IIe) were achieved.

We believe the alkylation method reported here has considerable potential, especially with polycyclic "cage" molecules.

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(5) (a) H. Stetter, M. Schwarz, and A. Hirschorn, *Ber.*, **92**, 1629 (1959); (b) H. Koch and J. Franken, *ibid.*, **96**, 213 (1963).

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(9) (a) R. Kuhn and H. Roth, *Ber.*, **66**, 1274 (1933); W. Kirsten and E. Stenhagen, *Acta Chem. Scand.*, **6**, 682 (1952). (b) Z. Majerski, A. P. Wolf, and P. von R. Schleyer, *J. Label. Compounds*, **5**, 168 (1970); S. Liggero, Z. Majerski, P. von R. Schleyer, A. P. Wolf, and H. Wynberg, *ibid.*, in press.

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(11) Z. Dolejšek, S. Hála, V. Hanuš, and S. Landa, *Collect. Czech. Chem. Commun.*, **31**, 435 (1966).

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(15) H. Stetter and P. Goebel, *Ber.*, **96**, 550 (1963).

(16) Prepared by refluxing diamantane with bromine (V. Z. Williams, Jr., A.B. Thesis, Princeton University, 1965); see ref 17.

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TABLE I
PRODUCTS OF THE COUPLING REACTION OF 1-BROMOADAMANTANES WITH GRIGNARD REAGENTS

Starting material	Grignard reagent, M (ethyl ether soln)	Molar ratio, RMgX/I	Coupling product, yield	Yield of adamantane[h]
Ia	CH_3MgBr, 3	3.2	IIa, 83%[a]	
Ia	CH_3MgI, 1.5	1.5	IIa, 70%[b]	
Ib	CH_3MgBr, 3	3.7	IIb, 92%[c]	
Ia	C_2H_5MgBr, 2	7.2	IIc, 39%[d]	36%[g]
Ia	*tert*-C_4H_9MgBr, 2	5.4	IId, 0%[e]	84%
Ia	$C_6H_5CH_2MgBr$, 2	2.0	IIe, 38%[f]	48%[g]
III[k]	CH_3MgBr, 3	3.5	IV, 87%[i]	
V[l]	CH_3MgBr, 3	3.5	VI, 90%[j]	

[a] Mp 102–103° (lit.[5a] mp 103°). [b] Mp 101–103°. 1-Iodoadamantane was formed in *ca.* 10% yield, mp 74–76° (lit.[12] mp 75.3–76.4°). [c] Bp 82° (13 mm) [lit.[5b] bp 88–89.5° (19 mm)]. [d] Separated by glc; nmr spectrum identical with literature.[3] [e] For a method of preparation of IId, see ref 13. [f] Mp 42–44° (lit.[14] mp 43–44°). [g] Yields by glc. [h] Reduction product; see text. [i] Mp 109–111°. [j] Mp 215–218°. See ref 8. [k] Reference 15. [l] Reference 16.

Experimental Section

General Procedure.—A high pressure aerosol glass bottle (Fischer and Porter Co.) was charged with 10 mm of the bromoadamantane (Ia or Ib[18]) and the quantities of the Grignard reagents are given in Table I. (It is important to use concentrated reagents. Lower yields are obtained with lower concentrations.) In the case of CH_3MgBr, commercial (Arapahoe Chemicals) reagent was used; otherwise the Grignard solutions in ethyl ether were prepared in the usual manner. The bottle was flushed with nitrogen and closed tightly. The reaction mixture was stirred magnetically while being heated in an oil bath at 90–100°. After about 10 min of heating, a white precipitate typically was observed; the total heating time was 20–30 min. After cooling, 20 ml of pentane was added and the excess Grignard reagent destroyed by cautious addition of 2% aqueous HCl at 0°. The layers were separated; the aqueous one was extracted with three 10-ml portions of pentane. The combined organic solutions were washed with 20 ml of 10% aqueous K_2CO_3, two 20-ml portions of water, and then dried over Na_2SO_4. After evaporation of the solvent through a Vigreux column, the product was isolated in an appropriate manner: sublimation *in vacuo* (IIa), distillation *in vacuo* (IIb), or preparative gas chromatography (20 ft × 0.25 in. 15% Carbowax 20M at 177°) (IIc and IIe). Table I provides further details. The identity of the products was confirmed by nmr and mass spectroscopy.[11,12]

Summary of Other Experiments. A. Refluxing Solvents.—Reaction of Ia with excess methylmagnesium bromide in refluxing ether solution gave only 13% IIa after 5 hr and 20% after 18 hr. If the ethyl ether was replaced by adding tetrahydrofuran and distilling off the lower boiling solvent, no IIa was observed after 50 min. A similar experiment employing dioxane in place of tetrahydrofuran led to the formation of a precipitate; refluxing this heterogenous mixture (after removal of ethyl ether) gave only 16% IIa in addition to unreacted starting material.

When 1-bromoadamantane (Ia) was refluxed with a 4 molar excess of methyllithium in ethyl ether, 1-methyladamantane (IIa) formed very slowly. The yields follow: after 2 days, 7%; 3 days, 14%; 5 days, 20%. The only other compound detected was starting material.

B. Use of $FeCl_3$ in Attempted Preparations of IId.—These reactions were carried out at *ca.* −65°.[19] Three attempts were made: anhydrous $FeCl_3$ (Fisher Scientific Co.) was dissolved in the ether solution of *tert*-C_4H_9MgBr and then Ia in ether added, $FeCl_3$ was added together with Ia to the Grignard solution, and $FeCl_3$ was added to the solution of Ia in the Grignard reagent. In no case did the nmr spectrum of the product show any significant formation of 1-*tert*-butyladamantane (IId).[13]

1-Methyladamantane-methyl-^{14}C.—1-Methyladamantane-methyl-^{14}C (specific activity 0.34 nCi/mg C) was obtained in 64% yield following the general procedure described above. Grignard reagent, prepared from 5.6 g (32 mmol) of $^{14}CH_3I$ (specific activity 3.80 nCi/mgC) and 730 mg (30 mg-atoms) of magnesium turnings in 20 ml of anhydrous ether, and 1-bromoadamantane (4.3 g, 20 mmol) were stirred at 100° for 30 min, followed by the usual isolation procedure.

The product was subjected to the Kuhn–Roth oxidation following the reported procedure.[9a] The acetic acid (isolated as thallous salt)[10] had a specific activity of 1.83 nCi/mg C. The Schmidt degradation[9b] of the TlOAc gave inactive CO_2 and methylamine which was assayed as *N*-phenyl-*N'*-methylthiourea (specific activity 0.46 nCi/mg C corresponding to 100.5% of the activity in the TlOAc).

1-Methyladamantane-methyl-^{13}C.—1-Methyladamantane-methyl-^{13}C was prepared as described for 1-methyladamantane-methyl-^{14}C using $^{13}CH_3I$ (70% ^{13}C). The (M + 1)/M ratio 151/150 (corresponding to 1-methyladamantane-^{13}C/1-methyladamantane) showed 71% of ^{13}C labeled molecules. The (M + 1)/M ratio 136/135 (corresponding to adamantyl-^{13}C/adamantyl) was found to be essentially the same as that of unlabeled 1-methyladamantane.

1-Benzyladamantane (IIe).—This compound had been prepared in the literature by a different route, but no spectral details were provided.[14] The mass spectrum shows a pattern characteristic of 1-alkyladamantane: the ring signal for the adamantyl cation (*m/e* 135) was the most intense. In addition, a strong molecular ion peak (*m/e* 226) and a strong peak from the benzyl group (*m/e* 91) were observed. Nmr spectrum in $CDCl_3$ showed C_6H_5 (m, δ 7.4–6.9, 5 H), $C_6H_5CH_2$ (s, 2.39, 2 H), adamantyl bridgehead protons (broad s, 1.9 3 H), adamantyl methylene protons (m, 1.4–1.7, 12 H).

3-Methylhomoadamantane (IV).—This compound was prepared from 3-bromohomoadamantane (III)[15] in 87% yield following the general procedure (above): mp 109–111°; nmr (15% in $CDCl_3$) CH_3 (s, δ 0.90, 3 H), the remainder of homoadamantane spectrum[20] appearing in the range δ 1.3–2.2 17 H; mass spectrum *m/e* 149 (base peak, $M^+ - CH_3$), 164 (M^+).

Anal. Calcd for $C_{21}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.46; H, 12.02.

1-Methyldiamantane (VI).[8]—1-Methyldiamantane[8] was prepared in 90% yield from 1-bromodiamantane[16] following the general procedure: mp 215–218°; nmr (~15% in $CDCl_3$) CH_3 (s, δ 0.93, 3 H), the remainder of the spectrum, δ 1.25–2.35, 19 H; mass spectrum *m/e* 187 (base peak, $M^+ - 15$), 202 (M^+).

Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96 Found: C, 89.32; H, 11.08.

Registry No.—IIe, 7131-11-5; IV, 26460-75-3; VI, 26460-76-4.

Acknowledgment.—This research was supported by grants from the National Institutes of Health (AI-07766) and the Petroleum Research Fund, administered by the American Chemical Society. The experiments with labeled 1-methyladamantane were carried out at Brookhaven National Laboratory in association with Dr. A. P. Wolf.

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(19) At higher temperatures $FeCl_3$ catalyzes a disproportionation of the adamantyl halides: F. N. Stepanov, G. I. Danilenko, V. M. Buzash, and K. Daisi, *Zh. Org. Khim.*, **5**, 2187 (1969); *Chem. Abstr.*, **72**, 66461u (1970).

(20) S. H. Liggero, P. von R. Schleyer, and K. C. Ramey, *Spectrosc. Lett.*, **2**, 197 (1969).

Anomalous Nitration in the 2,1,3-Benzothiadiazole Series

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Received April 22, 1970

Although examples of the replacement of nuclear bromine by a nitro group during nitration of aromatic bromo compounds have been known for several

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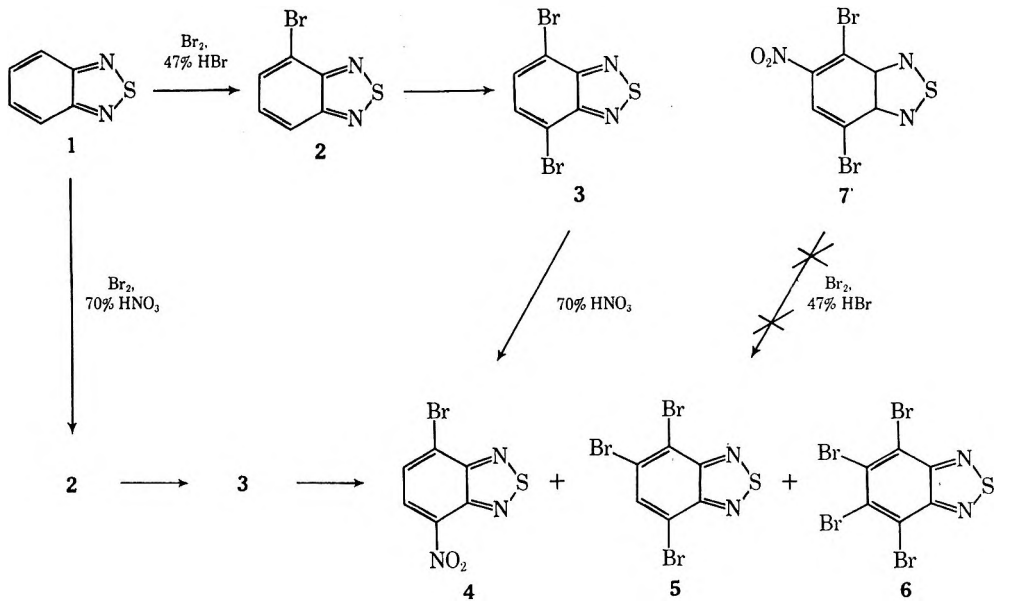
SCHEME I



years,[1-3] the mechanism of the displacement and the fate of the replaced bromine have not received much attention despite the synthetic usefulness of several of these reactions. Experimental data have now been obtained which give a clue to a probable reaction mechanism and which establish, in part, the fate of the displaced aromatic bromine.

We wish to report the direct observation of the formation and disappearance of 4,7-dibromo-2,1,3-benzothiadiazole (**3**) in the course of the bromination of 2,1,3-benzothiadiazole (**1**) in refluxing 70% nitric acid. In following the reaction by gas–liquid chromatography (glc) and thin layer chromatography (tlc), the formation of **3** *via* the monobromo analog **2** was shown to be very rapid (0.5–1 hr) until all of **1** is converted. Subsequently, **3** reacted more slowly (3–6 hr) to give a mixture of 4-bromo-7-nitro-2,1,3-benzothiadiazole **4**, 4,5,7-tribromo-2,1,3-benzothiadiazole (**5**), and 4,5,6,7-tetrabromo-2,1,3-benzothiadiozole (**6**) in the approximate molar proportion of 8:2:0.1 in 50–60% total yield.[4] Furthermore, it was demonstrated independently that treatment of **3** with refluxing 70% nitric acid over a period of 3–6 hr in the absence of bromine produces the same three compounds, **4**, **5**, and **6** in approximately the same ratio and yield. Fractional crystallization of the reaction mixture from acetone afforded **4**. Compounds **5** and **6** were separated by preparative tlc.[6] Compounds **4**[7a] and **5**[7b] were indistinguishable from authentic samples on the basis of comparisons of mixture melting points and thin layer and gas chromatograms.

It is important to note the failure to detect in the reaction mixture 4,7-dibromo-5-nitro-2,1,3-benzothiadiazole (**7**), which would result from electrophilic attack of nitrating species on the 5 position of **3**. Also striking is the observation that, when an authentic sample of **7** was treated with excess bromine in refluxing 70% nitric acid over a period of 5 hr, it was recovered unchanged.

The failure to observe **4** very early in the reaction of **1** with bromine in refluxing 73% nitric acid suggests that either the cationic bromine species is a much stronger acid and therefore a more powerful reagent in electrophilic substitution reactions than is the nitrating species or that by mass action the concentration of cationic bromine species is far in excess. The nitronium ion (NO_2^+) concentration in 100% nitric acid is about 4% and decreases with increasing water content.[8] It seems probable, therefore, that the nitrosonium ion (NO^+) which is a much less powerful reagent in electrophilic substitution reactions than the nitronium ion may be the substituting species, and one can see why cationic bromine species can compete with this weaker electrophile or any other than the nitronium ion. The resulting nitroso compound would be, in turn, very rapidly oxidized by nitric acid to the corresponding nitro compound **4**.

The formation of **5** can be characterized as nucleophilic displacement by the heterocycle **3** of the cationic bromine species formed in the above displacement step; the bromine atom, in its displacement by the nitrating species, may not assume a cationic charge but rather be accepted by **3** acting as a nucleophile to form **5**, a process which might be called an Se2 mechanism (Scheme I).

Experimental Section

Reaction of 4,7-Dibromo-2,1,3-benzothiadiazole (3) with Refluxing 70% Nitric Acid.—A mixture of 29.4 g (0.1 mol) of **3** in 150 ml of 70% nitric acid was heated under reflux with stirring. After 5 hr, the resulting clear solution was poured into 500 ml of ice water, and the product was filtered, washed well with water, and dried to give 14.2 g (50.8%) of light yellow crystalline solid. Gas–liquid chromatography indicated a mixture of two (major)

(1) D. V. Nightingale, *Chem. Rev.*, **40**, 117 (1947).
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(3) I. T. Barnish and M. S. Gibson, *J. Chem. Soc., C*, 8 (1968).
(4) When bromine was added dropwise at 126–130° to a mixture of **1** in 47% (constant boiling) hydrobromic acid, 4-bromo-2,1,3-benzothiadiazole (**2**) was formed exclusively at first. Toward the halfway point of the addition, glc indicated that the 4,7-dibromo analog, **3**, began to form. After completion of the bromination, **3** was isolated in almost quantitative yield.[5]
(5) K. Pilgram, M. Zupan, and R. D. Skiles, *J. Heterocycl. Chem.*, **7**, 629 (1970).
(6) Preparative tlc plates silica gel F_{254}, E. Merck A.G., Darmstadt, Germany. Solvent mixture (by volume): tetrahydrofuran (2), ethyl acetate (8), and *n*-hexane (40).
(7) (a) V. G. Pesin, A. M. Khaletskii, and V. A. Sergeev, *Gen. Chem. USSR*, **33** (2), 1714 (1963); (b) *ibid.*, **33** (2), 935 (1963).
(8) P. B. D. De la Mare and J. H. Ridd, "Aromatic Substitution–Nitration and Halogenation," Academic Press, New York, N. Y., 1959, pp 59–60. According to the referee, it is doubtful that any nitronium ion is present in 70% nitric acid.

components in the approximate ratio of 4:1 in addition to traces of **3** (starting material) and a third (minor) component. Fractional crystallization of the crude solid from acetone afforded 4.1 g of **4**: mp 214–218° (lit.[6a] mp 218–220°); ir spectrum (KBr pellet) intense bands at 1525 and 1350 cm^{-1} (NO_2).

Anal. Calcd for $C_6H_2BrN_3O_2S$: Br, 30.8; S, 12.3. Found: Br, 30.7; S, 12.6.

The combined mother liquors were concentrated to dryness. Fractional crystallization of the residual solid from ethanol gave 0.7 g of **5**, mp 155–157° (lit.[6b] mp 152–154°).

Anal. Calcd for $C_6HBr_3N_2S$: Br, 64.3; N, 7.5. Found: Br, 64.0; N, 7.7.

The combined mother liquors were concentrated to dryness. The residual solid (8.9 g) was resolved into its components by preparative tlc.[6] The first fraction, 120 mg (0.5%), consisted of **6**, a white crystalline solid melting at 144–145° (from methanol).

Anal. Calcd for $C_6Br_4N_2S$: C, 16.0; H, 0.0; Br, 70.8; N, 6.2; S, 7.1. Found: C, 16.0; H, 0.2; Br, 71.0; N, 6.2; S, 7.4.

The second fraction consisted of **3** (starting material) and was discarded. Fraction no. 3 consisted of 1.2 g of **5**; fraction 4 consisted of 5.1 g of **4**. The total yield of **4** was 35.3%; the total yield of **5** was 7.6%.

Reaction of 2,1,3-Benzothiadiazole (1) with Bromine in Refluxing 70% Nitric Acid.—A mixture of 27.2 g (0.2 mol) of 1 in 300 ml of 70% nitric acid was heated under reflux with stirring while 144 g (0.9 mol) of bromine was added within 30 min. After about 1 hr, a white crystalline solid precipitated from the refluxing solution; it was shown to be 4,7-dibromo-2,1,3-benzothiadiazole (**3**) (by glc), mp 188–189° (lit.[9] 184–185°). However, the precipitate redissolved gradually. After 6 hr, glc indicated that starting material 1 and intermediate **3** had disappeared. The cooled reaction mixture was poured into water and the product was filtered, washed well with water, and dried to yield 28.8 g (51.5%) of a light yellow crystalline solid consisting of a mixture of **4**, **5**, and **6** in the ratio of 84:14:2 (by glc).

Registry No.—**3**, 15155-41-6; **4**, 26460-78-6; **5**, 26460-79-7; **6**, 26460-80-0.

(9) V. G. Pesin, A. M. Khaletskii, and C. Chzhi-Chzhun, *J. Gen. Chem. (USSR)*, **27**, 1648 (1957).

Photolytic Studies on 4-Hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl, a Stable Nitroxide Free Radical

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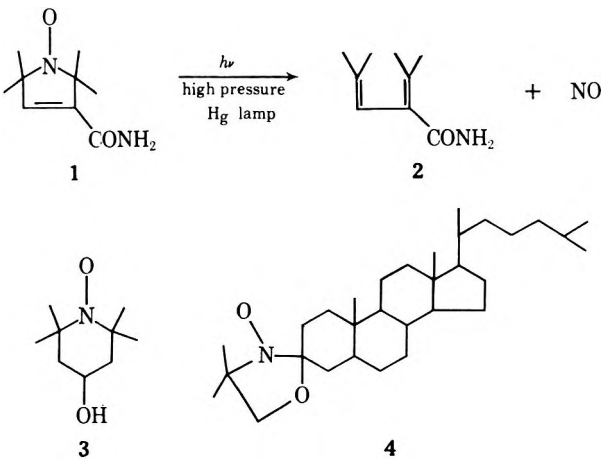
Received January 2, 1970

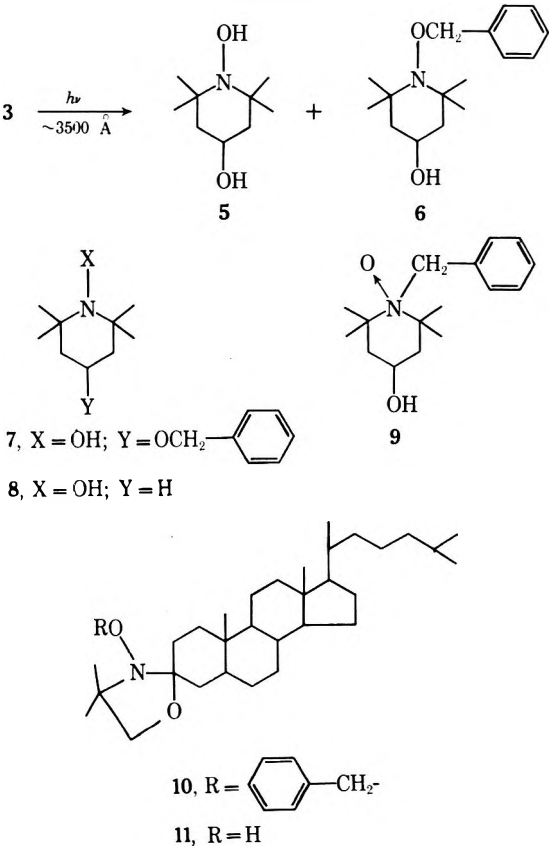
Recently,[3] we reported on the photolysis of the stable nitroxide, 3-carbamoyl-2,2,5,5-tetramethylpyrroline-1-oxyl (**1**), a process which afforded diene **2** in high yield. Under the same conditions the alcohol nitroxide **3** and the steroid nitroxide **4** underwent reaction at a much slower rate. We have now examined the photolysis of nitroxides **3** and **4** under somewhat different conditions. The products are in marked contrast to those derived from nitroxide **1** and are reported herewith.

Irradiation of a vacuum-degassed toluene solution



which was ~0.02 *M* in 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (**3**)[4] for 96 hr in sealed Pyrex tubes with ~3500 Å light resulted in almost complete (>98%) disappearance of starting material as estimated by esr spectroscopy. Removal of the solvent, followed by trituration of the resulting solid with benzene afforded a crystalline residue of 1,4-dihydroxy-2,2,6,6-tetramethylpiperidine (**5**)[5] (Chart I) (~50% crude yield).

CHART I



A recrystallized sample was shown to be identical with authentic **5**[5] by mixture melting point and spectral comparisons. Chromatography of the benzene-soluble

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(1) NDEA Graduate Fellow, 1966–1969; PRF Graduate Fellow, 1969–1970.

(2) Undergraduate Research Participant, 1966–1968.

(3) J. F. W. Keana and F. Baitis, *Tetrahedron Lett.*, 365 (1968).

(4) E. G. Rozantsev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **12**, 2187 (1964); *Chem. Abstr.*, **62**, 7721e (1965).

(5) E. G. Rosantsev and V. A. Golubev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **8**, 891 (1966); *Chem. Abstr.*, **65**, 10559e (1966).

fraction afforded 1-benzyloxy-4-hydroxy-2,2,6,6-tetramethylpiperidine (**6**) (50% crude yield), identified on the basis of analytical and spectral data (see Experimental Section) and the following observations.

That the substance was not 1-hydroxy-4-benzyloxy-2,2,6,6-tetramethylpiperidine (**7**) was shown by the failure of **6** to undergo oxidation to the corresponding nitroxide free radical upon treatment with air or *m*-chloroperoxybenzoic acid, oxidizing agents which readily oxidize, *inter alia*, *N*-hydroxy derivative **5** and 1-hydroxy-2,2,6,6-tetramethylpiperidine (**8**) to the corresponding nitroxides. The unlikely alternative *N*-oxide structure **9** for substance **6** was ruled out when it was demonstrated that substance **6** was thermally stable in dimethylacetamide at 170°. Compound **9** would have been expected to suffer a Meisenheimer rearrangement to structure **6** under these conditions.[6]

In a similar series of experiments a pale yellow toluene solution of steroid nitroxide **4**[7] was irradiated for 144 hr, affording a near colorless solution containing almost no (<2%) starting nitroxide (by esr). Since *N*-hydroxy derivative **11** appeared to suffer hydrolysis upon chromatography, a stream of dry oxygen was bubbled through the photolyzed solution prior to analysis in order to oxidize (see above) **11** back to stable nitroxide **4**. Chromatography at this point led to *N*-benzyloxy derivative **10** in 39% yield, identified on the basis of analytical and spectral data, and nitroxide **4** in 57% yield.

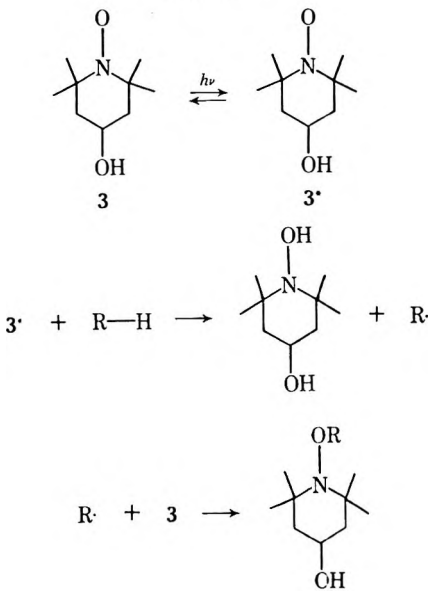
The nature of the photo products derived from nitroxides **3** and **4** suggests that the excited nitroxide is an effective hydrogen atom abstractor. Table I summarizes the results of a study of the effect of solvent on the rate of disappearance of nitroxide **3** upon irradiation of a $\sim 10^{-4}$ *M* solution while inside the cavity of an esr spectrometer. The light was from a PEK high pressure mercury lamp, filtered through Pyrex. The photolysis proceeded most rapidly in cumene and became progressively slower as the solvent was changed from cumene to toluene to cyclohexane to benzene, in qualitative accord with the respective hydrogen atom donor abilities of those solvents.[8] When the light was filtered so as to approximate the output of the Rayonet 3500-Å range lamps employed in the preparative experiments, the rate of disappearance of esr signal intensity in the solvents other than cumene proved too slow for convenient measurement.

TABLE I
RELATIVE RATES OF PHOTOLYSIS OF **3** IN VARIOUS SOLVENTS

Solvent	Relative rate
Cumene	420
Toluene	1.1
Cyclohexane	1.0
Benzene	0.52

A reaction sequence consistent with the above data and analogous to that proposed by Pitts[9] for the photoreduction of 2,2-diphenyl-1-picrylhydrazyl (DPPH) in hydrocarbons is shown in Scheme I. While no 1,2-diphenylethane was detected when irradiations were carried out in toluene, small amounts (~5%, based on starting **3**) of biphenyl could be isolated from the photolysis mixture by chromatography when benzene was the solvent, suggesting that excited nitroxide **3** is capable of abstracting a hydrogen atom from benzene to produce a phenyl radical.[10] Attack of phenyl radical on another benzene molecule followed by a disproportionation or oxidation step would afford biphenyl.[11] Benzyl radical, on the other hand, would not be expected to attack the aromatic ring of another toluene molecule and thus benzyl radical survives long enough to be scavenged by a molecule of nitroxide **3** to produce **6**.

SCHEME I



The ability of an excited nitroxide grouping to abstract a hydrogen atom could provide a novel method of functionalization at a site remote from the grouping in a large molecule, a possibility which we are presently investigating.

Experimental Section

Infrared spectra were recorded with a Beckman IR-5 spectrometer. The small letters in parentheses found after infrared maxima refer to the relative intensities of the peaks. Weak, moderate, and strong are referred to as w, m, and s, respectively.

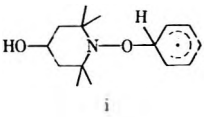
(6) See, *inter alia*, L. D. Quin, and L. A. Shelburne, *J. Org. Chem.*, **30**, 3135 (1965).

(7) J. F. W. Keana, S. B. Keana, and D. Beetham, *J. Amer. Chem. Soc.*, **89**, 3055 (1967).

(8) W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, p 170.

(9) J. N. Pitts, Jr., E. A. Schuck, and J. K. S. Wan, *J. Amer. Chem. Soc.*, **86**, 296 (1964).

(10) Alternatively, the process leading to biphenyl might be initiated by attack of an excited nitroxide on a benzene molecule to produce species i,



i

dimerization of which, followed by loss of two molecules of **5**, would afford biphenyl.

(11) D. F. DeTar, *J. Amer. Chem. Soc.*, **89**, 4058 (1967).

Nmr spectra were determined on a Varian Associates Model A-60 high-resolution spectrometer. Chemical shifts are recorded in parts per million (δ) downfield from internal TMS Elemental analyses were performed by either Alfred Berhardt Laboratories, Mullheim, Germany, or Micro-Tech Laboratories, Skokie, Ill. Preparative scale irradiations were conducted in a RPR-100 Rayonet photochemical apparatus employing the 3500-Å range lamps and fitted with a merry-go-round attachment.

Preparative Irradiation of 4-Hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (3).—Three Pyrex tubes were each charged with 40 mg of nitroxide **3**[4] and 10 ml of toluene. The solutions were vacuum-degassed three times, sealed in the tubes, and then irradiated for 96 hr at 30–40°. Removal of the toluene under reduced pressure afforded a residue which was triturated with benzene. The crystalline solid which remained, 69 mg (~50% crude yield), mp 144–150°, was recrystallized from hexane–ether to give 40 mg (30% yield) of pure diol **5**, mp 156–158° (lit.[5] mp 158°), no melting point depression upon admixture with authentic **5**.[5]

Immediate chromatography of the benzene-soluble fraction over basic alumina and elution with pentane afforded 109 mg (~50% crude yield) of a colorless oil which crystallized upon scratching. Recrystallization from pentane afforded 16 mg (8% yield) of 1-benzyloxy-4-hydroxy-2,2,6,6-tetramethylpiperidine (**6**) as white needles: mp 87–87.5°; nmr (CCl_4) 1.21 (s, 6, pair of methyl groups), 1.28 (s, 6, pair of methyl groups), 1.7 (m, 4, ring protons), 3.9 (m, 1, H-4), 4.78 (s, 2, benzylic protons), 7.24 (s, 5, aromatic protons); ir (CCl_4) 3350 (m), 3000 (s), 1450 (m), 1380 (s), 1250 (s), 1190 (m), 1045 (s), 1025 cm^{-1} (s).

Anal. Calcd for $C_{16}H_{25}NO_2$: C, 73.00; H, 9.51; N, 5.32. Found: C, 72.78; H, 9.57; N, 5.40.

Irradiation of Steroid Nitroxide 4.—Six Pyrex tubes were each charged with 40 mg of nitroxide **4**[7] and 10 ml of toluene. The solutions were vacuum-degassed three times, sealed in the tubes, and then irradiated for 144 hr at 30–40°. It could be estimated by esr spectroscopy that less than 2% of starting nitroxide **4** remained after the photolysis. Dried oxygen was then bubbled through the near colorless solutions for 24 hr. Removal of the toluene under reduced pressure afforded a pale yellow solid which was chromatographed over silica gel. Elution with 5:1 hexane–benzene afforded 113 mg (39% yield) of a white solid, mp 55–62°. Recrystallization from ether–methanol gave *N*-benzyloxy derivative **10** as white needles: mp 74–76°; nmr (CCl_4) 0.6–2.1 (m, 52), 3.43 (s, 2, oxazolidine ring protons), 4.65 (s, 2, benzylic protons), 7.28 (s, 5, aromatic protons).

Anal. Calcd for $C_{38}H_{61}NO_2$: C, 80.99; H, 10.83; N, 2.48. Found: C, 80.94; H, 10.80; N, 2.79.

Elution with benzene afforded 133 mg (57% yield) of a pale yellow solid which was recrystallized from ether–methanol and shown to be identical with starting **4** by ir and melting point comparisons.

Determination of Relative Rates of Photolysis of 3 in Various Solvents.—Rates of photolysis were determined on a Varian 4502 esr spectrometer equipped with a 50% transmittance cavity. The light source was a 100-W PEK high-pressure mercury lamp mounted on an optical bench about 50 cm from the cavity. The light was focused with quartz optics and passed through a Pyrex filter. Reagent grade cumene, toluene, cyclohexane, and benzene were carefully purified prior to use. Irradiations were conducted in stoppered quartz tubes and nitrogen was passed through the solutions immediately prior to irradiation. The photolysis exhibited cleanly first-order kinetics in each instance.

Registry No.—**3**, 2226-96-2; **4**, 78353-76-9; **6**, 26460-91-3; **10**, 26460-92-4.

Acknowledgment.—The authors wish to express their thanks to the National Science Foundation (GP10736), the National Institutes of Health (1-RO3 MH-17209-01), and the donors of the Petroleum Research Fund, administered by the American Chemical Society (Grant GF674), for generous financial support. Thanks are also due Professors O. H. Griffith, W. T. Simpson, and W. L. Peticolas for use of some of their equipment.

α-Ketols from Hydride Reduction of a Steroidal Enamino Ketone and the Corresponding α Diketone[1]

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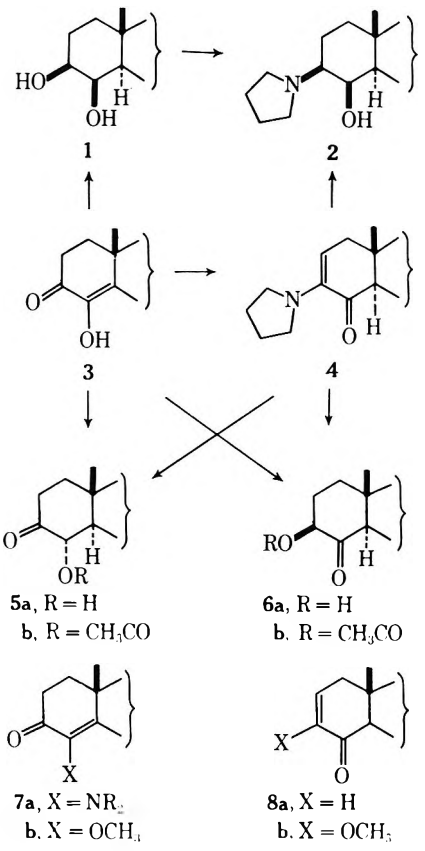
Received June 4, 1970

We describe here the reduction of the steroidal α diketone **3** and its derived enamine **4** with sodium borohydride, lithium aluminum hydride, and other reducing systems. Our interest in the reduction of the enamine **4** arose from the need to generate 3-amino-4-hydroxy steroids, both as precursors of steroidal heterocycles and as synthetic intermediates for naturally occurring steroid alkaloids. The pyrrolidyl enamine **4** seemed a convenient model compound for these studies, and the initial reduction results dictated additional experiments with the α diketone[2] **3**. The ultraviolet (λ_{max}^{MeOH} 277 nm, ϵ 12,500) and infrared ($\nu_{max}^{CHCl_3}$ 3484, 1672, and 1645 cm^{-1}) spectra of **3** testify to the enolized system and the nmr spectrum (no vinyl hydrogen) rules out the alternative 3-hydroxy-Δ^2-4-oxo system.[3] Reaction of **3** with pyrrolidine[4] gave, in high yield, the enamine–ketone **4**



* To whom correspondence should be addressed.

(1) This work was supported, in part, by U. S. Public Health Service Grant HE-08913 and GM 16492.

(2) A. Butenandt, G. Schramm, A. Wolff, and H. Kudszus, *Chem. Ber.*, **69**, 2779 (1936).

(3) *Cf.* D. P. Strike, D. Herbst, and H. Smith, *J. Med. Chem.*, **10**, 446 (1967).

(4) *Cf.* B. Camerino, D. Cattepan, U. Valcavi, and B. Patelli, *Gazz. Chim. Ital.*, **89**, 674 (1959).

which showed λ_{max}^{MeOH} 308 nm (ϵ 8700) and infrared absorptions at 1692 and 1626 cm^{-1}. A single vinyl hydrogen appeared at δ 5.4 in the nmr spectrum, supporting the 3-pyrrolidyl-Δ^2-4-oxo formulation for **4**. The C-19 hydrogens appeared at δ 0.85 supporting[5] the assignment of 5α configuration at the AB ring junction.

The ultraviolet spectrum of **4** (λ_{max}^{MeOH} 308 nm, ϵ 8700) deserves brief comment. The bathochromic effect of the α-dialkylamino group in the conjugated ketone **8a** (λ_{max} 226 nm) is +82 nm, while the effect of an α-methoxyl group[6] in the same system (**8b**) is +37 nm. In contrast, the bathochromic shifts caused by α-dialkylamino[7] and methoxyl[6] groups in a Δ^4-3 ketone (**7a** and **7b**, respectively) are +3 to +6 nm and +12 nm, respectively.

The small bathochromic effect of an α-methoxyl group in the Δ^4-3-ketone system relative to its effect in the Δ^2-4-ketone grouping has already been commented on.[6] Thus, Reusch suggested that for maximum bathochromic effect the bonding plane of the methoxyl oxygen should be parallel to the enone chromophore and pointed out that this condition is met in those α-methoxylenones (as **8**) which lack a β-alkyl substituent cis to the methoxyl group. He further noted that this condition *cannot* be met in the 4-methoxyl-Δ^4-3-ketone system, due to steric crowding of the methoxyl group by the C-6 methylene group and the carbonyl oxygen, which substantially prevents coplanarity.

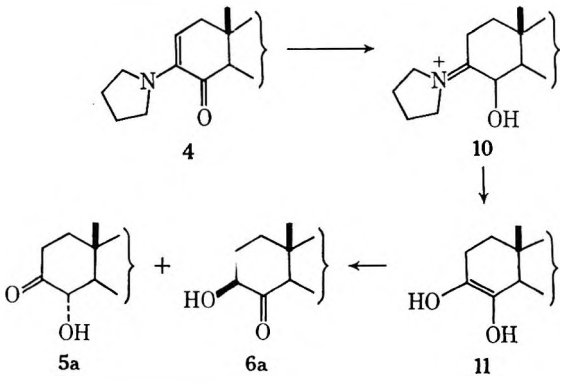
We note here that the very small bathochromic shifts of α-dialkylamino substituents (+3 to +6 nm) in the Δ^4-3-ketone grouping are consistent with even greater steric crowding of the large dialkylamino group by the C-6 methylene group, preventing efficient overlap of the nitrogen p electrons with the π system of the enone. On the other hand, the large (+82 nm) bathochromic shift shown by the α-dialkylamino substituent in the Δ^2-4-ketone system can presumably be taken as a maximal effect, as here the dialkylamino substituent can readily assume an unhindered conformation, permitting efficient overlap of the nitrogen p electrons with the enone π electrons.

We now turn to reduction experiments with the enamine **4** and the parent diosphenol **3**. Reductions of other steroidal enamines to amines using sodium borohydride[8] have been described, as have reductions of enamine salts with lithium aluminum hydride.[9] Repeated attempts to reduce the pyrrolidyl enamino ketone **4** with sodium borohydride under a variety of conditions proved disappointing. By using a large excess of sodium borohydride at room temperature, modest yields (*ca.* 16%) of the 3β-pyrrolidino-4β-ol, **2**, could be obtained. On some occasions, inexplicably, no reduction occurred under conditions which appeared to be identical with those in successful reductions. The gross constitution of **2** followed from elemental analysis, and the stereochemistry at C-3 and C-4 was assigned on the basis of nmr and infrared data. Thus, the nmr spectrum showed, in addition to the pyrrolidine–CH_2–N– resonances, a singlet at δ 1.04 (C-19 CH_3) and a multiplet centered on δ 3.75 ($W_{1/2}$ = 5.5 Hz, C-4 H). The C-19 methyl resonance at δ 1.04 is consistent with A/B trans stereochemistry and the presence of a 4β-hydroxyl group, while the width at half height (5.5 Hz) of the C-4 hydrogen testifies to its equatorial nature and hence to the axial (4β) configuration for the hydroxyl on the same carbon.

One must, then, be dealing with either a 3α,4β- or 3β,4β-disubstituted compound. Conclusive support for the 3β-pyrrolidyl-4β-hydroxy structure, **2**, came from infrared studies. At concentrations between 10^{-1} and 10^{-3} *M*, only associated hydroxyl absorption at 3462 cm^{-1} could be observed. Using 4β-hydroxycholestane as reference (ν_{OH} = 3631 cm^{-1}), the $\Delta\nu$ value in this system is 169 cm^{-1}, in good accord with literature data[10] for –OH --- N– bonding. For example, the $\Delta\nu$ for intramolecular hydrogen bonding in diethylaminoethanol is 170 cm^{-1}. Such bonding is clearly favored in the 3β-pyrrolidino-4β-hydroxy system (equatorial–axial) but ruled out in the alternative 3α,4β (diaxial) system.

Attempts to oxidize **2** to the amino ketone using chromium trioxide–acetic acid–hydrochloric acid gave material showing saturated carbonyl absorption in the infrared, but pure crystalline ketone could not be obtained.

In contrast to the sodium borohydride reduction of the enamino ketone **4**, reduction with lithium aluminum hydride in ether gave, after column and thick layer chromatography on silica gel, the two isomeric α-ketols, **5a** and **6a**. The structures of these hitherto undescribed and previously inaccessible ketols followed from the analytical and spectroscopic data, and from conversion of **5a** and **6a**, respectively, to the known[11,12] α-ketol acetates, **5b** and **6b**, with pyridine–acetic anhydride. A possible explanation for the formation of the 5α-cholestane-3,4-ketols from enamine **4** is shown below.



1,2 (or 1,4) addition of hydride to **4** might be expected to generate the iminium salt **10** on work-up. Decomposition of this salt could give rise to the α-ketols **5a** and **6a**, *via* protonation of the intermediate enediol **11**.

Attempts to reduce the enamino ketone **4** with other hydrides, *e.g.*, lithium aluminum tri-*tert*-butoxyhydride or trimethylamine borane were unsuccessful,

(5) Calculations from the Zürcher tables [R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963)], neglecting the effect of the nitrogen substituent at C-3, give δ values for the C-19 hydrogens as follows: 0.74 for a 5α-Δ^2-4-oxocholestane *vs.* 1.11 for the 5β-Δ^2-4-oxocholestane. The 5α-3-alkoxy-Δ^2-4-oxo compound[6] **8b** shows a value of 0.83 for the C-19 methyl hydrogens.

(6) W. Reusch and R. LeMahieu, *J. Amer. Chem. Soc.*, **85**, 1669 (1963).

(7) K. Irmscher, *Tetrahedron Lett.*, 2707 (1964).

(8) *Cf.* J. A. Marshall and W. S. Johnson, *J. Org. Chem.*, **28**, 421 (1963).

(9) *Cf.* G. Opitz and A. Griesinger, *Justus Liebigs Ann. Chem.*, **665**, 101 (1963).

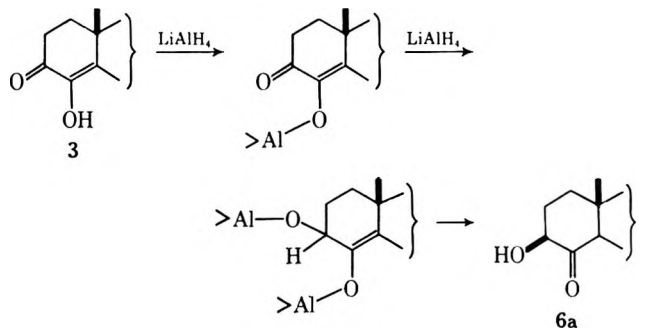
(10) See L. P. Kuhn, R. A. Wires, W. Ruoff, and H. Kwart, *J. Amer. Chem. Soc.*, **91**, 4790 (1969), for tabulation of amino alcohol frequency shifts and for prior references to hydrogen bonding in amino alcohols.

(11) K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).

(12) S. Lieberman and D. K. Fukushima, *J. Amer. Chem. Soc.*, **72**, 5211 (1950).

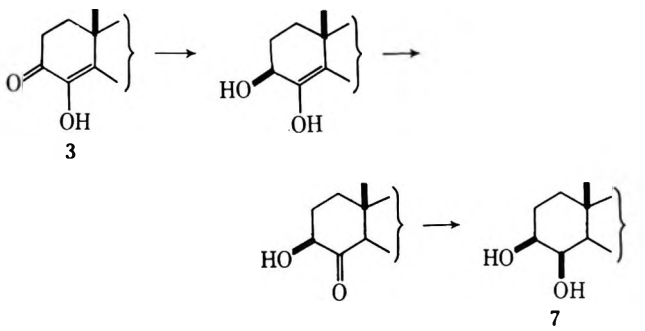
while the use of formic acid or Raney nickel gave unidentified polar products.

Work on another project involving the diosphenol **3** led us to study the reduction of the compound with lithium aluminum hydride and sodium borohydride and compare the results with those noted above for the enamine **4**. In the event reduction of compound **3** with lithium aluminum hydride in ether gave predominantly the 4-oxo-3β-ol, **6a**, this reduction possibly involving the path shown below.[13]



Thus, reaction of lithium aluminum hydride with the enol to give aluminum enolate may be followed by reduction at C-3 with lithium aluminum hydride, and the resulting intermediate could suffer cleavage of the O–Al bonds during work-up to give the observed product.

In contrast, sodium borohydride reduction of **3** in methanol gave, predominantly, the known 3β,4β-diol, **1**, characterized further as the 3,4-acetonide. This result is consistent with reduction of **3** first at C-3 to give 3β-ol, with subsequent ketonization of the resulting Δ^4-3β,4-diol in the protic medium and then reduction of the 3β-hydroxy-4 ketone so formed.[14]



The 3β,4β-diol **1** showed at high dilution, in CCl_4, OH stretching frequencies at 3587 (bonded OH) and 3631 cm^{-1} (free OH). These data giving a $\Delta\nu$ value of 44 cm^{-1} ($\Delta\nu$ = frequency of free OH − frequency of hydrogen-bonded OH) compare well with the value reported by Kuhn[15] for cyclohexane-1,2-diol ($\Delta\nu$ = 39 cm^{-1}).

Experimental Section[16]

3-*N*-Pyrrolidinocholest-2-en-4-one (4).—To a boiling solution of **3** (1.0 g) in methanol (100 ml) was added pyrrolidine (2.0 ml). The solution was heated for 30 min under reflux and then concentrated *in vacuo* to about 75 ml. The resulting suspension was filtered giving 873 mg of the enamine **4**. Two recrystallizations from methanol gave the analytical sample: mp 138–141°; $[\alpha]_D$ +80°; λ_{max} 308 nm (ϵ 8700); $\nu_{max}^{CHCl_3}$ 1692, 1626 cm^{-1}; nmr ($CDCl_3$) 0.66 (18-methyl), 1.09 (19-methyl), and 5.40 (q, 1, vinyl H).

Anal. Calcd for $C_{31}H_{51}NO$: C, 82.06; H, 11.33; N, 3.09. Found: C, 82.31; H, 11.33; N, 3.30.

3β-*N*-Pyrrolidino-5α-cholestan-4β-ol (2).—To the enamine **4** (615 mg) in methanol (250 ml) was added sodium borohydride (250 mg). After the mixture was stirred at room temperature for 15 min a further 250-mg portion of sodium borohydride was added, followed at 15-min intervals by two more 250-mg portions. After it was stirred for 18 hr more (total reaction time 19 hr), the solution was diluted with water and extracted with ether. The ethereal extract was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was chromatographed on silica gel (30 g), when elution with chloroform gave the diosphenol **3** (238 mg). Elution with chloroform–methanol–ammonia (132:12:0.9) mixture gave crude amino alcohol (**2**, 100 mg) which was recrystallized from methanol to give analytically pure **2**: mp 177–179°; $[\alpha]_D$ +41°; $\nu_{max}^{CCl_4}$ 3462 cm^{-1}; nmr ($CDCl_3$) δ 0.65 (s, 3, C-18 methyl), 1.04 (s, 3, C-19 methyl), 3.75 (m, 1, C-4 CHOH, $W_{1/2}$ = 5.5 Hz).

Anal. Calcd for $C_{31}H_{55}NO$: C, 81.33; H, 12.11; N, 3.06. Found: C, 81.03; H, 12.05; N, 3.42.

5α-Cholestane-3β,4β-diol (1) by Reduction of 4-Hydroxycholest-4-en-3-one (3) with Sodium Borohydride.—To a stirred solution of the diosphenol **3** (3.0 g) in methanol (800 ml) was added sodium borohydride (3.0 g) portionwise over 5 min. Stirring was continued at room temperature for 30 min, and the reaction mixture was neutralized with acid, concentrated *in vacuo* to about 100 ml, and diluted with water. The mixture was extracted with ether and the ethereal extract washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. Crystallization of the product from benzene gave the 3β,4β-diol, **1** (952 mg): mp 201–204°; $[\alpha]_D$ +18° (lit. mp 202–203°; $[\alpha]_D$ +19°); nmr ($CDCl_3$ δ 0.66 (s, 3, C-18 methyl), 1.03 (s, 3, C-19 methyl), 3.75 (m, 1, C-4 CHOH, $W_{1/2}$ = 6.5 Hz).

The diol (**1**, 73 mg) was converted to the 3,4-acetonide derivative by treatment with perchloric acid (0.15 ml, 70%) in acetone (25 ml) for 1.5 hr with stirring. The mixture was neutralized (solid $NaHCO_3$) and evaporated *in vacuo* to about 10 ml. Dilution with water and filtration gave 81 mg of crude product which was filtered, in benzene, through a short column of silica gel. The benzene eluates gave 5α-cholestane-3β,4β-diol acetonide: mp 150–151° (from acetone); $[\alpha]_D$ 0°; nmr ($CDCl_3$) δ 0.67 (s, 3, C-18 methyl), 1.05 (s, 3, C-19 methyl), 1.35 and 1.51 (s, 3 each, acetonide methyls), 4.0 (m, 1, C-4 CHO–, $W_{1/2}$ = 6 Hz).

Anal. Calcd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 81.06; H, 11.53.

Lithium Aluminum Hydride Reduction of 3-*N*-Pyrrolidinocholest-2-en-4-one (4), giving 5α-Cholestan-4α-ol-3-one (5a) and 5α-Cholestan-3β-ol-4-one (6a).—To a stirred solution of the enamine **4** (1.535 g) in ether (200 ml) was added lithium aluminum hydride (250 mg). After 4 hr the reaction mixture was cooled in ice and water was added cautiously. The ethereal layer was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to give 1.47 g of crude product. Chromatography on silica gel failed to separate the mixture. However, preparative tlc (petroleum ether–ethyl acetate, 4:1) of a 420-mg portion of the crude reaction product gave 5α-cholestan-4α-ol-3-one (**5a**, 94 mg): mp 162–170° (from benzene–methanol); $[\alpha]_D$ +50°; $\nu_{max}^{CHCl_3}$ 3521, 1718 cm^{-1}; nmr ($CDCl_3$) 0.67 (s, 3, C-18 methyl), 1.10 (s, 3, C-19 methyl), 3.97 (d, 1, C-4 CHOH, J = 11 Hz); mass spectrum, M^+ 402, and *m/e* 387, 384, 369.

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.44; H, 11.22.

Acetylation of **5a** (pyridine–acetic anhydride, room temperature, 18 hr) gave 5α-cholestan-4α-ol-3-one acetate (**5b**): mp 139–144° (from ethanol) undepressed on admixture with an authentic

(13) *Cf.* C. H. Snyder, *J. Org. Chem.*, **31**, 4220 (1966), who comments on possible mechanisms for the lithium aluminum hydride reduction of 1,2-cyclohexanedione to 2-hydroxycyclohexanone.

(14) *Cf.* reduction of the steroidal 2-hydroxy-Δ^1-3-oxo system: H. Mori, K. Shibata, K. Tsuneda, and M. Sawai, *Chem. Pharm. Bull.*, **15**, 460 (1967).

(15) L. P. Kuhn, *J. Amer. Chem. Soc.*, **74**, 2492 (1952).

(16) Melting points were determined on the Kofler block. Optical rotations were measured in chloroform solution by Janssen Pharmaceutica, Beerse, Belgium. Nmr spectra were recorded for deuteriochloroform solutions using Varian A-60 and HA-100 spectrometers, and chemical shifts were given in parts per million on the δ scale (tetramethylsilane = 0). Infrared spectra were recorded on a Perkin-Elmer 521 spectrophotometer using carbon tetrachloride solutions or potassium bromide disks, and on a Perkin-Elmer Infracord using chloroform solutions. Unless otherwise specified, infrared data refer to chloroform solutions. For thin layer chromatography (tlc) silica gel GF254 was used in 0.25-mm layers for analytical purposes and in 2-mm layers for preparative work.

sample[11,17] of **5b**; infrared spectrum (KBr) identical with that of the authentic sample and showing same R_f on tlc (petroleum ether–ethyl acetate, 9:1); ORD [methanol–dioxane (2:1)], 298–259 mμ, a = +39; nmr ($CDCl_3$) δ 0.66 (s, 3, C-18 methyl), 1.11 (s, 3, C-19 methyl), 2.11 (s, 3, acetate methyl), and 5.0 (d, 1, C-4 CHOAc, J = 12 Hz). The chemical shifts for the C-19 methyl and the C-4 hydrogen are considerably different from those reported, presumably because of solvent differences ($CDCl_3$ *vs.* CS_2).

There was also isolated from the above preparative tlc 5α-cholestan-3β-ol-4-one (**6a**, 64 mg): double mp 106–109° and 113–115° (from benzene–methanol); $[\alpha]D$ ±0°; $\nu_{max}^{CHCl_3}$ 3521, 1715 cm^{-1}; nmr ($CDCl_3$) δ 0.67 (s, 3, C-18 methyl), 1.10 (s, 3, C-19 methyl), 4.08 (m, 1, C-3 CHOH).

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.19; H, 11.37.

Acetylation of **6a** (pyridine–acetic anhydride, room temperature, 18 hr) gave 5α-cholestan-3β-ol-4-one acetate (**6b**): mp 120–121° (from acetone) undepressed on admixture with an authentic sample;[12,18] infrared spectrum (KBr) identical with that of the authentic material, showing the same R_f on tlc (petroleum ether–ethyl acetate, 9:1); the expected ORD [methanol–dioxane (2:1)] 305–265 mμ, a = −105; nmr spectrum ($CDCl_3$) δ 0.64 (s, 3, C-18 methyl), 0.73 (s, 3, C-19 methyl), 2.10 (s, 3, acetate methyl), and 5.10 (d, 1, C-3 CHOAc, J_{app} = 7 and 11.5 Hz).

Reduction of 4-Hydroxycholest-4-en-3-one (3) with Lithium Aluminum Hydride to Give 5α-Cholestan-3β-ol-4-one.—To a stirred solution of the diosphenol **3** (1.005 g) in ether (120 ml) was added lithium aluminum hydride (163 mg). After 4 hr, water was added cautiously to the cooled mixture and the ethereal phase was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to give 450 mg of crude product. Reextraction of the aqueous phases with chloroform gave a further 457 mg of crude product, total yield 907 mg.

A 450-mg portion of the crude material was acetylated (pyridine–acetic anhydride, room temperature for 18 hr) and chromatographed on silica gel (20 g). Elution with benzene and benzene–chloroform (95:5) gave mixtures (71 mg) rich in 5α-cholestan-3β-ol-4-one acetate **6b**, as judged by tlc. Further elution, with benzene–chloroform (1:1), gave pure **6b** (161 mg) identical in all respects with authentic material.

Although tlc revealed the presence of more **6b**, as well as minor amounts of the isomeric 4α-acetoxy-3 ketone (**5b**) and unidentified products in the other chromatogram fractions, further chromatography (both column and thick layer) gave only additional small quantities of **6b** in pure form.

Registry No.—**1**, 20834-99-5; **1** (acetonide), 26460-83-3; **2**, 26460-84-4; **4**, 26460-85-5; **5a**, 1105-27-7; **5b**, 16963-22-7; **6a**, 18897-84-2; **6b**, 1256-67-3.

Acknowledgments.—We thank Dr. D. P. Hollis for the 100-Hz nmr spectra, and Dr. H. Fales for the mass spectrum.

(17) We thank Professor W. S. Johnson (Stanford University) for kindly supplying us with an authentic specimen of the ketol **5b**.

(18) We thank Professor S. Lieberman (Columbia University) for kindly supplying us with an authentic sample of **6b**.

Photoinitiated Fragmentation of Cyclohexenols

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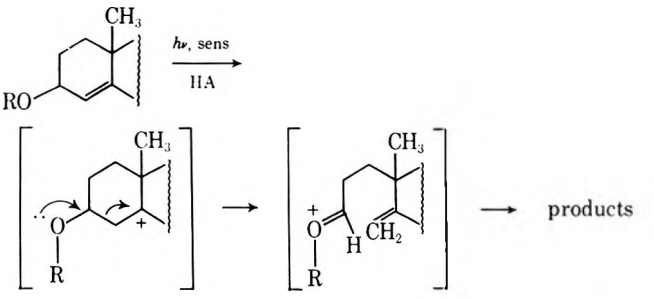
Several years ago we found that certain cyclic olefins undergo a photochemically initiated protonation reaction, thereby giving rise to products *via* carbonium ion pathways.[1] We have subsequently been engaged in studies aimed at the application of this novel finding to polyfunctional olefins wherein the initially formed cation, through interaction with a second functional group, could initiate further reactions. Scheme I shows

SCHEME I



a predicted reaction pathway for cyclohexenols[2,3] which constitutes the subject of this report.

Irradiation of the allylic alcohol **1** in aqueous acetic acid–1,2-dimethoxyethane (DME)–*p*-xylene afforded the oxetane **2** as the only observable product. In methanol–*p*-xylene, the aldehyde **4** was initially produced but this gradually gave way to oxetane **2** upon prolonged irradiation. When this latter irradiation was conducted in methanol which had not been freshly distilled from sodium carbonate, the acetal **7** was also observed. We therefore conclude that the acetal **7** arises *via* an acid-catalyzed ground-state reaction and that irradiation of undistilled methanol produces a strongly acidic substance which catalyzes this reaction. In fact, even acetic acid was found to promote the ground-state conversion of aldehyde **4** to acetal **7** in methanol, albeit somewhat inefficiently. In methanol–acetic acid–*p*-xylene, photolysis of the allylic alcohol **1** afforded a mixture of oxetane **2**, aldehyde **4**, and the dimethyl acetal **7**. Here again, prolonged irradiation produced increased amounts of the oxetane **2** at the expense of aldehyde **4**.

Aldehyde **4** was identified through its spectral properties and by independent synthesis from the known cyano ketone **5**[4] *via* condensation with triphenylmethylenephosphorane in dimethyl sulfoxide (DMSO)[5] followed by reduction with diisobutylaluminum hydride nad hydrolysis.[6] Irradiation of the aldehyde thus obtained afforded the oxetane **2**[7] (Scheme II). The stereochemistry of oxetane **2** has not been rigorously established, but steric considerations tend to favor the indicated structure wherein the propionaldehyde side chain of the unsaturated aldehyde precursor **4** can inter-

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(1) *Cf.* J. A. Marshall, *Accounts Chem. Res.*, **2**, 33 (1969); P. J. Kropp, *J. Amer. Chem. Soc.*, **91**, 5783 (1969), and references therein.

(2) For an example of a related homoallylic alcohol cleavage, see P. J. Kropp and H. J. Krauss, *ibid.*, **91**, 7466 (1969).

(3) Recently, J. A. Waters and B. Witkop [*J. Org. Chem.*, **34**, 3774 (1969)] reported on the conversion of cholesterol and 4-cholesten-3-ol to the steroidal counterpart of oxetane **2**. These authors suggested a mechanism involving C–C bond migration in the presumed intermediate tertiary cation leading to an *A*-nor primary cation which then underwent cyclization to the aforementioned oxetane.

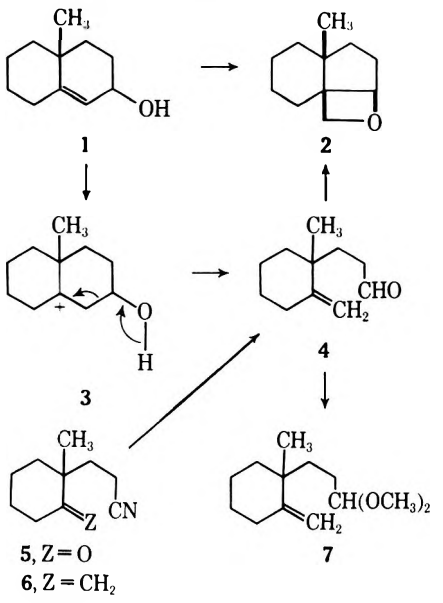
(4) R. L. Frank and R. C. Perle, *J. Amer. Chem. Soc.*, **73**, 724 (1951).

(5) *Cf.* E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1345 (1965).

(6) *Cf.* L. I. Zakharkin and I. M. Khorlina, *Dokl. Akad. Nauk SSSR*, **116**, 422 (1967); *Chem. Abstr.*, **52**, 8040*f* (1958).

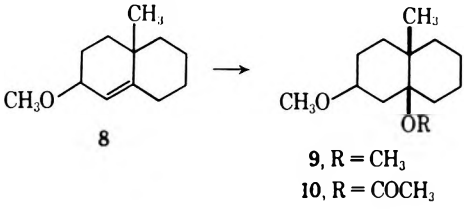
(7) For examples of carbonyl–olefin potochemical additions, see N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, New York N. Y., 1965, pp 208–211.

SCHEME II



act with the exocyclic double bond without undue strain in the developing bicyclo[3.2.0] ring system.

An attempt to extend the concept depicted in Scheme I to the methyl ether **8** was unsuccessful. Irradiation in methanol–acetic acid–*p*-xylene led to the addition products **9** and **10**.[1] None of the acetal **7** could be detected.



From a synthetic standpoint, the photoinitiated fragmentation of cyclohexenols described above represents a convenient route to polycyclic oxetanes or to ring-cleaved products such as **4** and **7**. The widespread occurrence of steroidal 4-en-3-ones makes the corresponding alcohols likely candidates for future studies.[3,7a]

Experimental Section[8]

Photolysis of Unsaturated Alcohol 1. A. In Methanol Acetic Acid.—A solution of 1.40 g of alcohol 1,[9] 5.0 ml of acetic acid, and 5.0 ml of *p*-xylene in 180 ml of methanol was irradiated[10] for 2 hr.[8a] The product was isolated with ether[8b] affording 1.3 g of a mixture shown by gas chromatography to contain, in order of increasing retention time, oxetane **2**, aldehyde **4**, acetal **7**, and alcohol **1** in the ratio 1:1:3:1. This mixture was separated *via* preparative gas chromatography to give the following pure components.

(1) **Oxetane 2** showed λ_{max}^{film} 9.78, 10.15, 11.00, 11.34, and 11.7 μ; $\delta_{TMS}^{CCl_4}$ 4.60 (multiplet, –OCH–), 4.09 (–OCH_2–, AB quartet, J_{AB} = 6 Hz, $\Delta\nu_{AB}$ = 34 Hz), and 0.90 ppm (CH_3).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.5; H, 10.9.

(2) **Aldehyde 4** showed λ_{max}^{film} 3.70, 5.80, 6.09, and 11.19 μ; $\delta_{TMS}^{CCl_4}$ 9.69 (CHO triplet, J = 1 Hz), 4.6 (C=CH_2 multiplet), and 0.97 ppm (CH_3).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46, H, 10.91. Found: C, 79.2; H, 10.9.

(3) **Acetal 7** showed λ_{max}^{film} 6.10, 8.91, 9.36, 9.50, and 11.19 μ; $\delta_{TMS}^{CCl_4}$ 4.65, 4.50 (C=CH_2), 4.18 (acetal α-H triplet, J = 6 Hz), 3.19 (CH_3O), and 1.0 ppm (CH_3).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.75; H, 11.2.

B. In Methanol.—A solution of 1.09 g of alcohol **1** and 5 ml of xylene in 175 ml of methanol was subjected to irradiation.[10] After 1 hr, gc analysis of aliquot indicated a 26:74 mixture of oxetane **2** and aldehyde **4**. After an additional 4 hr of irradiation, gc analysis showed that a 60:40 mixture of these two components was present.

C. In DME–Water–Acetic Acid.—A solution of 1.25 g of alcohol **1**, 5 ml of *p*-xylene, 5 ml of acetic acid, and 40 ml of water in 140 ml of DME was irradiated[10] for 4 hr.[8a] The product was isolated with ether[8b] aud distilled affording 0.75 g (60%) of oxetane **2** purified by preparative gas chromatography.

3-(2-Methylene-1-methylcyclohexyl)propanenitrile (6).—To a solution of methylenetriphenylphosphorane in DMSO[5] (50 ml of 2 *M*) was added 8.20 g (0.047 mol) of ketonitrile 5[4] in 5 ml of DMSO dropwise.[8a] The mixture was stirred overnight and poured into 250 ml of ice–water, and the product was isolated with pentane[8b] and chromatographed on alumina. Elution with hexane afforded 2.77 g (33%) of unsaturated nitrile **6**: λ_{max}^{film} 4.45, 6.08, and 11.14 μ; $\delta_{TMS}^{CCl_4}$ 4.70, 4.59 (C=CH_2), and 1.02 ppm (CH_3). The analytical sample, bp 55–60° (0.05 mm), was obtained *via* short-path distillation.

Anal. Calcd for $C_{11}H_{17}N$: C, 80.93; H, 10.50; N, 8.58. Found: C, 80.9; H, 10.4; N, 8.3.

3-(2-Methylene-1-methylcyclohexyl)propanecarboxaldehyde (4).—To a stirred solution of 900 mg (6.0 mmol) of nitrile **6** in 50 ml of hexane at −60° was added 10.0 ml of 0.9 *M* diisobutylaluminum hydride[6] in hexane.[8a] The solution was allowed to reach room temperature and, after 2 hr, 60 ml of saturated aqueous ammonium chloride was added. After 20 min, the mixture was poured into 20 ml of 5% aqueous sulfuric acid and the product was isolated with hexane[8b] and distilled affording 383 mg (42.5%) of aldehyde, bp 62–65° (0.07 mm). The infrared and nmr spectra exactly matched those of aldehyde **4** secured through photolysis of alcohol **1** as described above.

Photolysis of Aldehyde 4.—A solution of 315 mg (1.90 mmol) of aldehyde **4** and 3.0 ml of *p*-xylene in 105 ml of methanol was irradiated[10] for 2 hr.[8a] The product was isolated with ether[8b] and distilled affording 285 mg (90%) of a 9:1 mixture of oxetane **2** and aldehyde **4**. The material isolated by preparative gc exhibited infrared and nmr spectra which exactly matched those of the oxetane secured *via* photolysis of alcohol **1**.

3-(2-Methylene-1-methylcyclohexyl)propanecarboxaldehyde Dimethyl Acetal (7).—A solution of 80 mg (0.48 mmol) of aldehyde **4**, 0.5 ml of acetic acid, and 0.5 ml of trimethyl orthoformate in 6 ml of methanol was stirred at reflux for 18 hr. The product was isolated with ether[8b] and distilled (60°, 0.05 mm), to give 68 mg (66.7%) of acetal **7**, identical with the material described above.

Registry No.—**1**, 26675-10-5; **2**, 26675-09-2; **4**, 26675-11-6; **6**, 26731-50-0; **7**, 26675-12-7.

Acknowledgment.—We are indebted to the National Science Foundation for support of this work through a research grant.

(7a) NOTE ADDED IN PROOF.—Since submission of this note a study has appeared which likewise postulates the pathway depicted in Scheme I for steroidal allylic and homoallylic alcohol photolysis: D. Guénard and R. Beugelmans, *Tetrahedron Lett.*, 1705 (1970).

(8) (a) The apparatus described by W. S. Johnson and W. P. Schneider ("Organic Syntheses," Coll. Vol. IV, Wiley, New York, N. Y., 1963, p 132) was used to maintain a nitrogen atmosphere. (b) The isolation procedure consisted of thorough extraction with the specified solvent, washing the combined extracts with saturated brine solution, and drying the extracts over anhydrous magnesium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator. (c) Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.

(9) W. J. Vandenheuvel and E. S. Wallis, *J. Org. Chem.*, **27**, 1233 (1962).

(10) The irradiation was carried out with a 450-W Hanovia medium-pressure mercury arc (type L) in a water-jacketed Vycor immersion well. Mixing was effected by a fine stream of nitrogen introduced through a gas dispersion tube fitted in the bottom of the reaction vessel.

Epoxidation. II. Stereoselective Epoxidation of Methylenecyclohexanes *via* Bromohydrins[1]

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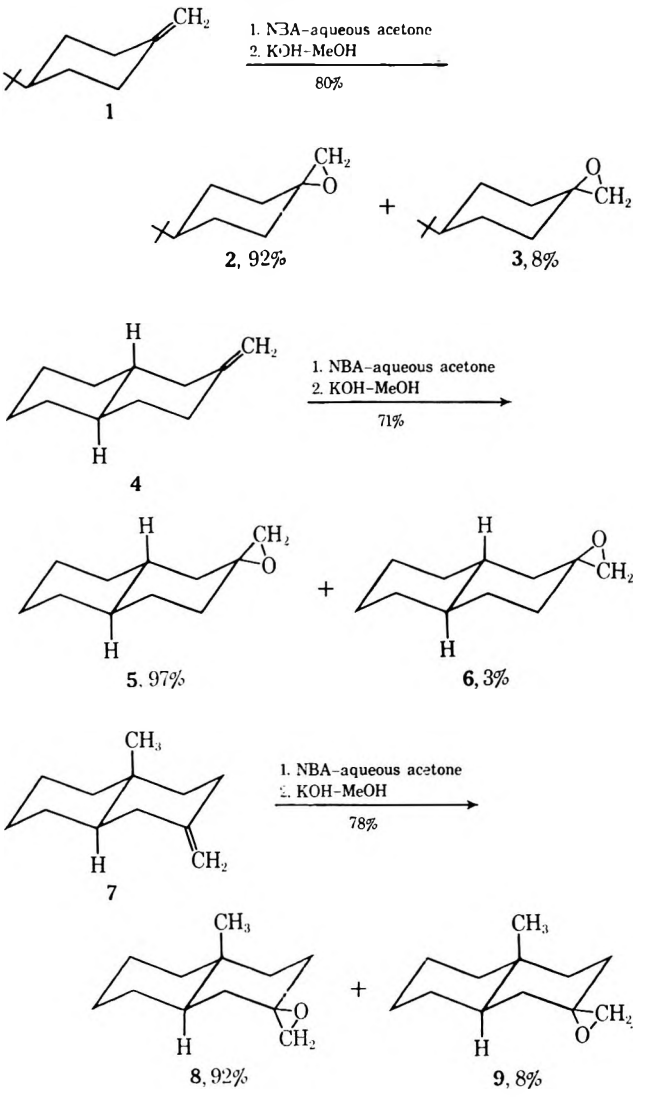
Received July 17, 1970

Our interest in the use of isomeric methylenecyclohexane oxides (*e.g.*, **2** and **3**) as intermediates for the synthesis of amino alcohols required for ring expansion reactions[3] prompted an earlier study[1] of methods for the stereoselective preparation of compounds of this type. This study revealed that epoxides with an equatorial methylene group (*e.g.*, **3**) could be prepared in good yield and with high stereoselectivity by treatment of the corresponding cyclohexanone with dimethyloxosulfonium methylide.[4] The isomeric epoxides with an axial methylene group (*e.g.*, **2**) were best prepared by epoxidation of the corresponding olefin with the alkaline hydrogen peroxide–benzonitrile system. This method gave at best a mixture of epoxides containing only about 70% of the epoxide with an axial methylene group and further purification, although possible, was quite tedious. We now wish to report that epoxides with an axial methylene group can be readily prepared from unhindered methylenecyclohexanes *via* bromohydrins.

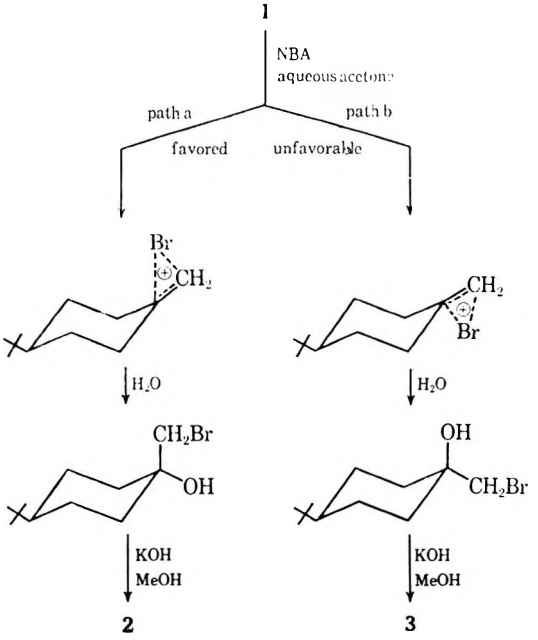
Treatment of the three representative olefins **1**, **4**, and **7** with *N*-bromoacetamide (NBA) in aqueous acetone produced the corresponding bromohydrins[5] which, without further purification, were converted to the epoxides by treatment with potassium hydroxide in methanol. This two-step procedure gave the corresponding epoxides **2**, **5**, and **8** in good yield and with a high degree of stereoselectivity (see Scheme I). Although a brief examination of the use of other solvent systems for the formation of the bromohydrins was made, aqueous acetone proved to be the most satisfactory.

These stereochemical results indicate that bromonium ion formation by electrophilic attack of NBA on the olefin occurs preferentially from the axial direction (path a, Scheme II) and in this respect is similar to other addition reactions to methylenecyclohexanes and cyclohexanones.[6]

SCHEME I



SCHEME II



Experimental Section

The preparation of the olefins and characterization of the epoxides has been previously reported.[1] The following general procedure was used for the preparation of the epoxides.

General Procedure.—To a solution of 4.14 g (30 mmol) of *N*-bromoacetamide and 3.75 g of sodium acetate in 120 ml of water was added a solution of the olefin (6.0 mmol) in 300 ml of acetone. The resulting mixture was stirred overnight at room temperature and extracted thoroughly with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated to give the crude bromohydrin (91–96%). The crude bromohydrin was dissolved in 10 ml of methanol, 10 ml of a 5% solution of potassium hydroxide in methanol was added, and the resulting mixture stirred for 90 min. The reaction mixture was diluted with water and ex-

(1) For part I, see R. G. Carlson and N. S. Behn, *J. Org. Chem.*, **32**, 1363 (1967).

(2) Alfred P. Sloan Foundation Research Fellow, 1970–1972. To whom correspondence should be addressed.

(3) R. G. Carlson and N. S. Behn, *J. Org. Chem.*, **33**, 2069 (1968).

(4) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

(5) For comments on the structure of the bromohydrin derived from methylenecyclohexane, see A. J. Sisti, *J. Org. Chem.*, **33**, 3953 (1968).

(6) For a recent discussion, see M. Cherest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968).

tracted with ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), and evaporated with ether to give the epoxide mixture which was analyzed by vpc.[1] The results are summarized in Scheme I.

Registry No.—**1**, 13294-73-0; **2**, 7787-79-3; **4**, 7787-72-6; **5**, 7787-77-1; **7**, 7787-73-7; **8**, 7787-80-6.

Acknowledgment.—R. A. gratefully acknowledges financial assistance from A. I. D., the Ford Foundation, and the University of Costa Rica.

Nuclear Magnetic Resonance Analysis of 5,12*H*-Dibenzo[*b*,*e*]-1,3a,6,6a-tetraazapentalene

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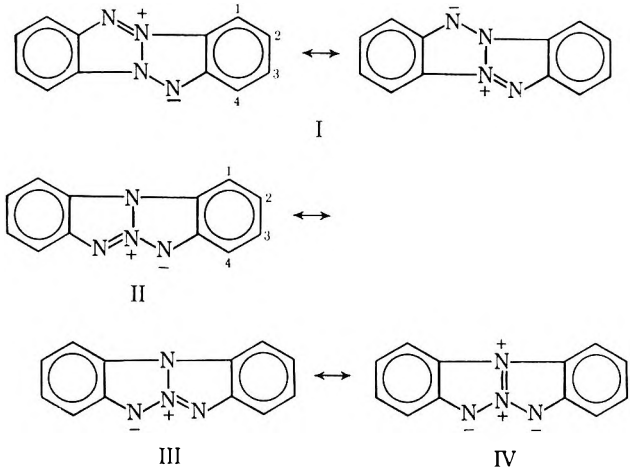
Received September 15, 1969

In an earlier paper,[1] the nmr spectrum of 5,6*H*-dibenzo[*b*,*f*]-1,3a,4,6a-tetraazapentalene (I) and two of its methyl derivatives was reported. In this paper, the analysis of the nmr of the isomeric 5,12*H*-dibenzo[*b*,*e*]-1,3a,6,6a-tetraazapentalene (II) is described.



I

II

III IV

Compound II was prepared by essentially the same procedure as has been reported by Carboni, *et al.*,[2] from 1-(2-azidophenyl)benzotriazole. The nmr spectrum of II was obtained in deuteriochloroform. The spectrum is shown in Figure 1. The experimental spectrum was matched with the calculated spectrum shown in Figure 1 using the LAOCN-3 program.[3] The calculated coupling constants and chemical shifts for II are tabulated in Table I. The data reported previously[1] for I are also tabulated in Table I for comparison purposes.

The coupling constants for both I and II are similar and of the order of magnitude expected for a normal benzenoid ring. The chemical shift of H_2 in each compound is furtherest upfield, a reflection of its location para to N-5, which carries a partial negative charge as seen in structures II–IV. H_4, which is ortho to N-5, is at nearly the same position in both I and II and in both cases is over 27 Hz downfield from H_2, a reflection of its closer proximity to the electronegative nitrogen. Apparently the inductive effect of the nitrogen in the ortho position decreases the effect of the partial negative charge on N-5 and results in the downfield shift. In both I and II, H_3 is located further downfield than H_2; however, in the II the difference between H_2 and H_3 is 7 cycles compared to 13 cycles in compound I. This result suggests that, whereas in compound I H_3 is located para to a nitrogen carrying a partial positive charge, in II the positive charge is much reduced; *i.e.*, structure IV contributes very little to the resonance hybrid. H_1 in compound II is 12 cps upfield compared to H_1 in compound I. This again suggests little contribution of structure IV to the resonance hybrid.

It is interesting to compare the observed chemical shifts of the protons in I and II with the molecular orbital calculations of Chia and Simmons.[4] In Figure 2 is shown a plot of the calculated electron densities *vs.* the observed chemical shifts. The chemical shifts of protons H_2 and H_3 in both I and II seem to correlate very well with the calculated electron densities. H_4 in both compounds falls nearly at the same point. This is not unexpected, since examination of structures I and II shows that in both H_4 has a similar electronic relationship to the nitrogens of the heterocyclic system. On the other hand H_1 in the compounds is in quite

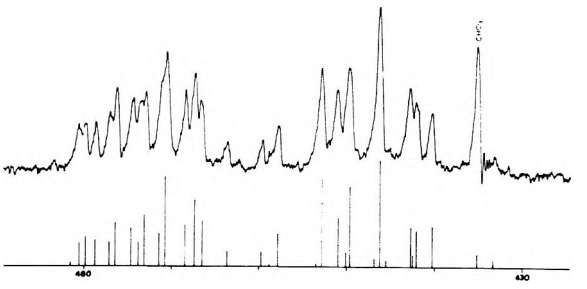


Figure 1.—Experimental and calculated spectra of 5,12*H*-dibenzo[*b*,*e*]-1,3a,6,6a-tetraazapentalene (II) in deuteriochloroform.

TABLE I
COUPLING CONSTANTS AND 60-MHz CHEMICAL SHIFTS

	Compd	
Chemical shifts[a]	I[b]	II
H_1	486.7	474.8
H_2	440.0	443.6
H_3	453.1	450.7
H_4	471.5	471.0
Coupling constants		
$J_{1,2}$	8.47	8.38
$J_{1,3}$	1.05	0.98
$J_{1,4}$	0.79	0.69
$J_{2,3}$	7.00	7.32
$J_{2,4}$	0.93	0.85
$J_{3,4}$	8.73	8.68

[a] Chemical shifts are in hertz downfield relative to internal tetramethylsilane. The values in this table were obtained by an iterative fitting using the LAOCN-3 program.[3] [b] Reference 1.

(1) J. H. Hall, J. G. Stephanie, and D. K. Nordstrom, *J. Org. Chem.*, **33**, 2951 (1968).

(2) R. A. Carboni, J. C. Kauer, J. E. Castle, and H. E. Simmons, *J. Amer. Chem. Soc.*, **89**, 2618 (1967).

(3) A. A. Bothner-By and S. Castellano, *J. Chem. Phys.*, **41**, 3863 (1964).

(4) Y. T. Chia and H. E. Simmons, *J. Amer. Chem. Soc.*, **89**, 2638 (1967).

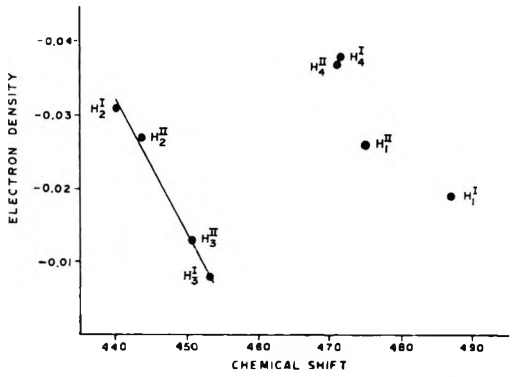


Figure 2.—Chemical shifts of protons in I and II *vs.* calculated electron densities. Electron densities are from ref 4 and the chemical shifts for I from ref 1.

different environments and there is observed a large chemical shift difference as well as a calculated electron density difference.

On the basis of the chemical shift data and transition state considerations,[5] one would predict a large preference for electrophilic aromatic substitution at H_2 with a much smaller reactivity at H_1 for each of these compounds. On the basis of the electron density calculations, one might expect the 2 and 4 positions to be about equally reactive or with a slight preference for the 4 position. Nitration, chlorination, bromination, and chlorosulfonation of I has been reported to give substitution at the 2 position.[5] Substitution at the 4 position is observed after positions 2 and 8 have been substituted. Although II has been nitrated and chlorosulfonated, the position of substitution has not been established.[6] These results suggest that the calculated electron densities at H_1 are too high relative to those at H_2.

Experimental Section

The nmr spectrum of II was taken in deuteriochloroform using a Varian A-56/60 spectrometer. The peak positions were determined relative to TMS by use of the side-band technique immediately preceding and immediately following the spectral scan. The initial peak assignments were based on similarities between the spectrum of II and the published spectrum of I.[1] The exact chemical shifts and couplings constants were calculated using the LAOCN-3 program.[3] In plotting the computed spectrum in Figure 1, lines closer together than 0.2 Hz were added together, since such lines would not normally be resolved.

5,12*H*-Dibenzo[*b*,*e*]-1,3a,6,6a-tetraazapentalene (II).—In 2 ml of decalin was placed 52.1 mg (0.221 mmol) of 1-(2-azidophenyl)benzotriazole.[2] The mixture was first warmed to dissolve the solid and then heated slowly up to the boiling point of the decalin. After 5 min of refluxing, the solution was cooled to room temperature. The needles which precipitated were filtered and washed thoroughly with petroleum ether, yield 26.5 mg (58%), mp 251–252° (lit.[2] 255°).

Registry No.—II, 2055-55-2.

Acknowledgment.—The author is indebted to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(5) R. A. Carboni, J. C. Kauer, W. R. Hatchard, and R. J. Harder, *J. Amer. Chem. Soc.*, **89**, 2626 (1967).

(6) J. C. Kauer and R. A. Carboni, *ibid.*, **89**, 2633 (1967).

Thermolysis of 3,3′,5,5′-Tetraphenyldiphenoquinone

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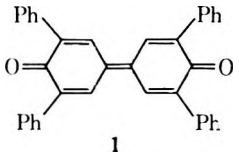
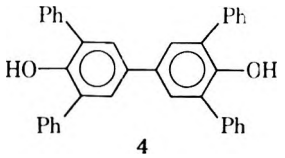
Received June 24, 1970

When 3,3′,5,5′-tetraphenyldiphenoquinone **1**[1] is



1

heated above its melting point, the melt which initially is an intense red color gradually fades and becomes almost colorless. Thin layer chromatography on silica gel using xylene as eluent shows the presence of three compounds, **2**, **3**, and **4**, with R_f values of 1, 0.7, and 0.5, respectively. By comparison with an authentic sample, **4** was identified as 2,2′,6,6′-tetraphenyl-*p*,*p*′-biphenol.



4

Superposition of the infrared spectra (in CS_2) of **2** and **4** gives a spectrum that is essentially identical with that of **3**. This is shown in Table I which lists the principal

TABLE I

PRINCIPAL INFRARED ABSORPTION BANDS (IN cm^{-1})

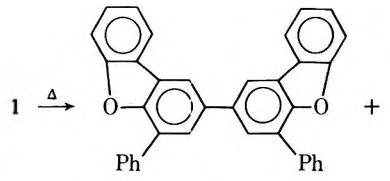
2			1188			772	745	691	
3	3538	1225	1188	1120	867	772	745	700, 691	565
4	3538	1225		1120	872	772		700, 691	571

absorption bands of the three compounds. Furthermore, the molar extinction coefficients of all the major bands of **3** are approximately one-half of the corresponding bands in **2** or **4**. The infrared spectrum of 2,6-diphenylphenol (**5**)[1] also shows a doublet at 685 and 695 cm^{-1} indicating the two phenyl groups are not equivalent.

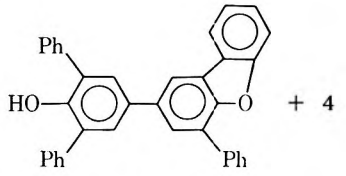
The spectrum of **2** is exceptionally simple. The strong C–O stretching absorption at 1188 cm^{-1}, which is also present in **3**, is also found in 4-phenyldibenzofuran (**6**, ν 1184 cm^{-1}) and dibenzofuran (**7**, ν 1195 cm^{-1}). The former also has a strong absorption at 691 cm^{-1}.

(1) J. Plesek, *Collect. Czech. Chem. Commun.*, **21**, 375 (1956).

Thus it is apparent that the course of the reaction is

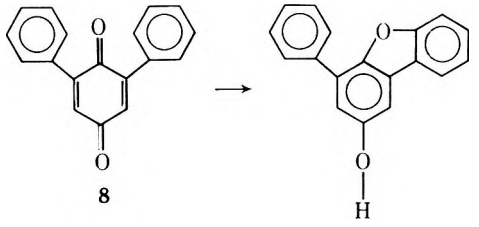


2



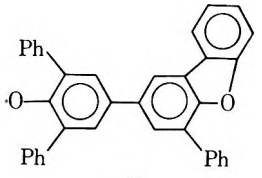
3

A related reaction has recently been observed. Hageman[2] irradiated 2,6-diphenyl-1,4-benzoquinone (**8**) in acetonitrile with ultraviolet light and isolated the dibenzofuran **9** in high yield.



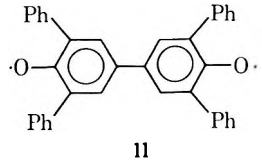
8 9

Separation of the bisdibenzofuran **2** from **3** and **4** is readily accomplished by column chromatography or alternatively by crystallization from benzene. Oxidation of the mixture of **3** and **4** with oxygen in alcohol solution in the presence of a copper–amine catalyst[3] converts **4** to insoluble **1**. By analogy, with the oxidation of 2,4,6-triphenylphenol to the stable phenoxy radical,[4] the oxidation of **3** should yield **10**, and thus reduction of the filtrate from the preceding step regenerates **3**.



10

Dimroth[5] has examined the esr spectrum of **1** and observed a weak signal at room temperature. It has also been demonstrated that diphenoquinones such as **1** are powerful oxidizing agents. The oxidation of diphenylmethane to *s*-tetraphenylethane proceeds readily in high yield at 150°.[6] Hence it appears reasonable to assume that species such as **11** on the quinhydrone are present especially at elevated temperatures. In the absence of a species to dehydrogenate, attack would occur on the pendant phenyl and subsequent aromatization by dehydrogenation would yield **2** or **3**.



11

(2) H. J. Hageman and W. G. B. Huysmans, *Chem. Commun.*, 837 (1969).
(3) A. S. Hay, *Advan. Polym. Sci.*, **4**, 496 (1967).
(4) K. Dimroth and A. Berndt, *Angew. Chem.*, **76**, 434 (1964).
(5) K. Dimroth, W. Unbach, and K. H. Blöcher, *ibid.*, **75**, 860 (1963).
(6) A. S. Hay, *Tetrahedron Lett.*, 4241 (1965).

Experimental Section

Preparation of 1.—Oxygen was passed through a vigorously stirred solution of 50 g (0.20 mol) of 2,6-diphenylphenol and 4.0 g of copper(I) chloride in 500 ml of *n*-butyronitrile at 100° for 5 hr. The reaction mixture was cooled and filtered to yield 42 g (0.086 mol, 85% yield) of **1**, mp 290° dec. Reduction with hydrazine in hot acetic acid gave the corresponding biphenol **4**, mp 196°. *Anal.* Calcd for $C_{36}H_{26}O_2$: C, 88.13; H, 5.34. Found: C, 88.30; H, 5.28.

Thermolysis of 1.—To a test tube was added 9.80 g (0.02 mol) of **1** which was then heated to 300° for 0.5 hr at which point the melt was light amber in color. The reaction mixture was cooled and diluted with 2 vol of benzene. The solution was chromatographed over activated alumina (column 2 in. in diameter, 12 in. long) using benzene as eluent. The first fractions obtained contained 2.56 g (0.0053 mol, 26.5% yield) of **2**, mp 231–234°. *Anal.* Calcd for $C_{35}H_{22}O_2$: C, 88.86; H, 4.56; mol wt, 486. Found: C, 88.7; H, 4.7; mol wt, 495.

Elution with ethanol–benzene gave a mixture of the two products, **3** and **4**. After evaporation of the solvents, the residue was dissolved in 150 ml of ethanol. To this solution was added 0.5 g of CuCl and 2 ml of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. Oxygen was passed through the vigorously stirred solution for 0.5 hr and then the green solid which separated was removed by filtration. The solid was dissolved in 250 ml of hot chloroform and filtered to separate copper salts, and the filtrate evaporated to yield 5.63 g (0.0115 mol, 57.5% yield) of **1**, identified by comparison with an authentic sample. The intense red-colored filtrate from the oxidation was treated with hypophosphorous acid until the red color of the reaction mixture disappeared and then flooded with water. The solid obtained was recrystallized from acetic acid to yield 1.24 g (0.0025 mol, 12.5% yield) of **3**, mp 196–198°. *Anal.* Calcd for $C_{36}H_{24}O_2$: C, 88.50; H, 4.95. Found: C, 88.6; H, 5.17.

Registry No. —**1**, 3550-01-4; **2**, 26675-14-9; **3**, 26675-15-0; **4**, 2416-96-8.

Intramolecular Hydrogen Bonding in β-Amino α,β-Unsaturated Esters

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Received May 21, 1970

This note comprises studies on hydrogen bonding of 1-ethylpyrazolyl-5-aminomethylenemalonic acid diethyl ester (Ia) and of its 3-methyl derivative (Ib) utilizing nmr and ir spectroscopy. These compounds could exist as II, III, or IV, where R′ is the pyrazol ring. Although nmr studies have been reported on closely related Schiff bases[1] and vinylogous imides,[2] studies on our system have not been previously reported.

* To whom correspondence should be addressed.

(1) G. O. Dudek and E. P. Dudek, *J. Amer. Chem. Soc.*, **88**, 2407 (1966), and preceding papers of the series.
(2) D. L. Ostercamp, *J. Org. Chem.*, **30**, 1169 (1964), and references cited therein.

Results[3]

The infrared spectra of Ia and Ib in deuteriochloroform ($CDCl_3$) and deuterioacetonitrile (CD_3CN) are very similar. The broad weak band at 3250 cm^{-1} is assigned to N–H stretching absorption, which was not affected by a 20-fold dilution of the concentrated $CDCl_3$ solution (0.071–0.003 *M*). No free NH stretching frequency in the 3400–3500-cm^{-1} region was observed.

In the ir spectra of Ia and Ib, the absorptions at 1711 (CD_3CN) and 1702 cm^{-1} ($CDCl_3$) are assigned to unassociated ester carbonyl, while the bands at 1691 (CD_3CN) and 1685 cm^{-1} ($CDCl_3$) are assigned to associated ester carbonyl.[4] The difference, $\Delta\nu$, of 15–20 cm^{-1} arises from participation of the C=O group in the hydrogen bonding. The absence of a large downward carbonyl shift suggests that the ionic resonance form, IV, does not contribute appreciably to the ground state.[5] The band at 1652 cm^{-1} is assigned to the C=C absorption frequency, while the absorption at 1612 cm^{-1} is assigned to NH bending (deformation) vibrations, based upon the disappearance of the latter band and the appearance, after deuteration, of a strong ND band at 1568 cm^{-1}. From ir results, it can be concluded that Ia and Ib exist predominantly as enamine, II, stabilized in intramolecular hydrogen bonding.

Proton resonance data for Ia and Ib are listed in Table I. The spectrum of Ia in $CDCl_3$ consists of two

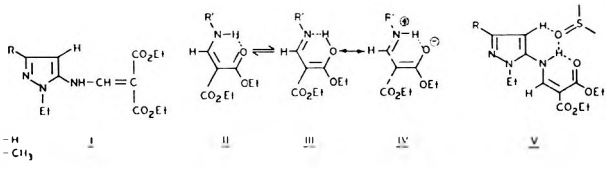
Table I
Proton Resonance Data

Compd	Solvent	Concn, *M*	δ, ppm: Ring protons 4 H[a]	3 R[a]	Vinyl H[b]	NH[b]
Ia	$CDCl_3$	0.36	6.04	7.42	8.16	11.08
		0.14	6.05	7.42	8.17	11.07
		0.08	6.03	7.39	8.16	11.07
		0.04	6.05	7.41	8.17	11.06
	DMSO-d_6	0.4	6.27	7.39	7.98	10.57
	CD_3CN	0.3	6.10	7.32	8.29	11.65[d]
	CF_3COOH	0.3	6.71	8.07	8.45[e]	*g*
	C_5D_5N	0.4	6.17	7.53	8.40[f]	11.27[f]
Ib	$CDCl_3$	0.05	5.88[c]	2.25	8.17	11.07
	DMSO-d_6	0.4	6.05[c]	2.12	7.99	10.56
	CD_3CN	0.3	5.90[c]	2.13	8.05	10.66[d]
	CF_3COOH	0.3	6.47[c]	2.53	8.42[e]	*g*
	C_5D_5N	0.4	5.92[c]	2.27	8.38[f]	11.23[f]

[a] Doublet with J = 2.0 Hz; in CF_3COOH, J = 3.0 Hz. [b] Doublet with J = 13.0 Hz. [c] Singlet when R = CH_3. [d] Broad doublet. [e] Fully collapsed or very broad resonance. [f] Broad singlet. [g] Not located.

doublets at δ 6.05 and 7.42, with spin–spin coupling constant, J = 2.0 Hz, which are assigned to protons at carbons 4 and 3 of the pyrazol ring, respectively. In Ib, the 3-methyl resonance occurs at δ 2.25, while the C_4 H appears as a singlet at δ 5.88, slightly upfield of the resonance in Ia because of substitution. The doublets at δ 8.17 and 11.08 are assigned to vinyl and hydrogen-bonded NH protons, respectively. The observed spin–spin coupling of 13.0 Hz indicates a trans spatial arrangement of the CH–NH moiety.[6] The variation in concentration from 0.36 to 0.04 *M* had no significant effect on the proton resonance spectrum of Ia. In dilute solutions, the trans coupling constant (J_{NH-CH}) of 13.0 Hz could still be observed, although the NH signal became somewhat broader. Dilution might be expected to influence the chemical shift of the NH proton resonance if it were intermolecularly hydrogen-bonded. In $CDCl_3$, the enaminic NH exchanged more slowly in the presence of D_2O than in dimethyl sulfoxide-d_6 (DMSO), due to the solubility differences of D_2O in the solvents. Usually, nonbonded NH protons exchange instantaneously under these conditions, which is another indication of intramolecular hydrogen bonding. Molecular models indicate a distance of *ca.* 1.5 Å for the NH–O=C bond in structure, II, which is a favorable distance for bonding.

Once it had been established that Ia and Ib exist mainly as the enamine, II, in $CDCl_3$, the effect of other solvents on the proton resonance spectrum was studied. Of particular significance are the results in DMSO, a hydrogen-bonding solvent. The coupling constants, J_{NH-CH} and $J_{H,H}$ were found to be insensitive to change of solvent. The upfield shift of 0.5 ppm in NH resonance includes about 0.2 ppm for diamagnetic anisotropic shielding, while the C_4 H shifted downfield by 0.2 ppm (equivalent to a total shift of 0.4 ppm). The preferred conformation of the pyrazol ring places the C_4 H



adjacent to the NH group. While the downfield shift of the C_4 H can be explained by anisotropy of DMSO, it is also possible that DMSO hydrogen bonds intermolecularly to the C_4H, at the same time bonding to the NH, with the concurrent weakening of the NH—O=C hydrogen bond, as depicted in V. In CD_3CN, the paramagnetic shift of 0.4 ppm of the NH indicates that the intramolecular hydrogen bond is weakened. In trifluoroacetic acid, a strong hydrogen-bonding medium, the NH proton resonance was probably obscured by the signal due to the solvent, but the broadening or collapse of the vinyl proton resonance indicates some perturbation of the NH—O=C bond.[7] The ring protons in Ia are shifted downfield by 0.65 ppm, with an increase in $J_{H,H}$ from 2.0 to 3.0 Hz because of protonation at nitrogen 1 and subsequent charge delocalization in the pyrazole ring. This conclusion is reinforced by the downfield shift (0.3 ppm) of the 3-methyl resonance in Ib. Finally, in pyridine, a proton acceptor base, NH and CH resonances appear as collapsed singlets with a downfield shift as a result of π-electron interaction (magnetic anisotropy) and proton exchange between NH and the solvent.

Our results confirm the observations of previous workers[1,2] who have shown that suitably substituted β-amino-α,β-unsaturated ketones were present as hydro-

(3) Nmr measurements were carried out on a Varian A-60 spectrometer using TMS as an internal reference. Perkin-Elmer Model 621 was used for ir studies. Both instruments were operated at ambient temperatures.

(4) The C=O absorption band at 1702 cm^{-1} in $CDCl_3$ was broad, with a shoulder at 1685 cm^{-1}, but was resolved in CD_3CN into two peaks.

(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1959, Chapter 14; "Advances in Infrared Group Frequencies," Methuen, London, 1968, Chapter 8.

(6) J_{NH-CH} of 13.0 Hz for trans and of 7.5 Hz for cis have been reported (ref 1).

(7) The infrared spectra of Ia before and after contact with trifluoroacetic acid were identical.

gen-bonded complexes of the type II at low concentrations. We have also shown the influence of various solvents on intramolecular hydrogen bonding.

Registry No.—Ia, 26823-99-4; Ib, 26824-00-0.

Acknowledgment.—We thank Dr. H. Höhn of Squibb Regensburg, Germany, for these compounds.

The Ultraviolet Irradiation of *S*-Phenyl Thiolacetate[1-3]

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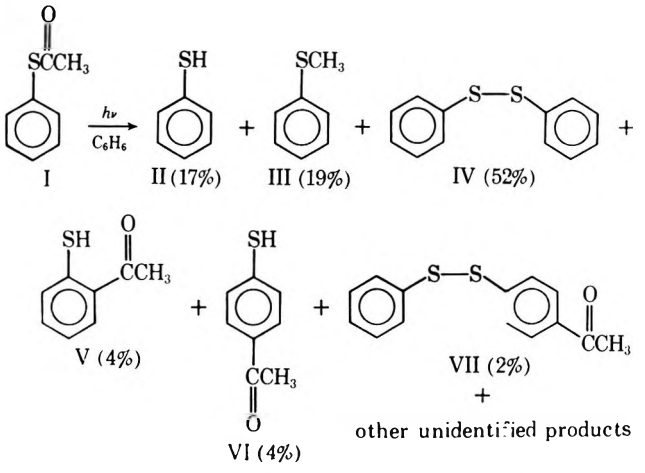
Received May 26, 1970

A recent communication[4] prompted us to report the results of our study of the ultraviolet irradiation of S-phenyl thiolacetate (I). When a 0.1 *M* solution of I in benzene was irradiated for 4 hr with a medium-pressure mercury lamp, the products shown in Scheme I were

SCHEME I



produced. Approximately 40% of the starting material was recovered. The products were isolated by preparative gas chromatography and identified by ir and nmr spectroscopy.

Products II, III, and IV were identified by comparison with authentic samples. The structure assignments for the photo-Fries reaction products (V and VI) were made from their ir and nmr spectra, which we believe are definitive. The nmr peak, attributable to the S–H proton, was shifted from δ 3.40 for VI to δ 5.10 for V. This type of shift is always observed when protons, which are capable of hydrogen bonding, are ortho to carbonyl groups.[5] The nmr of VI also exhibited a symmetrical AB pattern (really AA'XX') centered at δ 7.45. This is typical of benzene compounds which have different substituents in the para positions.[6] The structure assignment for compound VII is consistent with the spectral data. The ir of VII exhibited strong bands at 688 and 742 cm^{-1} which are indicative of the monosubstituted benzene moiety, as well as a strong band at 890 cm^{-1} which can be attributed to para-disubstituted benzene.[7] One of the small peaks which could not be isolated could be the ortho analog of VII.

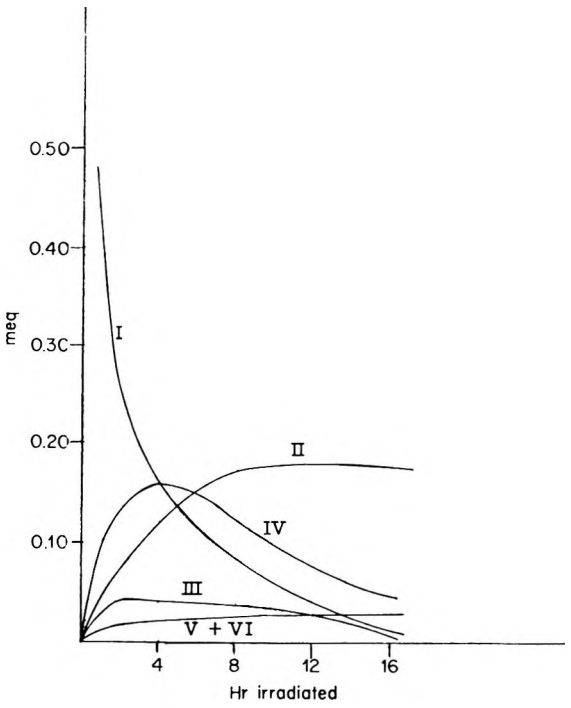


Figure 1.—0.1 *M* solution of *S*-phenyl thiolacetate in benzene.

The ratio of these products changed significantly as irradiation time was increased. As shown in Figure 1, the amount of II increased steadily while III and IV increased to a maximum at about 4 hr, then decreased in yield until the light was turned off after 16 hr. These results show that this is not a simple reaction. We feel the change in product ratios is due to secondary reactions. For example, diphenyl disulfide has been reported to form thiophenol when irradiated by ultraviolet light.[8] Compounds similar to thioanisole have been reported to form disulfides when irradiated.[9] The disulfide then would react to form thiols. We obtained thiophenol when we irradiated either thioanisole or diphenyl disulfide under our reaction conditions.

Table I gives a summary of the results of the irradiation of I in various solvents. The samples were irradiated until polymer build-up prevented further reaction. No products were observed when I was irradiated in either methyl carbitol ($CH_3OCH_2CH_2OH$) or ethanol. When a solution of I in benzene was irradiated by a low-pressure mercury lamp, the products were the same but ratios were different (see Table I). Apparently thioanisole is converted to diphenyl disulfide faster than the

* To whom correspondence should be addressed.

(1) Supported by the Brigham Young University Research Division and the United Fund of Utah County.

(2) Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer purchased under the National Science Foundation Grant GP-6837.

(3) Presented at the Pacific Northwest Regional Meeting of the American Chemical Society, Salt Lake City, Utah, June 1969.

(4) J. R. Grunwell, *Chem. Commun.*, 1437 (1969).

(5) See R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1967, p 122.

(6) See ref 5, p 127.

(7) See Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 26.

(8) Y. Schaofsma, A. F. Bickel, and E. Y. Kooyman, *Tetrahedron*, **10**, 76 (1960).

(9) W. Carruthers, *Nature*, **208**, 908 (1961).

TABLE I
IRRADIATION OF S-PHENYL THIOLACETATE USING A MEDIUM-PRESSURE LAMP

Solvent	Time, hr	% conversion	II	III	IV	V	VI	VII
Benzene	4	60	17	19	52	4	4	2
Benzene[a]	6	67	13	3	71	1	2	4
THF	48[b]	40	19	5	77	3	2	
Ether	48[b]	30	4	8	87	3	2	3
Cyclohexane	3	35	11	13	61	2	1	3

[a] A low-pressure Hanovia lamp was used. [b] Sample was in a quartz tube.

diphenyl disulfide is converted to thiophenol by the 2537-Å light.

We believe that the starting material cleaves under the influence of ultraviolet light to form C_6H_5S and $COCH_3$ radicals. The phenyl sulfide radical can then abstract a hydrogen atom to form thiophenol (II) or dimerize to form the disulfide IV. Occasionally, before the radicals separate, CO is liberated and the resulting phenylthiyl and methyl radicals combine to form thioanisole (III). Even less occasionally, the $COCH_3$ and phenyl sulfide radicals react to form the photo-Fries products V and VI. Intramolecular formation of products III, V, and VI has not been demonstrated; however, we believe that the reaction is intramolecular as are the corresponding esters.[10] Since irradiation of thiophenol did not yield diphenyl disulfide, we feel that VII was not formed by the irradiation of VI but rather by the combination of a phenylthiyl radical and *p*-acetylphenylthiyl radical. Thiophenol (II) is also formed by the secondary photolysis of III and IV as discussed above.

The source of the abstracted hydrogen (in thiophenol formation) is not known. Schaafsma and coworkers[11] have proposed that the hydrogen atom was abstracted from another phenylthiyl radical. Polymer would be a by-product of this reaction.[11] Polymer was observed in all our reactions. We observed no solvent dimer in any reaction which indicates that the solvent was not the source of the hydrogen atom.

Experimental Section

Materials and Apparatus.—Thiophenol and thioanisole were purchased from Aldrich Chemical Co. Diphenyl disulfide was purchased from Eastman Chemical Co. Benzene (Baker) was purified according to the procedure of Hammond.[12] Acetic anhydride (Matheson Coleman and Bell), cyclohexane and tetrahydrofuran (MCB), dimethylformamide (Baker), and anhydrous ethyl ether and methyl carbitol (Mallinckrodt) were reagent grade and used as received.

A Hanovia 450-W medium-pressure mercury lamp and a SC 2537 low-pressure mercury lamp were used. A quartz immersion reactor was used in all immersion reactions. All ir spectra were obtained on a Perkin-Elmer 457 spectrophotometer. The nmr spectra were obtained on a Varian A-60A spectrometer.[2] A Varian 202-B vapor phase chromatograph (vpc) was used to isolate all products. *S*-Phenyl thiolacetate was prepared by the procedure of Baker and Harris[13] and was purified by vacuum distillation: bp 55–60° (1 mm); ir 1710 cm^{-1}; nmr δ 2.20 (s, 3), 7.6 (s, 5).

Irradiation Procedure.—A 0.1 *M* solution of I in the appropriate solvent was placed in the immersion reactor. A small stream of pure nitrogen was sparged into the solution for 20–40 min before irradiation began and continued during the irradiation. The usual irradiation times were 2–4 hr. For irradiation times longer than 4 hr, polymeric material had to be removed from the well or the intensity of the light was greatly reduced. The solvent was then removed under the reduced pressure of a water aspirator at 50–60°. The remaining dark, foul-smelling liquid (5 ml) was placed in a vial under N_2 to prevent oxidation of the thiol (II) to disulfide (IV). The mixture was analyzed by vpc using a 3% SE-30 on Varaport 30 column and programming the temperature from 75 to 275°. Isolation was accomplished using 10% SE-30 on acid washed Chromosorb G. Chlorobenzene was used as an internal standard in determining product yields.

The runs in methyl carbitol, dimethylformamide, tetrahydrofuran, and ether were made in quartz tubes, degassed by three freeze–thaw cycles ($\sim 10^{-4}$ Torr). The tubes were irradiated for 24 hr on a "merry-go-round"[14] through a 1-cm^2 aperture and then 24 hr fully exposed to the low-pressure lamp. They were opened and analyzed by the same procedure as described above.

Analysis of the Products.—The products were isolated on the vpc and analyzed as follows. Fraction 1 (II), 2 (III), 3 (I), and 6 (IV) had ir and nmr spectra which were the same as authentic samples.

Fraction 4 (V) exhibited the following spectra: ir 3055, 2540 (SH), 1665 (C=O), 750 cm^{-1}; nmr (CCl_4) δ 2.55 (s, 3), 5.10 (s, 1), 7.45 (m, 4).

Fraction 5 (VI) exhibited the following spectra: ir 3050, 2550 (SH), 1680 (C=O), 820 cm^{-1}; nmr (CCl_4) δ 2.47 (s, 3), 3.40 (s, 1), 720 (d, 2), 7.70 (d, 2).

Fraction 7 (VII) exhibited the following spectra: ir 3055, 1675 (C=O), 890, 742, 688 cm^{-1}; nmr (CCl_4) δ 2.42 (s, 3), 7.4 (m, 9).

Registry No.—I, 934-87-2; V, 26824-02-2; VI, 3814-20-8; VII, 26824-04-4.

(10) M. R. Sandner, E. Hedaya, and D. J. Trecker, *J. Amer. Chem. Soc.*, **90**, 7249 (1968).

(11) Y. Schaafsma, A. F. Bickel, and E. C. Kooyman, *Tetrahedron*, **60**, 76, (1960).

(12) G. S. Hammond, S. C. Shim, and S. P. Van, *Mol. Photochem.*, **1**, 103 (1969).

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(14) P. J. Wagner and G. S. Hammond, *ibid.*, **88**, 1245 (1966).

A Reassignment of Structure to the Scholtz "Pyrrolo[1,2-*a*]indole"

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Received July 2, 1970

A literature search for examples of the pyrrolo[1,2-*a*]indole ring system, an important subunit of the mitomycin antibiotics,[2] revealed an early report of its preparation.[3] The *N*-acetylation and subsequent cyclodehydration of *N*-phenacylanthranilic acid (**1**) reportedly furnished the pyrrolo[1,2-*a*]indole **2a** (or some tautomer of it). This tricylic material was then hydrolyzed to the supposed indolylacrylic acid (**3a**). Our reinvestigation of these compounds, in the light of current spectroscopic structural analysis, has resulted in a reassignment of structure to these products. The phenacylanthranilic acid **1**, mp 183–184°, corresponding to the literature assignment, was prepared by alkylation of isatoic anhydride followed by hydrolysis rather than by

* To whom correspondence should be addressed.

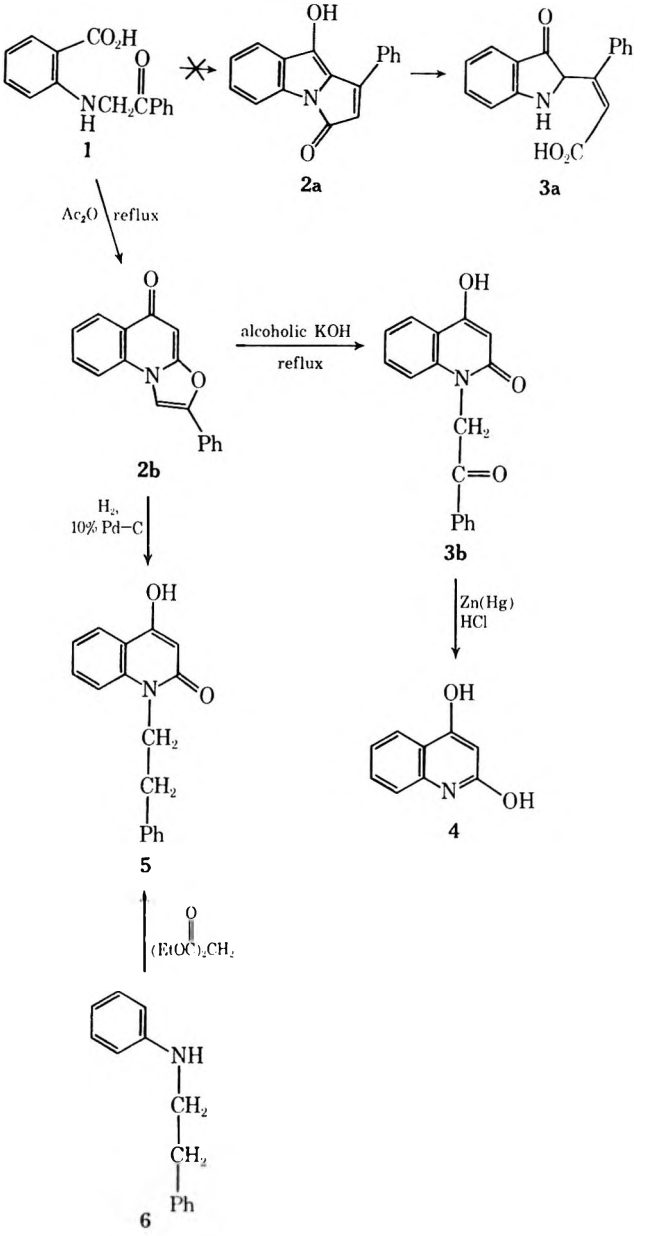
(1) This work was supported in part by Public Health Service Grants GM 12758 and CA 11421.

(2) G. O. Morton, G. E. Van Lear, and W. Fulmor, *J. Amer. Chem. Soc.*, **92**, 2588 (1970); the latest paper on the structural assignment of a member of the mitomycin class.

(3) (a) M. Scholtz, *Chem. Ber.*, **51**, 1645 (1918) (b) R. Wegscheider, *ibid.*, **52**, 1705 (1919).

the direct alkylation of anthranilic acid as in the original work. The cyclodehydration product, mp 276–278°, does not appear to have a carbonyl in a five-membered ring. It does not exhibit the characteristics of an enol. Its nmr spectrum reveals two uncoupled protons in deshielded environments which are not part of the aromatic envelope. In general, its uv and ir data are quite consistent with data for 2-alkoxy-4-quinolones.[4] We formulate the cyclodehydration product, mp 288°, as the oxazolo[3,2-*a*]quinoline **2b** (Scheme I). Thus, the

SCHEME I



hydrolysis product, mp 322–324° dec, of tricyclic **2b** is best formulated as the 4-hydroxy-1-phenacylcarbostyril **3b**, the spectral data of which are again in accord with the literature examples.[4] Further, zinc amalgam cleavage[5] of **3b** affords the parent quinoline **4**, identified by its superimposable ir and undepressed mixture melting point with an authentic sample.[6] This experiment demonstrates that **3b** has a quinoline framework. However, **3b** is obtained by base treatment of **2b** and one could argue that these conditions can effect retro-aldol and retro-Michael reactions followed by recyclizations, with the result being that the quinoline framework of **3b** is not at all related to **2b**. Thus, **2b** was subjected to catalytic hydrogenolysis, the product of which proved to be 4-hydroxy-1-phenethylcarbostyril (**5**), which was identical with a sample which was independently synthesized from phenethylaniline **6** and diethyl malonate.[7] To the best of our knowledge, **2b** is the first example of a neutral oxazolo[3,2-*a*]quinoline, although the ring system as the oxazolo[3,2-*a*]quinolinium perchlorate has been prepared.[8]

Experimental Section

***N*-Phenacylanthranilic Acid (1).**—To a mixture of 27.7 g (0.17 mol) of isatoic anhydride dissolved in 200 ml of dimethylformamide and 18 g (0.22 mol) of sodium carbonate was added 26.2 g (0.17 mol) of phenacyl chloride dissolved in 200 ml of dimethylformamide. The reaction mixture was allowed to stir vigorously over a 24-hr period at room temperature. After the excess sodium carbonate was filtered off, the reaction mixture was poured into 230 ml of 10% sodium hydroxide and acidified to pH 5 with 0.5 *N* aqueous hydrochloric acid. The crude product precipitated from the acidified solution and was subsequently filtered. After recrystallization from 95% ethanol, a total of 14.1 g (33%) of *N*-phenacylanthranilic acid was collected: mp 183–184° (lit.[3a] mp 190°); uv max (95% C_2H_5OH) 224 mμ (log ε 4.56), 254 (4.37), 282 (3.58), and 330 (3.79); ir (KBr) 1684, 1694, 2934, and 3339 cm^{-1}; nmr (acetone-d_6) δ 4.91 (s, 2 H), and 6.51–8.88 ppm (br envelope, 11 H).

Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.45; H, 5.14; N, 5.38.

2-Phenyl-5-oxooxazolo[3,2-*a*]quinoline (2b).—*N*-Phenylacylanthranilic acid (1) [12.10 g (0.047 mol)] was refluxed with 121 ml of acetic anhydride for 3 hr. The reaction mixture was then poured into 150 ml of water and yielded a flaky substance after hydrolysis of the anhydride. The crude material was recrystallized from boiling pyridine, yielding 6.64 g (54%) of 2-phenyl-5-oxooxazolo[3,2-*a*]quinoline: sublimes 180–190° (0.2 mm); mp 276.5–278° (lit.[3a] mp 288°); uv max (95% C_2H_5OH) 218 mμ (log ε 3.96), 221 (4.01), 259 (3.52), 290 (3.66), and 340 (3.92); ir (KBr) 1200, 1550, 1580, 1620, 1655, and 3070 cm^{-1}; nmr (glacial acetic acid) δ 6.73 (s, 1 H), 7.13–8.46 (br envelope, 9 H), and 8.65 ppm (s, 1 H).

Anal. Calcd for $C_{17}H_{11}NO_2$: C, 78.15; H, 4.24; N, 5.36. Found: C, 77.99; H, 4.25; N, 5.48.

4-Hydroxy-1-phenacylcarbostyril (3b).—A mixture of 6.01 g (0.023 mol) of 2-phenyl-5-oxooxazolo[3,2-*a*]quinoline (**2b**), 90 ml of 95% ethanol, and 15 g of potassium hydroxide dissolved in 30 ml of water was refluxed. After complete solution of the solid (*ca.* 40 min), the liquid was evaporated on a rotary vacuum evaporator leaving a solid mass which was dissolved in hot water and recovered by acidification of the solution to pH 5 with 0.5 *N* aqueous hydrochloric acid. Recrystallization from glacial acetic acid yielded 5.75 g (90%) of 4-hydroxy-1-phenacylcarbostyril: sublimes 265–285° (760 mm); 322–324° dec (lit.[3a] 300° dec); uv (95% C_2H_5OH) 205 mμ (log ε 3.31), 231 (3.60), 274 (2.92), 284 (2.92), and 319 (2.67); ir (KBr) 1545, 1565, 1595, 1640, 2920, and 3424 cm^{-1}; nmr (trifluoroacetic acid) δ 6.06 (s, 2 H), 7.00 (s, 1 H), and 7.21–8.60 ppm (br envelope, 10 H).

Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.01. Found: C, 72.99; H, 4.76; N, 5.08.

Hydrogenation of 2-Phenyl-5-oxooxazolo[3,2-*a*]quinoline (2b).—A sample of 0.301 g (1.15 mmol) of 2-phenyl-5-oxooxazolo[3,2-*a*]quinoline (**2b**) was dissolved in 5 ml of glacial acetic acid and added *via* a dropping funnel to the prereduced catalyst, 0.046 g of 10% Pd–C in acetic acid. As the reaction proceeded, the hydrogenated material precipitated out of the solvent. Hydrogen (2 equiv) was absorbed over a period of 10 hr. At the end of this time, the reaction mixture was removed from the hydrogena-

(4) H. Rapoport and K. G. Holden, *J. Amer. Chem. Soc.*, **82**, 4395 (1960).
(5) J. B. Hendrickson and C. Kandall, *Tetrahedron Lett.*, 343 (1970).
(6) Available commercially as the sodium salt from K and K Laboratories, Plainview, N. Y.
(7) E. Ziegler and R. Wolf, *Monatsch. Chem.*, **96**, 418 (1965).
(8) (a) C. K. Bradsher and M. F. Zinn, *J. Heterocycl. Chem.*, **4**, 66 (1967); (b) A. Lawson and D. H. Miles, *J. Chem. Soc.*, 2865 (1959).

tor and was heated until the precipitated material redissolved. After the mixture was allowed to stand overnight at room temperature, pure 4-hydroxy-1-phenethylcarbostyril **5** (85%) was collected. This material, mp 255–256°, was identical (uv, ir, and nmr) with that prepared *via* *N*-phenethylaniline (**6**).

4-Hydroxy-1-phenethylcarbostyril (5) *via* *N*-Phenethylanilin (6).—A solution of 3.00 g (0.015 mol) of *N*-phenethylaniline (**6**) and 1.034 g (0.0076 mol) of diethyl malonate was placed under an atmosphere of nitrogen. The system was heated slowly in a Wood's metal bath to a temperature of 250–260°. The reaction mixture liberated 0.4 ml of ethanol within 15 min which was collected in a Dean–Stark apparatus; this quantity, however, was only one-half the expected amount. Therefore, the system was heated for an additional 20 min at the same temperature but failed to produce any additional ethanol. The reaction mixture was allowed to cool to room temperature, and *ca.* 10 ml of acetone was then added which caused a precipitate to form which was filtered, yielding 0.0801 g (4%) of product which was identified as 4-hydroxy-1-phenethylcarbostyril: mp 255–256°; uv (95% C_2H_5OH) 213 mμ (log ε 4.05), 226 (4.34), 232 (4.35), 275 (3.58), and 285 (3.45); ir (KBr) 1635, 2910, and 3390 cm^{-1}; nmr (trifluoroacetic acid) δ 3.20 (t, 2, J = 7 Hz), 4.86 (t, 2, J = 7 Hz), 6.92 (s, 1 H), and 7.00–8.60 ppm (br envelope, 10 H).

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.82; H, 5.68; N, 5.34.

Further heating of the mother liquors at 140° for 4 hr with polyphosphoric acid brought the overall yield of **5** obtained from the reaction to 25%.

***N*-Phenethylaniline (6).**[9]—A mixture of 26.12 g (0.28 mol) of freshly distilled aniline, 6.61 g (0.078 mol) of sodium bicarbonate, and 10 ml of water was refluxed under an atmosphere of nitrogen. Freshly distilled phenethyl bromide [12.88 g (0.069 mol)] was added by means of an addition funnel during the first 2 hr of reflux; the mixture was allowed to reflux an additional 2.25 hr. The reaction mixture was then allowed to come to room temperature and filtered, and the aqueous and organic layers separated. The latter was washed with a saturated solution of sodium chloride. The amines were dried over sodium sulfate and again filtered. Separation of the amines was accomplished by vacuum distillation using a fractionating column; one fraction distilled at 26–28° (0.025 mm) and was identified as aniline.

The other fraction contained 8.45 g (54%) of *N*-phenethylaniline which distilled at 120–125° (0.025 mm): uv (95% C_2H_5OH) 212 mμ (log ε 4.32), 250 (4.39), and 295 (3.52); ir (CCl_4) 1600, 2925, 3020, and 3400 cm^{-1}; nmr (CCl_4) δ 2.75 and 3.25 (A_2B_2, J = 7 Hz, 4 H), 3.39 (s, 1 H), and 6.28–7.34 ppm (br envelope, 10 H). An exchangeable proton was seen at δ 3.39 with the appearance of a water peak at δ 4.67.

Anal. Calcd for $C_{14}H_{15}N$: C, 85.24; H, 7.66; N, 7.10. Found: C, 85.30; H, 7.62; N, 7.18.

2,4-Dihydroxyquinoline (4) *via* *N*-Phenacyl-2,4-dihydroxyquinoline (3b).—A mixture of 0.25 g of mossy zinc, 0.025 g of mercuric chloride, 0.01 ml of concentrated hydrochloric acid, and 0.4 ml of water was refluxed for 5 min in a 10-ml round-bottom flask, followed by the addition of 0.2 ml of water, 0.25 ml of toluene, 0.01 ml of glacial acetic acid, and 0.200 g (0.0007 mol) of *N*-phenacyl-2,4-dihydroxyquinoline (**3b**), respectively. The mixture was refluxed continuously for 24 hr with the addition of 0.4 ml of concentrated hydrochloric acid every 6 hr. After the mixture was cooled to room temperature, 0.082 g (73%) of pure product precipitated and was identified by its melting point and superimposable ir as 2,4-dihydroxyquinoline.

2,4-Dihydroxyquinoline (4) *via* Hydrolysis of Its Sodium Salt.—A sample of 6.471 g of the sodium salt of 2,4-dihydroxyquinoline was dissolved in about 40 ml of hot water. Material that remained after the solution came to room temperature was filtered off. The aqueous filtrate was acidified to pH 5–6 by dropwise addition of 5% aqueous hydrochloric acid. In this manner, 4.215 g (76%) of 2,4-dihydroxyquinoline was collected: mp 354–355° (lit.[10] mp 355°); ir (KBr) 1230, 1325, 1670, 2850, and 3350 cm^{-1}.

Registry No.—**1**, 732-64-9; **2b**, 26630-29-5; **3b**, 26630-30-8; **5**, 26630-31-9; **6**, 1739-00-0.

(9) H. Gilman, Ed., "Organic Syntheses," Coll. Vol. 1, Wiley, New York, N. Y., 1932, p 97.

(10) E. H. Rodd, Ed., "Chemistry of Carbon Compounds," Vol. 4A, Elsevier, New York, N. Y., 1957, p 624.

A Study of the Mechanism of the Photoisomerization of 2-Phenylisatogen to 2-Phenyl-4*H*-3,1-benzoxazin-4-one[1]

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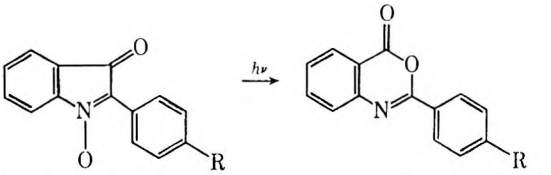
Received December 11, 1969

Recently we have described the photoisomerization of 2-phenylisatogen (**1a**) to 2-phenyl-4*H*-3,1-benzoxazin-4-one (**2a**) (eq 1), in various solvents with various



(1)

1a, R = H; **b**, R = Br **2**

light sources.[3] With 5.6×10^{-3} M concentration of 2-phenylisatogen in cyclohexane, there is almost quantitative conversion to **2a** after 3 hr of irradiation with a 450-W medium-pressure total immersion lamp.

The reaction, followed by ultraviolet spectra at several stages, shows isosbestic points at 255 and 300 mμ in solvents cyclohexane, cyclohexene, chloroform, absolute ethanol, 95% ethanol, and glacial acetic acid. The presence of isosbestic points indicates that there is no photostationary intermediate (*i.e.*, there is no intermediate with a lifetime of more than several seconds).

Unusual behavior at 2537-Å irradiation was displayed in solvents benzene, toluene, acetone, and methylisobutyl ketone. In each solvent, irradiation at 2537 Å gives rise to a photostationary intermediate, with absorption maxima in benzene solution at 356, 378, and 400 mμ (vibronic spacing = 1450–1475 cm^{-1}). Upon continued irradiation the intermediate is consumed and 2-phenyl-4*H*-3,1-benzoxazin-4-one, **2a**, is almost quantitatively formed. With 3500-Å-irradiation the intermediate is not formed in these solvents and the superimposed uv spectra of the reaction at various times show an isosbestic point (at 300 mμ) identical with the first six solvents.

It appears that the reaction proceeds by way of a singlet mechanism and that the aromatic and ketonic solvents behave as triplet sensitizers, thus allowing another reaction to take place.

Quantum yields were found to be independent of time and intensity of irradiation, and the presence of oxygen, but dependent on wavelength, concentration, solvent, and temperature.

The quantum yields of formation of **2a** in cyclohexane solution are shown in Table I. The decreased quantum yield in the presence of 10^{-2} M *m*-methoxyacetophenone can be accounted for by the fact that *m*-methoxyaceto-

(1) Part of this work was presented as a paper at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, ORGN 13.

(2) To whom all inquiries should be addressed: Department of Chemistry, York College, Flushing, N. Y. 11365.

(3) D. R. Eckroth and R. H. Squire, *Chem. Commun.*, 312 (1969); D. R. Eckroth, *ibid.*, 465 (1970).

TABLE I

Φ_{dis} OF 1a[a]

Solvent	Temp, °C	λ, mμ (±15 mμ)	$\Phi_{dis} \times 10^3$	Molar concn of 1a
Cyclohexane	25	254	15.1	1×10^{-3}
Cyclohexane	25	265	12.5	1×10^{-3}
Cyclohexane	25	295	8.0	1×10^{-3}
Cyclohexane	25	302	5.6	1×10^{-3}
Cyclohexane	25	305	6.2	1×10^{-3}
Cyclohexane	25	350	0.0	4×10^{-3}
Cyclohexane	45	305	7.2	1×10^{-3}
Cyclohexane	60	254	16.0	1×10^{-3}
Cyclohexane	60	265	14.3	1×10^{-3}
Cyclohexane	60	295	9.2	1×10^{-3}
Cyclohexane	60	305	7.4	1×10^{-3}
Cyclohexane with 10^{-2} *M* *m*-methoxyacetophenone	25	302	3.2	1×10^{-3}
Ethyl bromide–cyclohexane (1:2 vol ratio)	25	305	4.6	1×10^{-3}
Absolute ethanol	25	254	6.0	1×10^{-3}

Φ_{dis} of 1b[a]

Solvent	Temp, C°	λ, mμ (±15 mμ)	$\Phi_{dis} \times 10^3$	Molar concn of 1b
Cyclohexane	25	254	9.1	1×10^{-3}
Cyclohexane	25	305	4.5	1×10^{-3}
Cyclohexane	60	305	5.5	1×10^{-3}

[a] Φ_{dis} measured by disappearance of absorption maximum of 1a at 442 mμ and that of 1b at 450 mμ. Maximum error of Φ_{dis} is ±10%.

phenone is absorbing approximately half of the light at 3025 Å.

In the presence of ethyl bromide, intermolecular spin orbit coupling[4] presumably allows rapid intersystem crossing which slows the apparently singlet reaction. Intramolecular spin orbit coupling[5] is demonstrated by the reduced quantum yields of product from 2-(*p*-bromophenyl)isatogen (1b).[6]

The quantum yields from benzene solutions, shown in Table II, indicate strong concentration dependence.[7]

TABLE II

Φ_{dis} OF 1a[a]

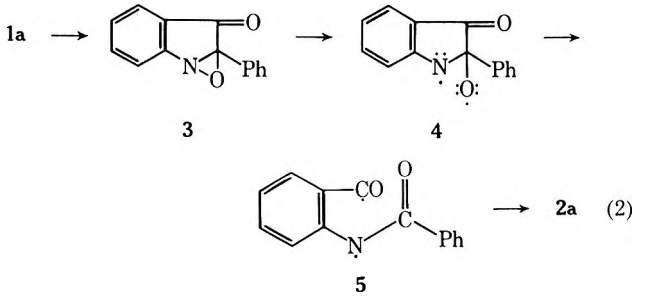
Solvent	Temp, °C	λ, mμ (±15 mμ)	$\Phi_{dis} \times 10^4$	Molar concn of 1a
Benzene	25	254	15.7	1×10^{-3}
Benzene	25	295	24.7	1×10^{-3}
Benzene	25	302	20.6	1×10^{-3}
Benzene	25	305	23.5	1×10^{-3}
Benzene	25	305	6.2	5×10^{-3}
Benzene	25	305	4.3	1×10^{-2}
Benzene	25	305	0.4	5×10^{-2}
Benzene with 10^{-2} *M* thioxanthone	25	302	12.9	1×10^{-3}
Benzene with 10^{-2} *M* *m*-methoxyacetophenone	25	302	9.8	1×10^{-3}

[a] Φ_{dis} measured by disappearance of absorption maximum of 1a at 442 mμ. Maximum error of Φ_{dis} is ±10%.

Triplet sensitizers such as thioxanthone and *m*-methoxyacetophenone reduce the quantum yield considerably at 3025 Å, but this is in part due to the fact that at their concentrations, they absorb roughly half of the light.

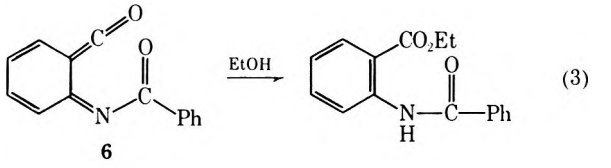
The fact that the quantum yield depends upon the concentration[8] of isatogen suggests that the reaction is sufficiently slow and that the deactivation of excited isatogen molecules with ground-state molecules occurs; *i.e.*, the compound apparently undergoes self-quenching.[7]

A possible reaction scheme could have initial conversion of the isatogen to the oxaziridine, **3**,[9] followed by N–O bond cleavage which could lead to a diradical **4**, with unpaired electrons on nitrogen and oxygen.[10] A homolytic cleavage of the C_2–C_3 bond could lead to diradical **5**. Bond formations at C_3–O and C_2–N could then lead to the benzoxazinone **2a** (eq 2). There is



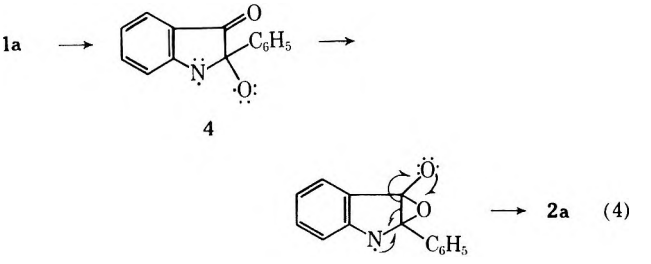
(2)

difficulty in rationalizing this scheme in that intermediate **5** is a form of the imine–ketene **6**, which should be trapped by a polar solvent such as ethanol in the same way as that described by Ege[11] (eq 3).



(3)

It appears that the diradical **4** must form a C_3–O bond either before or in concert with C_3–C_2 bond cleavage, in order to prevent imine–ketene formation *via* **5**[12] (eq 4).



(4)

Experimental Section

Materials.—**2-Phenylisatogen** (1a) was prepared according to a procedure outlined by Jones,[13] and recrystallized twice from ethanol, mp 188–190° (lit.[13] mp 189.5–190°).

2-(4′-Bromophenyl)isatogen (1b) was prepared by a modification of Jones'[13] procedure with α,*p*-dibromotoluene and recrystallized twice from ethanol, mp 183° (lit.[14] mp 183–184°).

(4) M. Kasha and S. P. McGlynn, *Annu. Rev. Phys. Chem.*, **7**, 403 (1956).

(5) S. P. McGlynn, T. Azumi, and M. Kinoshita, "Molecular Spectroscopy of the Triplet State," Prentice-Hall, Englewood Cliffs, N. J., p 183.

(6) There is almost quantitative conversion of **1b** to **2b**.

(7) O. L. Chapman and G. Wampfler, *J. Amer. Chem. Soc.*, **91**, 5390 (1969).

(8) Beer's law is obeyed at every concentration.

(9) For an excellent review, see G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, **70**, 231 (1970).

(10) Competitive thermal processes **3** → **4** and **3** → **1a** might account for the temperature dependence.

(11) G. Ege, *Angew. Chem.*, **77**, 723 (1965). R. K. Smalley, H. Suschitsky, and E. M. Tanner, *Tetrahedron Lett.*, 2465 (1966), showed that imine–ketenes structurally similar to **6** can easily dimerize.

(12) A similar suggestion was made in the case of photochemistry of silyl ketones by A. G. Brook and J. M. Duff, *J. Amer. Chem. Soc.*, **89**, 454 (1967).

(13) D. A. Jones, Ph.D. Dissertation, University of Minnesota, 1961.

(14) F. Kröhnke and I. Vogt, *Ber.*, **86**, 376 (1952).

2-Phenyl-4*H*-3,1-benzoxazin-4-one (2a) was synthesized independently according to the procedure described by Bogert, *et al.*,[15] mp 124° (lit.[15] mp 124.5°).

2-(4′-Bromophenyl)-4*H*-3,1-benzoxazin-4-one (2b) was synthesized by a modification of Bogert's[15] procedure with *p*-bromobenzoyl chloride, mp 185–189° (lit.[16] mp 183–184°).

The cyclohexane, chloroform, benzene, and acetone were spectroscopic grade. They were further dried over magnesium sulfate and distilled through a 30-cm column. Only the middle cuts were used. The cyclohexene, toluene, and methylisopropyl ketone were reagent grade and were purified as described above. The 95% ethanol was made from absolute ethanol and distilled water. The acetic acid was reagent grade.

Typical Irradiation Experiments. With Rayonet 2537-and 3500-Å Lamps.—1a or 1b (0.5 g) was dissolved in 650 ml of solvent, placed in a quartz reaction vessel fitted with a magnetic stirrer, and irradiated for an extended period of time.

With Hanovia 450-W Medium-Pressure Immersion Lamp (No Filter).—One gram of 1a or 1b was dissolved in 750 ml of solvent, placed in a water-cooled reaction chamber, and irradiated for 1–3 hr. The benzoxazinone (2a or 2b) was separated from the unreacted starting material by sublimation (95°, 0.1 mm, 30 hr).

Quantum Yields.—For quantum-yield determinations light from a Bausch and Lomb high-intensity monochromator equipped with an Osram HBO-200W super-pressure mercury source was employed. The monochromator settings were at 254, 265, 295, 302, 305, and 350 mμ and the exit slits were set at 4 mm. Under these conditions the maximum band width was 29.6 mμ. The light passed directly into a standard glass-stoppered 10 × 10 mm silica cuvette which served as the reaction vessel. The cell was held 5.5 cm from the exit port of the monochromator in a metal compartment maintained at constant temperature by flowing water. Light incident on the reaction solution was determined by irradiating samples of actinometer solution both before and after irradiation of the reaction solution. The extent of reaction was determined by the decrease in absorbance at 442 mμ with 1a and 450 mμ with 2a, and the period of irradiation was such that the reaction proceeded less than 10% to completion. Calculations of quantum yields were performed with the procedure described by Calvert and Pitts.[17]

Spin Orbit Coupling.—Irradiation of a 10^{-4} *M* solution of 1b in cyclohexane showed a decreased rate of reaction from that of the nonbrominated material, 1a (see Table I).[6] In order to determine the nature of this rate retardation as a spin orbit effect,[5] a cyclohexane solution of 13 ml of 1.08×10^{-4} *M* 1a and 1 ml of ethyl bromide was irradiated in reference to a sample of 10^{-4} *M* 1a in cyclohexane without ethyl bromide. An observed rate decrease in the former solution seemed to establish the intermolecular spin orbit effect.[4]

Registry No.—1a, 1969-74-0; 2a, 1022-46-4.

Acknowledgment.—One of us (D. R. E.) wishes to express his indebtedness to Professor O. L. Chapman for many helpful discussions.

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A Facile Synthesis of New Heterocycles from Glutaraldehyde

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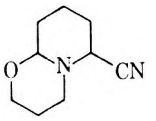
Received June 8, 1970

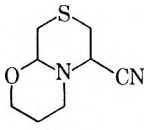
The reaction of glutaraldehyde dicyanohydrin with 3-aminopropanol to give the reduced pyrido[2,1-*b*][1,3]-oxazine (1) has been reported.[1] The apparent resemblance of this reaction to the remarkable Robinson–Schöpf synthesis[2] of pseudopelletierine from methylamine, acetone dicarboxylic acid, and glutaraldehyde suggested the following extensions.



1

The reported procedure has been simplified and the yields improved by the use of a phosphate buffer and by the generation of the cyanohydrin *in situ* rather than in a separate step.[3] Thus an 80% yield of 1 is obtained when potassium cyanide (1.5 mol), glutaraldehyde (1.0 mol), and 3-aminopropanol (1.07 mol) are stirred in a phosphate buffer at pH 4 for 4 hr compared with 67% after 20 hr from the pure dicyanohydrin.[1] The reaction is pH sensitive and proceeds best between pH 3 and 7, only resinous products being formed at high pH. This pH dependence has also been reported for the synthesis of pseudopelletierine[4] and suggests that both reactions share a Mannich-like mechanism.

The following heterocycles were prepared by this simplified procedure.



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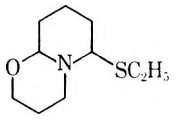
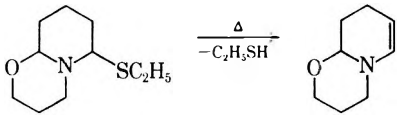


3

Compound 2, a new ring system, was prepared in 45% overall yield from thiodiacetaldehyde diethylacetal.[5] Replacement of potassium cyanide in the synthesis by ethanethiol gave the product 3 in 88% yield. Although this product is thermally unstable and fails to give crystalline products with hydrochloric, perchloric, or picric acids, a concentrate with the proper ir spectrum was obtained. The ir spectrum of the distillation product showed a band at 1630 cm^{-1} which indicated that the enamine 4 had been formed. All attempts to characterize this labile enamine failed. Attempts to prepare more stable products by using diethyl malonate or ethyl cyanoacetate with glutaraldehyde and 3-aminopropanol in aqueous alcoholic solution instead of cyanide led only to intractable gums. As expected, amines (ammonia, benzylamine) and succinimide failed to give the corresponding bicyclic 1,1-diamine derivatives. An unusual 1,1-diamine, 5, was, however, prepared by sub-



4

(1) H. E. Johnson, U. S. Patent 3,375,249 (1968), to Union Carbide Corporation.

(2) Sir R. Robinson, *J. Chem. Soc.*, **111**, 762, 876 (1917); C. Schöpf and G. Lehmann, *Justus Liebigs Ann. Chem.*, **518**, 1 (1935); C. Schöpf, *Angew. Chem.*, **50**, 779, 797 (1937); L. A. Paquette and J. W. Heimaster, *J. Amer. Chem. Soc.*, **88**, 763 (1966).

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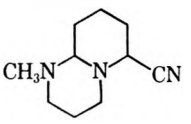
stituting *N*-methylpropane-1,3-diamine for 3-aminopropanol in the synthesis of **1**. The diamine was suffi-



5

ciently stable in neutral or basic, aqueous solution to be readily isolated but no crystalline salts could be prepared.

These reactions are further examples of intramolecular Mannich reactions some of which have been described by Leonard[6] and elegantly exploited by Wenkert[7] in the synthesis of alkaloids. The successive generation of two imine (or iminium) groups by reaction of a primary amine with a dialdehyde in the presence of a nucleophile appears to provide a versatile synthetic tool which has yet to be widely used. Tricyclic products[8] have already been reported from this type of reaction and Lichtenthaler reports[9] an analogous reaction of glutaraldehyde, nitromethane, and benzylamine to give a cyclohexane derivative.

Experimental Section

Melting points are uncorrected. Nmr spectra were recorded on a Varian HA-100 nmr spectrometer.

6-Cyano-3,4,7,8,9,9a-hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]-oxazine (1).—A solution of potassium cyanide (24.45 g, 0.375 mol) in water (150 ml) was brought to pH 7 by the addition of 17 ml of 85% phosphoric acid. A 50% aqueous solution of glutaraldehyde (50 g, 0.25 mol) was added at 20° causing some turbidity. 3-Aminopropanol (20 g, 0.267 mol) was then added dropwise. During the addition, the temperature rose to 38° and was accompanied by a temporary rise in pH to 8 followed by a decrease to pH 7. After standing for 4 hr, the pale yellow solution was extracted with five 25-ml portions of methylene chloride. The combined extracts were dried (Na_2SO_4), concentrated, and distilled, giving 32.4 g (78%) of the product **1**: bp 128–130° (0.5 mm); ir (film) 2941, 2857, 2739 (CH), 2222 (C≡N), 1265, 1258, 1142, 1123, 1092, 1069, 1061 (OCN);[10] nmr ($CDCl_3$) δ 1.3–2.2 (m, 9), 2.6–3.25 (m, 2), 3.4–4.1 ppm (m, 4). Treatment of **1** with anhydrous hydrogen chloride in ether and recrystallization from ether gave the hydrochloride: mp 145–146°; ir (KBr) 2958, 2915, 2739 (CH), 2500 (broad, NH, obscuring C≡N), 1298, 1156, 1096, 1070 cm^{-1} (COC).[10]

Anal. Calcd for $C_9H_{15}N_2OCl$: C, 53.33; H, 7.46; N, 13.82. Found: C, 53.15; H, 7.52; N, 14.02.

6-Ethylthio-3,4,7,8,9,9a-hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]-oxazine (3).—A 50% aqueous solution of glutaraldehyde (255 g, 1.3 mol) was added with stirring to a mixture of ethanethiol (78.9 g, 1.27 mol), methanol (90 ml), and water (300 ml) at 0°. 3-Aminopropanol (90 g, 1.2 mol) was added dropwise with stirring during which time the temperature rose to 32° and the mixture became heterogeneous and bright yellow. After stirring overnight, the mixture was basified (NaOH) and extracted with six 100-ml portions of methylene chloride. The dried (Na_2SO_4) extract was filtered through activated charcoal and concentrated to give a clear orange oil (211.9 g, 88% based on 3-aminopropanol), ir (film) 2941, 2857, 2732 (CH), 1312, 1273, 1149, 1126, 1098 cm^{-1} (COC).[10]

Anal. Calcd for $C_{10}H_{19}NOS$: C, 59.67; H, 9.52; N, 6.96. Found: C, 60.00; H, 9.43; N, 6.68.

Attempted distillation of the product from a Woods metal bath at 155° gave a small amount of yellow liquid (crude **4**): bp 62–66° (1.75 mm); ir (film) 1630 (C=C), 1200–1100 cm^{-1} (COC).[10]

6-Cyano-1-methyl-1,2,3,4,7,8,9,9a-octahydro-6*H*-pyrido[1,2-*a*]-pyrimidine (5).—The pH of a solution of potassium cyanide (24.45 g, 0.375 mol) in water (150 ml) was brought to 7 by the addition of 17 ml of 85% phosphoric acid. A 50% aqueous solution of glutaraldehyde (50 g, 0.25 mol) was added, followed by the dropwise addition of 24.2 g (0.275 mol) of *N*-methyl-1,3-propanediamine. The diamine caused an exothermic reaction to 55° and an increase in pH which was controlled by dropwise addition of 85% phosphoric acid.

After the addition was complete, the heterogeneous mixture was allowed to stand for 4 hr, basified with 40% sodium hydroxide solution, and extracted with three 100-ml portions of ether. The dried (Na_2SO_4) extracts were concentrated and distilled giving 10 g of **5** (20.2%): bp 136–137° (2.5 mm); ir (film) 2941, 2857, 2793, 2710, 2577 (CH), 2222 cm^{-1} (C≡N).

Anal. Calcd for $C_{10}H_{17}N_3$: C, 66.99; H, 9.57; N, 23.44. Found: C, 66.99; H, 9.39; N, 23.17.

A further 5.1 g, bp 137–143° (2.5 mm), of material with a virtually identical ir spectrum was collected bringing the total yield to 30.5%.

6-Cyano-3,4,6,7,9,9a-hexahydro-2*H*-1,4-thiazino[3,4-*b*][1,3]-oxazine (2).—Thiodiacetaldehyde tetraethylacetal[6] (50 g, 0.188 mol) was stirred with 250 ml of water containing 5 ml of concentrated hydrochloric acid at 55°. The mixture became homogeneous in 10 min and was stirred for a further 50 min. After cooling to 0°, a solution of 18.8 g (0.29 mol) of potassium cyanide in 50 ml of water at 0° was added, the pH being kept below 7.5 by concurrent addition of cold 50% aqueous phosphoric acid (30 ml). A flocculent white precipitate remained suspended in the mixture. 3-Aminopropanol (14.1 g, 0.188 mol) dissolved in 25 ml of water was then added, the pH again being maintained between 6.5 and 8 by the addition of 50% aqueous phosphoric acid (10 ml required). The temperature was allowed to rise to 25° during the addition and the precipitate virtually dissolved leaving a pale yellow solution. The mixture was allowed to stand overnight and was then basified and extracted with three 75-ml portions of methylene chloride. The dried ($MgSO_4$) extract was concentrated to give 21.4 g of a yellow oil which crystallized on standing. Recrystallization from ethanol gave 15.6 g (45%) of crude product, mp 116–119°, which on further recrystallization gave pure **2**, mp 126–127°. The mother liquors smelled strongly of hydrogen cyanide: ir (KBr) 2980, 2898, 2857, 2777, 2739, 2666 (CH), 2257 (C≡N), 1282, 1257, 1234, 1219, 1206, 1183, 1145, 1111, 1003, 1070 cm^{-1} (COC);[10] nmr ($CDCl_3$) δ 1.6 (m, 1), 2.1 (m, 1), 2.6–3.3 (m, 6), 3.6 (m, 1), 4.1 (m, 3).

Anal. Calcd for $C_8H_{12}N_2OS$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.00; H, 6.53; N, 14.99.

Registry No.—**1**, 19791-32-3; **1** hydrochloride, 26693-23-2; **2**, 15311-74-7; **3**, 26731-49-7; **4**, 26693-20-9; **5**, 26693-21-0.

Acknowledgments.—The author wishes to thank the following: Professors H. O. House and H. H. Wasserman for helpful discussions; Mr. C. B. Strow and Mr. H. L. Joyce and their colleagues for the nmr and ir spectra.

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Ring Strain Effects on Aromatic Reactivity. A Molecular Orbital Treatment

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Received June 29, 1970

The first theoretical discussion of the reduced reactivity of the α position of strained benzocycloalkenes was advanced by Mills and Nixon[1] over 40 years ago.

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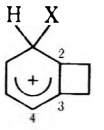
Their model, along with others presented recently, has proven to be inaccurate.[2] Recently, two generalizations have been put forth to explain the observed reactivity. Vaughan[3] has offered a bond order argument. He points out that in the Wheland intermediate for α substitution, the bond common to both rings has $^2/_3$ double bond character, while for β substitution it has only $^1/_3$ double bond character. This tends to decrease the bond length for α substitution but increase it for β substitution. Accordingly, he argues that as strain is increased in the fused ring, the transition state for α attack will be destabilized relative to the transition state for β attack. Streitwieser[4] has offered an explanation based on a rehybridization–polarization argument. In this model, it is suggested that the ring juncture carbons will have to rehybridize to accommodate the small bond angles of the strained ring. Thus, the σ bonds in the strained ring will have increased p character and the remaining σ bonds to the aromatic carbons α to the fused ring will have more s character. This increase in orbital electronegativity results in a polarization of σ electrons away from the α carbons. The net result is a decrease in reactivity of the α position toward electrophiles. In addition, the observed increase in acidity of the α protons with increased strain is explained.[4,5] Markgraf's[6] observation of reduced basicity of the lone pair of electrons of a nitrogen α to a strained ring is also explained.

We have demonstrated that Streitwieser's model can also be used to explain changes in half-wave reduction potentials[7,8] and changes in spin densities[9,10] of aromatic radical anions. We have been able to correlate this data within the Hückel framework by making the α carbons more electronegative with increased strain and the ring juncture carbons more electropositive. In this paper, we would like to point out that use of simple perturbation theory[11] within the Hückel framework plus the parameters derived from the epr and polarographic data can explain the observed decrease in reactivity of the α position of benzocyclobutene.

The energy of the neutral molecule in simple perturbation theory is equal to that of the unperturbed molecule, benzene, plus the change in energy due to changes in coulomb integrals of the atomic orbitals.[12] The energies of the Wheland intermediates for α and β substitution are equal to the unperturbed pentadienyl cation, E^+, plus the energy changes caused by the changes in coulomb integrals of the atomic orbitals.[13]

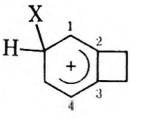
$$\alpha_1 = \alpha_4 = \alpha_0 + h_1\beta$$
$$\alpha_2 = \alpha_3 = \alpha_0 + h_2\beta$$
$$E^0 = E_{benzene} + h_1\beta + h_2\beta + h_3\beta + h_4\beta$$
$$E^0 = E_{benzene} + 2h_1\beta + 2h_2\beta$$



I

$$E^I = E^+ + {}^2/_3h_2\beta + h_3\beta + {}^2/_3h_4\beta$$
$$h_1 = h_4 \text{ and } h_2 = h_3$$
$$E^I = E^+ + {}^2/_3h_2\beta + h_2\beta + {}^2/_3h_1\beta$$
$$E^I = E^+ + {}^2/_3h_1\beta + {}^5/_3h_2\beta$$

The energy of activation for α and β attack can then be approximated by substracting the energy of the neutral molecule from that of each of the Wheland intermediates. In order to explain the observed preference of β attack, it follows that $\Delta E_I > \Delta E_{II}$; if we ignore common terms



II

$$E^{II} = E^+ + {}^2/_3h_1\beta + h_2\beta + {}^2/_3h_3\beta + h_4\beta$$
$$h_1 = h_4 \text{ and } h_2 = h_3$$
$$E^{II} = E^+ + {}^2/_3h_2\beta + h_2\beta + {}^2/_3h_2\beta + h_1\beta$$
$$E^{II} = E^+ + {}^5/_3h_1\beta + {}^5/_3h_2\beta$$

ΔE for α attack

$$\Delta E_I = E^I - E^0 = E^+ - E_{benzene} - {}^4/_3h_1\beta - {}^1/_3h_2\beta$$

ΔE for β attack

$$\Delta E_{II} = E^{II} - E^0 = E^+ - E_{benzene} - {}^1/_3h_1\beta - {}^1/_3h_2\beta$$

the inequality shown below must hold. This demonstrates that h_1 must be positive and greater than zero.

$$(4h_1 + h_2) > (h_1 + h_2)$$

Thus the carbon atoms α to the strained, fused ring have become more electronegative with respect to the π electrons; this is implied by Streitwieser's Model[4] and has been demonstrated by our epr and polarographic studies.[7-10] The parameters for naphtho[*b*]cyclobutene[8] derived from polarographic studies were $h_1 = 0.1$ and $h_2 = -0.3$. If one used these parameters in conjunction with the expressions derived above for the energies of activation and a value of -18 kcal/mol for β,[14] one predicts that β substitution will occur approximately 50:1 over α substitution. In addition, the simple theory predicts that electrophilic substitution at the β position will occur faster than electrophilic substitution of benzene while substitution at the α position will occur almost at the same rate as benzene. Recently,

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(9) R. D. Rieke, C. F. Meares, and L. I. Rieke, *Tetrahedron Lett.*, 5275 (1968).

(10) R. D. Rieke and W. E. Rich, *J. Amer. Chem. Soc.*, **92**, 7349 (1970).

(11) N. V. Riggs, "Quantum Chemistry," Macmillan, New York, N. Y., 1969, p 184.

(12) In simple perturbation theory, the change in total π energy of a molecule caused by a change of one or more coulomb integrals is given by the product of the total electron density at a particular atom (i) and the change in the coulomb integral for that atom, $h_i\beta$.

(13) Using the nonbonding molecular orbital of the pentadientyl system, the total π-electron densities of $^2/_3$ for positions 2, 4, and 6 are easily determined. The π-electron densities at positions 3 and 5 are found to be unity.

(14) The value of -18 kcal/mol is frequently used in simple molecular orbital theory. The basic conclusions of the paper are not dependent on the value of β and essentially the same results will be obtained if one uses one of the other values for β found in the literature.

Eaborn[15] published the relative rates of protodesilylations of a series of benzocycloalkenes. He found that in benzocyclobutene the β position underwent protodesilylation ten times faster than the α position; this is remarkably close to what the simple molecular orbital calculations predict. He also found that the β position was 154 times as reactive as benzene while the α position was only 16 times as reactive. Once again, these results are close to those predicted by the above treatment.

The only other strained aromatic hydrocarbon for which there is any electrophilic substitution data is naphtho[*b*]cyclobutene.[9,16] Cava has reported that upon nitration of naphtho[*b*]cyclobutene the major product isolated is the 1-nitronaphtho[*b*]cyclobutene.[16] We found that the major product upon bromination is 1-bromonaphtho[*b*]cyclobutene.[9] There are, however, no relative rate studies available for this molecule. However, if one applies the simple perturbation calculations to this molecule, one finds that using $h_1 = 0.08\beta$ and $h_2 = -0.38\beta$ will give preferred electrophilic attack α to the fused, four-membered ring rather than in the adjacent benzene ring. These parameters are essentially the same as those derived from the polarographic data for this molecule.

One could make the simple MO calculations agree even better with the electrophilic substitution data by arbitrarily varying the parameters. Due to the semiempirical nature of this approach, this would add nothing to the argument. The remarkable thing about this model of ring strain and the derived parameters is that they adequately describe such diverse chemical and physical properties as epr and polarographic data,[7-10] acidity and basicity,[4-6] and relative rates of electrophilic substitution.[15] Vaughan's model, on the other hand, is not based on a firm theoretical basis and is not able to explain the changes in physical properties of aromatic hydrocarbons with strain.

Registry No.—Benzocyclobutene, 694-87-1.

Acknowledgment.—Financial support of this investigation by the University of North Carolina Materials Research Center under Contract SD-100 with the Advanced Research Projects Agency is gratefully acknowledged.

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Photocoronopilin-A, a Cleaved Pseudoguaianolide from the Photolysis of Coronopilin

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Received July 20, 1970

In our continuing study of the photochemical transformations of sesquiterpene lactones[1] we wish to report a C_4–C_5 cleaved photolytic product from the pseudoguaianolide coronopilin (**1**). The product, which we named photocornopilin-A,[2] was of particular interest since we had previously discovered a series of naturally occurring C_4–C_5 cleaved pseudoguaianolides, the psilostachyins, in various *Ambrosia* species.[3,4] For example, *Ambrosia psilostachya* DC. plants which occur on a chain of islands which line the Texas gulf produce only cleaved pseudoguaianolides while plants of the same species which were collected on the adjacent mainland contained only typical pseudoguaianolides including coronopilin.[5] Furthermore, the major island constituent psilostachyin-A (**2**) could be derived directly by treatment of coronopilin with peracetic acid.

A benzene solution of coronopilin (*c* 0.08) was irradiated at 253.7 nm for 2.5 hr.[6] A major photo product, photocoronopilin-A (**3**) (mp 93–97°, $C_{15}H_{20}O_4$), was isolated in about 40% yield based upon the amount of coronopilin consumed. The presence of an α,β'-conjugated γ-lactone function and a hydroxyl group in the photoproduct was evident from the uv, ir, and nmr data: λ_{max} 211 nm (ϵ 8900); ir bands 3500–3600, 1752, 1655, and 1640 cm^{-1}; nmr (see Experimental Section). Moreover, the nmr data indicated that while the C_{10} secondary methyl group was still present, the C_5 methyl group had disappeared. Acetylation of photocoronopilin-A gave an acetate whose nmr spectrum (see Experimental Section) was best interpreted on the basis of formula **4**. Accordingly, photocoronopilin-A would be represented by structure **3**.

Confirmation of structure **3** for photocoronopilin-A was provided by CrO_3 oxidation of photocoronopilin-A to the known anhydropsilostachyin (**5**), a substance previously prepared from psilostachyin-A (**2**).[3]

Photocoronopilin-A appears, for the following reasons, to be a 1:1 mixture of C_4 epimers: (1) The C_{13}-methylene and C_{10}-methyl proton signals of photocoronopilin-A are each overlapped doublets. (2) A stereospecific hemiacetal formation during photolysis does not appear to be likely.

Experimental Section[7]

The photolytic reaction was carried out using a Rayonet reactor, Model PRP-100 equipped with ultraviolet lamps (35-W; wavelength 253.7 nm) and a quartz reactor vessel (50.8 nm internal diameter, 33-cm length). Nmr spectra were recorded on a Varian A-60 spectrometer in $CDCl_3$ using TMS as an internal reference.

Photocoronopilin-A (3) from Coronopilin (1) (Scheme I).—Coronopilin (1) (400 mg) was dissolved in 500 ml of benzene which had been preflushed by bubbling a stream of nitrogen through the solution for 2 hr. The solution was irradiated at 35° under nitrogen for 2.5 hr. The residue obtained upon evaporation of the solvent was chromatographed over a column of

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(1) H. Yoshioka, T. J. Mabry, and A. Higo, *J. Amer. Chem. Soc.*, **92**, 923 (1970).

(2) The designation A is employed for the photolytic product from coronopilin since Dr. J. Kagan has informed us that he obtained this same substance along with two other compounds by the photolysis of coronopilin under conditions different from those described here.

(3) T. J. Mabry, H. E. Miller, H. B. Kagan, and W. Renold, *Tetrahedron*, **22**, 1139 (1966).

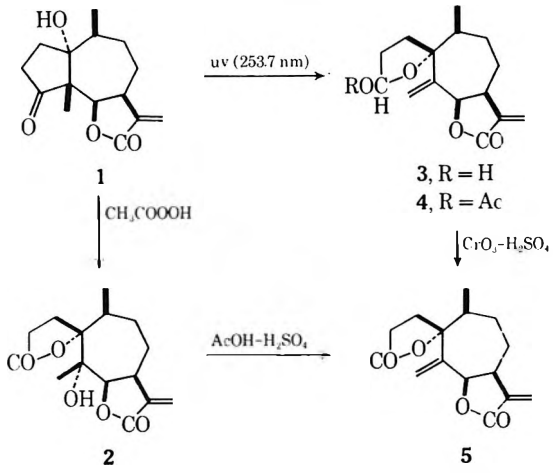
(4) For a recent review of the distribution of sesquiterpene lactones in *Ambrosia*, see T. J. Mabry in "Phytochemical Phylogeny," J. B. Harborne, Ed., Academic Press, New York, N. Y., 1970, Chapter 12, pp 269–298.

(5) H. E. Miller, T. J. Mabry, B. L. Turner, and W. W. Payne, *Amer. J. Bot.*, **55**, 316 (1968).

(6) An acetic acid solution of coronopilin did not undergo any significant photolysis under similar irradiation.

(7) Melting points are uncorrected. The analysis was determined by Dr. Alfred Bernhardt, Mikronalytisches Laboratorium, Elbach über Engelskirchen, West Germany.

SCHEME I



silica gel (35 g) packed in ether–$CHCl_3$ (2:3). Elution of the column with the same solvent yielded 140 mg of crude photocoronopilin-A (**3**). Further elution of the column recovered 79 mg of coronopilin (**1**). Photocoronopilin-A (**3**) had the following: mp 93–97° (from isopropyl ether); $[\alpha]^{25}D$ −105° (*c* 0.53, EtOH); uv (EtOH) λ_{max} 211 mμ (ε 8900); ir ($CHCl_3$) 3600–3500 (hydroxyl), 1752 (carbonyl), 1655 and 1640 cm^{-1} (double bonds); nmr (ppm, δ scale) 5.4–5.6 (H_4 and H_6), 4.90 and 5.32 (c, $C_5 = CH_2$), 3.15 (c, H_7), 0.87 (C_{10}-Me, d, J = 7 Hz) and 0.90 (C_{10}-Me, d, J = 7 Hz), 5.56 (m, $H_{13a \text{ and } b}$) and 6.23 ($H_{13a \text{ and } b}$, d, J = 2 Hz), 6.24 (d, J = 2 Hz), and 3.5 (c, OH). *Anal.* Calcd for $C_{15}H_{20}O_4$: C, 68.14; H, 7.63; O, 24.21. Found: C, 68.03; H, 7.54; O, 24.14.

Acetylation of **3** with acetic anhydride and pyridine under standard conditions yielded the acetate **4** as an oil: nmr 6.2 (m, H_4), 4.83 and 5.28 (c, $C_5 = CH_2$), 5.22 (H_6, d tr, J = 10 and 1.5 Hz), 3.17 (c, H_7), 0.87 (C_{10}-Me, d, J = 7 Hz), 5.50 ($H_{13a \text{ and } b}$, d, J = 2.2 Hz), 6.15 (d, J = 2.4 Hz), and 1.97 (s, acetyl-Me).

Anhydropsilostachyin (5) from Photocoronopilin-A (3).—A solution of 40 mg of **3** in 1 ml of acetone was treated at room temperature with three drops of the CrO_3–H_2SO_4 reagent.[8] After a half minute, the mixture was diluted with 10 ml of water and extracted with two 3-ml portions of CH_2Cl_2. The CH_2Cl_2 extract was washed (aqueous $NaHCO_3$) and dried (Na_2SO_4). The crystals obtained upon evaporation of the solvent were recrystallized from isopropyl ether–acetone: yield of **5**, 25 mg; mp 158°. The specimen was identical with an authentic sample of anhydropsilostachyin prepared from psilostachyin[3] (**2**) by nmr, ir, and mixture melting point.

Registry No.—**3**, 26823-94-9; **4**, 26823-95-0.

Acknowledgments.—This investigation was supported by the Robert A. Welch Foundation (Grant F-130), the National Science Foundation (Grant GB-5548X), and the National Institutes of Health (Grant HD 04488).

(8) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1548 (1956).

Isolation and Chemistry of the Invertomers of *N*-Chlorobenzoylphenylaziridine

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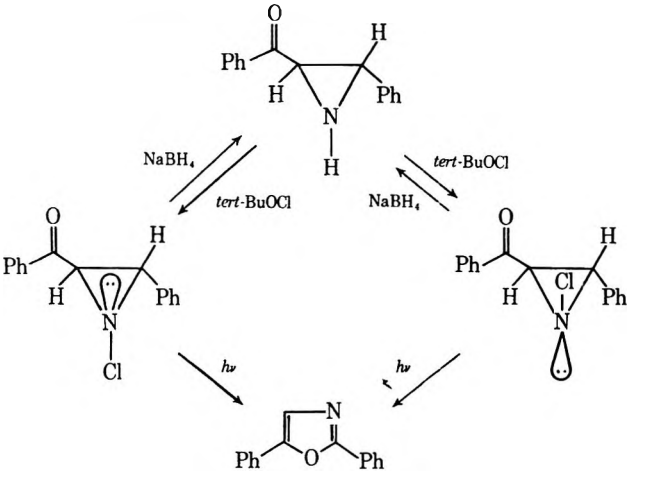
Received June 19, 1970

Recent nmr studies have shown that inversion about nitrogen is a relatively slow process for *N*-haloaziridines.[2-4] The high energy barrier for inversion has been ascribed to a combination of inductive and electrostatic factors which stabilize the pyramidal configuration.[2,5] In fact, the rate of pyramidal inversion about nitrogen is sufficiently slow to permit separation of the two invertomers in the cases of 7-chloro-7-azabicyclo[4.1.0]heptane[5] and *N*-chloro-2-methylaziridine.[6,7] At this time we wish to disclose our results on the preparation of the two invertomers of *N*-chlorobenzoylphenylaziridine as well as to report on some of the chemical properties of this system.

Treatment of *trans*-benzoylphenylaziridine with *tert*-butylhypochlorite in methylene chloride at 25° for 2 hr afforded a mixture of the two invertomers of *N*-chlorobenzoylphenylaziridine (Ia and Ib). A clean separation of the two components could be achieved by thick layer chromatography. The structure of these materials was established by elemental analysis, as well as by ir and nmr spectra. The mass spectra of both components show a peak at *m/e* 222 which corresponds to the loss of chlorine from the parent peak. The nmr spectrum of the fast moving component, mp 86–86.5°, shows an AB quartet at τ 5.80 (J = 5.8 Hz) while the slow moving component, mp 83.5–84°, has the AB quartet located at τ 5.91 (J = 5.5 Hz). Both components revert back to *trans*-benzoylphenylaziridine on reduction with sodium borohydride in methanol.



As part of our continuing probe into the excited state behavior of small ring ketones, we attempted to dehydrochlorinate I in order to study the photochemistry of the benzoylphenylazirene system. Preliminary efforts to dehydrohalogenate either aziridine were unsuccessful. All attempts led to the formation of *trans*-benzoylphenylaziridine.

In view of Gassman's recent results on the solvolysis of *N*-chloroaziridines,[7] it was expected that I would solvolyze at a rapid rate. However, both aziridines could be recovered unchanged from a silver nitrate–methanol solution. Thus it would appear that this

(1) Fellow of the Alfred P. Sloan Foundation; to whom correspondence should be addressed.

(2) S. J. Brois, *J. Amer. Chem. Soc.*, **90**, 506 (1968).

(3) J. M. Lehn and J. Wagner, *Chem. Commun.*, 148 (1968).

(4) R. G. Kostyanovsky, Z. E. Samojlova, and I. I. Tcheruin, *Tetrahedron Lett.*, 719 (1969).

(5) D. Felix and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, **7**, 224 (1968).

(6) S. J. Brois, *J. Amer. Chem. Soc.*, **90**, 508 (1968).

(7) P. G. Gassman, D. K. Dygos, and J. E. Trent, *ibid.*, **92**, 2084 (1970).

particular *N*-chloroaziridine system is reluctant to form a nitrenium ion and undergo ring cleavage. This might be attributed to the presence of the electron deficient benzoyl group attached to the adjacent carbon atom.

Irradiation of a solution of Ia (or Ib) in benzene at 25° in a Pyrex immersion apparatus with a 450-W Hanovia lamp for 7 hr led to complete disappearance of starting material. Conventional isolation procedures afforded 2,5-diphenyloxazole in high yield. The formation of the oxazole and the complete absence of the isooxazole ring suggest that the reaction proceeds by exclusive C–C bond scission. Subsequent ring closure to a 2,3-dihydrooxazole followed by dehydrochlorination readily accounts for the observed product.

Experimental Section

***N*-Chloro-2-benzoyl-3-phenylaziridine (Ia and Ib).**—To a solution of 2.0 g of 2-benzoyl-3-phenylaziridine[8] in 50 ml of methylene chloride was added 2.0 g of *tert*-butyl hypochlorite. After stirring for 2 hr at room temperature, the solvent was removed under reduced pressure and the crude solid was subjected to preparative thick layer chromatography.[9] Elution with benzene afforded two bands which were taken up in acetone. Removal of the solvent from the lower band gave material with mp 83.5–84°.

Anal. Calcd for $C_{15}H_{12}ClNO$: C, 69.89; H, 4.69; N, 4.45; Cl, 13.75. Found: C, 69.71; H, 4.75; N, 5.52; Cl, 13.73.

The nmr spectrum showed an AB quartet centered at τ 5.91 (J = 5.5 Hz) and a multiplet centered at τ 2.20 (10 H). Removal of the solvent from the upper band of the thick layer plate gave an isomeric material, mp 86–86.5°.

Anal. Calcd for $C_{15}H_{12}ClNO$: C, 69.89; H, 4.69; N, 5.45; Cl, 13.75. Found: C, 69.75; H, 4.75; N, 5.50; Cl, 13.73.

The nmr spectrum showed an AB quartet at τ 5.80 (J = 5.8 Hz) and a multiplet for the aromatic hydrogens.

Photolysis of *N*-Chloro-2-benzoyl-3-phenylaziridine.—A solution of 1.0 g of Ia (or Ib) in 1 l. of benzene was irradiated with an internal water-cooled mercury arc lamp (450-W) using a Pyrex filter. After 7 hr the solution was concentrated to give a brown oil. The residue was dissolved in benzene and chromatographed on a Florisil column. Elution with benzene gave 2,5-diphenyloxazole (80%) as white needles. Further elution of the column afforded only ill-defined tars.

Attempted Dehydrohalogenation and Solvolysis of *N*-Chloro-2-benzoyl-3-phenylaziridine.—In a typical case, 0.10 g of I was dissolved in 10 ml of methanol. To the above solution was added 5 ml of a 10% sodium methoxide–methanol solution. The mixture was allowed to stir for 12 hr. The resulting solution was washed with water, extracted with CH_2Cl_2, and dried (Na_2SO_4). Removal of the solvent under reduced pressure, followed by infrared and nmr analysis showed the presence of only *trans*-benzoylphenylaziridine. Similar results were obtained when sodium hydride, phenyl lithium, 1,5-diazabicyclo[4.3.0]non-5-ene, and potassium *tert*-butoxide were used as bases.

In an attempt to investigate the solvolytic behavior of I, a 0.10-g sample of I was added to a 10% aqueous methanol solution containing 0.85 g of silver nitrate. The resulting solution was allowed to stir for 12 hr at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in benzene and washed with water, and the extracts were dried. Removal of the solvent showed only the presence of unreacted starting material.

Registry No.—**1a**, 26823-97-2; **1b**, 26823-98-3.

Acknowledgment.—We thank the U. S. Public Health Service, Research Grant No. CA-12195-04 from the National Cancer Institute, National Institutes of Health, for support.

(8) N. H. Cromwell, N. G. Barker, R. H. Wankel, P. Vanderhorst, F. W. Olson, and J. H. Anglin, *J. Amer. Chem. Soc.*, **73**, 1044 (1951).

(9) Thick layer plates were prepared by spreading a slurry of 150 g of Merck $HF_{254,366}$ silica gel and 350 ml of water onto 10 × 20 cm glass plates to an average thickness of 1.5 cm. The plates were allowed to dry at room temperature for 24 hr.

Stereochemistry of the Palladium-Catalyzed Hydrogenation of 3-Oxo-4-ene Steroids. III. The Effects of the Functional Groups at C-11, C-17, and C-20 on the Hydrogenation[1,2]

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Received June 12, 1970

It has been previously reported from our laboratories that during the hydrogenation of 4-cholesten-3-one (**9**) and testosterone (**3a**) with palladium catalyst in alcohols, acetic acid, or in these solvents containing mineral acid, a larger amount of 5β ketone was formed from **9** than from **3a**. In comparison with **3a**, testosterone acetate (**3b**) gave the 5β ketone in considerably higher yield. Such an increase in the yield of 5β ketone on changing a 17β-hydroxyl group to a 17β-acetoxyl group was also observed in the corresponding compounds of the 19-nor series, which led to the suggestion that the effect of a 17β-hydroxyl group is to decrease the formation of 5β ketones.[2,4] Such influence of substituents, which lie far from the reaction site, on the stereochemistry of hydrogenation has already been noted by Pataki, Rosenkranz, and Djerassi[5] during the hydrogenation of 11β-hydroxy- and 11-oxo-substituted 3-oxo-4-ene steroids, and similar observations were made by other investigators[6,7] while our work was in progress. It seems rather difficult to explain these phenomena in terms of steric effect alone.

With the aim of getting more quantitative and systematic information on the influence of functional groups on hydrogenation, we have now hydrogenated 25 3-oxo-4-ene steroids with or without functional groups at C-11, 17, or 20 over prereduced palladium hydroxide. Products were analyzed by gas–liquid chromatography.

The results are given in Table I. From the Table it is seen that 17β-acetoxy-11β-hydroxy-4-androsten-3-one (**5**), 11β-hydroxy-4-androstene-3,17-dione (**7a**), and 11β-hydroxyprogesterone (**15a**), which are all 3-oxo-4-ene steroids containing an 11β-hydroxyl group, afford apparently rather different ratios of 5β to 5α ketone. However, when the results are compared with those for

(1) Presented in part at the 20th Annual Meeting of the Chemical Society of Japan in Tokyo, Japan, April 1967, and the 21st Annual Meeting of Chemical Society of Japan in Osaka, Japan, April 1968.

(2) For Part II, see S. Nishimura, M. Shimahara, and M. Shiota, *Chem. Ind. (London)*, 1796 (1966).

(3) (a) To whom correspondence should be addressed: National Institute of Industrial Health; (b) Science University of Tokyo; (c) Tokyo University of Agriculture and Technology; (d) Ochanomizu University.

(4) S. Nishimura, M. Shimahara, and M. Shiota, *J. Org. Chem.*, **31**, 2394 (1966).

(5) J. Pataki, G. Rosenkranz, and C. Djerassi, *J. Biol. Chem.*, **195**, 751 (1952).

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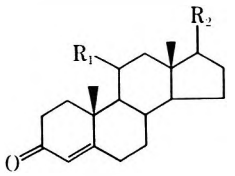
(7) M. G. Combe, H. B. Henbest, and W. R. Jackson, *J. Chem. Soc. C*, 2467 (1967).

TABLE I
RATIO OF 5β TO 5α KETONE IN THE HYDROGENATION OF 3-OXO-4-ENE STEROIDS WITH PALLADIUM CATALYST



Compd	Solvent			
	i-PrOH	i-PrOH–HCl	AcOH	AcOH–HCl
1, $R_1 = R_2 = H$	1.0	0.95	1.1	3.4
2a, $R_1 = H$; $R_2 = \alpha$-OH	4.1	4.0	3.2	2.3
2b, $R_1 = H$; $R_2 = \alpha$-OAc	2.7	2.9	2.7	3.1
2c, $R_1 = H$; $R_2 = \alpha$-OBz	3.5	3.5	6.9	8.8
3a, $R_1 = H$; $R_2 = \beta$-OH	0.73	0.57	0.84	0.63
3b, $R_1 = H$; $R_2 = \beta$-OAc	1.9	2.3	1.3	2.5
3c, $R_1 = H$; $R_2 = \beta$-OBz	1.5	1.3	2.6	3.1
4, $R_1 = H$; $R_2 = O$	0.55	0.91	1.3	1.3
5, $R_1 = \beta$-OH; $R_2 = \beta$-OAc	0.62	0.48	1.3	2.0
6, $R_1 = O$; $R_2 = \beta$-OAc	0.13	0.20	0.30	0.47
7a, $R_1 = \beta$-OH; $R_2 = O$	0.26	0.19	0.69	1.0
7b, $R_1 = \beta$-OAc; $R_2 = O$	0.27	0.33	0.91	1.1
8, $R_1 = O$; $R_2 = O$	0.09	0.07	0.17	0.27
9, $R_1 = H$; $R_2 = \beta$-C_8H_{17}	1.5	0.86	0.89	3.9
10, $R_1 = H$; $R_2 = \beta$-C_2H_5	2.7	1.2	2.2	3.5
11a, $R_1 = H$; $R_2 = \beta$-CH_3CH (α-OH)	1.3	0.67	2.3	1.6
11b, $R_1 = H$; $R_2 = \beta$-CH_3CH (α-OAc)	0.58	0.37	2.8	2.3
12a, $R_1 = H$; $R_2 = \beta$-CH_3CH (β-OH)	1.4	1.0	1.7	2.5
12b, $R_1 = H$; $R_2 = \beta$-CH_3CH (β-OAc)	1.0	0.67	0.98	2.7
13, $R_1 = H$; $R_2 = \beta$-CH_3CO	0.34	0.21	0.48	0.62
14a, $R_1 = \alpha$-OH; $R_2 = \beta$-CH_3CO	0.38	0.28	0.59	0.66
14b, $R_1 = \alpha$-OAc; $R_2 = \beta$-CH_3CO	0.71	0.28	0.68	1.1
15a, $R_1 = \beta$-OH; $R_2 = \beta$-CH_3CO	0.16	0.08	0.32	0.35
15b, $R_1 = \beta$-OAc; $R_2 = \beta$-CH_3CO	0.33	0.22	0.84	0.86
16, $R_1 = O$; $R_2 = \beta$-CH_3CO	0.03	0.02	0.04	0.04

the corresponding parent steroids without the substituent at C-11, it appears that the 11β-hydroxyl group has a tendency to decrease the formation of the 5β ketone (compare **5**, **7a**, and **15a** with **3b**, **4**, and **13**, respectively).

In order to describe our observations on the effect of various substituents, we will define an effect which increases the proportion of 5β isomers in the product as positive and the reverse effect as negative.[8]

The ratio of ketones obtained from **9** (with a 17β-C_8H_{17} side chain) is almost the same as that from 4-androsten-3-one (**1**) with no substituent at C-17. A 17β-ethyl group appears to have a positive effect, but the result in acetic acid containing hydrochloric acid is the same as that for **1** (compare **10** with **1**).

With respect to the effect of hydroxyl groups, the 11α-hydroxyl group has scarcely any effect and 20α- and 20β-hydroxyl groups show slightly negative effects (compare **14a** with **13**; **11a** and **12a** with **10**). While 11β- and 17β-hydroxyl groups have certainly negative effects, some difference is found between them when the solvent is changed (compare **5**, **7a**, and **15a** with **3b**, **4**, and **13**, respectively; **3a** with **1**). It is difficult to estimate which of the substituents at C-11 and C-17 has a more significant effect on the stereochemistry. Although Pataki, Rosenkranz, and Djerassi[5] observed the perponderant formation of 5α ketones for 11β-hydroxyl derivatives (corticosterone acetate and cortisol acetate), it has been pointed out by Liston and Howarth[6] that hydrogenation of 11β-ols (11β-hydroxy-4-androsten-3-one and **5**) results in predominant formation of 5β ketones. Certainly the 11β-hydroxyl group has the effect of decreasing the formation of 5β ketone as compared with the result obtained by hydrogenating the parent compounds. However, when the parent compound produces a very large amount of the 5β ketone as in the case of **3b**, introduction of an 11β-hydroxyl group may still result in predominant formation of the 5β ketone in acetic acid and acetic acid containing hydrochloric acid, even though the ratio is smaller. By contrast, when the parent compound already contains a 20-oxo group which considerably inhibits the formation of 5β ketone, introduction of an 11β-hydroxyl group results in predominant formation of 5α ketone due to combined effect of the effects of the substituents as in **15a**. On the other hand, the 17α-hydroxyl group has a positive effect (compare **2a** with **1**).[9] The order of the substituent effects of the hydroxyl groups is as follows: 17α-OH > 11α-OH > H > 20α-OH ≅ 20β-OH > 17β-OH ≅ 11β-OH.

Among ketones, the 17-oxo group has a barely negative effect, while the 20-oxo and 11-oxo groups have much more negative effects which are also much greater than those of the corresponding hydroxyl groups (compare **4** with **1**; **13** with **10**; **6**, **8**, and **16** with **3b**, **4**, and **13**, respectively). The negative effect is more pronounced for the 11-oxo group than for the 20-

(8) It is convenient to use the ratio of $(5\beta/5\alpha)_R$ to $(5\beta/5\alpha)_H$. $(5\beta/5\alpha)_R$ is 5β/5α ketone of hydrogenated products of 3-oxo-4-ene steroid with substituent R. $(5\beta/5\alpha)_H$ is 5β/5α ketone of hydrogenated products of parent steroid without substituent.

(9) Such behavior slightly decreases in the hydrogenation in acetic acid, and even a negative effect is observed in acetic acid containing hydrochloric acid or hydrobromic acid.

oxo group.[10] Consequently, the order of substituent effects of the oxo groups is as follows: H > 17-oxo > 20-oxo > 11-oxo.

Finally, concerning the acetoxyl groups, the 11α-acetoxyl group gives a slightly more positive effect than the 11α-hydroxyl groups, and 5β-ketone formation in an 11α-acetoxyl derivative increases in comparison with that from the corresponding parent compound (compare **14b** with **13**). The 11β- and 17β-acetoxyl groups have certainly less negative effects than those of the corresponding β-hydroxyl groups, the 17β-acetoxy compound giving the 5β ketone in even greater yield than the parent compound (compare **7b** and **15b** with **4** and **13**, respectively; **3b** with **1**). The 17α-acetoxyl group provides a strongly positive effect except when hydrochloric acid in acetic acid is added, although the effect is somewhat smaller than that of the hydroxyl group (compare **2b** and **2a** with **1**). The effects of 20α- and 20β-acetoxyl groups are similar to those of the corresponding hydroxyl groups and more negative than that of 11β-acetoxyl group (compare **11b** and **12b** with **10**; **7b** and **15b** with **4** and **13**, respectively). The order of substituent effects of the acetoxyl groups is therefore as follows: 17α-OAc > 17β-OAc ≅ 11α-OAc > H > 11β-OAc > 20α-OAc ≅ 20β-OAc.

The fact that the equatorial 11α-acetoxyl group has a slightly more positive effect than an equatorial 11α-hydroxyl group which shows nearly the same effect as that of 11α hydrogen, does not contradict the concept of steric effect. On the other hand, the 11β-hydroxyl (axial) group has a more negative effect than the corresponding acetoxyl group, while the 17α-hydroxyl (quasiaxial) group has definitely a more positive effect than the 17α-acetoxyl group. These result cannot be interpreted in steric terms. The negative effect of the quasiequatorial 17β-hydroxyl group is as great as that of the axial 11β-hydroxyl group, but such an effect is scarcely noticeable when a 17β-acetoxyl group is present. These facts suggest that the effect of hydroxyl groups is electronic rather than steric. The large negative effect of the oxo group is also considered as arising from electronic factors.[11]

Experimental Section

Materials.—4-Androsten-3-one (**1**) was supplied from Teikoku Hormone Manufacturing Company, Ltd. Testosterone (**3a**), testosterone acetate (**3b**), and 4-cholesten-3-one (**9**) were described in a previous paper.[4] Epitestosterone (**2a**), progesterone (**13**), 11α-hydroxyprogesterone (**14a**), and 11-oxoprogesterone (**16**) were obtained commercially and recrystallized. 17β-Acetoxy-11β-hydroxy-4-androsten-3-one (**5**),[12] 11β-hydroxy-4-androstene-3,17-dione (**7a**),[13] 11β-acetoxy-4-androstene-3,17-dione (**7b**),[14] 4-androstene-3,11,17-trione (**8**),[13] 4-pregnene-3-one (**10**),[15] 20α-hydroxy-4-pregnen-3-one (**11a**),[16] 20β-hydroxy-4-pregnen-3-one (**12a**),[17] 11β-hydroxyprogesterone (**15a**),[18] and 11β-acetoxyprogesterone (**15b**)[14] were prepared by published procedures. Epitestosterone acetate (**2b**), 20α-acetoxy-4-pregnen-3-one (**11b**), 20β-acetoxy-4-pregnen-3-one (**12b**), 11α-acetoxyprogesterone (**14b**), epitestosterone benzoate (**2c**), testosterone benzoate (**3c**), 4-androstene-3,17-dione (**4**), and 17β-acetoxy-4-androstene-3,11-dione (**6**) were prepared from the corresponding hydroxy steroids by acetylation, benzoylation, or oxidation in the usual way. Purity of these compounds was checked by gas–liquid partition chromatography (glpc). Palladium hydroxide was prepared as previously described.[4,19]

Hydrogenation and Analysis.—The steroid (10 mg) was hydrogenated in the solvent (10 ml) with prereduced palladium hydroxide (5 mg) at 25° and under atmospheric pressure. After hydrogenation of the catalyst in isopropyl alcohol or acetic acid, 3 *N* hydrochloric acid (0.05 ml), if necessary, was added to the suspension. After the steroid had been hydrogenated for 0.5 hr, the reaction was stopped to analyze the products by glpc. A Shimazu Seisakusho Model GC-4APF gas chromatograph equipped with dual flame detectors was employed. The glass columns (2 m × 4 mm inside diameter) contained 1.5% OV-17 on 80–100 mesh Shimalite W (Shimazu Co.) washed with acid and silanized with dichlorodimethylsilane. The carrier gas was nitrogen at a flow rate of 70 ml/min and the column tempearature was suitably selected for each product between 205 and 260°. Quantitative estimation of the products was carried out by multiplying the height of the peak by the width at half-height.

Acknowledgment.—The authors are grateful to Teikoku Hormone Manufacturing Company, Ltd., for providing 4-androsten-3-one.

(10) Since the negative effects of the oxo groups are great, **8** with an 11,17-dioxo group and especially **16** with an 11,20-dioxo group mainly lead to the formation of the 5α ketones.

(11) *Cf.* D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier, Amsterdam, London, New York, N. Y., 1968, p 16.

(12) O. Mancera, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 2189 (1953).

(13) C. J. W. Brooks and J. K. Norymberski, *Biochem. J.*, **55**, 371 (1953).

(14) A. L. Nussbaum, G. Brabazon, E. P. Oliveto, and H. B. Hershberg, *J. Org. Chem.*, **22**, 977 (1957).

(15) Huang-Minlon, *J. Amer. Chem. Soc.*, **71**, 3301 (1949).

(16) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1922 (1949).

(17) F. Sondheimer, C. Amendolla, and G. Rosenkranz, *J. Amer. Chem. Soc.*, **75**, 5930 (1953).

(18) B. J. Magerlein and R. H. Levin, *ibid.*, **75**, 3654 (1953).

(19) The ratio of 5β to 5α ketone is somewhat changed using different batches of catalyst, particularly in isopropyl alcohol.

An Improved Synthesis of Phenyl Benzohydroxamate and Its Conversion to Phenyl *O*-Phenyl- and *O*-Ethylbenzohydroxamate

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Although alkyl benzohydroxamates may be prepared by simple alkylation,[2] aryl benzohydroxamates are not readily accessible and, in fact, only two representatives of this class of derivatives have been previously reported. Thus, arylation of potassium benzohydroxamate with diphenyliodonium bromide gave phenyl benzohydroxamate in 24% yield,[3] while treatment of the same salt with 2,4-dinitrofluorobenzene gave 2,4-dinitrophenyl benzohydroxamate in 20% yield.[4]

We have recently reported[5] the formation of an unstable *N*-chlorosulfite by reaction of thionyl chloride with 1-hydroxy-2(1*H*)-pyridone; subsequent treatment with thallium(I) carboxylates gave 1-acyloxy-2(1*H*)-pyridones. Extension of this reaction to open-chain hydroxamic acids would have provided simple access to aryl hydroxamate derivatives. In order to explore this possibility, we treated an ethereal solution of benzo-

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(1) NRCC Postdoctoral Fellow, 1968–1970.

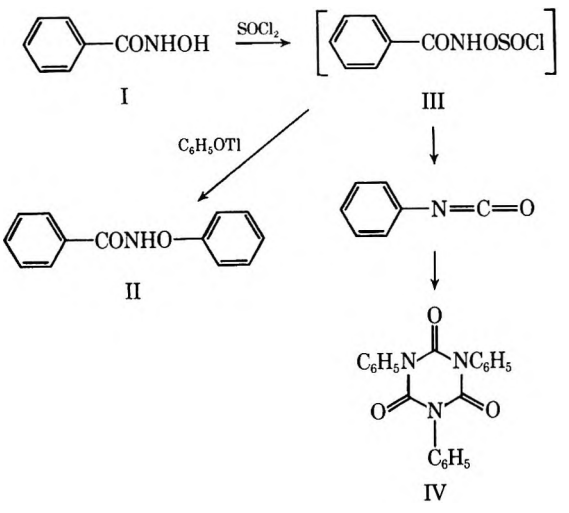
(2) P. A. S. Smith, "The Chemistry of Open-chain Nitrogen Compounds," Vol. II, W. A. Benjamin, New York, N. Y., 1966.

(3) J. S. Nicholson and D. A. Peak, *Chem. Ind. (London)*, 1244 (1962).

(4) P. M. Gallop, S. Seifter, M. Lukin, and E. Meilman, *J. Biol. Chem.*, **235**, 2619 (1960).

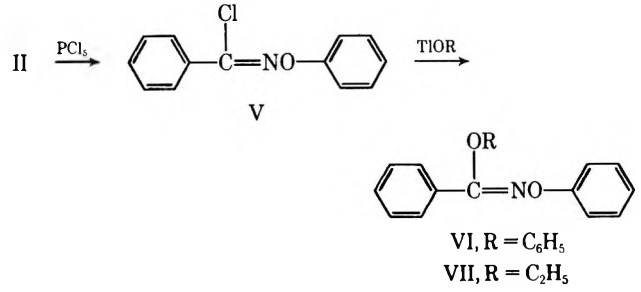
(5) E. C. Taylor, F. Kienzle, and A. McKillop, *J. Org. Chem.*, **35**, 1672 (1970).

hydroxamic acid (I) at 0° with thionyl chloride. Evaporation of the ether followed by treatment of the residual syrup with thallium(I) phenoxide in benzene gave phenyl benzohydroxamate (II) in 6.2% yield, indicating the probable intermediacy of *N*-chlorosulfite III. The principle product (22.5%) isolated, however, was triphenyl isocyanurate (IV) which probably arose by trimerization of phenyl isocyanate, the product of a Lossen rearrangement of III.[6]

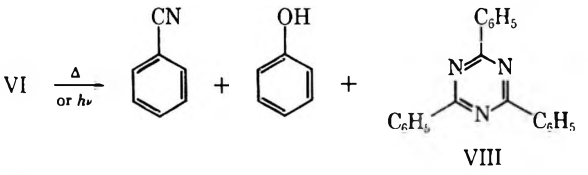


Phenyl benzohydroxamate (II) could, however, be prepared in satisfactory yield (66%) by reaction of thallium(I) benzohydroxamate with diphenyliodonium chloride. This is a considerable improvement over the previously reported method[3] for the preparation of this compound.

Reaction of II with phosphorus pentachloride gave *O*-phenylbenzohydroximoyl chloride (V) in 77% yield. Subsequent nucleophilic displacement of chlorine was readily achieved by treatment of V with thallium(I) phenoxide[7] and thallium(I) ethoxide to give, respectively, phenyl *O*-phenylbenzohydroximate (VI)[8] and phenyl *O*-ethylbenzohydroximate (VII). Alkyl *O*-alkylbenzohydroximates have been synthesized previously,[2] but neither aryl *O*-aryl- nor aryl *O*-alkylbenzohydroximates are known. Compounds VI and VII, therefore, represent the first examples of these new classes of hydroximate derivatives.



The tendency of hydroxamic and imido acid derivatives to rearrange is well known,[2] and we therefore briefly examined the stability of VI. It was found that VI, when heated or irradiated with 3000-Å light, gave as major products benzonitrile and phenol; no rearrangement products were observed. Under both sets of conditions, 2,4,6-triphenyl-1,3,5-triazine (cyaphenine) (VIII) was isolated in small amounts.[9]



Experimental Section[10]

Phenyl Benzohydroxamate (II).—To a solution of 13.7 g (0.1 mol) of benzohydroxamic acid in 250 ml of ethanol was added, with vigorous stirring, 24.9 g (0.1 mol) of thallium(I) ethoxide. Thallium(I) benzohydroxamate immediately precipitated. After 10 min of continued stirring, diphenyliodonium chloride (31.7 g, 0.1 mol) was added, and the reaction mixture heated gently under reflux for 4 hr, and then cooled and filtered. Evaporation of the filtrate gave a liquid residue which was taken up in 150 ml of ether. The ether solution was extracted with four 50-ml portions of 1 *N* NaOH. Crude phenyl benzohydroxamate (14.1 g, 66%, mp 125–131°) was precipitated upon acidification of the combined alkaline extracts with dilute hydrochloric acid. Recrystallization from absolute alcohol raised the melting point to 136–137° (lit.[3] mp 137.5–139°).

***O*-Phenylbenzohydroximoyl Chloride (V).**—Crude phenyl benzohydroxamate (13.9 g, 0.065 mol) was suspended in cold carbon tetrachloride (500 ml) and phosphorus pentachloride (14.6 g, 0.07 mol) was added. The reaction mixture was stirred at 0° until most of the suspended solid had dissolved (6 hr). The resulting yellow solution was then evaporated, the residue dissolved in 200 ml of ether, and the ether solution washed once with 50 ml of water. Evaporation gave a syrup which crystallized on treatment with aqueous ethanol to give practically pure V, 11.6 g (76.5%), mp 34–35°. The analytical sample, mp 35–36°, was prepared by recrystallization from aqueous ethanol.

Anal. Calcd for $C_{13}H_{10}NOCl$: C, 67.40; H, 4.35; N, 6.05. Found: C, 67.20; H, 4.50; N, 6.18.

A mass spectrum showed a strong parent peak *m/e* 231 in addition to a medium intensity peak at *m/e* p + 2; ir 1592, 1260, 980, 948, 750, and 685 (strong), 1560, 1195, 1155, 1020, 1000, 825, and 705 cm^{-1} (medium).

Phenyl *O*-Phenylbenzohydroximate (VI).—*O*-Phenylbenzohydroximoyl chloride (5.78 g, 0.025 mol) was mixed well with thallium(I) phenoxide (7.44 g, 0.025 mol), 15 ml of dimethyl sulfoxide added, and the mixture heated on a steam bath for 5 hr. It was then cooled to room temperature and diluted with 150 ml of ether, and the insoluble thallium(I) chloride filtered off. The filtrate was extracted with four 20-ml portions of water and evaporated, and the residual brown syrup was taken up in 75 ml

(6) Treatment of hydroxamic acids with thionyl chloride has been reported to give isocyanates: R. Marquis, *C. R. Acad. Sci., Ser. C*, **143**, 1163 (1906); G. B. Bachman and J. E. Goldmacher, *J. Org. Chem.*, **29**, 2576 (1964).

(7) The advantages of thallium(I) *vs.* alkali metal salts of phenols in acylation, aroylation, and tosylation reactions have been stressed previously [E. C. Taylor, G. W. McLay, and A. McKillop, *J. Amer. Chem. Soc.*, **90**, 2422 (1968)]. In addition, thallium(I) phenoxide is a crystalline, stable solid which offers considerable manipulative advantages over deliquescent sodium phenoxide.

(8) Hydrolysis of this compound in alcoholic hydrochloric acid gave *O*-phenylhydroxylamine hydrochloride, mp 134° (lit.[3] mp 136°), thus confirming structure VI and excluding the possibility that a Chapman rearrangement (see ref 14) might have taken place under the reaction conditions.

(9) Benzonitrile is known to give rise to cyaphenine upon treatment with a variety of reagents, such as concentrated H_2SO_4, alcoholic HCl, Br_2 in a sealed tube, boiling sodium, etc. (Beilstein's "Handbuch der organischen Chemie," Vol. 26, Springer, Berlin, 1937, p 97). Since our reaction described above was carried out on pure VI, without the presence of catalysts, we favor a mechanism for the formation of VIII involving some activated nitrile species (*e.g.*, a triplet nitrile, R—C=N:).

(10) Evaporations were carried out *in vacuo* (35–40° bath temperature). Melting points were determined on a Thomas–Hoover apparatus and are uncorrected. Infrared data refer to Nujol mull spectra taken on a Perkin-Elmer 237B grating infrared spectrometer.

of ethanol. Water was added to incipient turbidity. After 20 hr at 0°, 5.42 g of slightly colored but nearly pure VI, mp 50–51°, was collected by filtration. Addition of water to the mother liquor gave a second crop (0.25 g, mp 46–48°), total yield 79%. The combined material was dissolved in hexane and the solution passed through a short column of silica gel. Evaporation of the eluate and crystallization of the residue from aqueous ethanol gave 4.75 g of colorless prisms: mp 53–54°; ir 1585, 1322, 1195, 1160, 1070, 965, 755, and 685 (strong), 1625, 1300, 1025, 1000, 925, and 770 cm^{-1} (medium).

Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.75; H, 5.29; N, 5.02.

Phenyl *O*-Ethylbenzohydroximate (VII).—*O*-Phenylbenzohydroximoyl chloride (1.00 g, 4.3 mmol) was dissolved in 20 ml of ethanol and thallium(I) ethoxide (1.07 g, 4.3 mmol) was added. The mixture was heated under reflux for 4 hr, thallium(I) chloride filtered off, and the filtrate evaporated. The residue was dissolved in ethyl acetate–hexane (1:1) and the solution passed through a short column of silica gel. Evaporation of the eluate and crystallization of the residue from aqueous ethanol gave 550 mg (53%) of flat prisms: mp 43–44°; ir 1590, 1320, 1215, 755, and 695 (strong), 1625, 1575, 1300, 1155, 1105, 1075, 1025, 955, 930, and 770 cm^{-1} (medium).

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.62; H, 6.27; N, 5.81. Found: C, 74.60; H, 6.24; N, 5.88.

Reaction of Benzohydroxamic Acid with Thionyl Chloride and Thallium(I) Phenoxide.—To a suspension of 1.37 g (0.01 mol) of benzohydroxamic acid in 150 ml of cold anhydrous ether was added 1.30 g (0.011 mol) of thionyl chloride. The resulting clear solution was stirred for 1 hr at 0° and evaporated (bath temperature 20°), and the residual syrup dissolved in 100 ml of dry, cold benzene. Thallium(I) phenoxide (2.97 g, 0.01 mol) was added (slight exothermic reaction) and the mixture stirred at room temperature for 2 hr. Filtration and evaporation of the filtrate gave a syrup which crystallized upon trituration with ethyl acetate–petroleum ether to give 250 mg (23%) of triphenyl isocyanurate, mp 275° (lit.[11] mp 275°).

Addition of more petroleum ether to the mother liquors gave 180 mg (6%) of impure phenyl benzohydroxamate, mp 120°, mmp (with pure II) 130°. The yield of this material was not increased when the reaction of benzohydroxamic acid with thionyl chloride and thallium(I) phenoxide was carried out at lower temperatures.

Thermolysis of Phenyl *O*-Phenylbenzohydroximate (VI).—Compound VI (1.00 g) was placed in a small round-bottom flask equipped with a condenser and immersed into a Wood's metal bath at 180°. The reaction mixture, which immediately started to boil violently, was maintained at 180° for 30 min and then cooled to room temperature. The partly crystalline product was dissolved in ethyl acetate–methanol (1:1) and the solution left at 0° for 20 hr. Filtration then gave 15 mg of 2,4,6-triphenyl-1,3,5-triazine (VIII), mp 231–232° (*m/e* 309) (lit.[12] mp 230°). Evaporation of the filtrate and chromatography of the residue on a silica gel column [eluent, hexane–ethyl acetate (5:1)] gave benzonitrile (250 mg) (containing a little VI and VIII), phenol (80 mg), and 170 mg of a mixture of at least three different, unidentified compounds.

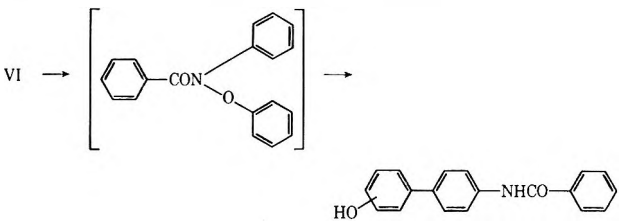
Photolysis of Phenyl *O*-Phenylbenzohydroximate (VI).—Compound VI (2.00 g) was dissolved in hexane (500 ml) and irradiated with 3000-Å light (Rayonet photochemical reactor) for 3 hr. Some insoluble brown material was filtered off and the filtrate irradiated for an additional 4 hr. Filtration gave a second crop of hexane-insoluble material, total yield 400 mg.[13] Evaporation of the filtrate gave a syrup which was separated on a silica gel column into VIII (12 mg), unreacted starting material (740 mg, containing a little benzonitrile), benzonitrile (50 mg), phenol (350 mg), 40 mg of a solid, recrystallized from water to give an amide (5 mg, mp 215–220°),[14] and 45 mg of an unidentified aromatic compound (no OH, NH, CO).

(11) A. W. Hofmann, *Ber.*, **18**, 3217 (1885).

(12) A. Pinner, *ibid.*, **22**, 1611 (1889).

(13) This material was insoluble in water, but it could be dissolved in hot benzene and precipitated again upon addition of petroleum ether to give a dark red powder, mp 140–150° dec. Its ir spectrum showed a medium strong absorption band at 1650 cm^{-1}. Its nmr spectrum (in DMSO-d_6) showed only one broad symmetrical peak at τ 3.05. The compound thus appears to be diphenoquinone, which is known to be unstable and to decompose at 165° [R. Willstätter and L. Kalb, *ibid.*, **38**, 1235 (1905)]. It also liberated iodine from an acidic potassium iodide solution, a characteristic reaction of diphenoquinone.

(14) Its ir spectrum showed NH absorption at 3340 cm^{-1}, strong bands at 1655 (amide I) and 1545 cm^{-1} (amide II), and additional bands at 1590, 1510, 825, and 725 cm^{-1}, suggesting the presence of phenyl groups. It has been shown [J. R. Cox, Jr., and M. F. Dunn, *Tetrahedron Lett.*, 985 (1963)] that *N*-acetyl-*O*,*N*-diphenylhydroxylamine rearranges spontaneously to 4- (and 2-) hydroxy-4′-acetylaminobiphenyl. It seems reasonable to suggest, therefore, that VI may have rearranged first by a Chapman-type rearrangement to phenyl *N*-phenylbenzohydroxamate, which subsequently underwent a further rearrangement to 4′-benzoylamino-hydroxybiphenyl according to the following scheme.



4′-Benzoylamino-4-hydroxybiphenyl melts at 284° [L. C. Raiford and E. P. Clark, *J. Amer. Chem. Soc.*, **48**, 483 (1926)]; our compound could be the unknown 2-hydroxy isomer.

Registry No.—II, 4380-77-2; V, 26630-25-1; VI, 26630-26-2; VII, 26630-27-3.

Tautomerism in 1,5-Dianilino-4,8-naphthoquinones

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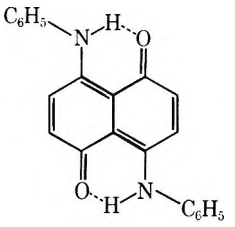
Received May 27, 1970

While studying a number of 1,5-bis(alkylamino)-4,8-naphthoquinones,[1] we noted that the absorption spectra of the dianilide (1) was solvent dependent (Figure 1 and



1

Table I). In polar, associating solvents, the absorption at 661 nm of the dianilide is of maximum intensity and decreases with decreasing solvent associating ability. Conversely, the band at ~560 nm (broad) increases in intensity. The alkyl-substituted aminonaphthoquinones, however, have a limited dependence of the electronic spectrum upon solvent, the effects being in the range considered normal (for example, ϵ_0 shifting from 2.42 to 2.28 × 10^3 between ethanol and pyridine).[1]

Dähne and Paul discussed the strong solvent dependency of the electronic spectra of 1,8-diamino-2,7-naphthoquinones.[2] They attributed the solvent effect to mesomerism from the quadrapolar nature of the mole-

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(1) S. M. Bloom and G. Dudek, *Tetrahedron*, **26**, 1267 (1970).

(2) S. Dähne and H. Paul, *Chem. Ber.*, **97**, 1625 (1964).

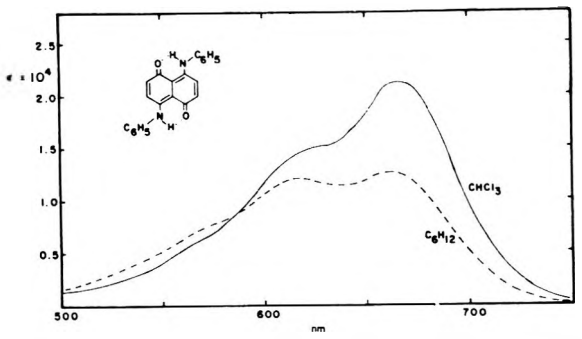


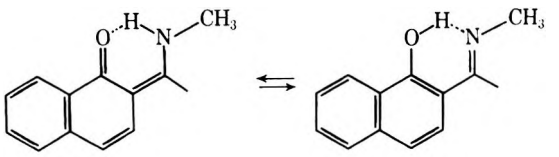
Figure 1.—The electronic spectra of 1,5-dianilino-4,8-naphthoquinone. For clarity, only the extremes of the solvent effect are shown.

TABLE I
ELECTRONIC SPECTRAL DATA

Compd	Solvent	λ_{nm}	$\epsilon \times 10^4$	λ_{nm}	$\epsilon \times 10^4$
1	CH_3OH	620 (s)[a]	1.52	660	2.20
	$CHCl_3$	625	1.51	667	2.14
	C_2H_5OH	625	1.55	661	2.14
	CH_3SOCH_3	625	1.38	667	1.81
	C_5H_5N	628	1.37	671	1.75
	CH_3COCH_3	628	1.35	668	1.63
	CCl_4	624	1.31	668	1.59
	C_6H_{12}	618	1.21	663	1.26
3	$CHCl_3$	620	1.51	673	2.38
	CCl_4	620 (s)	1.44	673	1.94

[a] (s) = shoulder.

cule. However, the behavior of the dianilide is more like that of systems[3] such as 2-(*N*-methylacetimidoyl)-1-naphthol (**2**). A band at 420 nm in **2** decreases in intensity with decreasing solvent association and a weak band at 380 nm, also observed as a shoulder, increases.



2a **2b**

The solvent dependency of **2** has been ascribed to the tautomeric shift of the proton from nitrogen to oxygen (**2a** ⇋ **2b**). Confirmation of this equilibrium was obtained through the proton magnetic resonance spectrum of the ^{15}N-substituted compound.[3] In nonexchanging compounds, such as amides, the ^{15}NH spin coupling is about 88–99 Hz which decreases as the residence time of the proton on the nitrogen decreases.

Accordingly, the ^{15}N analog of **1** was synthesized using 99% ^{15}N-enriched aniline. In chloroform solution, the ^{15}NH spin coupling is 76.5 Hz at 27° (Table II) and only 62.0 Hz in carbon tetrachloride solution. These ^{15}NH spin couplings are appreciably smaller than the value of 88–90 Hz frequently measured.[3,4] The chemical shift of the NH is at δ 14.28 ppm, indicative of a strong hydrogen bond. The utilization of pyridine as a solvent little affects the strength of the association.

Although reduced spin couplings may be attributed to intermolecular proton exchange, the strong intermolecular hydrogen bond, the parallel solvent dependent of the electronic spectra, and the normal behavior

(3) G. Dudek and E. Dudek, *J. Amer. Chem. Soc.*, **88**, 2407 (1966).
(4) A. J. Bourn and E. W. Randall, *Mol. Phys.*, **8**, 567 (1964).

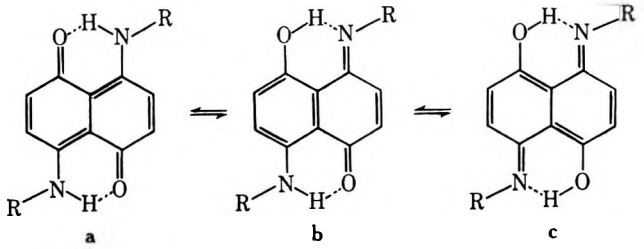
TABLE II
PMR SPECTRAL DATA (IN PPM)[a]

Compd	Solvent, temp, °C	Acidic proton	Aromatic protons
1[b]	$CDCl_3$, (27)	14.28 (76.5)[c]	7.01 (10.0)[c]
	(40)	14.21 (74.7)	
	(50)	14.15 (72.3)	
	C_5H_5N, (27)	14.33 (61.3)	
	CCl_4, (27)	13.72 (62.0)	6.89 (10.2)
3	$CDCl_3$	14.29	

[a] From tetramethylsilane as reference. [b] Labeled with ^{15}N. [c] Spin coupling in Hz.

of the alkyl substituted compound suggest the presence of a keto–enol tautomeric process. The existence of a keto–enol equilibrium is verified by the parallel solvent dependency of the electronic spectra.

The tautomeric shift of the dianilide may involve three species. If the equilibrium involves only a and b,



a **b** **c**

then the observed $J_{^{15}NH}$ will vary between 90 and 45 Hz, while a and c would have $J_{^{15}NH}$ varying between 90 and 0 Hz.[5] If all three forms are present, the quantitative aspects of both the nmr and uv spectra will be complex.

The synthesis of 1,5-bis(4′-ethoxyaniline)-4,8-naphthoquinine (**3**) provides a compound with a negative σ for comparison.[6] The ethoxy substituent on the phenyl stabilizes the amino tautomer as the solvent dependency of this derivative is less marked, but an equilibrium is still observable. Regrettably, the insolubility of the compound limited the solvents that could be utilized.

Since derivatives of the dianilinonaphthoquinones are important commercial dyestuffs,[7] these findings suggest the color of the dyes can be markedly affected through a tautomeric shift. The color and intensity of the product would depend strongly upon the material being colored.

The double bond proton–proton spin coupling of 10.0 Hz suggests little bond delocalization (aromaticity) in the system.[8] The small change in this value from 10.0 Hz in $CDCl_3$ to 10.2 Hz in CCl_4 solution indicates the other tautomers have even less bond delocalization than the predominate tautomer a.

This has a possibility of being construed as evidence for elimination of b as an important tautomer. In b one ring should possess a significant degree of aromaticity.

Infrared Spectra.—The infrared spectra of the ^{15}N-labeled anilide (**1**) was compared with that of the unlabeled compound so the frequencies indicating the

(5) Assuming of course, that the tautomeric process is rapid on an nmr time scale.
(6) R. W. Taft in "Steric Effects In Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 556.
(7) E. Merian, *Chimia*, **13**, 181 (1959).
(8) M. A. Cooper and S. L. Manatt, *J. Amer. Chem. Soc.*, **91**, 6325 (1969).

TABLE III
IR SPECTRA OF 1,5-BISANILINO-1,4-NAPHTHOQUINONE[a]

^{14}N	^{15}N
1608	1606.5
1592	1592
1553	1554
1537 (s)[b]	1525
1491	1491
1423.5	1423.5
1289 (b)[c]	1284
1147	1147
949.5	949.5

[a] $CDCl_3$ solution. [b] s, shoulder. [c] b, broad.

nitrogen could be identified. In Table III it can be seen that the strong band at 1537 cm^{-1} and the one at 1289 cm^{-1} shift appreciably upon isotopic substitution and these are the only absorptions observed with appreciable shifts.

Experimental Section

Spectra were taken as previously described.[1]

Compound 1.—To 54 mg (0.3 mmol) of 1,5-diamino-4,8-naphthoquinone was added 166 mg, 1.2 mmol, of aniline and 1 ml of acetic acid. The solution was gently refluxed for 4 hr and then the solvent was removed. The residue was crystallized from toluene–hexane, wt 86 mg, mp 220–221°.[9]

The ^{15}N compound was synthesized in the same manner, employing 99.5% aniline-^{15}N.

Compound 3.—This compound was synthesized as 1. The material was crystallized from xylene, mp 220–222°. *Anal.* Calcd for $C_{26}H_{24}O_4N_2$: C, 72.88; H, 5.69; N, 6.54. Found: C, 72.77; H, 7.53; N, 6.43.

Registry No. —**1**, 26823-92-7; **3**, 26823-93-8.

(9) C. Neudecker, Thesis, Würzburg, Germany, 1930.

The Reaction of α-Sulfonyl Carbanions with Carbon Disulfide

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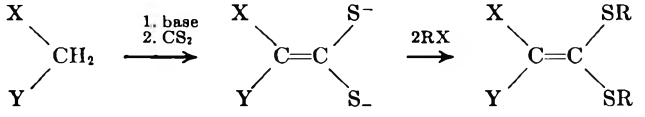
Received February 18, 1970

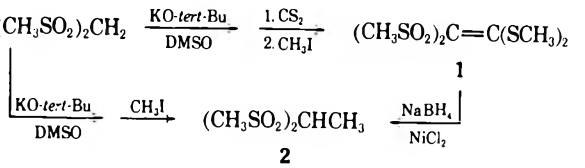
The base-induced reaction of activated methylene groups with carbon disulfide followed by alkylation of the intermediate dithiolate anion has been used for the preparation of 1,1-di(alkylmercapto)ethenes.[1-6]



This reaction has now been investigated as a synthetic route to structures of the type $RSO_2(R')C{=}C(SR'')_2$ and $(RSO_2)_2C{=}C(SR')_2$, starting with the appropriate sulfone or disulfone.

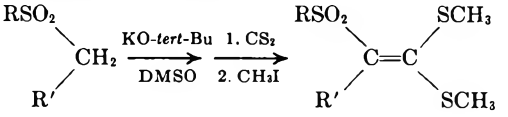
(1) R. Gompper and W. Topfl, *Chem. Ber.*, **95**, 2861 (1962).
(2) E. Soderback, *Acta Chem. Scand.*, **17**, 362 (1963).
(3) R. Gompper, E. Kutter, and W. Topfl, *Justus Liebigs Ann. Chem.*, **659**, 90 (1962).
(4) A. Thuillier and J. Vialle, *Bull. Soc. Chim. Fr.*, 2182, 2194 (1962).
(5) D. C. Dittmer, H. E. Simmons, and R. D. Vest, *J. Org. Chem.*, **29**, 497 (1964).
(6) K. A. Jensen and L. Henriksen, *Acta Chem. Scand.*, **22**, 1107 (1968).

The expected product, 1,1-di(methylsulfonyl)-2,2-di(methylmercapto)ethene (**1**), was isolated in 11.5% yield when di(methylsulfonyl)methane was treated with carbon disulfide in dimethyl sulfoxide in the presence of potassium *tert*-butoxide, followed by methylation. The structure of **1** was demonstrated by reduc-



tion of the double bond with simultaneous desulfurization of the mercaptal unit by treatment with the sodium borohydride–nickelous chloride system.[7] The resulting 1,1-di(methylsulfonyl)ethane (**2**)[8] was identical with an authentic sample prepared by methylation of di(methylsulfonyl)methane. An attempt to extend this sequence to di(*p*-tolylsulfonyl)methane led only to methylated starting material, 1,1-di(*p*-tolylsulfonyl)ethane.

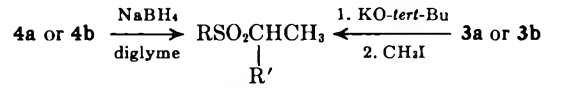
Treatment of the monosulfones benzyl phenyl sulfone (**3a**), benzyl *p*-tolyl sulfone (**3b**), and methyl *p*-tolyl sulfone (**3c**) in a like manner afforded products **4a–c** in 30, 50, and 2.5% yields, respectively.



3a, R = Ph; R′ = Ph
b, R = *p*-$CH_3C_6H_4$; R′ = Ph
c, R = *p*-$CH_3C_6H_4$; R′ = H

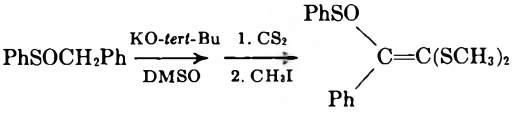
4a, R = Ph; R′ = Ph
b, R = *p*-$CH_3C_6H_4$; R′ = Ph
c, R = *p*-$CH_3C_6H_4$; R′ = H

Reduction of **4a** and **4b** with sodium borohydride in diglyme produced the α-methyl benzyl sulfones, **5a** and **5b**, which were prepared independently by methylation of the benzyl sulfones.



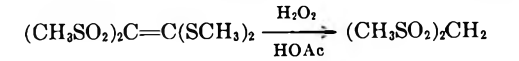
5a, R = Ph; R′ = Ph
b, R = *p*-$CH_3C_6H_4$; R′ = Ph

Application of the reaction sequence to benzyl phenyl sulfoxide gave a material whose spectral characteristics were in accord with 1-phenyl-1-(phenylsulfinyl)-2,2-di(methylmercapto)ethene (**6**). The initial product **6**



decomposed to a pungent black oil which was not further investigated.

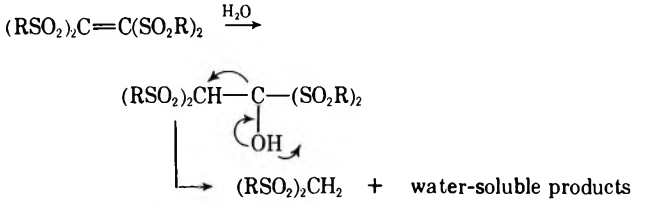
Oxidation of **1** with hydrogen peroxide in glacial acetic acid produced di(methylsulfonyl)methane. This result



is analogous to that of oxidation of 1,1,2,2-tetra(*p*-tolylmercapto)ethene[9] and 1-nitro-2,2-di(methylmercapto)-ethene.[10] The products of the oxidation reactions

(7) W. E. Truce and F. M. Perry, *J. Org. Chem.*, **30**, 1316 (1965).
(8) D. T. Gibson, *J. Chem. Soc.*, 2640 (1931).
(9) W. E. Truce and B. Groten, *J. Org. Chem.*, **27**, 128 (1962).
(10) K. A. Jensen, O. Buchardt, and C. Lohse, *Acta Chem. Scand.*, **21**, 2797 (1967).

are believed to arise by hydration of an initially formed intermediate tri- or tetra(alkylsulfonyl)ethene, followed by cleavage of the hydrate to the observed product and to water-soluble products which were not recovered.



Experimental Section[11]

Starting Materials.—Di(methylsulfonyl)methane,[12] di(*p*-tolylsulfonyl)methane,[13] benzyl phenyl sulfone,[14] benzyl *p*-tolyl sulfone,[15] and benzyl phenyl sulfoxide[14] were prepared by known methods. Methyl *p*-tolyl sulfone, potassium *tert*-butoxide, and methyl iodide were commercially available and used without further purification. Commercial grade carbon disulfide was distilled before use.

General Procedure for Dimercaptomethylation.—To a stirred solution of potassium *tert*-butoxide in dimethyl sulfoxide, under nitrogen, was added a solution of the sulfone in dimethyl sulfoxide. After the solution was stirred for 10 min, carbon disulfide was added, after which the solution became dark red to purple. Methyl iodide was added dropwise to the solution, whereupon the color changed to yellow. The resulting solution was stirred from 1.5 to 3 hr, poured into water, and extracted with methylene chloride, and the extracts were washed with water. After drying ($MgSO_4$), the solvent was removed *in vacuo* and the red oil remaining was dissolved in hot methanol, decolorized, and cooled. Recrystallization afforded the pure product.

1,1-Di(methylsulfonyl)-2,2-di(methylmercapto)ethene (1).—This was prepared from 11.2 g (0.10 mol) of potassium *tert*-butoxide, 8.6 g (0.05 mol) of di(methylsulfonyl)methane, 3.2 ml (0.05 mol) of carbon disulfide, and 6.2 ml (0.10 mol) of methyl iodide, according to the above procedure. Work-up gave 1.8 g of solid which was recrystallized from toluene to afford 1.6 g (11.5%) of **1**: mp 153–154°; nmr ($CDCl_3$) δ 2.69 (s, 6 H, CH_3S), 3.33 ppm (s, 6 H, CH_3SO_2).

Anal. Calcd for $C_6H_{12}O_4S_4$: C, 26.08; H, 4.35; S, 46.38. Found: C, 26.24; H, 4.66; S, 46.01.

1-Phenyl-1-(phenylsulfonyl)-2,2-di(methylmercapto)ethene (4a).—This was prepared, as above, from 11.6 g (0.05 mol) of benzyl phenyl sulfone. Work-up and recrystallization from methanol gave 5.10 g (30%) of product: mp 120–121°; nmr ($CDCl_3$) δ 2.20 (s, 6 H, CH_3S),[16] 7.1–8.0 ppm (m, 10 H, aromatic protons).

Anal. Calcd for $C_{16}H_{16}O_2S_3$: C, 57.15; H, 4.76; S, 28.57. Found: C, 57.32; H, 5.03; S, 28.43.

1-Phenyl-1-(*p*-tolylsulfonyl)-2,2-di(methylmercapto)ethene (4b).—Treatment of 12.3 g (0.05 mol) of benzyl *p*-tolyl sulfone as described above afforded 7.1 g (50%) of product: mp 104–106°; nmr ($CDCl_3$) δ 2.15 (s, 3 H, CH_3S), 2.21 (s, 3 H, CH_3S), 2.39 (s, 3 H, $CH_3C_6H_5$), 7.15–7.81 ppm (m, 9 H, aromatic protons).

Anal. Calcd for $C_{17}H_{18}O_2S_3$: C, 58.35; H, 5.14; S, 27.42. Found: C, 58.73; H, 5.31; S, 27.27.

1-(*p*-Tolylsulfonyl-2,2-di(methylmercapto)ethene (4c).—This was prepared as described above from 8.5 g (0.05 mol) of methyl *p*-tolyl sulfone. Work-up and recrystallization from methanol afforded 0.35 g (2.5%) of light yellow crystals: mp 137–138°; nmr ($CDCl_3$) δ 2.32 (s, 6 H, CH_3S),[16] 2.39 (s, 3 H, $CH_3C_6H_4$), 6.00 (s, 1 H, vinyl proton), 7.21–7.95 ppm (m, 4 H, aromatic protons).

Anal. Calcd for $C_{11}H_{14}O_2S_3$: C, 48.18; H, 5.15; S, 35.00. Found: C, 48.28; H, 5.27; S, 35.30.

1-Phenyl-1-(phenylsulfinyl)-2,2-di(methylmercapto)ethene (6).—This was prepared in 10% yield from 10.80 g (0.05 mol) of benzyl phenyl sulfoxide, using the procedure given above. The crude oil isolated after work-up was dissolved in boiling benzene, and hexane was added until cloudiness persisted. Cooling gave light yellow crystals which were recrystallized several times from hexane to afford **6**: mp 89–90°; nmr ($CDCl_3$) δ 2.15 (s, 3 H, CH_3S), 2.55 (s, 3 H, CH_3S), 6.90–7.60 (m, 10 H, aromatic protons). This material decomposed to a pungent black oil over a period of 4 days.

Anal. Calcd for $C_{16}H_{16}OS_3$: C, 59.97; H, 4.99; S, 30.00. Found: C, 59.36; H, 4.59; S, 29.51.

Reduction of 1,1-Di(methylsulfonyl)2,2-di(methylmercapto)-ethene.—To a stirred slurry of 6.15 g of pulverized nickelous chloride hexahydrate and 0.35 g (0.0013 mol) of **1** in 30 ml of absolute ethanol was slowly added a solution of 3.0 g (0.08 mol) of sodium borohydride in water (stabilized by adding a few drops of 10% sodium hydroxide). A vigorous reaction ensued as the borohydride solution was added. The black reaction mixture was allowed to reflux for 20.5 hr and was filtered. The precipitate was washed with acetone. A white solid (mp >300°) precipitated from the filtrate. It was removed by filtration and the filtrate was evaporated *in vacuo* to give 0.8 g of a white solid which was extracted with boiling acetone. Evaporation of the acetone extracts afforded 0.2 g of **2**: mp 119.5–122.5° (lit.[8] mp 122°); nmr ($CDCl_3$) δ 1.87 (d, 3 H, J = 7.2 cps, CH_3CH), 3.20 (s, 6 H, CH_3SO_2), 4.19 (q, 1 H, J = 7.2 cps, CH_3CH).

Reduction of 1-Phenyl-1-(*p*-tolylsulfonyl)-2,2-di(methylmercapto)ethene.—To a solution of 0.25 g (0.0066 mol) of sodium borohydride in 60 ml of rigorously dried diglyme was added a solution of 2.0 g (0.006 mol) of **4b** in 45 ml of diglyme, and the resulting solution heated at 50° for 17 hr. The cloudy mixture was poured into 600 ml of ice water to which a few drops of sulfuric acid had been added. The precipitate which formed was filtered, dissolved in hot methanol, and filtered while hot to remove a small amount of insoluble material. Cooling the methanol solution produced **5b**: mp 131–133.5° [lit.[17] mp 133–135° (*dl* mixture)]; nmr ($CDCl_3$) δ 1.73 (d, 3 H, J = 7.5 cps, CH_3CH), 2.39 (s, 3 H, $CH_3C_6H_4$), 4.18 (q, 1 H, J = 7.5 cps, CH_3CH), 7.04–7.42 ppm (m, 9 H, aromatic protons).

Reduction of 1-Phenyl-1-(phenylsulfonyl)-2,2-di(methylmercapto)ethene.—The above procedure was followed using 1.92 g (0.0057 mol) of **4a**, 0.25 g (0.0066 mol) of sodium borohydride, and 100 ml of diglyme. The mixture was heated to 64° for 17 hr, and work-up as above gave 0.90 g (75%) of **5a**: mp 113–115° (lit.[18] mp 114–115°); nmr ($CDCl_3$) δ 1.80 (d, 3 H, J = 7.5 cps, CH_3CH), 4.25 (q, 1 H, J = 7.5 cps, CH_3CH), 7.30 ppm (m, 10 H, aromatic protons).

1,1-Di(methylsulfonyl)ethane (2).—To a stirred solution of 2.80 g (0.025 mol) of potassium *tert*-butoxide in 25 ml of dimethyl sulfoxide, under nitrogen, was added a solution of 4.3 g (0.025 mol) of di(methylsulfonyl)methane in 20 ml of dimethyl sulfoxide. After the solution was stirred at room temperature for 20 min, 1.6 ml (0.025 mol) of methyl iodide was added. The solution was stirred for 1.75 hr, poured into 100 ml of water, and extracted with methylene chloride. The extracts were washed with water and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The resulting solid was recrystallized twice from methanol to afford 1.8 g (42%) of **2**, mp 121–123° (lit.[8] mp 122°). In a similar manner, α-methylbenzyl phenyl sulfone (**5a**), mp 113–114°, and α-methylbenzyl *p*-tolyl sulfone (**5b**), mp 132–133°, were prepared.

Oxidation of 1,1-Di(methylsulfonyl)-2,2-di(methylmercapto)-ethene.—To a suspension of 0.5 g (0.0018 mol) of **1** in 4 ml of glacial acetic acid was added 1.5 ml of 30% hydrogen peroxide. The stirred mixture was heated at reflux for 2 hr during which time the suspension changed to a clear yellow solution and finally to a clear colorless solution. On pouring the reaction mixture

(11) All melting points and boiling points are uncorrected. Microanalyses were performed by Dr. C. S. Yeh and staff. The nmr spectra were obtained using a Varian A-60 spectrometer with tetramethylsilane as an internal standard.

(12) H. Bohme and R. Marx, *Chem. Ber.*, **74**, 1667 (1941).

(13) E. Fromm, A. Forster, and B. V. Scherschewitzki, *Justus Liebigs Ann. Chem.*, **394**, 343 (1912).

(14) R. L. Shriner, H. C. Struck, and W. J. Joreson, *J. Amer. Chem. Soc.*, **52**, 2060 (1930).

(15) R. Otto, *Chem. Ber.*, **13**, 1272 (1880).

(16) Apparently, the barriers to rotation about the double bonds in **4a** and **4c** are sufficiently low to allow rotation and subsequent equivalence of these protons. When the nmr spectrum of **4a** was taken at −25°, the methylmercapto signals appeared at δ 2.03 (s, 3 H) and 2.18 ppm (s, 3 H). For a discussion of similar behavior of other 1,1-dimethylmercaptoethenes, see G. Isakson, J. Sandstrom, and I. Wennerbeck, *Tetrahedron Lett.*, 2233 (1967).

(17) C. L. Arcus, M. P. Balfe, and J. Kenyon, *J. Chem. Soc.*, 485 (1938).

(18) F. Ashworth and G. N. Burkhardt, *ibid.*, 1797 (1928).

into ice, no precipitate was produced. Evaporation of the solution to near dryness produced white crystals which were diluted with water and filtered producing 0.2 g (67%) of product, mp 142–146°. The infrared spectrum was identical with that of di(methylsulfonyl)methane.

Registry No.—Carbon disulfide, 75-15-0; **1**, 26958-44-1; **4a**, 26958-45-2; **4b**, 26958-46-3; **4c**, 26958-47-4; **6**, 26958-48-5.

Acknowledgment.—This investigation was supported by the U. S. Army Research Office under Grant No. DA-31-124-ARO-D-211, and by Public Health Service Research Grant No. CA-04536-07 from the National Cancer Institute.

Solvent Effects on the Energy of the Principal Electronic Transition of *p*-Nitrotoluene-α-d_3 and *p*-Methylanisole-α-d_3

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Received May 29, 1970

In recent years it has been postulated that the experimental finding that is called the Baker–Nathan effect owes its origin to direct solvent influences rather than to an inherent predominance of C–H hyperconjugation, other modes of electronic stabilization such as C–C hyperconjugation, and the inductive effect. One group has attributed the Baker–Nathan effect to steric hindrance to solvation near bulkier alkyl groups.[1,2] Another has attributed it to solvent enhancement of C–H over C–C hyperconjugation, through incipient hydrogen bonding of the α hydrogens of the alkyl substituent with the solvent.[3] The observation that the inductive order of principal electronic transition energies found for *p*-alkyl nitrobenzenes and acetophenones in the gas phase and in inert solvents tends to be inverted in basic solvents is qualitatively consistent with either viewpoint.[2,4] It therefore appeared desirable to try to find direct evidence for solvent enhancement of C–H hyperconjugation in the effect of a number of solvents on the relative principal electronic transition energies of *p*-nitrotoluene and *p*-nitrotoluene-α-d_3. The principal electronic transition of the nitrobenzenes is highly electronic demanding on the para substituent, the electron migration being in the long axis of the molecule and away from the substituent.[5] Also included here are solvent studies on the energy of the principal electron transition of *p*-methylanisole and *p*-methylanisole-α-d_3, in which the electron migration is toward the substituent.[5]

An increase in excitation energy spread between *p*-nitrotoluene and *p*-nitrotoluene-α-d_3 in basic solvents could be considered as direct evidence for solvent enhancement of C–H hyperconjugation. On the other hand, the absence of such a finding does not prove that solvent enhancement of C–H hyperconjugation is absent in other systems, *e.g.*, in chemical transitions. That is, in the present system, in contrast to chemical systems, the upper (electronic) state that originally arises is not an "equilibrium state." In the short time of the electronic excitation of a molecule (*ca.* 10^{-16} sec), nuclear relaxation (*ca.* 10^{-13} sec) is minimal (Franck–Condon principle). Thus, orientation of basic portions of solvent molecules to the α hydrogens of the polar excited state species may be minimal, since such orientation is essentially that pertaining in ground state species.

The only trend discernible is a slight increase in $\nu_{CD_3} - \nu_{CH_3}$ in highly acidic solvents, a trend that accompanies a large increase in $\nu_H - \nu_{CH_3}$, the excitation energy difference between nitrobenzene and *p*-nitrotoluene (Table I). In fact, a plot of $\nu_H - \nu_{CD_3}$ against $\nu_H - \nu_{CH_3}$ is linear to a high degree of precision. This indicates that in the transition to the nonequilibrium Franck–Condon excited state, differential solvent perturbation of the CH_3 and CD_3 groups is negligible. The slope of the line is 1.036 with a standard deviation of ± 0.002 and a correlation coefficient of 0.999+. In terms of the Hammett relationship, the slope is the substituent constant ratio, $\sigma_{CH_3}/\sigma_{CD_3}$,[6] and the value of the slope can be taken as meaning that the methyl group has a greater absolute σ value than the CD_3 group.[8]

TABLE I

VALUES OF ν_H, $\nu_H - \nu_{CH_3}$, AND $\nu_{CD_3} - \nu_{CH_3}$ IN cm^{-1} FOR *p*-$RC_6H_4NO_2$ IN VARIOUS SOLVENTS[a-c]

Solvent	ν_H	$\nu_H - \nu_{CH_3}$	$\nu_{CD_3} - \nu_{CH_3}$
Gas phase	41,820	1850	80[d]
Heptane	39,700	1810	50
n-$BuNH_2$	38,200	1920	40
tert-BuOH	38,790	1960	40
Dioxane	38,650	2090	30
EtOH	38,530	2090	30
H_2O	37,440	2280	50
52% $HClO_4$	36,810	2480	60
70% $HClO_4$	35,720	2750	70
96% H_2SO_4	34,580	2710	70

[a] Values of ν_{max}, determined as previously described,[5] are averages of three determinations, duplicable to ±15 cm^{-1} or better except where noted. [b] Compound preparation and purification also previously described.[5] [c] The isotopic composition of the sample of *p*-nitrotoluene-α-d_3 was: d_3, 85.4%; d_2, 13.9%; d_1, 0.7%; d_0, 0%.[5] [d] Value of ref 5, duplicable to ±20–30 cm^{-1}.

The effect of a few solvents on the excitation energy of *p*-methylanisole-α-d_3 is shown in Table II. Within

* To whom correspondence should be addressed.

(1) W. M. Schubert and D. F. Gurka, *J. Amer. Chem. Soc.*, **91**, 1443 (1969), and preceding papers.

(2) W. M. Schubert, J. Robins, and J. Haun, *ibid.*, **79**, 910 (1957).

(3) V. J. Shiner, Jr., and C. J. Verbanic, *ibid.*, **79**, 373 (1957); V. J. Shiner, Jr., *Tetrahedron*, **5**, 243 (1959).

(4) A quantitative treatment of the data in twelve widely varying solvents, dealing with the relative linearity of plots of $\nu_H - \nu_R$ against ν_H was considered to favor the steric hindrance to solvation argument.[2]

(5) W. M. Schubert, R. B. Murphy, and J. Robins, *J. Org Chem.*, **35**, 951 (1970), and references therein.

(6) Since ν is proportional to energy, the Hammett relationship for electronic transitions can be written $\nu_H - \nu_{CH_3} = \sigma_{CH_3}\rho'$, where ρ' is dependent on the solvent and the units of energy used.[7] By combining this equation with the corresponding one for CD_3 one obtains $\nu_H - \nu_{CH_3} = (\sigma_{CH_3}/\sigma_{CD_3})(\nu_H - \nu_{CD_3})$, which is the equation of the line.

(7) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).

(8) It is to be noted that the various kinds of σ values that have been assigned to alkyl substituents, all negative, have the wrong sign for the principal electron transition of anisoles, phenols, and anilines.[5,9]

(9) W. M. Schubert, R. B. Murphy, and J. Robins, *Tetrahedron*, **17**, 199 (1962).

TABLE II

VALUES OF ν_H, $\nu_H - \nu_{CH_3}$, AND $\nu_{CD_3} - \nu_{CH_3}$ IN CM^{-1} FOR p-$RC_6H_4OCH_3$ IN VARIOUS SOLVENTS[a-c]

Solvent	ν_H	$\nu_H - \nu_{CH_3}$	$\nu_{CD_3} - \nu_{CH_3}$
Gas phase	46,510	1010	130[d]
Heptane	45,530	1090	80
MeCN	45,530	770	80
Dioxane	45,350	730	80
EtOH	45,570	860	80
H_2O	46,180	910	100

[a] Values of ν_{max}, determined as previously described,[5] are averages of two determinations, duplicable to ± 20 cm^{-1} except where noted. [b] Compound preparation and purification also previously described.[5] [c] The isotopic composition of the sample of p-methylanisole-α-d_3 was: d_3, 85.0%; d_2, 9.8%; d_1, 0.7%; d_0, 4.5%.[5] [d] Value of ref 5, duplicable to ± 20–30 cm^{-1}.

experimental error no solvent effect on $\nu_{CD_3} - \nu_{CH_3}$ is discernible. The interesting fact that p-alkyl lowers the principal electronic excitation energy of anisole and similar compounds,[8] and that both for compounds of the anisole type and nitrobenzene, p-CD_3 derivatives have a slightly higher excitation energy than the p-CH_3 derivatives, has been commented upon previously.[5,9]

Although base solvation of p-CH_3 is indetectable in this particular system, the pronounced lowering of the excitation energy of each nitrobenzene as solvent acidity is increased[10] indicates that acidic hydrogen bond solvation of the nitro oxygens is highly important in the total solvent effect.[2] The *increase* in excitation energy of the anisoles in proceeding from heptane to water solvent is attributable to acidic hydrogen bond solvation of the ether oxygen.[5]

Registry No.—p-Nitrotoluene-α-d_3, 23346-24-9; p-methylanisole-α-d_3, 23346-26-1.

Acknowledgment.—Financial support by the Office of Ordnance Research, U. S. Army, is gratefully acknowledged.

(10) For nitrobenzene itself, the excitation energy is 14.6 kcal mol^{-1} less in 96% sulfuric acid than in heptane.

Protonation and Methylation of Dianions Derived from 1,4-Bisbiphenylenebutatriene and 1,4-Bisbiphenylene-1,3-butadiene

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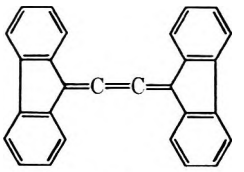
Received February 18, 1970

It was the purpose of this investigation to extend our knowledge of the chemical reactions of the dianions generated from aryl-substituted butatrienes. The chemical reactivity of the dianion derived from tetraphenylbutatriene has been the subject of several papers.[1]

The butatriene chosen for the present study was 1,4-bisbiphenylenebutatriene (II). It is a planar molecule

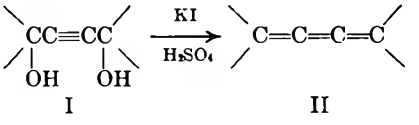


II

and extensive resonance delocalization is possible. This fact is clearly indicated by the colors of tetraphenylbutatriene and 1,4-bisbiphenylenebutatriene. The first is bright yellow and absorbs in the visible at 408 mμ, whereas the second is deep red with a visible absorption at 483 mμ. Due to some steric inhibition of resonance, delocalization is less in the first compound.

1,4-Bisbiphenylenebutatriene was prepared from 1,4-bisbiphenylene-2-butyne-1,4-diol by the potassium iodide–sulfuric acid method described by Wolinski[2] (Scheme I).

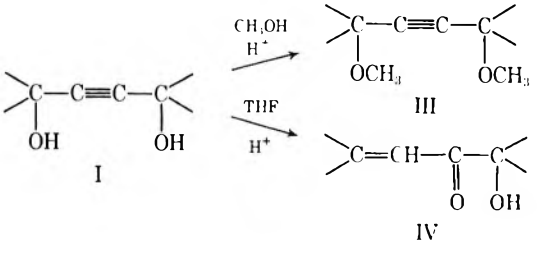
SCHEME I



I II

The dimethyl ether of I was readily prepared by treating the diol with methanol and sulfuric acid. The yellow color produced during the reaction was due to the formation of a small amount of 1,4-bisbiphenylene-1-buten-3-one-4-ol. The latter was formed as the result of an allylic-type rearrangement followed by a tautomeric shift to a keto structure. The keto alcohol was the main product when tetrahydrofuran was used in place of methanol (Scheme II).

SCHEME II



I III IV

The hybrid dianion, $[C\cdots C\equiv C\cdots C]^{2-}$ may be obtained directly from 1,4-bisbiphenylenebutatriene by treatment with sodium–potassium alloy but it is more readily prepared by treating the dimethyl ether III with sodium–potassium alloy.

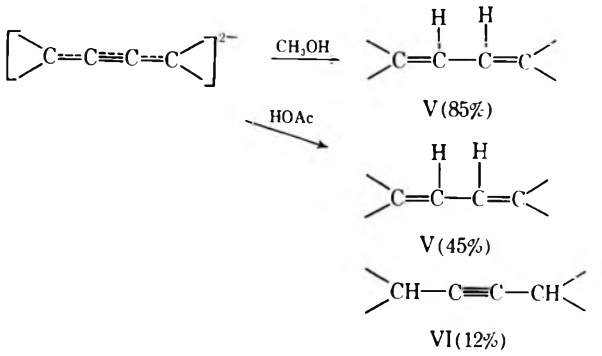
Protonation of the dianion was first accomplished by the addition of methanol. The protonation was slow as evidenced by the very slow decolorization of the dianion solution. Only 1,4-bisbiphenylene-1,3-butadiene (V) was obtained from this reaction. When acetic acid was used as the protonating agent, decolorization occurred almost at once. In addition to the 1,3-diene V, 1,4-bisbiphenylene-2-butyne (VI) was isolated (Scheme III).

* To whom correspondence should be addressed.

(1) (a) A. Zweig and A. Hoffman, *J. Amer. Chem. Soc.*, **84**, 3278 (1962); (b) R. Nahon and A. R. Day, *J. Org. Chem.*, **30**, 1973 (1965); (c) S. Sisenwine and A. R. Day, *ibid.*, **32**, 1770 (1967).

(2) J. Wolinski, *Rocz. Chem.*, **29**, 23 (1955).

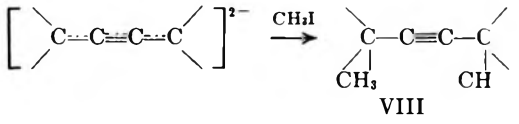
SCHEME III



Small amounts of impure 1,4-bisbiphenylene-1,2-butadiene (VII) were obtained from both methods of protonation. This was indicated by a strong infrared absorption at 1950 cm^{-1}, but a pure sample of VII could not be obtained. It was shown earlier[1c] that in the protonation of the dianion from tetraphenylbutatriene, an allene, 1,1,4,4-tetraphenyl-1,2-butadiene, was the kinetically favored product and could be obtained in good yields at low temperatures. The fact that no appreciable amount of the 1,2-diene could be obtained from the dianion corresponding to 1,4-bisbiphenylenebutatriene, even at low temperatures, suggests a greater increase in resonance stabilization when the entire system becomes conjugated than was the case with the tetraphenyl system.

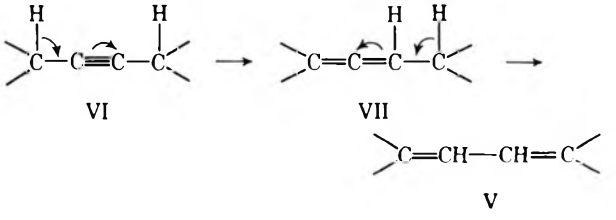
Methylation of the dianion obtained from III, with methyl iodide, gave 2,5-bisbiphenylene-3-hexyne (VIII) as the only product (Scheme IV).

SCHEME IV



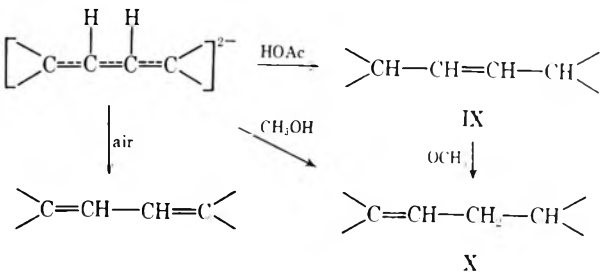
It is probable that protonation and methylation involve the same initial step, namely 1,4 addition. The 1,4-dihydro compound VI rearranges to the more stable system V, whereas the 1,4-dimethyl product VIII is stable under the conditions used (Scheme V).

SCHEME V



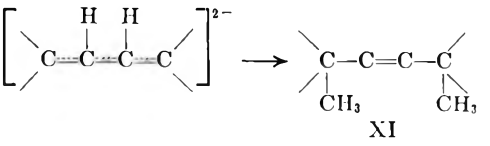
Protonation of the dianion derived from 1,4-bisbiphenylene-1,3-butadiene (V) led to some interesting results. Protonation with acetic acid gave an excellent yield of 1,4-bisbiphenylene-2-butene (IX). The compound was too insoluble for nmr analysis. The presence of an absorption at 957 cm^{-1} in the infrared indicated the 2-butene to be in the trans form. Protonation of the dianion from V with methanol gave only 1,4-bisbiphenylene-1-butene (X) (Scheme VI). In the conversion of V to X a small amount of 1,4-bisbiphenylene-1,3-butadiene (V) was isolated. This undoubtedly resulted from an electron-transfer reaction with air (O_2), since the conversion is efficiently accomplished by bubbling air through the solution.

SCHEME VI



Methylation of the dianion from V, with methyl iodide, gave an excellent yield of 2,4-bisbiphenylene-3-hexene (XI) (Scheme VII).

SCHEME VII



Experimental Section

All melting points were taken in a Thomas–Hoover capillary melting point apparatus. The infrared spectra were obtained with a Perkin-Elmer 521, double beam, recording spectrophotometer using KBr disks, Nujol mulls, or thin films on sodium chloride disks. The ultraviolet spectra were recorded on a Cary 14 spectrophotometer. Nuclear magnetic resonance spectra were determined with a Varian Associates Model A-60A spectrophotometer at 60 MHz with tetramethylsilane as an internal standard.

Purification of Solvents.—Tetrahydrofuran and 1,2-dimethoxyethane were refluxed over lithium aluminum hydride and then distilled. The distillate was then redistilled over sodium–potassium alloy. Several crystals of benzophenone were added to the alloy–solvent mixture to signal complete dryness. If the intense blue-violet color of the anion–radical of the benzophenone disappeared at any time during the distillation, the drying process was repeated.

Preparation of Sodium–Potassium Alloy.—Four parts (12.0 g) of potassium and one part of sodium (3 g) were added to a 100-ml flask containing 60–70 ml of freshly distilled 1,2-dimethoxyethane. After refluxing for 2–3 hr, the flask was cooled and the liquid alloy was stored under nitrogen in the same flask in which it was prepared. The alloy was removed as needed with a glass pipet (eye dropper type) and transferred to a weighed, stoppered, 25-ml erlenmeyer flask containing 10 ml of dry tetrahydrofuran. The entire contents of this flask were then emptied into the reaction flask when needed.

1,4-Bisbiphenylene-2-butyne-1,4-diol (I).—This diol was prepared from fluorenone and acetylenedimagnesium bromide.[3]

1,4-Bisbiphenylenebutatriene (II).—This compound was prepared from I by the sulfuric acid–potassium iodide method.[1c,2] The red product was washed with ethanol, water, and again with ethanol, yield 78%, mp 316° (from xylene).[4] The ir spectrum of the triene was identical with that obtained by Otting.[5]

Anal. Calcd for $C_{28}H_{16}$: C, 95.41; H, 4.59. Found: C, 95.36; H, 4.64.

(3) E. Bergmann, H. Hoffman, and D. Winter, *Chem. Ber.*, **50**, 3349 (1956).

(4) The melting points reported in the literature vary widely. Bergmann, Hoffman, and Winter (ref 3) report >300°; Wolinski[2] gives 324–336°; R. Kuhn and G. Platzer [*Chem. Ber.*, **73**, 1410 (1940)] report 330°; C. R. Hauser and D. Lednicer [*J. Org. Chem.*, **22**, 1248 (1957)] give 309°; D. Y. Curtin and E. W. Flynn [*J. Amer. Chem. Soc.*, **81**, 4714 (1959)] give 279–282°; and D. Lavie and E. D. Bergmann [*J. Org. Chem.*, **18**, 367 (1953)] report 300–302°.

(5) W. Otting, *Chem. Ber.*, **87**, 611 (1954).

1,4-Bisbiphenylene-1,4-dimethoxy-2-butyne (III).—This ether was prepared by a previously reported method.[1c] The yield was 75%: mp 200° (from ethanol); ir (KBr) 2990–2820 (CH_3), 1090–1060 cm^{-1} (COC); nmr aromatic multiplet at δ 7.3 (16) and a methyl proton singlet at δ 3.0 (6).

Anal. Calcd for $C_{30}H_{22}O_2$: C, 86.92; H, 5.35. Found: C, 86.95; H, 5.40.

1,4-Bisbiphenylene-3-oxo-1-buten-4-ol (IV).—A tetrahydrofuran solution of sulfuric acid (2 ml of 96.4% H_2SO_4 in 10 ml of THF) was added with stirring to a solution of III (2 g, 0.005 mol) in 30 ml of THF. After refluxing for 30 min, the solution was poured into water. The resulting orange oil was taken up in ether, and washed with water, 10% $NaHCO_3$, and water, and dried ($CaCl_2$). The ether was evaporated and the resulting solid was recrystallized from petroleum ether (60–110°): yield 63%, orange crystals; mp 175°; ir (KBr) 1670 (C=CC=O) and 3440 cm^{-1} (OH); nmr aromatic multiplet at δ 7.2 (16), olefin proton singlet at δ 6 (1), and a hydroxyl proton singlet at δ 4.95 (1).

Anal. Calcd for $C_{28}H_{18}O_2$: C, 87.02; H, 4.69. Found: C, 86.89; H, 4.79.

Preparation of the Dianion from 1,4-Bisbiphenylene-1,4-dimethoxy-2-butyne (III).—Tetrahydrofuran (250 ml) was distilled, in a nitrogen atmosphere, into a dry 500-ml erlenmeyer flask containing a magnetic stirrer. Compound III (2.9 g, 0.007 mol) was then added and the flask was capped with a serum cap. The Na–K alloy (1.44 g, 0.042 g-atom), was preweighed in a 25-ml erlenmeyer flask containing 10 ml of dry THF and added quickly to the solution of III. The mixture was stirred for 12 hr at which time the solution was dark reddish brown (the color of the dianion). Stirring was continued for an additional 10 hr.

Protonation of the Dianion, from III, with Methanol. Preparation of 1,4-Bisbiphenylene-1,3-butadiene.—The dianion solution was transferred, under nitrogen, to another dry flask and protonation carried out as described in the protonation of the dianion from tetraphenylbutatriene.[1c] The solution was stirred for 1 hr and evaporated to about one-third of its initial volume. The solid so obtained was washed with methanol, water, and methanol and recrystallized from xylene, yield 85%, orange needles, mp 381°.[6] The ultraviolet spectrum for V was almost identical with that reported by Wieland and Kraus:[5] uv (dioxane) 241 mμ (log ϵ 4.82), 268 (4.71), 278 (4.65), 415 (4.63), and 442 (4.60).

Anal. Calcd for $C_{28}H_{18}$: C, 94.87; H, 5.13. Found: C, 94.78; H, 5.17.

Protonation of the Dianion from III with Acetic Acid. Preparation of 1,4-Bisbiphenylene-1,3-butadiene and 1,4-Bisbiphenylene-2-butyne (VI).—The only change in the above procedure was the use of acetic acid in place of methanol. The resulting solid was refluxed in THF and filtered hot to remove the 1,3-diene V which was identified by its melting point and uv spectrum. The filtrate deposited colorless crystals of 1,4-bisbiphenylene-2-butyne which were recrystallized from benzene until spectrally free of the 1,3-diene (uv) and of the 1,2-diene (no 1950 cm^{-1} absorption in the ir), yield 12%, mp 255–257°. A mixture melting point determination with an authentic sample, prepared by an aluminum amalgam–water reduction of bisbiphenylenebutatriene,[7] showed no depression.

Methylation of the Dianion from III. Preparation of 2,5-Bisbiphenylene-3-hexyne (VIII).—A solution of the dianion, prepared in the usual manner, was cooled in Dry Ice–acetone and 7 ml of methyl iodide was added by way of a syringe. The solution was stirred for 1 hr and cooled and the inorganic salts were removed. The filtrate was evaporated and the resulting solid was recrystallized from ethanol: yield 82%; mp 231°; ir (KBr) 2970–2860 cm^{-1}; nmr an aromatic multiplet at δ 7.4 (16) and a methyl proton singlet at δ 1.5 (6).

Anal. Calcd for $C_{30}H_{22}$: C, 94.20; H, 5.80. Found: C, 94.28; H, 5.87.

Protonation of the Dianion from 1,4-Bisbiphenylene-1,3-butadiene with Methanol. Preparation of 1,4-Bisbiphenylene-1-butene (X).—Methanol was added to the cold (0°) dianion solution, prepared in the usual way[1c] from V, and the solution stirred for 1 hr. The mixture was filtered and the filtrate was evaporated. The resulting oil was taken up in benzene and a small amount of the 1,3-diene V (orange crystals, mp 381°) was removed. The benzene filtrate was evaporated and a yellow oil remained which crystallized from methanol. The product was recrystallized from ethanol: yield 85%, pale yellow needles; mp 163°; nmr an aromatic multiplet at δ 7.35 (16), an olefinic proton triplet at δ 6.45 (1, J = 7 Hz), a tertiary proton at δ 4.15 (1, J = 7 Hz), and a methylene proton triplet at δ 3.35 (2, J = 7 Hz); ir (KBr) 957 cm^{-1} (trans form).

Anal. Calcd for $C_{28}H_{20}$: C, 94.34; H, 5.66. Found: C, 94.25; H, 5.69.

Protonation of the Dianion from 1,4-Bisbiphenylene-1,3-butadiene with Acetic Acid. Preparation of 1,4-Bisbiphenylene-2-butene (IX).—Acetic acid was added to the dianion solution from V at 0°. After stirring for 1 hr, the mixture was allowed to come to room temperature and was then filtered. The filtrate was evaporated to small volume and cooled and the solid removed. This solid was recrystallized from benzene, yield 84%, pale yellow crystals, mp 268° (Lavie and Bergmann[4] reported 267–268°). A mixture melting point determination with an authentic sample, prepared by the zinc–acetic acid reduction of 1,4-bisbiphenylene-1,3-butadiene,[4] showed no depression.

Base-Catalyzed Isomerization of 1,4-Bisbiphenylene-2-butene (IX) to 1,4-Bisbiphenylene-1-butene (X).—1,4-Bisbiphenylene-2-butene (0.1472 g, 0.004 mol) was dissolved in 10 ml of warm tetrahydrofuran and 0.121 g of sodium methoxide was added. Three drops of water were added to dissolve the sodium methoxide. After stirring for 15 min, the mixture was partially evaporated to give an orange product. After recrystallization from xylene this proved to be 1,4-bisbiphenylene-1,3-butadiene, yield 8%, mp 381°. The addition of methanol to the tetrahydrofuran filtrate precipitated a light yellow product which was recrystallized from ethanol, yield 43%, mp 163°. A mixture melting point determination proved this product to be bisbiphenylene-1-butene.

Methylation of the Dianion from 1,4-Bisbiphenylene-1,3-butadiene (V). Preparation of 2,5-Bisbiphenylene-3-hexene (XI).—Methyl iodide (10 ml) was added to the cold (0°) dianion solution. After stirring for 1 hr, the mixture was allowed to come to room temperature and filtered. The filtrate was evaporated and the resulting oil was crystallized by stirring with methanol. The product was recrystallized from methanol: yield 76%; mp 158°; nmr (CS_2) δ 7.7–7.1 (m, 16), 5.65 (s, 2, CH=CH), 1.4 (s, 6, CH_3).

Anal. Calcd for $C_{30}H_{24}$: C, 93.71; H, 6.29. Found: C, 93.61; H, 6.25.

Registry No.—Dianion of II, 12441-29-1; IV, 26924-10-7; V, 4551-02-4; dianion of V, 12441-28-0; VIII, 26963-81-5; X, 26924-12-9; XI, 26924-13-0.

(6) The melting points reported in the literature differ considerably from our value. Lavie and Bergmann (ref 4) report 355°; H. Wieland and E. Krause [*Justus Liebigs Ann. Chem.*, **443**, 129 (1925)] report 360°; and E. Bergmann and Y. Hirshberg [*Bull. Soc. Chim. Fr.*, **17**, 1091 (1950)] give 373°.

(7) R. Kuhn and H. Fischer, *Chem. Ber.*, **94**, 3060 (1961).

The Synthesis of Nitrotrifluoromethylphenols and Related Compounds from Nitrotrifluoromethylchlorobenzenes

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Received January 26, 1970

The use of nitrotrifluoromethylchlorobenzenes as precursors for nitrotrifluoromethylphenols is of interest owing to the commercial availability[1] of the former and the lack of general synthesis procedures for the latter. In addition, nitrotrifluoromethylphenols are useful

(1) The various nitrotrifluoromethylchlorobenzenes used as starting materials in the present work were obtained from Sherwin Williams Chemicals, Fine Chemicals Dept., Cincinnati, Ohio.

TABLE I

PRODUCTS FROM NUCLEOPHILIC SUBSTITUTIONS OF NITROTRIFLUOROMETHYLCHLOROBENZENES IN DMSO

Chlorobenzene substituents	Reagent	Temp, °C (time, hr)	Product	Yield, %	Mp, °C	Ref
2-NO_2-4-CF_3-	NaOH	20–25 (8)	2-Nitro-4-(trifluoromethyl)phenol	96.2	*a*	
4-NO_2-2-CF_3-	NaOH	20–25 (8)[b]	4-Nitro-2-(trifluoromethyl)phenol	40	133–134[g]	*h*
2,6-(NO_2)$_2$-4-CF_3-	NaOH	20–25 (4)[c]	2,6-Dinitro-4-(trifluoromethyl)phenol	92	46–48	*i*
4-NO_2-3-CF_3	NaSH	20–25 (8)	Bis(4-nitro-3-(trifluoromethyl)-phenyl) disulfide	45	119–120.5	*d*
2-NO_2-4-CF_3-	NaSCH	45–50 (22)	2-Nitro-4-(trifluoromethyl)phenyl-thiocyanate	70	74–77	*e*
4-NO_2-3-CF_3-	NaOH	20–25 (8)	5-Chloro-2-nitrophenol	93[f]	38.5–39	*j*

[a] The product is a dark red oil at 20°. [b] The product was actually isolated from the crude product oil after having been stored for 2 months at 20–25°. [c] Reverse addition required, with dinitro compound being added to a DMSO slurry of NaOH, in order to control extreme exotherm (fire). [d] *Anal.* Calcd for $C_{14}H_6F_6N_2O_4S_2$: S, 14.43. Found: S, 14.52. [e] *Anal.* Calcd for $C_8H_3F_3N_2O_2S$: S, 12.9; F, 23.0. Found: S, 12.9; F, 23.19. [f] The other major product was identified as fluoroform. [g] On several occasions, a solid, mp 63.5–64°, was isolated which on the basis of nmr spectrum and elemental analysis appears to be a 1:1 adduct of DMSO and 4-nitro-2-(trifluoromethyl)phenol (*Anal.* Calcd for $C_9H_{10}F_3NO_4S$: C, 37.89; H, 3.53; N, 4.91; F, 19.98. Found: C, 37.92; H, 3.95; N, 4.62; F, 19.84). [h] See ref 5. [i] L. M. Yaguipolskii and V. S. Mospan, *Ukr. Khim. Zh.*, 21, 81 (1955); *Chem. Abstr.*, 49, 8867*c* (1955). [j] Laubenheimer, *Chem. Ber.*, 9, 768 (1876).

commercially as lamprecides,[2] agricultural chemicals,[3] and dyestuff intermediates.[4]

In the present work, nitrotrifluoromethylphenols were readily prepared by the reaction of sodium hydroxide with nitrotrifluoromethylchlorobenzenes in dimethyl sulfoxide. In general, the reactions proceeded best when 3 mol of sodium hydroxide was used for 1 mol of nitrotrifluoromethylchlorobenzene (see Table I).

Phenols of the type described are not new but have been prepared previously by tedious multistep reactions.[5]

Others[6] have attempted to produce nitrotrifluoromethylphenols directly in one step from nitrotrifluoromethylchlorobenzenes and hydroxide ions but in all cases found that the trifluoromethyl groups had been hydrolyzed. This is consistent with reports[7] that a trifluoromethyl group is invariably hydrolyzed by strong bases and with extraordinary facility if amino or hydroxyl groups are located ortho or para to the trifluoromethyl group. Such behavior has been attributed to "no-bond" resonance.[8]

In the course of this investigation, a novel reaction was observed when 4-nitro-3-trifluoromethylchlorobenzene was treated with sodium hydroxide in dimethyl sulfoxide. Upon the addition of the first portion of sodium hydroxide, gas evolution was noted. The two major products from this reaction were identified as fluoroform and 5-chloro-2-nitrophenol.

It is noteworthy that reaction of sodium sulfhydrate with 4-nitro-3-trifluoromethylchlorobenzene in dimethyl sulfoxide was normal.

In addition to the reactions described above, it was found that the use of sodium thiocyanate in place of sodium hydroxide produced nitrotrifluoromethylbenzenes containing the SCN moiety.

(2) O. Scherer, H. Frensch, and G. Stahler, German Patent 1,068,505 (Nov 5, 1969).

(3) J. Walker, M. Kerchersid, and M. Merkle, *J. Agr. Food Chem.*, **16**, 143 (1968).

(4) J. Dickey and J. McNally, U. S. Patent 2,442,345 (June 1, 1948).

(5) R. Filler, B. Khan, and C. W. McMullen, *J. Org. Chem.*, **27**, 4660 (1962).

(6) R. Filler and H. Novar, *ibid.*, **26**, 2707 (1961); *Chem. Ind. (London)*, 468, 1273 (1960).

(7) R. G. Jones, *J. Amer. Chem. Soc.*, **69**, 2346 (1947); J. Boynstein, S. A. Leone, W. F. Sullivan, and O. F. Bennett, *ibid.*, **79**, 1745 (1957).

(8) J. D. Roberts, R. L. Webb, and E. A. McElhill, *ibid.*, **72**, 408 (1950).

Experimental Section[9]

The preparation of 2-nitro-4-trifluoromethylphenol well illustrates the general technique followed in the preparation of those compounds shown in Table I. A 112.5-g (0.5 mol) quantity of 2-nitro-4-trifluoromethylchlorobenzene was dissolved in 150 ml of dimethyl sulfoxide, and 60 g (1.5 mol) of finely powdered sodium hydroxide was added with stirring over an 8-hr period. The reaction mixture was kept at 20–25° throughout the sodium hydroxide addition period. After standing overnight without stirring, the reaction mixture was poured into 1 l. of cold water, filtered through Dicalite, and acidified to pH 1 with concentrated hydrochloric acid. A dark red oil separated and was removed, dissolved in 50 ml of ether, and dried over Na_2SO_4; the ether was removed under reduced pressure. There remained 100 g (96.2% yield) of product, the ir spectrum of which was identical with the ir spectrum of a known pure sample of 2-nitro-4-trifluoromethylphenol.

Registry No.—2-Nitro-4-(trifluoromethyl)phenol, 400-99-7; 4-nitro-2-(trifluoromethyl)phenol, 1548-61-4; 2,6-dinitro-4-(trifluoromethyl)phenol, 393-77-1; bis-(4-nitro-3-(trifluoromethyl)phenyl) disulfide, 27006-08-2; 2-nitro-4-(trifluoromethyl)phenylthiocyanate, 26958-51-0; 5-chloro-2-nitrophenol, 611-07-4; 1:1 adduct of DMSO and 4-nitro-2-(trifluoromethyl)phenol, 26958-52-1.

(9) Melting points are corrected and were determined in a Thomas-Hoover capillary melting point apparatus. Infrared spectra were obtained with a Perkin-Elmer infracord spectrophotometer and all compounds prepared had infrared spectra which agreed with the assigned structures. Microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. The mass spectrometric analysis was performed by Morgan-Schaffer Corp., Quebec, Canada.

A New Route to Brex-4-ene

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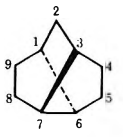
Received April 17, 1970

The continuing interest in the synthesis and rearrangements of alicyclic structures[1] has provided considerable information on the behavior of ionic intermediates in stereochemically defined systems. Several

(1) P. de Mayo, "Molecular Rearrangements," Interscience, New York, N. Y., 1963.

years ago, the synthesis of a new tricyclic ring system, brexane (tricyclo[4.3.0.0.^{3,7}]nonane) (**1**), was announced by Nickon, *et al.*[2]

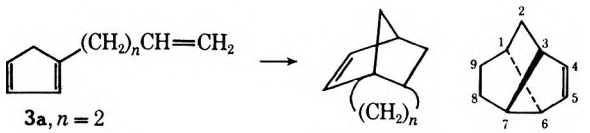
In our systematic pursuit of synthetic applications of the intramolecular Diels–Alder reaction,[3] we have found a convenient synthesis of the unsaturated derivative brex-4-ene (**2**).



1

Results and Discussion

The application of the intramolecular Diels–Alder reaction to a substituted cyclopentadienylhexene has been reported previously.[3a] A related synthetic application was reported by Corey,[4] utilizing 1-(4-pentenyl)-1,3-cyclopentadiene. On extending this reaction to the corresponding 1-(3-butenyl)-1,3-cyclopentadiene (**3a**), the product formed in quantitative yield was not the expected, albeit strained, tricyclo[4.2.1.0^{1,4}]-non-7-ene (**4a**) but instead the isomeric brex-4-ene (**2**).[5]



3a, $n = 2$
b, $n = 3$
c, $n = 4$

4a, $n = 2$
b, $n = 3$
c, $n = 4$

2

Presumably the starting olefin, **3a**, isomerizes to the 1-substituted cyclopentadiene prior to cyclization permitting the formation of the less strained brex-4-ene. The equilibration of alkylcyclopentadienes is well established, the free-energy difference between 1-methyl- and 5-methylcyclopentadiene being approximately 2.0–2.5 kcal/mol.[6] The structure of product **2** was established by direct gas chromatographic and spectroscopic comparison (ir and nmr) with an authentic sample.[7]

To confirm further the structure of the olefin, **2** was catalytically hydrogenated to the parent hydrocarbon brexane (**1**), identical with an authentic sample.[7] The presence of the double bond offers an opportunity or the introduction of other functional groups.[4]

(2) A. Nickon, H. Kwasnik, T. Swartz, R. O. Williams, and J. B. Di Giorgio, *J. Amer. Chem. Soc.*, **87**, 1613 (1965).

(3) (a) G. Brieger, *ibid.*, **85**, 3783 (1963); (b) G. Brieger, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, p D-29.

(4) E. J. Corey and R. S. Glass, *J. Amer. Chem. Soc.*, **89**, 2600 (1967).

(5) H. Scharf and G. Weisgerber, *Tetrahedron Lett.*, **16**, 1567 (1967).

(6) S. McLean and P. Haynes, *Tetrahedron*, **21**, 2329 (1965).

(7) Comparison with authentic samples of brex-4-ene and brexane was kindly performed by Professor A. Nickon.

Experimental Section[8]

1-(3-Butenyl)-1,3-cyclopentadiene (3a).—A solution of 3.25 g (0.0825 mol) of sodium amide in 85.0 ml of tetrahydrofuran was added, under nitrogen, to a stirred solution of 11.0 ml (0.125 mol) of cyclopentadiene in 10 ml of tetrahydrofuran with cooling. 4-Bromobutene, 11.1 g (0.0822 mol), was added over a 45-min period. The mixture was stirred for an additional 2.5 hr. The mixture was then extracted with 150 ml of petroleum ether. The extract was washed three times with water, dried ($MgSO_4$), and distilled to give 4.52 g (44.5% yield) of **3a**: bp 52–53° (14 mm); ir 3.30 (m), 3.48 (s), 6.12 (m), 6.24 (w), 6.98 (m), 7.34 (m), 10.06 (m), 10.55 (w), 10.98 (s), 12.33 (w), 13.38 (w), 14.81 μ (s); nmr δ 6.4–5.4, multiplet (4 H), 4.95, triplet (2 H), 2.82, doublet (2 H), 2.36, singlet (4 H).

Anal. Calcd for C_9H_{12}: C, 89.94; H, 10.06. Found: C, 89.83; H, 10.23.

1-(4-Pentenyl)-1,3-cyclopentadiene (3b).—The same procedure as above was followed, utilizing 5-bromopentene, for the preparation of **3b**, yield 77%, bp 69–71° (15 mm).[4]

1-(5-Hexenyl)-1,3-cyclopentadiene (3c).—The above procedure was followed for the preparation of **3c**, utilizing 5-bromohexene: yield 73%; bp 87–89° (12 mm); ir 3.27 (m), 3.41 (s), 6.10 (m), 6.20 (w), 6.97 (m), 7.32 (m), 10.07 (m), 10.53 (w), 10.97 (s), 11.12 (s), 12.34 (w), 13.62 (w), 14.85 μ (m); nmr δ 6.2–5.0, complex (4 H), 4.45, doublet, 4.95, singlet (2 H), 2.55, doublet (2 H), 2.3–1.22, complex (8 H).

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 88.96; H, 11.04.

Brex-4-ene (2).—A 5.0% solution of **3a** in benzene was heated in a sealed tube at 180° for 4 hr. According to gas–liquid chromatographic analysis (15 ft × 0.25 in. column with 25% TCEPE/Chromosorb W), there was quantitative conversion to **5**. A sample collected by preparative glc had the following properties: ir 3.28 (m), 3.38 (s), 6.21 (w), 6.36 (w), 7.49 (m), 7.96 (w), 7.86 (w), 10.97 (w), 11.14 (w), 11.83 (m), 12.38 (m), 13.29 (w), 14.18 μ (s); nmr δ 5.94 doublet, (2 H), 2.40, singlet (1 H), 2.56, singlet (1 H), 2.08, singlet, (1 H), 1.8–0.6, several bands (7 H).[7]

Tricyclo[5.2.1.0^{1,5}]dec-8-ene (4b) was prepared as described above for **2** from **3b**. A quantitative conversion was noted.[4]

Tricyclo[6.2.1.0^{1,6}]undec-9-ene (4c) was prepared as above for **2** from **3c**: ir 3.29 (w), 3.42 (s), 3.51 (w), 6.91 (m), 7.49 (w), 11.0 (w), 11.71 (w), 13.35 (w), 14.20 μ (m); nmr δ 5.95–5.68, complex (2 H), 2.68, singlet (1 H), 2.4–1.0, complex (13 H).

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 88.89; H, 11.12.

Brexane (1).—**2** (0.5 g) was hydrogenated in a Parr hydrogenator in 60.0 ml of diethyl ether with 0.5 g of 10% Pd/C. The ether was removed by distillation and the product analyzed by gas chromatography as above. A 95% yield was obtained: ir 3.38 (s), 3.47 (sh), 6.84 (w), 7.62 μ (w); nmr δ 2.88, singlet (4 H), 1.46, multiplet (8 H), 1.03, singlet (2 H).[7]

Registry No.—**2**, 15782-76-0; **3a**, 27017-52-3; **3c**, 27017-53-4; **4c**, 27017-54-5.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(8) The boiling points are uncorrected. Infrared spectra in μ were determined as liquid films unless otherwise indicated. Nmr spectra were determined with a Varian T-60 spectrometer, 10% solutions in CCl_4 with TMS internal reference (δ = 0 ppm). Analyses were made by Spang Microanalytical Laboratories, Ann Arbor, Mich.

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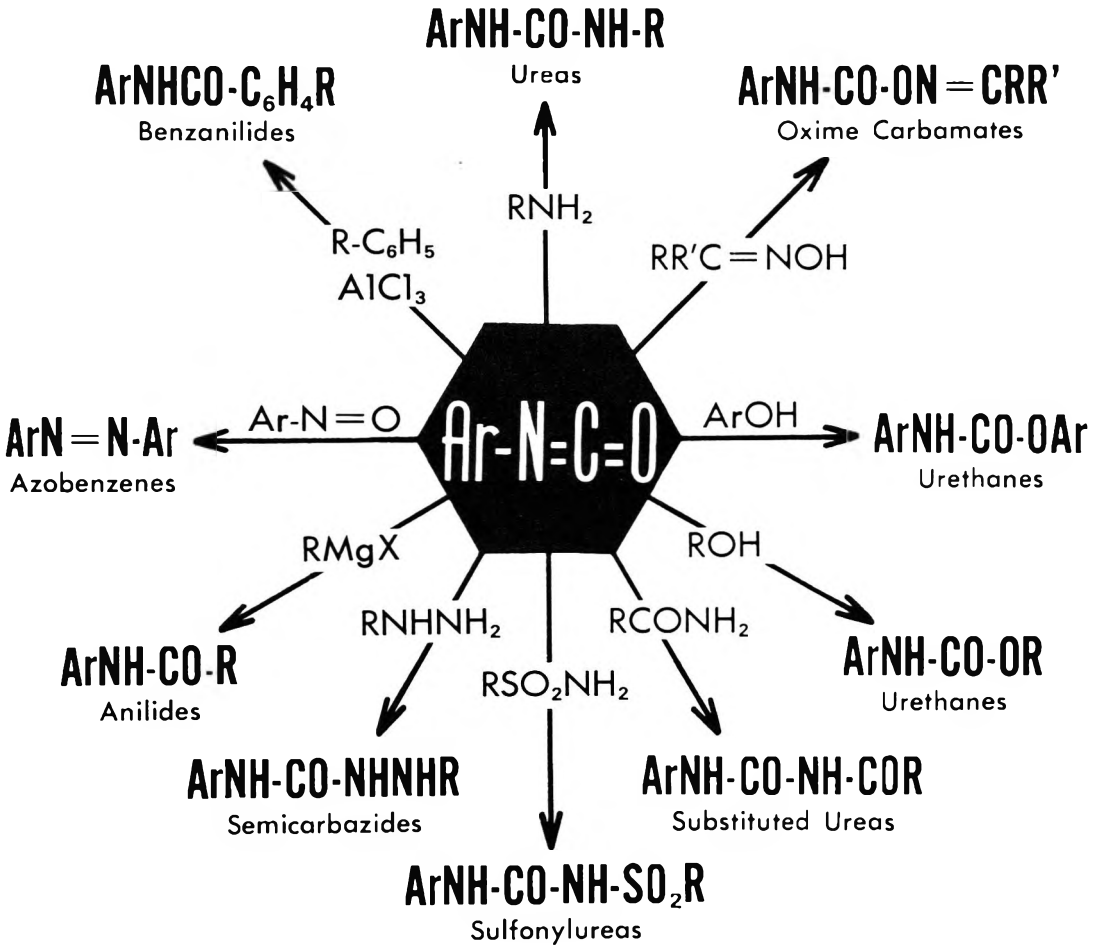

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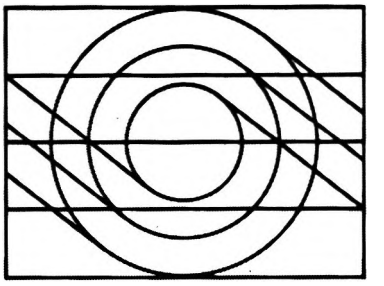

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