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THE JOURNAL OF Organic Chemistry®

VOLUME 37, NUMBER 22

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Steroid Total Synthesis. IX.[1] Alternative Routes to (±)- and (+)-Estr-4-ene-3,17-dione and (±)-13β-Ethylgon-4-ene-3,17-dione *via* Novel Nitrile Intermediates

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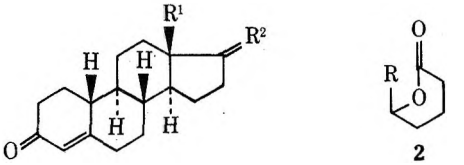
Received May 2, 1972

Total syntheses of (±)-estr-4-ene-3,17-dione [(±)-**1a**] and (±)-13β-ethylgon-4-ene-3,17-dione [(±)-**1b**] are described using the known and readily available compound 2,2-di(3-cyanopropyl)-1,3-dioxolane (**5**) as a starting material. The key step in the sequence involves condensation of amine **10** (derived from **5** *via* δ-lactone **9**) with 2-methyl- or 2-ethyl-1,3-cyclopentanedione giving mixtures of the racemic dienes **12a–13a** and **12b–13b** in which the trans isomers **12a** and **12b** predominate. In the optically active series, (+)-estr-4-ene-3,17-dione [(+)-**1a**] was synthesized *via* resolution of base 11 giving the diastereomer **23**. Condensation of **23** or the related ketone **26** with 2-methyl-1,3-cyclopentanedione afforded predominantly the trans diene (−)-**12a** possessing the natural C_{13} configuration. Conversion of the dienes **12** to the title 19-nor steroids was efficiently achieved in 8 stages *via* the intermediates **14–19**. Treatment of the triketone intermediates **15a** and **15b** with *p*-toluenesulfonic acid gave rise to the novel hetero steroids **20a**, **20b** and **21a**, **21b**.

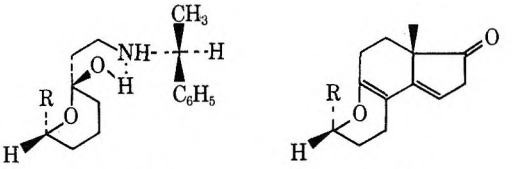
Previous publications from our laboratories have described novel total syntheses of (±)- and (−)-17β-hydroxyde-*A*-androst-9-en-5-one,[2,3] (−)-9β,10α-testosterone,[4] (±)-13β-ethyl-17α-ethynyl-17β-hydroxygon-4-en-3-one (**1c**),[5] (+)- and (±)-estr-4-ene-3,17-dione (**1a**),[1,6–8] and (±)-13β-ethylgon-4-ene-3,17-dione (**1b**).[6] The key intermediates leading to the important optically active steroids are the dienes **4**[1,4,7] which are formed upon condensation of the Mannich bases **3** (or certain related 4-hydroxyalkyl vinyl ketone precursors obtained from the δ-lactones **2**) with 2-methyl-1,3-cyclopentanedione. These reactions, which occur with substantial asymmetric induction give predominantly the trans dienes possessing the natural C_{13} configuration. In this paper we wish to describe a related route to the 19-nor steroid (+)-**1a** *via* the intermediates **2–4** [R = $(CH_2)_3CN$] as well as model studies leading to (±)-**1a** and (±)-**1b** (Chart I). A novel feature of the present work involves the efficient generation of nine carbon atoms (C_1–C_3 and C_5–C_{10}) of the steroid molecule starting from γ-butyrolactone and sodium cyanide.

CHART I

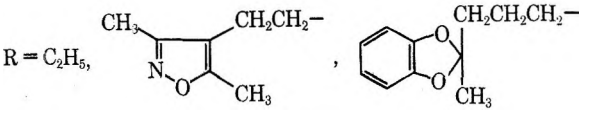


2

1a, $R^1 = CH_3$; $R^2 = O$
b, $R^1 = C_2H_5$; $R^2 = O$
c, $R^1 = C_2H_5$; $R^2 = -OH$, $\cdots C{\equiv}CH$



3 **4**

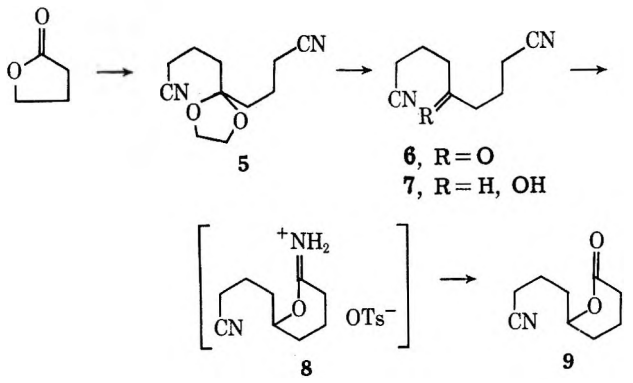


Results and Discussion

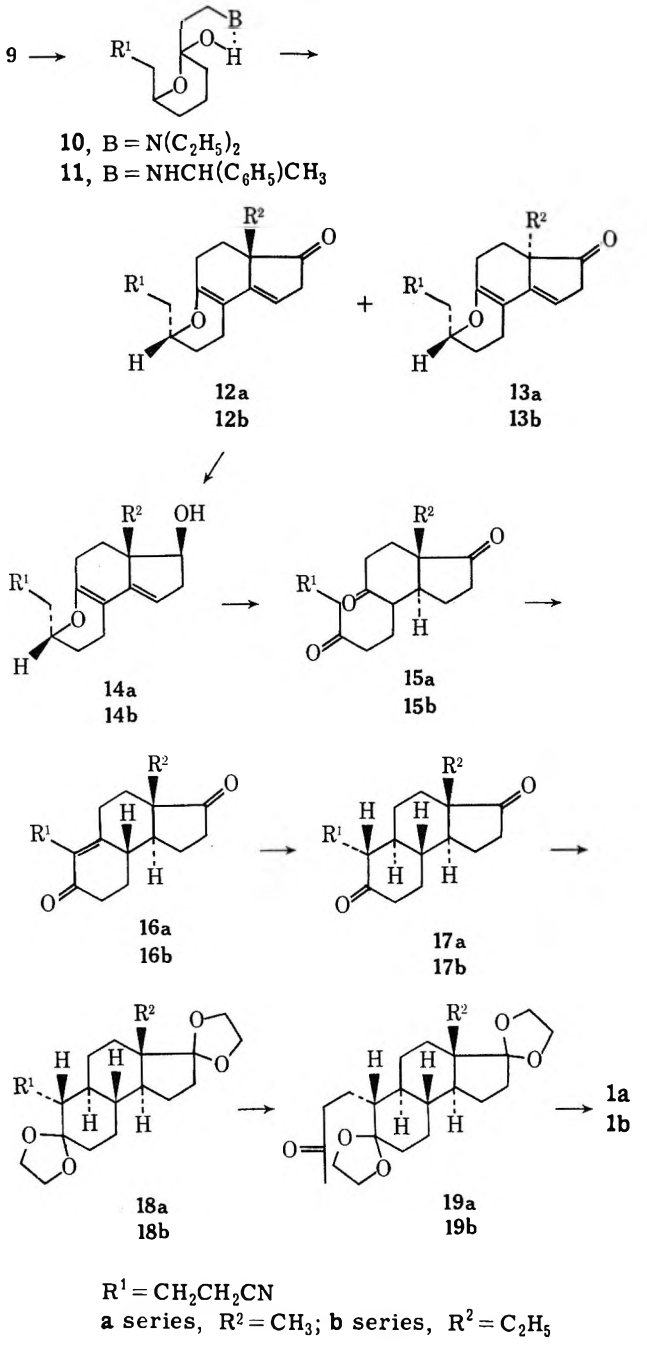
In 1962, Hartley[9] reported a synthesis of 2,2-di(3-cyanopropyl)-1,3-dioxolane (**5**) (Scheme I) in high yield by reaction of 1,7-dichloroheptan-4-one ethylene ketal with sodium cyanide. The required dichloro ketone is, in turn, readily available from γ-butyro-

(1) Part VIII: M. Rosenberger, R. Borer, R. Mueller, and G. Saucy, *Helv. Chim. Acta*, in press.
(2) Part I: G. Saucy, R. Borer, and A. Furst, *ibid.*, **54**, 2034 (1971).
(3) Part II: G. Saucy and R. Borer, *ibid.*, **54**, 2121 (1971).
(4) Part III: G. Saucy and R. Borer, *ibid.*, **54**, 2517 (1971).
(5) Part IV: M. Rosenberger, T. P. Fraher, and G. Saucy, *ibid.*, **54**, 2857 (1971).
(6) Part V: J. W. Scott and G. Saucy, *J. Org. Chem.*, **37**, 1652 (1972).
(7) Part VI: J. W. Scott, R. Borer, and G. Saucy, *ibid.*, **37**, 1659 (1972).
(8) Part VII: M. Rosenberger, A. Duggan, and G. Saucy, *Helv. Chim. Acta*, **55**, 1333 (1972).
(9) D. Hartley, *J. Chem. Soc.*, 4722 (1962).

SCHEME I



SCHEME II



lactone.[10] We reasoned that **5** would be a valuable starting material for the production of 19-nor steroids (using appropriate modifications of the previously reported schemes)[1,6-8] if its conversion into the lactone **9** [2, R = $(CH_2)_3CN$] could be readily accomplished. It was hoped that utilization of the cyanoethyl moiety in **9** as an A-ring synthon (C_1–C_3) would eliminate the often troublesome requirements imposed by protected or disguised carbonyl functions. Furthermore, the nitrile function appeared to offer sufficient stability to survive the reaction conditions required throughout the synthetic scheme and would allow facile conversion to a methyl ketone by, for example, reaction with methyllithium at a suitable stage late in the sequence.

The required lactone **9** was synthesized as shown in Scheme I. Acid hydrolysis of ketal **5** gave the dicyano ketone **6** which was subsequently reduced with sodium borohydride affording the alcohol **7**. Selective transformation of only one of the two equivalent nitrile functions in **7** was most conveniently achieved by treatment of this material with 1 equiv of *p*-toluenesulfonic acid monohydrate in refluxing toluene. In this way, the lactone **9** was readily produced in an overall yield of 42% based on γ-butyrolactone. The facile conversion of **7** to **9** most likely involves the initial formation of the cyclic imino ether salt **8** which then hydrolyzes to the lactone and ammonium *p*-toluenesulfonate.

The 19-nor steroids (±)-**1a** and (±)-**1b** were produced as shown in Scheme II. Reaction of **9** with vinylmagnesium chloride at −50 to −60° [3] followed by immediate treatment of the resultant vinyl ketone with diethylamine gave the Mannich base (±)-**10** in 81% yield. Under these conditions, the nitrile function was untouched by the Grignard reagent even though an excess of the latter was employed. By substituting (*S*)-(−)-α-methylbenzylamine for diethylamine in this sequence, a mixture of diastereomeric Mannich bases **11** was obtained which could be resolved[4] and used for the synthesis of (+)-**1a** (see below).

Condensation of amine **10** with 2-methyl-1,3-cyclopentanedione in refluxing toluene–acetic acid[2] afforded a mixture of the dienes (±)-**12a** and (±)-**13a** in 85% yield, recrystallization of which allowed isolation of the major (trans) isomer (±)-**12a** in pure form. Further transformations were performed using the major isomer so obtained.[11] Thus, reduction with sodium borohydride furnished the alcohol (±)-**14a** which by a sequence[2,3] involving regio- and stereoselective catalytic hydrogenation [14,15-carbon–carbon double bond (steroid numbering)] then hydration and oxidation[12] subsequently gave the oily triketone (±)-**15a**. Cyclization of the latter material was best accomplished using a catalytic amount of potassium hydroxide. In this way the tricyclic enedione (±)-**16a** was secured in 46.5% overall yield based on the diene (±)-**12a**.

By an analogous set of transformations, the homologous enedione (±)-**16b** was produced starting from Mannich base **10** and 2-ethyl-1,3-cyclopentanedione[13] *via* the racemic intermediates **12b**–**15b**. In this case, the diene mixture (±)-**12b**–(±)-**13b** was noncrystalline and was used without separation.[11]

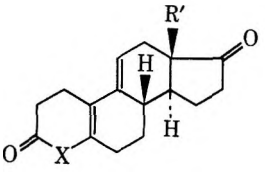
(10) O. E. Curtis, Jr., J. M. Sandri, R. E. Crocker, and H. Hart, *Org. Syn.*, **38**, 19 (1958).

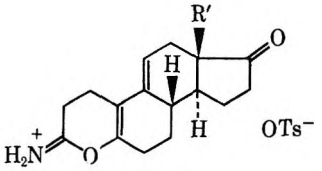
(11) For the purpose of synthesizing racemic 19-nor steroids the separation of these dienes is unnecessary since both lead ultimately to the same racemic intermediates **16a** and **16b**.

(12) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, **39** (1946).

(13) H. Schick, G. Lehmann, and G. Hilgetag, *Angew. Chem.*, **79**, 378 (1967).

When the triketonitriles (±)-**15a** and (±)-**15b** were cyclized under the influence of *p*-toluenesulfonic acid monohydrate in refluxing toluene, the aza steroids (±)-**20a** and (±)-**20b** and oxa steroids (±)-**21a** and (±)-**21b** were isolated in addition to the enediones (±)-**16a** and (±)-**16b**. These hetero steroids probably arise from further acid catalyzed reactions of the enediones. In fact, when (±)-**16a** was heated with *p*-toluenesulfonic acid monohydrate, (±)-**20a** and (±)-**21a** were produced in 24 and 47% yields, respectively. The synthesis of dihydro-2-pyridones (*e.g.*, **20**) from δ-ketonitriles under acidic conditions is well known.[14-16] The formation of the oxa steroids probably involves facile enolization of the α,β-unsaturated ketone function in **16** leading to an imino ether salt such as **22** which then hydrolyzes to the isolated diene lactone.





20a, X = NH; R′ = CH_3
b, X = NH; R′ = C_2H_5
21a, X = O; R′ = CH_3
b, X = O; R′ = C_2H_5

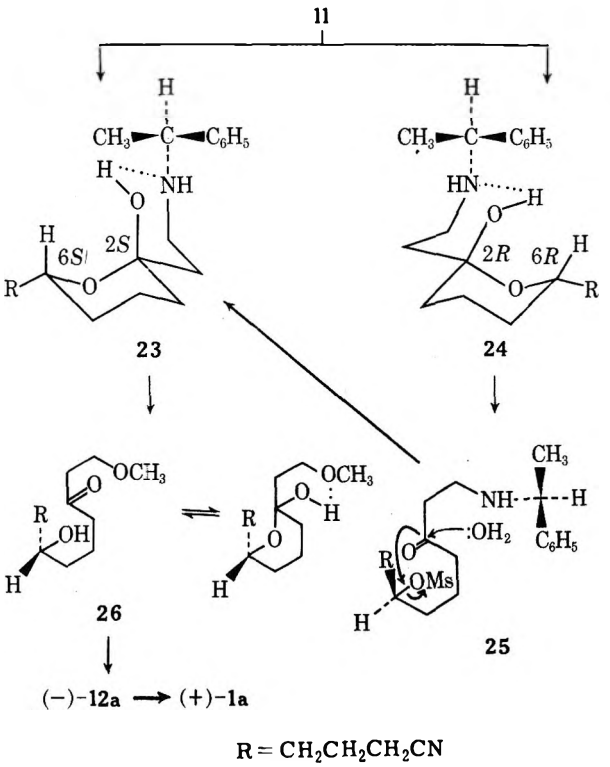
22

Catalytic hydrogenation of the enediones (±)-**16a** and (±)-**16b** over palladium on carbon in the presence of triethylamine[6] gave the expected saturated diketonitriles (±)-**17a** and (±)-**17b**. Conversion of these materials to the bisketals (±)-**18a** and (±)-**18b** was followed by reaction with methyllithium affording the known[6] keto bisketals (±)-**19a** and (±)-**19b**. Finally, exposure of the latter substances to refluxing methanolic hydrochloric acid yielded the desired diones (±)-**1a** and (±)-**1b** in 40 and 47% overall yields, respectively, based on the tricyclic diketones (±)-**16a** and (±)-**16b**.

In order to synthesize (+)-**1a**, the Mannich base **11** was resolved by crystallization of the oxalic acid salt. This led to the oxalate of the oily 2*S*,6*S* diastereomer **23**[17] [**3**, R = $(CH_2)_3CN$] (Scheme III) in 21–27% weight yield based on **9** (42–54% of theory). From the mother liquor of this recrystallization the 2*R*,6*R* base **24** was obtained in crystalline form. In an effort to increase the yield of the desired base **23**, an inversion cycle[1] was employed. Thus, treatment of **25** with a mixture of methanesulphonyl chloride, methanesulfonic acid and pyridine led to the unstable *O*-mesylate **25** which usually was not isolated. Under these conditions N-mesylation was not observed. When the mesylation mixture was simply treated with water and heated, stereochemical inversion occurred, possibly as shown giving the base **23**. Incorporation of this inversion sequence allowed the isolation of **23** oxalic acid salt in an overall yield of 44% based on lactone **9**.

Following prior art,[4] base **23** was treated with benzaldehyde and sodium bicarbonate in refluxing methanol giving the β-methoxy ketone **26** (mixture of keto and hemiketal forms) in 92% yield as well as the Schiff base derived from α-methylbenzylamine and benzaldehyde. Condensation[4] of **26** with 2-methyl-1,3-cyclopentanedione in refluxing toluene–acetic acid[2] then furnished the mixture of dienes **12a** and **13a** in optically active form.[18] By direct crystallization, the major (trans) isomer (−)-**12a** [**4**, R = $(CH_2)_3CN$] was isolated in 38% yield based on **24**. The minor isomer **13a**, of unnatural C_{13} configuration, was never obtained in pure form. The mixture of dienes **12a** and **13a** could also be obtained by reaction of **23** directly with 2-methyl-1,3-cyclopentanedione. In a sequence which completely parallels that employed in the racemic series, the diene (−)-**12a** was finally converted to (+)-estr-4-ene-3,17-dione [(+)-**1a**][7] in an overall yield of 39.6%, *via* the optically active intermediates **14a**–**19a**.

SCHEME III



Experimental Section[19]

5-Oxoazeleonitrile (6).—A solution of 347.4 g (1.67 mol) of the dicyano ketal **5**[9] in 1.5 l. of acetone was cooled to 10° and treated with 1 l. of cold (10°) 3 *N* aqueous hydrochloric acid. The mixture was allowed to stand at room temperature for 18 hr then concentrated to a volume of approximately 1.5 l. at 40° and aspirator pressure. The organic materials were isolated with

(14) A. I. Meyers and G. Garcia-Munoz, *J. Org. Chem.*, **29**, 1435 (1964).
(15) J. J. Vill, T. R. Steadman, and J. J. Godfrey, *ibid.*, **29**, 2780 (1964).
(16) N. P. Shusherina, A. V. Golovin, and R. Ya. Levina, *Zh. Org. Khim.*, **30**, 1762 (1960).
(17) The configuration of this material (which leads ultimately to **1a** of natural configuration) is assigned by analogy with similarly produced optically active Mannich bases from the previous work; see ref 3, 4, and 7.
(18) The mechanism of this crucial, stereoselective annelation reaction has been discussed previously; see ref 4.
(19) Unless otherwise noted, reaction products were isolated by addition of brine and extraction with the specified solvent. Organic solutions were then washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated at water aspirator pressure at 40–50°. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. All reactions except hydrogenations were carried out under an atmosphere of nitrogen. Column chromatography was performed using Merck (Darmstadt) silica gel 0.05–0.2 mm. Varian A-60 or HA-100 spectrometers were used to obtain the pmr spectra. Infrared spectra were recorded on a Beckman IR-9 spectrophotometer. The uv spectra were recorded on a Cary Model 14M spectrophotometer. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Thin layer chromatography was performed using Brinkmann silica gel G plates with uv indicator. Plates were developed with 1:1 benzene–ethyl acetate. Spots were detected with uv light, iodine vapor, or *p*-toluenesulfonic acid spray followed by heating.

methylene chloride giving 276 g of cily ketodinitrile **6**. A sample of this material on distillation yielded pure **6**, bp 137–140° (0.05 mm), as a colorless liquid: ir ($CHCl_3$) 2250 (C≡N) and 1710 cm^{-1} (ketone C=O).

Anal. Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 66.08; H, 7.46; N, 17.07.

5-Hydroxyazeleonitrile (7).—A solution of 276 g (1.67 mol) of crude ketodinitrile **6** in 500 ml of methanol and 500 ml of water was added to a cooled (5°), stirred solution of 33 g (0.873 mol) of sodium borohydride in 300 ml of water. The temperature was held at 5–10° during the addition. After addition was complete, the mixture was stirred at room temperature for 90 min. Dilute aqueous sulfuric acid solution (4 *N*) was added to the reaction mixture with cooling (10°) until pH 2–3 was obtained. The organic materials were isolated with methylene chloride giving 272 g (98%) of hydroxydinitrile **7** as a colorless, mobile liquid. A sample of this material on evaporative distillation gave an analytical specimen: bp 145–175° (bath temperature) (0.01 mm); ir ($CHCl_3$) 3625, 3500 (OH), and 2250 cm^{-1} (C≡N).

Anal. Calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.92; H, 8.35; N, 16.68.

(±)-8-Cyano-5-hydroxyoctanoic Acid Lactone (9).—A solution of 272 g (1.64 mol) of crude hydroxydinitrile **7** in 1.5 l. of toluene was treated with 312 g (1.64 mol) of *p*-toluenesulfonic acid monohydrate and the mixture was stirred and heated at reflux for 1 hr. The starting materials dissolved and were replaced by a precipitate of ammonium tosylate which, after cooling, was filtered with suction and washed with fresh toluene. The combined filtrate and washes were washed with water, dried and concentrated *in vacuo*. The residue on distillation furnished pure lactone **9** (214 g, 78.2%): bp 162–165° (0.2 mm); ir ($CHCl_3$) 2250 (C≡N), 1730 (δ-lactone C=O), and 1250 cm^{-1}.

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.63; H, 7.89; N, 8.18.

(±)-2-(2-Diethylaminoethyl)-6-(3-cyanopropyl)tetrahydropyran-2-ol (10).—A stirred solution of 8.35 g (0.05 mol) of lactone **9** in 40 ml of dry THF was cooled to −70° and treated over 14 min with 38 ml (0.076 mol) of a 2 *M* solution of vinylmagnesium chloride in THF. The mixture was stirred for 6 min at −50°, cooled to −65°, and decomposed first with 2 ml of methanol and subsequently with 50 ml of 5% aqueous ammonium chloride solution. Sufficient acetic acid was added to yield two clear layers yet keeping the pH above 7.

The organic layer was separated and the aqueous layer was extracted with THF. The combined THF solutions were treated with 10 ml of diethylamine and left at room temperature for 1.5–2 hr. Removal of solvents *in vacuo* yielded the crude, oily Mannich base (17 g).

This material was treated with 50 ml of 10% aqueous acetic acid and 20 ml of ether. The aqueous layer was reextracted with 20 ml of additional ether and the combined ether extracts were reextracted with 10% aqueous acetic acid then discarded. The combined aqueous acid extract was made alkaline with 10% aqueous sodium carbonate solution and the product was isolated by extraction with methylene chloride affording the pure product **10** (10.84 g, 81%) as a mobile, pale yellow oil: ir ($CHCl_3$) 3150, 3450 (bonded OH and NH), 2250 (C≡N), 1710 cm^{-1} (w, C=O of open form).

Anal. Calcd for $C_{15}H_{28}N_2O_2$: C, 67.12; H, 10.52; N, 10.44. Found: C, 67.15; H, 10.37; N, 10.28.

(±)-*trans*-3-(3-Cyanopropyl)-6a-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*][*l*]benzopyran-7(8*H*)-one [(±)-12a].—A solution of 18.92 g (0.0706 mol) of Mannich base **10**, 8.72 g (0.0778 mol) of 2-methyl-1,3-cyclopentanedione, 64 ml of glacial acetic acid, and 253 ml of toluene was stirred and heated at reflux for 1.5 hr. After cooling, the solution was washed twice with water, once with 0.5 *N* aqueous HCl, twice with saturated aqueous sodium bicarbonate, then dried, filtered, and concentrated *in vacuo* giving 16.3 g (85.4%) of orange, crystalline diene mixture (±)-**12a** and (±)-**13a**. Recrystallization from 20 ml of ethanol gave 11.54 g (60.4%) of pale orange crystals, mp 95–99° [mainly (±)-**12a**]. By further recrystallization of a sample from ethanol, an analytical specimen of (±)-12a was obtained as pale yellow crystals: mp 100–101.5°; uv max (95% EtOH) 253 nm (ε 19,500); ir ($CHCl_3$) 2250 (C≡N), 1730 (C=O), 1630 cm^{-1} (C=C); nmr ($CDCl_3$) δ 5.47 (t, 1, J = 2 Hz, HC=C), 3.85 (m, 1, HCO), 1.14 ppm (s, 3, C_{6a} CH_3); mass spectrum m/e 271 (M^+).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.36; H, 7.75; N, 5.03.

(±)-*trans-anti*-6-(2-Cyanoethyl)-3a-methyl-1,2,3a,4,5,9,9a,9b-octahydro-3*H*-benz[*e*]indene-3,7(8*H*)-dione [(±)-16a].—A solution of 6 g (0.0222 mol) of diene (±)-**12a** in 35 ml of benzene was added dropwise, over a 10 min period to an ice-cold solution of 0.864 g (0.0228 mol) of sodium borohydride in 50 ml of ethanol and 5 ml of water. The resulting mixture was stirred with ice-bath cooling for 25 min then the cooling bath was removed and the mixture was stirred at ambient temperature for an additional 15 min. Isolation with ether gave 6 g of yellow, crystalline alcohol (±)-**14a**: ir ($CHCl_3$) 3450, 3600 (OH), 2250 (C≡N), 1640 cm^{-1} (C=C).

A solution of this alcohol in 35 ml of toluene and 25 ml of THF was hydrogenated over 1 g of preequilibrated 5% palladium on carbon[20] at room temperature and 1 atm for 23 hr. A total of 543 ml of hydrogen was consumed (555 ml theory). The catalyst was filtered with suction on a pad of Celite and the filter cake was washed well with toluene. The combined filtrate and washes were concentrated at reduced pressure giving 6.65 g of pale yellow foam: ir (film) 3480 (OH), 2250 (C≡N), 1680 cm^{-1} (enol ether).

This material was dissolved in 165 ml of acetone and treated with 15 ml of 0.5 *N* aqueous sulfuric acid. The resulting solution was stirred at room temperature for 3.25 hr, then cooled (ice bath), and treated with 16.5 ml of Jones reagent[12] dropwise, over 15 min. The ice bath was removed and the resulting red mixture was stirred at room temperature for 3.25 hr. After decomposition of the excess oxidant with sodium bisulfite, the product was isolated with benzene (the organic solution was additionally washed with saturated aqueous sodium bicarbonate solution) giving 5.93 g (92.5%) of triketone (±)-**15a** as an orange oil: ir (film) 2250 (C≡N), 1745 (cyclopentanone C=O), 1715 cm^{-1} (cyclohexanone and aliphatic C=O).

A solution of 3.983 g (0.01 mol) of this triketone in 20 ml of methanol was treated with 10 ml of 0.1 *M* methanolic potassium hydroxide solution. The resulting dark brown solution was stirred and heated at reflux for 2 hr. After cooling, the product was isolated with methylene chloride giving 2.8 g (93.8%) of crude enedione (±)-**16a** as a brown solid. Recrystallization from ethanol gave 1.5 g (50.2%) of pale yellow crystals, mp 105–107°. The analytical specimen was obtained as colorless crystals, mp 106–107°, by further recrystallization of a sample from ethanol: ir ($CHCl_3$) 2250 (C≡N), 1740 (cyclopentanone C=O), 1665 (cyclohexenone C=O), 1605 cm^{-1} (C=C); uv max (95% EtOH) 245 nm (ε 15,640); nmr ($CDCl_3$) δ 1.03 ppm (s, C_{3a} CH_3).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.51; H, 7.99; N, 5.08.

(±)-*trans-anti-trans-anti*-6-(2-Cyanoethyl)-3a-methyl-1,2,3a,4,5,5a,8,9,9a,9b-decahydrobenz[*e*]indene-3,7(6*H*)-dione [(±)-17a].—A solution of 1.03 g (3.82 mmol) of enedione (±)-**16a** in 25 ml of dry THF and 0.7 ml of triethylamine was stirred in an atmosphere of hydrogen over 0.25 g of preequilibrated 5% palladium on carbon.[20] After 40 min, 102 ml of hydrogen was absorbed (96 ml theory) and the hydrogenation was stopped. The catalyst was filtered and washed with ether and the combined filtrate and washings were concentrated at reduced pressure giving 1 g of colorless, solid residue. This was recrystallized from ethanol giving 0.805 g (77.4%) of colorless crystals, mp 130–132°. An analytical specimen was obtained, mp 132–133°, by further recrystallization from ethanol: ir ($CHCl_3$) 2250 (C≡N), 1740 (cyclopentanone C=O), 1710 cm^{-1} (cyclohexanone C=O); nmr ($CDCl_3$) δ 0.98 ppm (s, C_{3a} CH_3); mass spectrum m/e 273 (M^+).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.49; H, 8.49; N, 5.05.

(±)-*trans-anti-trans-anti*-3,3,7,7-Bis(ethylenedioxy)-3a-methyl-6-(2-cyanoethyl)perhydro-1*H*-benz[*e*]indene [(±)-18a].—A solution of 0.1 g (0.366 mmol) of diketone (±)-**17a** in 5 ml of dry THF was treated with 0.226 g (3.66 mmol) of ethylene glycol, 0.2 ml of trimethyl orthoformate and 0.01 ml of concentrated sulfuric acid. The resulting solution was stirred at room temperature for 1.5 hr then poured into excess 10% aqueous sodium hydroxide solution. The product was isolated with ether giving 0.133 g of colorless, crystalline bisketal (±)-**18a**.

This material was combined with the product from an identical run (0.111 g, 0.244 g total) and chromatographed on 25 g of

(20) A 5% palladium-on-carbon catalyst prepared at F. Hoffmann-La Roche and Co., AG, Basle, Switzerland, and designated AK-4 was employed for this hydrogenation.

silica gel. The fractions eluted with 1:1 benzene–ether gave 0.229 g (86.8%) of pure (±)-**18a** as a colorless solid. Two recrystallizations from ether gave colorless crystals: mp 118.5–120.5°; ir ($CHCl_3$) 2250 (C≡N), 1160, 1105, 1050 cm^{-1}; nmr ($CDCl_3$) δ 3.94, 3.86 (2 s, 8, OCH_2CH_2O), 0.87 ppm (s, C_{3a} CH_3); mass spectrum *m/e* 361 (M^+).

Anal. Calcd for $C_{21}H_{31}NO_4$: C, 69.77; H, 8.65; N, 3.88. Found: C, 69.87; H, 8.39; N, 3.86.

(±)-*trans-anti-trans-anti*-**3,3,7,7-Bis(ethylenedioxy)-3a-methyl-6-(3-oxo-1-butyl)perhydro-1*H*-benz[*e*]indene** [(±)-**19a**].—An ethereal methyllithium solution (4.3 ml, 2 *M*, 8.6 mmol) was cooled to −10° (ice–salt bath) and stirred while a solution of 0.711 g (1.97 mmol) of bisketal nitrile (±)-**18a** in 15 ml of anhydrous ether and 5 ml of anhydrous THF was added over a 3-min period. The reaction mixture was stirred at −5° for 1 hr then 10 ml of water was added and stirring was continued at room temperature for 30 min. Isolation with ether gave 0.719 g (96.5%) of essentially pure keto bisketal (±)-**19a** as a colorless solid.

A sample was chromatographed on silica gel and recrystallized from ether giving fluffy white crystals: mp 122–123° (lit.[6] mp 126.5–128°); ir ($CHCl_3$) 1715 (ketone C=O), 1160, 1105, 1050, 1040, 950 cm^{-1}.

(±)-**Estr-4-ene-3,17-dione** [(±)-**1a**].—A solution of 0.538 g (1.47 mmol) of bisketal (±)-**19a** in 20 ml of methanol and 6 ml of 4 *N* aqueous hydrochloric acid was stirred and heated at reflux for 4 hr then cooled. The product was isolated with ether giving 0.352 g (87%) of colorless, crystalline product. Recrystallization from aqueous methanol gave 0.254 g (62.7%) of colorless crystals: mp 155–156.5° (lit.[6] mp 157–159.5°, lit.[8] mp 155–157°); uv max (95% EtOH) 240 nm (ε 17,400). This material was identical by ir and tlc analysis with a sample of (±)-**1a** prepared previously.[8]

(±)-**4-Azaestra-5(10),9-diene-3,17-dione** [(±)-**20a**].—A solution of 2.853 g (0.01 mol) of crude triketone (±)-**15a** and 0.637 g of *p*-toluenesulfonic acid monohydrate in 130 ml of toluene was stirred and heated at reflux, using a Dean-Stark trap for 4.5 hr after vigorous refluxing began. The mixture was allowed to stir at room temperature for 13.5 hr, then washed twice with saturated aqueous sodium bicarbonate solution. The combined washings were back extracted twice with methylene chloride. The combined organic solutions were dried, filtered, and concentrated *in vacuo* giving 2.728 g of an orange semisolid residue.

This material was triturated with ethyl acetate and the solid was suction filtered and washed until essentially colorless with ethyl acetate giving 0.708 g (26.4%) of off-white, solid (±)-**20a**, mp 259–262° dec. The combined filtrate and washings were concentrated at reduced pressure and the residue chromatographed as described in the following experiment.

A 0.3-g sample of the dienol lactam prepared in this manner was recrystallized from acetonitrile giving a colorless solid: mp 261–264° dec; ir ($CHCl_3$) 3425, 3225 (NH), 1735 (cyclopentanone C=O), 1680 (lactam C=O), 1650 cm^{-1} (C=C); uv max (95% EtOH) 216 nm (ε 7280), 284 (14,360); nmr ($CDCl_3$) δ 8.65 (m, 1, NH), 5.46 (m, 1, C_{11} H), 0.90 ppm (s, 3, C_{13} CH_3); mass spectrum *m/e* 271 (M^+).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.36; H, 8.02; N, 5.20.

(±)-**4-Oxaestra-5(10),9-diene-3,17-dione** [(±)-**21a**].—The residue (2.02 g) from the preceding experiment [after removal of (±)-**20a**] was chromatographed on 100 g of silica gel. Elution with 9:1 benzene–ether gave 0.223 g of semicrystalline material rich in dienol lactone (±)-**21a**. The analytical specimen was obtained by several recrystallizations from acetonitrile as colorless prisms: mp 167–169°; ir ($CHCl_3$) 1770 (lactone C=O), 1740 (cyclopentanone C=O), 1665 (C=C), 1160, 1120 cm^{-1}; uv max (95% EtOH) 254 nm (ε 12,300), sh 230 (ε 9400); nmr ($CDCl_3$) δ 5.53 (m, 1, C_{11} H), 0.90 ppm (s, 3, C_{13} CH_3); mass spectrum *m/e* 272 (M^+).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.79; H, 7.51.

The fractions eluted with 4:1 benzene–ether gave 0.866 g (32.3%) of crystalline enedione (±)-**16a**. This was recrystallized from ethanol giving 0.681 g of pale yellow solid, mp 105–107°.

Conversion of Dione (±)-16a to Aza Steroid (±)-20a and Oxa Steroid (±)-21a.—A mixture of 1 g (3.69 mmol) of enedione (±)-**16a**, 0.7 g (3.69 mmol) of *p*-toluenesulfonic acid monohydrate and 40 ml of xylene was stirred and heated at reflux for 5 hr. After cooling the resultant slurry was filtered and the solid was washed with methylene chloride and dried giving 0.534 g (76.6%) of ammonium tosylate.

The filtrate and washes were combined and washed with aqueous sodium bicarbonate then dried, filtered and concentrated *in vacuo* giving 1 g of semisolid residue. This material was chromatographed on 50 g of silica gel. Elution with 9:1 benzene–ether gave 0.467 g (46.7%) of crystalline lactone (±)-**21a**. This material was identical (tlc) to the lactone produced in the preceding experiment.

Elution with ethyl acetate afforded 0.242 g (24.2%) of crystalline lactam (±)-**20a** which was identical (tlc) to the lactam produced in the preceding experiment.

(±)-*trans-* **and** *-cis-***3-(3-Cyanopropyl)-6a-ethyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*][*l*]benzopyran-7(8*H*)-one** [(±)-**12b and** (±)-**13b**].—An 18.0 g (0.143 mol) sample of 2-ethylcyclopentane-1,3-dione[13] was dissolved in 500 ml of 4:1 toluene–glacial acetic acid and treated with a solution of 20.15 g (0.075 mol) of Mannich base **10** in 200 ml of 4:1 toluene–glacial acetic acid. The resulting solution was stirred and heated under reflux for 0.5 hr then water was removed azeotropically for 1.5 hr using a Dean-Stark trap. After cooling to room temperature, the mixture was diluted with 100 ml of toluene and washed with water, and saturated brine then dried, filtered, and concentrated in *vacuo* giving 20.38 g (93.5%) of an orange oil.

From an experiment on a smaller scale, using the same procedure as above, the crude product was purified by chromatography on silica gel. Elution with 9:1 and 4:1 benzene–ether gave the pure diene mixture: ir ($CHCl_3$) 2250 (C≡N), 1730 (cyclopentanone C=O), 1640 cm^{-1} (C=C); uv max (95% EtOH) 254 nm (ε 12,650); nmr ($CDCl_3$) δ 5.51 (t, 1, *J* = 2 Hz, CH=C), 3.80 (m, 1, C_3 H), 2.94 (m, 2, C_8 H), 0.83 ppm (t, 3, *J* = 8 Hz, C_{6a} CH_2CH_3).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.50; H, 7.88; N, 4.76.

(±)-*trans-anti*-**6-(2-Cyanoethyl)-3a-ethyl-1,2,3a,4,5,9,9a,9b-octahydro-3*H*-benz[*e*]indene-3,7(8*H*)-dione** [(±)-**16b**].—The crude diene mixture [(±)-**12b** and (±)-**13b**] from the preceding experiment (20.38 g) dissolved in 120 ml of benzene was added to a stirred solution of 6 g (0.159 mol) of sodium borohydride in 150 ml of ethanol and 15 ml of water at 0°. The reaction mixture was stirred at 0° for 30 min then at room temperature for 1 hr. The product was isolated with benzene giving 21.7 g of yellow-orange oil [mainly (±)-**14b** but containing some of the C_{3a} epimer]: ir (film) 3450 (OH), 2250 (C≡N), 1650 cm^{-1} (C=C).

This material was dissolved in 500 ml of toluene and hydrogenated over 4 g of 5% palladium on carbon[20] at room temperature and 1 atm for 6 hr. A total of 1725 ml of hydrogen was absorbed during this period. The catalyst was filtered with suction through Celite and the filter cake was washed well with fresh toluene. The combined filtrate and washings were concentrated at reduced pressure giving 20.15 g of yellow oil: ir (film) 3475 (OH), 2250 (C≡N), 1680 cm^{-1} (enol ether).

This crude enol ether was dissolved in 200 ml of acetone containing 25 ml of 1 *N* aqueous sulfuric acid. The solution was stirred at room temperature for 1 hr then the reaction mixture was cooled to 0–5° (ice bath) while 80 ml of Jones reagent[12] was added dropwise over 20 min. After stirring at room temperature for 3 hr, the excess oxidizing agent was decomposed with sodium bisulfite solution. Isolation of the product with benzene (the organic solution was additionally washed with saturated aqueous sodium bicarbonate solution) gave 14.2 g (66%) of oily trione (±)-**15b**: ir (film) 2250 (C≡N), 1740 (cyclopentanone C=O), 1715 cm^{-1} (aliphatic and cyclohexanone C=O).

A 6.0 g sample of this triketone was dissolved in 50 ml of methanol and 25 ml of 0.1 *N* methanolic potassium hydroxide then the reaction mixture was stirred and heated at reflux for 1.5 hr. The methanol was evaporated at reduced pressure and the product was isolated with benzene giving 5.3 g of dark red, oily, crude (±)-**16b**: uv max (95% EtOH) 246 nm (ε 10,300), 300 (915).

This material was chromatographed on 250 g of silica gel. The fractions eluted with 4:1 and 2:1 benzene–ether which were homogeneous on tlc analysis gave 2.55 g of pale yellow oil. The other fractions (1.10 g) showed the presence of a more polar impurity.

One of the purer fractions was rechromatographed on silica gel giving a colorless oil with the following physical properties: ir ($CHCl_3$) 2255 (C≡N), 1740 (cyclopentanone C=O), 1670 cyclohexenone C=O), 1600 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.86

ppm (t, 3, J = 8 Hz, $C_{3a}CH_2CH_3$); uv max (95% EtOH) 245 nm (ϵ 12,600).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.79; H, 7.99; N, 4.91.

(±)-*trans-anti-trans-anti*-6-(2-Cyanoethyl)-3a-ethyl-1,2,3a,4,-5,5a,8,9,9a,9b-decahydrobenz[*e*]indene-3,7(6*H*)-dione [(±)-17b].—A 1.15-g (4.04 mmol) sample of pure enedione (±)-**16b** was dissolved in 40 ml of dry THF containing 1 ml of triethylamine and hydrogenated over 0.2 g of 5% palladium on carbon[20] at room temperature and 1 atm for 2.5 hr. The hydrogen uptake amounted to 121 ml. The catalyst was filtered through Celite and the filtrate was concentrated at reduced pressure giving 1.14 g of colorless oil.

This material was chromatographed on 50 g of silica gel. The fractions eluted with 9:1, 4:1, and 2:1 benzene–ether afforded 0.906 g (78.5%) of colorless crystals. Recrystallization from 2-propanol gave the analytical specimen of (±)-**17b** as colorless crystals: mp 118.5–121°; ir ($CHCl_3$) 2250 (C≡N), 1740 (cyclopentanone C=O), 1715 cm^{-1} (cyclohexanone C=O).

Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.40; H, 9.07; N, 4.87.

(±)-*trans-anti-trans-anti*-3,3,7,7-Bis(ethylenedioxy)-3a-ethyl-6-(2-cyanoethyl)perhydro-1*H*-benz[*e*]indene [(±)-18b].—A 0.2 g (0.695 mmol) sample of dione (±)-**17b** was dissolved in 5 ml of dry THF and treated with 0.5 ml of ethylene glycol, 0.5 ml of trimethyl orthoformate and 0.01 ml of concentrated sulfuric acid. The resulting solution was stirred at room temperature for 5.5 hr. After addition of several drops of triethylamine then 2 ml of 10% aqueous sodium hydroxide, the product was isolated with benzene giving 0.264 g (100%) of crude (±)-**18b** as a beige powder. Recrystallization from 2-propanol gave 0.214 g of colorless crystals: mp 127.5–129.5°; ir ($CHCl_3$) 2250 (C≡N), 1160, 1100, 1050 cm^{-1}; nmr ($CDCl_3$) δ 3.96, 3.86 ppm (2 s, 8, OCH_2CH_2O).

Anal. Calcd for $C_{22}H_{33}NO_4$: C, 70.37; H, 8.86; N, 3.73. Found: C, 70.32; H, 8.56; N, 3.52.

(±)-*trans-anti-trans-anti*-3,3,7,7-Bis(ethylenedioxy)-3a-ethyl-6-(3-oxo-1-butyl)perhydro-1*H*-benz[*e*]indene [(±)-19b].—A solution of 0.164 g (0.437 mmol) of nitrile (±)-**18b** in 25 ml of anhydrous ether was added dropwise from a syringe to a solution of 2 ml of 2 M ethereal methyllithium in 5 ml of anhydrous ether at −15°. The mixture was stirred at −10° for 1.75 hr then decomposed by the addition of 2 ml of water at 0°. After stirring at room temperature for 1.5 hr the product was isolated with ether giving 0.165 g (97%) of (±)-**19b** as a beige solid.

This material was recrystallized from 2-propanol giving 0.082 g of colorless, fluffy crystals: mp 116–119° (lit.[6] mp 117.5–119.5°); ir ($CHCl_3$) 1710 (ketone C=O), 1155, 1100, 1055 cm^{-1}.

(±)-13β-Ethylgon-4-ene-3,17-dione [(±)-1b].—A solution of 0.124 g (0.33 mmol) of ketone (±)-**19b** in 7 ml of methanol and 2 ml of 4 N aqueous hydrochloric acid was refluxed for 4 hr. After cooling to room temperature, the product was isolated with benzene giving 0.110 g of crude, yellow, crystalline (±)-**1b**.

This material was chromatographed on 5 g of silica gel. The fractions eluted with 2:1 and 1:1 benzene–ether gave 0.083 g (92%) of pale yellow crystalline material. Recrystallization from methanol afforded 0.056 g (62%) of pure (±)-**1b** as colorless crystals: mp 156–159° (lit.[6] mp 158–161°); ir ($CHCl_3$) 1735 (cyclopentanone C=O), 1670 (conjc ketone C=O), 1625 cm^{-1} (C=C); uv max (95% EtOH) 240 nm (ϵ 18,000). This material was identical by ir and tlc analysis with a sample of (±)-**1b** prepared previously.[6]

(±)-13-Ethyl-4-azagona-5(10),9-diene-3,17-dione [(±)-20b].—A 4.0-g (0.0132 mol) sample of the crude triketone (±)-**15b** was dissolved in 200 ml of toluene and 0.90 g of *p*-toluenesulfonic acid monohydrate was added. The mixture was stirred and brought to reflux over 1 hr then heated at reflux with azeotropic removal of water (Dean-Stark trap) for 4 hr. After cooling to room temperature, the reaction mixture was washed with saturated aqueous sodium bicarbonate and saturated brine. The organic solution was dried, filtered and concentrated *in vacuo* giving 3.5 g of an orange semisolid residue.

This material was triturated with ethyl acetate and the solid was filtered off and washed well with ethyl acetate until nearly colorless giving 0.674 g (18%) of an off-white powder. Recrystallization from methanol–chloroform afforded 0.593 g of colorless crystals: mp 275–286° dec; ir ($CHCl_3$) 3400, 3225 (NH), 1730 (cyclopentanone C=O), 1680 (lactam C=O), 1650 cm^{-1} (C=C); uv max (95% EtOH) 212 nm (ϵ 7280), 282 (14,020); nmr ($CDCl_3$) δ 8.25 (s, 1, NH), 5.40 (m, 1, $C_{11}H$), 0.80 ppm (t, 3, J = 8 Hz, CH_2CH_3).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 9.90. Found: C, 75.91; H, 8.06; N, 9.99.

The combined filtrate and washings from the above purification were concentrated *in vacuo* and the residue was purified as in the following experiment.

(±)-13-Ethyl-4-oxagona-5(10),9-diene-3,17-dione [(±)-21b].—The residue (2.8 g) from the preceding experiment was chromatographed on 140 g of silica gel. The fractions eluted with 9:1 benzene–ether gave 0.32 g (8.5%) of yellow powder. Recrystallization from 2-propanol afforded 0.161 g of beige, crystalline (±)-**21b**: mp 142.5–145.0°; ir ($CHCl_3$) 1770 (lactone C=O), 1735 (cyclopentanone C=O), 1662 (C=C), 1150, 1120 cm^{-1}; uv max (95% EtOH) 253 nm (ϵ 12,380), 228 (sh, 9440); nmr ($CDCl_3$) δ 5.47 ppm (m, 1, $C_{11}H$).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.62; H, 7.59.

The fractions eluted with 4:1 and 2:1 benzene–ether gave 0.95 g (25.2%) of pale yellow oil. The ir spectrum and tlc mobility of this material were identical to those of enedione (±)-**16b**. Four other fractions gave 0.63 g of pale yellow oil showing two spots (1:1 mixture) on tlc analysis, the faster moving of which corresponded to (±)-**16b**.

(2*S*,6*S*)-2-{2-[(*S*)-α-Phenethylamino]ethyl}-6-(3-cyanopropyl)-tetrahydropyran-2-ol (23).—A 16.7-g (0.1 mol) sample of lactone **9** was treated with 76 ml (0.16 mol) of 2.1 M vinylmagnesium chloride solution in THF using the procedure described above for the synthesis of Mannich base **10**. After the same work-up, the THF extracts (containing the vinyl ketone intermediate) were treated with 12.1 g (0.1 mol) of *l*-(−)-α-methylbenzylamine and left at room temperature for 3 hr. The solvents were removed *in vacuo* and the residue was dissolved in a mixture of 125 ml of acetone and 125 ml of 1.5 N aqueous sulfuric acid solution. After 15 min at room temperature this mixture was extracted with *n*-hexane and the hexane extract was reextracted with 1:1 acetone–aqueous sulfuric acid (1N).

The combined acid aqueous extract was made alkaline with 10% aqueous sodium carbonate solution and the precipitated Mannich base mixture **11** was isolated by ether extraction giving 28.5 g of oily product. This material was dissolved in 65 ml of acetone, added to a solution of 9.2 g of anhydrous oxalic acid in 65 ml of acetone, and left at room temperature for 24 hr. The solids were filtered with suction, washed with 25 ml of acetone and 60 ml of 1:1 acetone–isopropyl ether and dried under high vacuum. The white solid was recrystallized from 50 ml of acetonitrile to yield 9.33 g (46%) of pure **23** oxalate: mp 108–12° (hot stage); $[\alpha]^{25}D$ −36.6° (*c* 2.26, CH_3OH). The analytical specimen, obtained by several recrystallizations of a sample from acetone showed mp 108–109° (capillary); $[\alpha]^{25}D$ −35.28° (*c* 1, CH_3OH).

Anal. Calcd for $C_{19}H_{28}N_2O_2 \cdot C_2H_2O_4$: C, 62.05; H, 7.44; N, 6.89. Found: C, 62.37; H, 7.65; N, 6.84.

To a suspension of 6.1 g of this salt in 60 ml of water, sodium carbonate was added until the mixture showed pH 9. The free base was then isolated by ether extraction giving 4.65 g of the free base **23** as a light yellow oil: $[\alpha]^{25}D$ −20.39° (*c* 1, C_6H_6); ir ($CHCl_3$) 3100 (bonded OH, NH), 2250 cm^{-1} (C≡N).

Anal. Calcd for $C_{19}H_{28}N_2O_2$: C, 72.11; H, 8.92; N, 8.85. Found: C, 72.17; H, 8.85; N, 9.05.

(2*R*,6*R*)-2-{2-[(*S*)-α-Phenethylamino]ethyl}-6-(3-cyanopropyl)-tetrahydropyran-2-ol (24).—The mother liquor from the first crystallization of **23** oxalate (obtained from a preparation similar to that described in the preceding experiment) was concentrated *in vacuo*. The residue was diluted with water and made alkaline with aqueous sodium carbonate solution. The liberated base was isolated by extraction with ether. A 135-g sample of this material was percolated through a column of grade III alumina (500 g) in 1:1 hexane–ethyl acetate (2.2 l.). The eluate was concentrated *in vacuo* and the residue (110 g) was recrystallized twice from isopropyl ether giving 27 g of pure base **24**: mp 62–63°; $[\alpha]^{25}D$ −52.4° (c 1.37, C_6H_6); ir ($CHCl_3$) 3150 (NH, OH), 2250 cm^{-1} (C≡N); nmr ($CDCl_3$) δ 7.40 (s, 5, C_6H_5), 3.85 (m, 1, >CHO), 1.35 ppm (d, 3, J = 6 Hz, $CH_3CH<$); mass spectrum m/e 316 (M^+).

Anal. Calcd for $C_{19}H_{28}N_2O_2$: C, 72.11; H, 8.92; N, 8.85. Found: C, 72.15; H, 8.83; N, 8.79.

Mannich Base 23 Oxalate Using an Inversion Cycle.—The crude oily diastereomeric base mixture **11** (75.3 g), obtained as described above from 41.8 g (0.25 mol) of lactone **9**, was dissolved

in 167 ml of acetone and treated with a solution of 25.7 g (0.286 mol) of anhydrous oxalic acid in 167 ml of acetone. The resulting solution was seeded with the oxalate of **23** and kept at room temperature for 3 hr and 4° for 40 hr. The solids were filtered, washed with 1:1 isopropyl ether–acetone (200 ml) and dried giving 50.6 g of salt. Recrystallization from 240 ml of acetonitrile yielded 33.15 g of pure **23** oxalate: mp 106–109°; $[\alpha]^{25}D$ −34.0° (*c* 2.15, CH_3OH).

The mother liquor from the first crystallization was concentrated *in vacuo* and the residue was dissolved in 100 ml of water and extracted with ether (ether solutions discarded). The aqueous solution was made alkaline (pH 9) with 10 *N* aqueous sodium hydroxide and the liberated base was isolated by ether extraction giving 29.5 g of crystalline product rich in **24**.

This material was dissolved in 250 ml of THF and treated at −10° with a solution (prepared at 0°) of 7.35 ml of methanesulfonic acid in 40 ml of THF. After the addition of 74 ml of pyridine, the mixture was cooled to −20° and stirred while 48 ml of methanesulfonyl chloride was added over a 10-min period. The reaction mixture was kept at room temperature for 5 hr then 250 ml of water was added and the resulting mixture was heated at reflux for 3 hr. After cooling, the mixture was made alkaline (pH 9) with 10 *N* aqueous sodium hydroxide and the organic layer was separated. The aqueous phase was extracted with methylene chloride. By isolation in the usual manner, there was obtained 29.6 g of dark brown, oily Mannich base **23** from the combined organic solutions.

This material was dissolved in 66 ml of acetone and treated with a solution of 10 g of anhydrous oxalic acid in 66 ml of acetone. The solution was seeded with **23** oxalate and kept at 4° for 24 hr. The resulting solid was filtered and recrystallized from 88 ml of acetonitrile yielding 12.28 g of pure **23** oxalate: mp 110–115°; $[\alpha]^{25}D$ −34.5° (c 2.04, CH_3OH). The total amount of 45.43 g of **23** oxalate produced by this sequence corresponds to a 44.5% yield based on lactone 9.

In a separate experiment, the mesylate intermediate **25** was isolated before the hydrolysis–inversion step by careful basification of the mesylation mixture with 10% aqueous sodium carbonate followed by extraction with methylene chloride. This afforded an unstable oil which showed the following spectral properties: ir ($CHCl_3$) 3350 (NH), 2250 (C≡N), 1718 (ketone C=O), 1340, 1150 cm^{-1} (SO_2O); nmr ($CDCl_3$) δ 7.3 (s, 5, C_6H_5), 4.18 (m, 1, NH exchangeable with D_2O), 3.00 (s, 3, CH_3SO_2), 1.42 ppm (d, 3, *J* = 6 Hz, CH_3CH).

(3*S*,6a*S*)-(−)-3-(3-Cyanopropyl)-6a-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*][*l*]benzopyran-7(8*H*)-one [(−)-12a].—A mixture of 4.55 g (0.0144 mol) of the free base derived from pure **23** oxalate, 110 ml of methanol, 0.46 g of sodium bicarbonate, and 2.0 g of freshly distilled benzaldehyde was stirred and heated at reflux for 8.5 hr. The reaction mixture was then concentrated to a volume of 10 ml and the products were isolated with methylene chloride giving 6.4 g of an oil. This material was chromatographed on 65 g of silica gel. Elution with ether, 4:1 and 2:1 ether–ethyl acetate afforded 3.07 g (92%) of pure β-methoxy ketone **26** as an oil: ir (film) 3470 (OH), 2250 (C≡N), 1720 cm^{-1} (ketone C=O).

In subsequent experiments the Schiff base of benzaldehyde and α-methylbenzylamine was isolated by dilution of the cooled reaction mixture with an equal volume of water followed by extraction with hexane. The product **26** was then isolated by saturation of the aqueous methanol phase with sodium chloride and extraction with methylene chloride.

A mixture of 2.27 g (0.01 mol) of **26**, 1.35 g (0.012 mol) of 2-methylcyclopentane-1,3-dione, 40 ml of toluene, and 20 ml of glacial acetic acid was stirred and heated at 110° for 5 hr. The bath temperature was then raised to 140° for 1 hr during which time azeotropic distillation of water into a Dean–Stark trap was carried out. The cooled mixture was washed with water, saturated aqueous sodium bicarbonate, and brine then dried, filtered, and concentrated *in vacuo* yielding 2.8 g of an orange, crystalline mixture of optically active dienes **12a** and **13a** which was chromatographed on 250 g of silica gel. The fractions eluted with 19:1 benzene–ether furnished 2.02 g of solid: mp 72–96°; $[\alpha]^{25}D$ −150.86° (*c* 0.92, $CHCl_3$).

This material was recrystallized from 2-propanol giving 1.02 g (37.7%) of pure (−)-**12a**: mp 101–104°; $[\alpha]^{25}D$ −182.0° (*c* 1.0, $CHCl_3$). A sample was recrystallized several times to afford the analytical specimen as pale yellow solid: mp 102–104°; $[\alpha]^{25}D$ −184.42° (c 1.03, $CHCl_3$); ir ($CHCl_3$) 2250 (C≡N), 1740 (cyclopentanone C=O) and 1640 cm^{-1} (C=C); uv max (95% EtOH) 254 nm (ε 18,800); nmr ($CDCl_3$) δ 5.41 (t, 1, *J* = 2 Hz, HC=), 3.78 (m, 1, C_3H), 1.10 ppm (s, 3, C_{3a} CH_3).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80. Found: C, 75.17; H, 7.95.

In another experiment, a mixture of 10 g (0.0246 mol) of **23** oxalic acid salt, 200 ml of toluene, 90 ml of glacial acetic acid, 10 ml of water, 40 ml of pyridine, and 3.5 g (0.031 mol) of 2-methyl-1,3-cyclopentanedione was stirred and heated at reflux for 16 hr. A Dean-Stark trap was then inserted into the system and heating at reflux was continued for 40 min with water removal. After cooling, the reaction mixture was diluted with toluene then washed successively with water, 1 *N* aqueous sulfuric acid and 10% aqueous sodium carbonate solution. After drying of the organic layer and removal of the solvents *in vacuo* there was obtained 6.2 g of red solid product. Two recrystallizations from 2-propanol gave 2.3 g (34.6%) of reddish crystals of (−)-**12a**: mp 102–103°; $[\alpha]^{25}D$ −178.0° (c 2.14, $CHCl_3$).

(+)-*trans-anti*-6-(2-Cyanoethyl)-3aβ-methyl-1,2,3a,4,5,9,9a,-9b-octahydro-3*H*-benz[*e*]indene-3,7(8*H*)-dione [(+)-16a].—A solution of 27.1 g (0.1 mol) of dienone (−)-**12a** in 150 ml of toluene was added over 35 min to a cold (5°), stirred solution of 2.5 g (0.066 mol) of sodium borohydride in 20 ml of water and 80 ml of ethanol. After the mixture had stirred for 40 min at room temperature, brine was added and the toluene layer was removed. The aqueous layer was extracted twice more with toluene; then the toluene solutions were combined, washed with brine, and dried. After filtration, the toluene solution [400-ml total volume containing alcohol (−)-**14a**] was treated with 2 ml of triethylamine and 2.5 g of 5% palladium on carbon[20] and stirred in an atmosphere of hydrogen for 5.24 hr (2.53 l. of hydrogen consumed). The catalyst was filtered and the filtrate was concentrated *in vacuo* to yield 30 g of colorless glass: ir (film) 3620 (OH), 2250 (C≡N), 1680 cm^{-1} (enol ether).

This material was dissolved in 300 ml of acetone and treated with 30 ml of 1 *N* aqueous sulfuric acid. After standing at room temperature for 1 hr the solution was cooled to −5° and stirred while a freshly prepared solution of 30 g of sodium dichromate dihydrate and 21.3 ml of concentrated sulfuric acid diluted to 75 ml with water was added over 8 min. The resulting mixture was stirred at 0–2° for 30 min, then allowed to warm to room temperature, and stirred at room temperature for 2 hr. After decomposition with aqueous sodium bisulfite solution and brine, the product was isolated with toluene in the usual manner (the combined organic extracts were additionally washed with saturated aqueous sodium carbonate solution) giving 27 g of crude, optically active triketone **15a**.

Without further purification, this material was dissolved in 50 ml of methanol and treated with a solution of 1.32 g (0.02 mol) of potassium hydroxide in 100 ml of methanol. After stirring and heating under reflux for 40 min, the mixture was cooled and diluted with brine and the product isolated with toluene affording 24.2 g of crude enedione (+)-**16a**. Recrystallization from 2-propanol yielded 13.3 g (49.2%) of solid: mp 112–114°; $[\alpha]^{25}D$ +54.0° (*c* 1.0, $CHCl_3$). An analytical specimen was obtained by further recrystallization of a sample from 2-propanol as colorless crystals: mp 116–119°; $[\alpha]^{25}D$ +53.9° (*c* 0.9, $CHCl_3$); ir ($CHCl_3$) 2250 (C≡N), 1740 (cyclopentanone C=O), 1665 (cyclohexenone C=O), 1605 cm^{-1} (C=C); uv max (95% EtOH) 245 nm (ε 13,400); nmr ($CDCl_3$) δ 1.04 ppm (s, C_{3a} CH_3).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 74.98; H, 7.71; N, 5.00.

Concentration of the mother liquor from the above crystallization gave 9.2 g of material which was reoxidized and cyclized as above to give an additional 4.3 g of (+)-**16a**: mp 112–114°; $[\alpha]^{25}D$ +55.6° (total yield 17.6 g, 65%).

The intermediate alcohol (−)-**14a** was isolated from a similar preparation:

(3*S*,6a*S*,7*S*)-(−)-3-(3-Cyanopropyl)-6a-methyl-1,2,3,5,6,6a,7,-8-octahydrocyclopenta[*f*][*l*]benzopyran-7-ol [(−)-14a].—Pale yellow crystals were obtained from 2-propanol at −15°: mp 116–119°; $[\alpha]^{25}D$ −194.57° (*c* 1.01, $CHCl_3$); ir ($CHCl_3$) 3650 (OH), 2250 (C≡N), 1640 cm^{-1} (C=C); uv max (95% EtOH) 254 nm (ε 19,300); nmr ($CDCl_3$) δ 5.01 (m, 1, HC=), 3.93 (m, HCO), 3.73 (m, HCO), 0.93 ppm (s, 3, C_{6a} CH_3).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48. Found: C, 74.55; H, 8.61.

(+)-Estr-4-ene-3,17-dione [(+)-1a].—A solution of 2.71 g (0.01 mol) of enedione (+)-**16a** in 30 ml of THF containing 1% triethylamine was treated with 0.25 g of 5% palladium on car-

bon[20] and stirred in an atmosphere of hydrogen for 5.75 hr (267 ml hydrogen consumed). The catalyst was filtered and the filtrate was concentrated *in vacuo* giving 2.8 g of dione (+)-**17a**.

This material was dissolved in 30 ml of THF and treated with 2.5 ml of ethylene glycol and 2.5 ml of trimethyl orthoformate. After the mixture cooled to 5°, 0.1 ml of concentrated sulfuric acid was added and the solution was kept at room temperature for 1 hr. Sequential addition of 3 ml of triethylamine, 10 ml of 2 *N* aqueous sodium hydroxide and brine was followed by isolation of the product with toluene. This gave 3.61 g of crystalline bisketal (+)-**18a**.

Without purification, this material was dissolved in 70 ml of anhydrous ether and added over 10 min to 23 ml of stirred, cold (−20°) 1.75 *M* ethereal methyllithium solution. After stirring at room temperature for 30 min, the mixture was again cooled and decomposed with water. Isolation of the product with ether yielded 3.8 g of crude keto bisketal (−)-**19a**.

This material was dissolved in 30 ml of methanol and 20 ml of 2 *N* aqueous hydrochloric acid was added. After heating at reflux for 2 hr, the methanol was removed *in vacuo* and the product was isolated with toluene giving 2.71 g of crude (+)-**1a**. Recrystallization from methylene chloride–isopropyl ether gave 1.65 g (60.6%) of colorless crystals: mp 167–171°; $[\alpha]^{25}D$ +140.0° (*c* 1.00, $CHCl_3$) {lit.[7] mp 172–173°; $[\alpha]^{25}D$ +139.5° (*c* 0.95, $CHCl_3$)}; uv max (95% EtOH) 240 nm (ε 17,000); ir ($CHCl_3$) 1740 (cyclopentanone C=O), 1665 (conjd ketone C=O), 1620 cm^{-1} (C=C). This material was identical with an authentic sample of (+)-**1a** by tlc and ir analysis.

The intermediates (+)-**17a**, (+)-**18a**, and (−)-**19a** were isolated from a similar preparation.

(+)-*trans-anti-trans-anti*-**6-(2-Cyanoethyl)-3aβ-methyl-1,2,3a,4,5,5a,8,9,9a,9b-decahydrobenz[*e*]indene-3,7(6*H*)-dione** [(+)-**17a**].—Colorless crystals were obtained from 2-propanol: mp 135–136°; $[\alpha]^{25}D$ +78.91° (*c* 1.03, $CHCl_3$); ir ($CHCl_3$) 2250 (C≡N), 1740 (cyclopentanone C=O), 1710 cm^{-1} (cyclohexanone C=O); nmr ($CDCl_3$) 0.97 ppm (s, C_{3a} CH_3).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.60; H, 8.79; N, 5.13.

(+)-*trans-anti-trans-anti*-**3,3,7,7-Bis(ethylenedioxy)-3aβ-methyl-6-(2-cyanoethyl)perhydro-1*H*-benz[*e*]indene** [(+)-**18a**].—A colorless solid was obtained from 2-propanol: mp 130–131°; $[\alpha]^{25}D$ +0.67° (*c* 1.04, $CHCl_3$); ir ($CHCl_3$) 2250 cm^{-1} (C≡N); nmr ($CDCl_3$) δ 3.96, 3.86 (2 s, 8, OCH_2CH_2O), 0.88 ppm (s, C_{3a} CH_3).

Anal. Calcd for $C_{21}H_{31}NO_4$: C, 69.77; H, 8.65; N, 3.88. Found: C, 69.93; H, 8.50; N, 3.91.

(−)-*trans-anti-trans-anti*-**3,3,7,7-Bis(ethylenedioxy)-3aβ-methyl-6-(3-oxo-1-butyl)perhydro-1*H*-benz[*e*]indene** [(−)-**19a**].—A colorless solid was obtained: mp 77–81°; $[\alpha]^{25}D$ −6.2° (*c* 1.0, $CHCl_3$) (lit.[7] mp 83.5–86.5°; $[\alpha]^{25}D$ −16.0° (*c* 1.17, C_6H_6)); ir ($CHCl_3$) 1720 cm^{-1} (ketone C=O).

(+)-**4-Azaestra-5(10),9-diene-3,17-dione** [(+)-**20a**].—This material was prepared by treatment of crude, optically active triketone **15a** (4.6 g; 0.016 mol) with *p*-toluenesulfonic acid monohydrate (1.0 g) in toluene (200 ml) as described above for the racemic modification. Trituration of the crude product (4.0 g) with ethyl acetate afforded 0.62 g (13.4%) of colorless solid lactam: mp 282–285° dec; $[\alpha]^{25}D$ +431.2° (*c* 1.0, $CHCl_3$). Recrystallization from methanol gave 0.45 g of pure (+)-**20a**: mp 283–287°d; $[\alpha]^{25}D$ +434.9° (*c* 0.93, $CHCl_3$); ir ($CHCl_3$) 3400, 3240 (NH), 1740 (cyclopentanone C=O), 1680 (lactam C=O), 1650 cm^{-1} (C=C); uv max (95% EtOH) 213 nm (ε 7500), 281 (13,640); nmr ($CDCl_3$) δ 8.36 (s, 1, NH), 5.42 (m, 1, C_{11} H), 0.90 ppm (s, 3, C_{13} CH_3).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.37; H, 7.86; N, 5.03.

Chromatography of the material remaining after removal of lactam (+)-**20a** gave the enedione (+)-**16a**, eluted with 4:1 and 2:1 benzene–ethyl acetate.

(+)-**4-Oxaestra-5(10),9-diene-3,17-dione** [(+)-**21a**].—A mixture of 1.0 g (3.69 mmol) of enedione (+)-**16a** was treated with 0.7 g (3.69 mmol) of *p*-toluenesulfonic acid monohydrate in 40 ml of xylene as described above in the racemic series. The crude product (0.967 g) was chromatographed on 50 g of silica gel. Elution with 9:1 and 4:1 benzene–ether gave 0.584 g (58.1%) of the crystalline diene lactone (+)-**21a**. Recrystallization from 2-propanol gave colorless crystals: mp 105.5–107.5°; $[\alpha]^{25}D$ +327.23° (*c* 1.06, $CHCl_3$); ir ($CHCl_3$) 1770 (lactone C=O), 1745 (cyclopentanone C=O), 1670 cm^{-1} (C=C); uv max (95% EtOH) 254 nm (ε 11,500), 220 (sh, 8300); nmr ($CDCl_3$) δ 5.50 (m, 1, C_{11} H), 0.89 ppm (s, 3, C_{13} CH_3).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.21; H, 7.47.

Elution with 9:1 chloroform–ethyl acetate gave 0.174 g (17.4%) crystalline diene lactam (+)-**20a**.

Registry No.—(±)-**1a**, 5972-59-8; (+)-**1a**, 734-32-7; (±)-**1b**, 23477-67-0; **6**, 35341-69-6; **7**, 35341-70-9; **9**, 35337-27-0; **10**, 35341-71-0; (±)-**12a**, 35337-28-1; (−)-**12a**, 35378-22-4; (±)-**12b**, 35337-29-2; (±)-**13b**, 35337-30-5; (−)-**14a**, 35378-23-5; (±)-**16a**, 35337-31-6; (+)-**16a**, 35378-24-6; (±)-**16b**, 35378-25-7; (±)-**17a**, 35337-32-7; (+)-**17a**, 35337-33-8; (±)-**17b**, 35337-34-9; (±)-**18a**, 35337-35-0; (+)-**18a**, 35337-36-1; (±)-**18b**, 35427-25-9; (±)-**20a**, 35337-37-2; (+)-**20a**, 35337-38-3; (±)-**20b**, 35337-39-4; (±)-**21a**, 35337-40-7; (+)-**21a**, 35378-26-8; (±)-**21b**, 35341-65-2; **23**, 35341-66-3; **23** oxalate, 35341-67-4; **24**, 35341-68-5.

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The Synthesis of (±)-Norketoagarofuran

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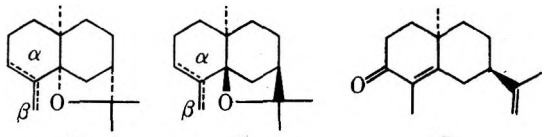
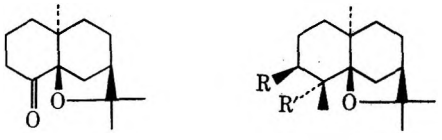
(±)-Norketoagarofuran (**4**) has been synthesized by a short, highly stereoselective route from **10**. Formic acid–hydrogen peroxide hydroxylation of **10** gives **18**, which is oxidized to **36**. Treatment of **36** with ethylene glycol and acid gives **37**, which is transesterified to **35**. The crucial epimerization–lactonization **35** → **41** → **38** is effected by lithium methoxide in dioxane but only if the reaction is driven to completion by continually removing the methanol as it is formed in the closure **41** → **38**. Without isolation **38** is treated successively with methyllithium and aqueous acid to afford **4**, presumably *via* **42**. A discussion of the factors affecting the conversion of **35** to **38** and related reactions is presented.

In 1963 Bhattacharyya and coworkers reported[2] the isolation and characterization of six closely related decalinic sequiterpenes found in agar-wood oil isolated from fungus-infected *Aquillaria agallocha* Roxb. Most of the degradative work was carried out on α- and β-agarofuran, which were assigned the structures and stereochemistry depicted by **1**. On the basis of both chemical and biogenetic considerations Barrett and Büchi deduced[3] that the geometric disposition of the tetrahydrofuran ring was more likely that shown in **2** and supported their conclusion by synthesizing α-agarofuran from (−)-epi-α-cyperone (**3**). Because



1 **2** **3**

of correlations carried out by Bhattacharyya, *et al.*,[2] the revised structures of the other naturally occurring agarofurans are norketoagarofuran (**4**), dihydroagarofuran (**5**),[4] 4-hydroxydihydroagarofuran (**6**), and 3,4-dihydroxydihydroagarofuran (**7**). In addition to the

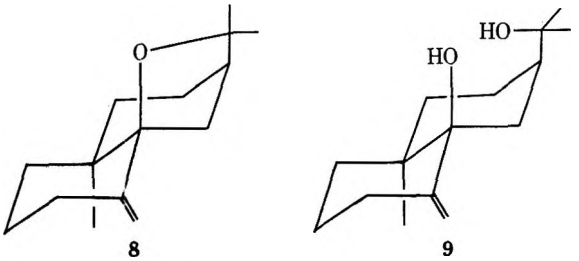


4

5, R = R′ = H
6, R = H; R′ = OH
7, R = R′ = OH

work of Barrett and Büchi[3] and the synthesis reported herein,[5] syntheses of various agarofurans have also been described by Marshall and Pike[6] and Asselin, Mongrain, and Deslongchamps.[4]

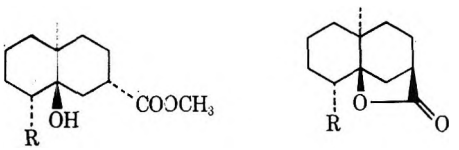
In considering approaches to the synthesis of the agarofurans the primary difficulty would appear to involve construction of the tetrahydrofuran ring. All successful syntheses have postponed forming the ether ring until the decalin framework has been fashioned. Since geometrical restrictions demand that the ether ring be diaxially fused to the decalin skeleton (*cf.* **8**), the isopropyl moiety (*cf.* **9**) must be located in the unstable axial position for ring closure (*i.e.*, **9** → **8**)



8 **9**

to occur. In all of the other syntheses[3,4,6] this problem was solved by using as starting material the readily available (−)-epi-α-cyperone (**3**) or its equivalent in which the β orientation of the isopropenyl grouping is already fixed.

Since earlier work[7,8] in these laboratories had shown that hydroxy esters **10** and **11** are converted into lactones **12** and **13** upon treatment with methanolic sodium methoxide, it was felt that such an epimerization–lactonization approach might provide an alternative route to the agarofurans.[9] Diol ester **14**, which is readily available from unsaturated acid **15**,[10] was selected as starting material.



10, R = H
11, R = CH_3
14, R = OH

12, R = H
13, R = CH_3

Treatment of **15** with performic acid[11] gives a mixture of diol acid monoformates **16** from which **17** can be isolated. Saponification of mixture **16** affords diol acid **18**, identical with material of known[7] stereochem-

(1) (a) Address correspondence to Department of Chemistry, Boston College, Chestnut Hill, Mass. 02167. (b) National Science Foundation Trainee, 1965–1968.

(2) (a) M. L. Maheshwari, K. R. Varma, and S. K. Bhattacharyya, *Tetrahedron*, **19**, 1519 (1963). (b) M. L. Maheshwari, T. C. Jain, R. B. Bates, and S. C. Bhattacharyya, *ibid.*, **19**, 1079 (1963). (c) Recently the structures of a number of sesquiterpene alkaloids which contain the tricyclic agarofuran ring system have been reported: S. M. Kupchan, R. M. Smith, and R. F. Bryan, *J. Amer. Chem. Soc.*, **92**, 6667 (1970); A. Klásek, Z. Samek, and F. Santavy, *Tetrahedron Lett.*, 941 (1972), and references cited therein.

(3) H. C. Barrett and G. Büchi, *J. Amer. Chem. Soc.*, **89**, 5665 (1967).

(4) The assignment of β stereochemistry to the C-4 methyl of **5** is due to A. Asselin, M. Mongrain, and P. DesLongchamps, *Can. J. Chem.*, **46**, 2817 (1968).

(5) A preliminary account describing some of this work has appeared: C. H. Heathcock and T. R. Kelly, *Chem. Commun.*, 267 (1968).

(6) J. A. Marshall and M. T. Pike, *J. Org. Chem.*, **33**, 434 (1968).

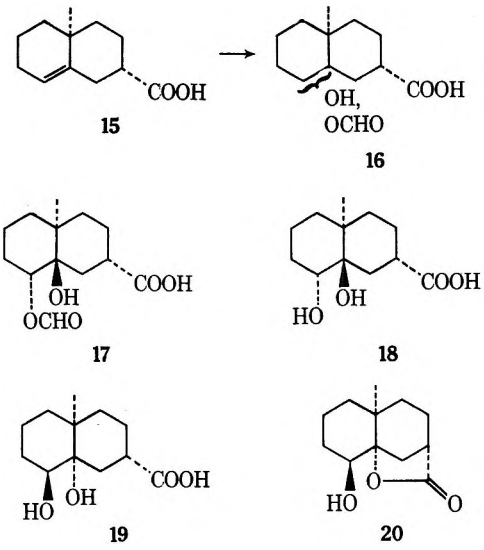
(7) C. H. Heathcock and T. R. Kelly, *Tetrahedron*, **24**, 3753 (1968). A second synthesis of lactone **12** has recently been reported: D. J. Dunham and R. G. Lawton, *J. Amer. Chem. Soc.*, **93**, 2075 (1971).

(8) C. H. Heathcock and Y. Amano, *Tetrahedron*, **24**, 4917 (1968).

(9) Although all compounds whose synthesis is reported herein are racemic, only that enantiomer corresponding to the natural configuration of the agarofurans is depicted. In previous papers[7,8,10] some of these racemic compounds were represented by the structure of the enantiomer.

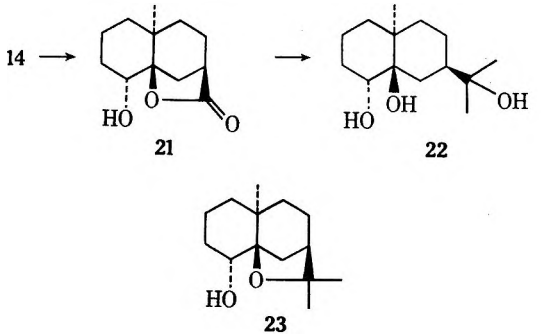
(10) C. H. Heathcock and T. R. Kelly, *Tetrahedron*, **24**, 1801 (1968).

(11) L. F. Fieser and S. Rajagopalan, *J. Amer. Chem. Soc.*, **71**, 3938 (1949).

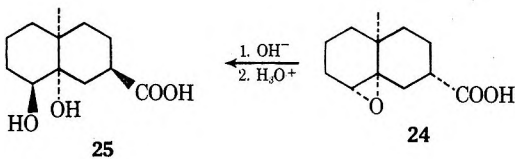


istry. In one run a small amount of another diol acid was obtained. This compound was assigned structure **19** on the basis of mechanistic considerations and the fact that upon heating it forms a γ-lactone ($\nu_{C=O}$ 1775 cm^{-1}), presumably **20**. Diol acid **18** reacts with ethereal diazomethane to give the desired diol ester **14**.

Treatment of **14** with methanolic sodium methoxide did not afford lactone **21**, but, when dioxane was substituted for methanol, epimerization and lactonization did take place, giving the desired hydroxy lactone **21**. The crude lactone, when treated successively



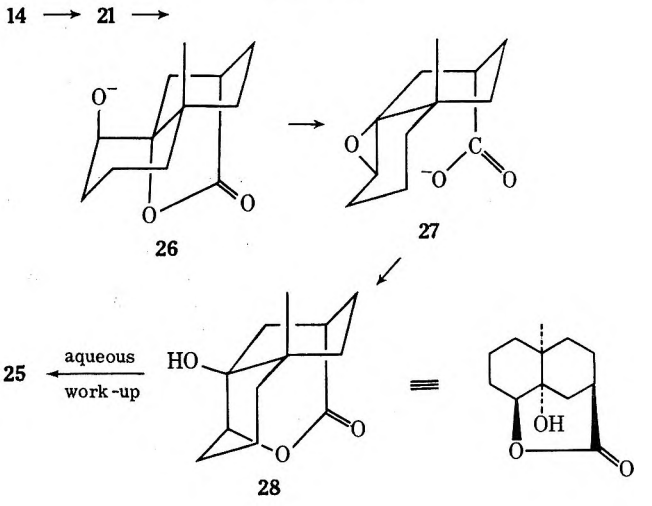
with methyllithium and Jones reagent,[12] was transformed into norketoagarofuran (**4**), presumably *via* **22** and **23**, with the acidic nature of the oxidant serving to catalyze ether formation. Unfortunately, numerous attempts to repeat the conversion of **14** to **21** were unsuccessful. An examination of the products from unsuccessful attempts at lactonization of **14** with sodium methoxide indicated the presence of a diol acid which we had previously prepared[7] from epoxy acid **24** and assigned structure **25**. A possible mech-



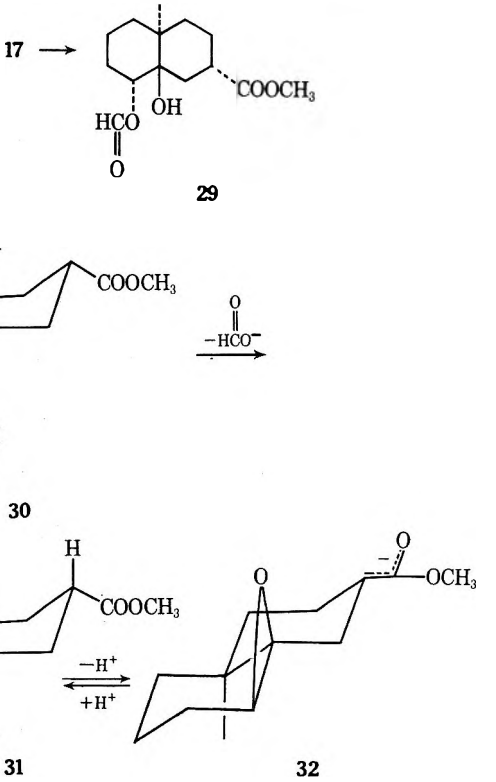
anism for the conversion of **14** into **25** is outlined in Scheme I.

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

SCHEME I



Support for the intramolecular displacement of carboxylate (**26** → **27**) is found in the observation that diol ester monoformate **29**, prepared from **17** by esterification with diazomethane, affords the known[7] epoxy ester **31** in 70% yield under similar conditions. Epoxide formation almost certainly results from an intramolecular displacement of formate (**30** → **31**), although it is surprising that such a reaction is preferred over transesterification of the formate to give **14**. Under the reaction conditions epoxy ester **31** is apparently converted to anion **32**, as carbonyl absorption in the

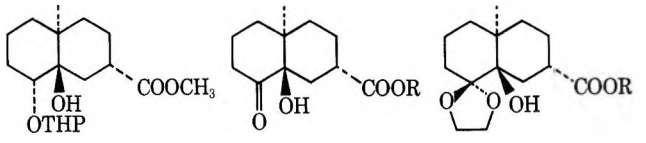


ir spectrum gradually disappears with the simultaneous appearance of absorption attributed[13] to enolate anions. Upon work-up, anion **32** suffers axial protonation, giving back **31**.

These considerations suggested that the secondary hydroxyl group in diol ester **14** should be replaced with

(13) H. Lenormant, *Ann. Chim. (Paris)*, **5**, 516 (1950).

some function incapable of participating in displacement reactions such as 26 → 27. The tetrahydropyranyl ether **33** could not be synthesized and ketol ester **34**, prepared by Jones oxidation[12] of diol ester **14**, appeared to be essentially inert to sodium methoxide in dioxane. Since the potential[14] for rearrangement inherent in the α-ketol moiety argues against subjecting **34** to forcing conditions, the corresponding ketal **35** was prepared. Jones oxidation[12] of diol acid **18**



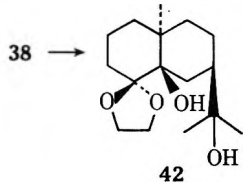
33 **34**, R = CH_3 **35**, R = CH_3
36, R = H **37**, R = CH_2CH_2OH

affords ketol acid **36**. Treatment of the latter with ethylene glycol and *p*-toluenesulfonic acid gives **37**, which is converted into the desired hydroxy ketal ester **35** upon transesterification with methanolic sodium methoxide.

When **35** is treated with lithium methoxide in refluxing dioxane, no reaction occurs. However, when methanol is removed by causing the condensed vapor to pass through a modified Soxhlet extractor[15] equipped with a thimble containing calcium hydride during its return to the reaction flask, lactone formation occurs. The simplest explanation of this result is that lactone **38** is less stable than hydroxy ester **35** and that the position of the equilibrium (**35** ⇄ **38** + CH_3OH) is driven to the right as methanol is removed.

Alternatively, **38** could be more stable than **35** but lithium methoxide may not be a sufficiently strong base to catalyze the conversion at an appreciable rate. In this event removal of methanol could result in the formation of greater amounts of tertiary alkoxide **39**, which should be sufficiently basic to promote the formation of enolate **40** (Scheme II). Enolate **40** could then suffer intermolecular protonation to give **41**, which would lactonize to give **38**.

Since it was anticipated that ketal lactone **38** would be sensitive to hydrolysis, no attempt was made to isolate it but rather the crude material was treated directly with methyllithium to give ketal diol **42**.



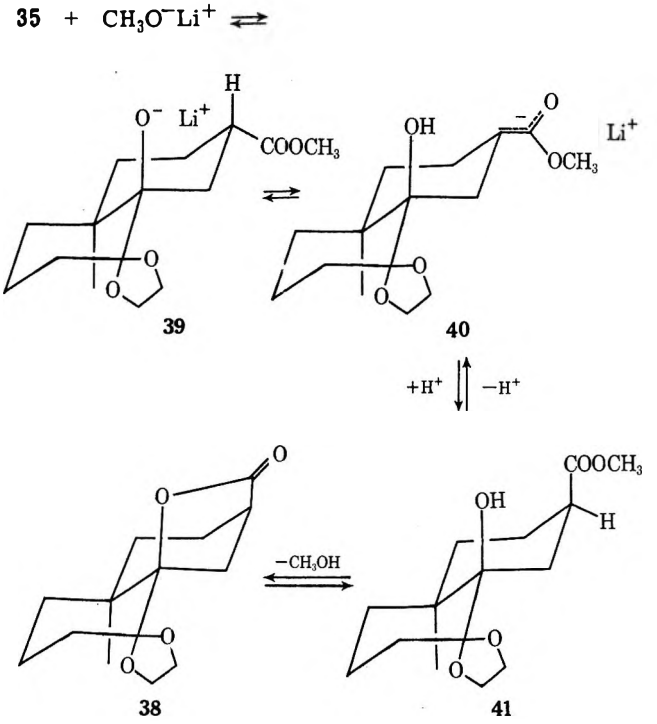
42

Without isolation, this compound was treated with aqueous acid to effect both deketalization and cyclization to racemic norketoagarofuran (**4**). The synthetic material exhibited nmr and ir spectra identical with those reported[2a] for the optically active material.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer 237 infrared spectrometer. Nmr spectra were determined on a Varian A-60 instrument. Chemical shifts are given in parts per million downfield from internal tetramethylsilane. Vpc analyses were performed with an Aerograph A-90-P instrument. Melting points (Pyrex capillary) and boiling points are uncorrected. Microanalyses were performed by the University of California Microanalytical Laboratory, Berkeley, Calif.

SCHEME II



39 **40** **38** **41**

4aβ-Methyl-8β,8aα-dihydroxydecahydronaphth-2β-oic Acid (18) and 4aβ-Methyl-8α,8aβ-dihydroxydecahydronaphth-2β-oic Acid (19).—To 20.00 g of 4aβ-methyl-1,2,3,4,4a,5,6,7-octahydronaphth-2β-oic acid (**15**), partially dissolved in 500 ml of 88% formic acid, was added 40 ml of 30% hydrogen peroxide.[11] After the reaction mixture was stirred at room temperature for 17 hr, volatile material was removed at or below 25° on a rotary evaporator connected to a vacuum pump. The residual crude diol acid monoformate (**16**, 32 g) was dissolved in 275 ml of 0.9 *M* sodium hydroxide. The resulting solution was heated on a steam bath for 2.5 hr and then allowed to cool. The alkaline solution was layered with methylene chloride (200 ml) and acidified. The voluminous precipitate was collected by filtration and the filtrate was set aside (*vide infra*).

The solid was taken up in methanol and dried over sodium sulfate. Removal of the methanol afforded 15.30 g of white solid, mp 200–220°. Recrystallization from acetone gave 11.75 g (50%) of diol acid **18** in several crops, mp 208–212, which was shown to be identical by mixture melting point and spectral comparison with a sample of **18** prepared by an independent route.[7]

The above-mentioned two-phase filtrate was separated and the aqueous layer was extracted several times with methylene chloride. After drying over $MgSO_4$ the combined methylene chloride layers were evaporated to afford 1.7 g of semisolid, which was triturated with methylene chloride. Filtration yielded 500 mg (2%) of analytically pure diol acid **19**: mp 143.5–146.5° (gas evolution); nmr (methanol) δ 1.03 (angular methyl); ir (KBr) 3570, 3490, 3300–2400, 1695 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.16; H, 8.77. Found: C, 62.89; H, 8.90.

4aβ-Methyl-8β-formyloxy-8aα-hydroxydecahydronaphth-2β-oic Acid (17).—In one run a portion of the semisolid mixture of diol acid monoformates **16** was crystallized from water to afford crude diol acid monoformate **17**, mp 110–140°. Recrystallization from benzene afforded material with mp 143.5–147.5°. The overall yield from unsaturated acid **15** is on the order of 25%. Further recrystallization from benzene afforded analytically pure material: mp 145.8–147.0°; ir (KBr) 3490, 3200–2500, 1710 (broad), and 1205 cm^{-1}; nmr (methanol) δ 1.20 (angular methyl), 8.02 (HCO_2^-).

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 61.28; H, 8.09.

(14) Y. Mazur and M. Nassim, *Tetrahedron Lett.*, 817 (1961).

(15) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, revised, D. C. Heath, Boston, Mass., 1955, p 50, Figure 7-2.

4aβ-Methyl-8α,8aβ-dihydroxydecahydronaphth-2β-oic Acid Lactone (20).—Diol acid **19** (66 mg) was heated at 150–160° for 15 min, at which point gas evolution had ceased. After partial cooling 0.5 ml of benzene was added and the solid material was removed by filtration and washed with 0.5 ml of hexane. The combined filtrate and wash were diluted with 10 ml of hexane. Cooling of this solution gave 32 mg (52%) of lactone **20**, mp 101–105°. Analytically pure material (mp 101.3–103.4°) was obtained upon recrystallization from hexane: ir ($CHCl_3$) 3600, 3450, and 1775 cm^{-1}; nmr ($CDCl_3$) δ 1.02 (angular methyl), 4.25 (very broad, axial[16] C_8 proton).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.43; H, 8.47.

Methyl 4aβ-Methyl-8β,8aα-dihydroxydecahydronaphth-2β-oate (14).—A solution of 1.025 g of diol acid **18** in 25 ml of methanol was esterified at 5° with ethereal diazomethane. The solvent was evaporated on a steam bath and the residue was taken up in ether and dried over $MgSO_4$. Removal of solvent afforded 1.00 g (92%) of ester **14**, mp 106–110°. Recrystallization from benzene–hexane afforded analytically pure material: mp 108.2–109.9; nmr ($CDCl_3$) δ 1.23 (angular methyl), 3.65 (OCH_3); ir ($CHCl_3$) 3600, 3490, and 1725 cm^{-1}.

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.53; H, 9.20.

Conversion of Diol Ester 14 to (±)-Norketoagarofuran (4).—A solution of 500 mg of diol ester **14** in 20 ml of dry dioxane was refluxed for several hours under nitrogen through a modified Soxhlet extractor[15] equipped with a thimble containing calcium hydride. After the dioxane solution was cooled to room temperature, approximately 1 equiv of sodium methoxide was added and the resulting suspension was refluxed. The reaction was monitored by ir. After 20 hr the reaction appeared to have stopped. An ir spectrum of the reaction mixture showed peaks at 1780 and 1730 cm^{-1} in a ratio of 3:1. The reaction mixture was allowed to cool to room temperature and 25 ml of dry ether was added followed by 5 ml of 1.5 *M* methyllithium in ether. After the mixture was stirred at room temperature for 3 hr, residual methyllithium was destroyed by the dropwise addition of brine. The organic phase was washed once with brine, dried over $MgSO_4$, and evaporated to give 500 mg of oil.

The crude oil was dissolved in acetone and oxidized with Jones reagent. After the usual work-up the crude product was chromatographed on activity III neutral alumina. Elution with benzene afforded approximately 30 mg of (±)-norketoagarofuran (**4**) whose ir and nmr spectra were identical with those previously reported.[2]

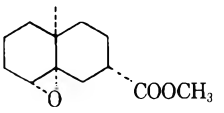
Attempts to repeat the conversion of diol ester **14** into lactone **21** were unsuccessful. In one run diol acid **25** was isolated from the reaction.

A solution of 600 mg of diol ester **14** in 30 ml of dry dioxane was refluxed through the calcium hydride equipped Soxhlet extraction as above. Then a suspension of 200 mg of sodium methoxide in 7 ml of dioxane containing 100 μl of ethyl benzoate (water scavenger) which had been heated at 60° for 12 hr was added to the solution of diol ester **14**. The resulting suspension was refluxed for 1 hr, at which time an ir spectrum of the reaction mixture showed no absorption in the carbonyl region. The reaction was allowed to cool and the dioxane was removed under vacuum. Water was added to the residue and the resulting solution was acidified with dilute sulfuric acid and extracted twice with ether. The combined ether extracts were dried over $MgSO_4$ and evaporated to give 700 mg of semisolid which was triturated with benzene. Filtration gave 110 mg (19%) of solid, mp 175–180°, with gas evolution. This material was shown to be identical with diol acid **25** which had been prepared in another manner[7] by comparison of spectra of both it and the derived lactone **28**.

Methyl 4aβ-Methyl-8β-formyloxy-8aα-hydroxydecahydronaphth-2β-oate (29).—A solution of 1.50 g of acid **17** in 50 ml of ether was esterified with ethereal diazomethane. After the ether was evaporated on a steam bath the crude ester was dissolved in ether and dried over magnesium sulfate. Removal of the ether afforded 1.53 g of oil which crystallized. One recrystallization from hexane gave 1.41 g (89%) of ester **29**, mp 88.0–90.2°. The analytical sample (mp 88.8–90.4°) was obtained upon one additional recrystallization from hexane: ir ($CHCl_3$) 3600, 3500, 1730, 1160 cm^{-1}; nmr ($CDCl_3$) δ 1.19 (angular methyl), 3.63 (CH_3O–), 4.82 ($W_{1/2}$ = 8 cps, equatorial[16] C_8 proton), 8.05 (HCO_2–).

Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 61.92; H, 7.92.

Reaction of Diol Ester Monoformate 29 with Lithium Methoxide.—To 20 ml of dry dioxane under a dry nitrogen atmosphere was added 1.5 ml of 1.5 *M* methyllithium in ether. Then a slight molar excess (90 μl) of methanol was added dropwise. After gas evolution had ceased (15 min), approximately 450 mg of formate ester **29** was added and the resulting cloudy solution was refluxed. The reaction was monitored by observing the infrared spectrum in the carbonyl region. After 4 hr, the ir spectrum showed essentially no absorption in the carbonyl region, but a broad band centered at *ca.* 1500 cm^{-1} was evident. The latter absorption is characteristic[13] of enolate anions. Heating was ceased and the reaction was allowed to cool overnight. The cooled solution was evaporated and 20 ml of water was added. The resulting two-phase mixture was thrice extracted with ether. The combined extracts were dried over $MgSO_4$ and evaporated, giving 260 mg (70%) of essentially pure epoxy ester **31**. The structure assignment was based on comparison of nmr and ir spectra of this material and those of a previously prepared 3:1 mixture of epoxy ester **31** and its epimer **43**. The analytical sample was



43

obtained by distillation at 0.1 mm (bath temperature 95°): nmr (CCl_4) δ 1.10 (angular methyl), 3.48 (OCH_3); ir (CCl_4) 1735 and 1025 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.28; H, 9.03.

Attempted Formation of the Tetrahydropyranol Ether of Diol Acid 18.—To a solution of 5.0 g of dihydropyran in 50 ml of dry ether was added 700 mg of diol acid[18] (mp 204–210°) and 5 drops of concentrated HCl. The diol acid did not appear to be soluble. After it had been stirred at room temperature for 18 hr the reaction mixture appeared unchanged and 20 ml of dry glyme was added which caused most of the suspended solid to dissolve. After 2.5 days the reaction was worked up in the usual manner. An nmr spectrum of the product (920 mg) showed several resonances attributable to angular methyl groups. No other attempts to prepare the THP ether were made.

Methyl 4aβ-Methyl-8-oxo-8aα-hydroxydecahydronaphth-2β-oate (34).—A solution of 300 mg of diol ester **14** in 15 ml of acetone was oxidized at 5° with 0.5 ml of Jones reagent.[12] The two-phase reaction mixture was added to 50 ml of saturated NaCl containing 1 ml of 10% aqueous $NaHSO_3$. The resulting two-phase mixture was thrice extracted with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated to give 290 mg of oil which crystallized. Recrystallization from hexane afforded 220 mg of keto ester **34** in two crops, mp 84–88°. One additional recrystallization from hexane gave analytically pure material: mp 87.0–88.7°; nmr ($CHCl_3$) δ 0.85 (angular methyl), 3.66 ($-OCH_3$); ir (CCl_4) 3590, 3490, 1735, 1715 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.03; H, 8.71.

Attempted Lactonization of Ketol Ester 34.—To 20 ml of dioxane under dry nitrogen was added 0.75 ml of 1.5 *M* CH_3Li in ether and 50 μl of methanol. After the resulting solution was stirred for 30 min, 50 μl of ethyl benzoate (water scavenger) was added and the solution was heated at 70° for 5 hr. The solution was cooled to room temperature, 110 mg of dry ketol ester **34** was added, and the reaction mixture was refluxed. An ir spectrum of the reaction mixture after 7 hr of reflux showed no absorption characteristic of a γ-lactone. The reaction was worked up in the usual manner to give material whose nmr spectrum indicated that it was mainly unreacted **34**.

4aβ-Methyl-8-oxo-8aα-hydroxydecahydronaphth-2β-oic Acid (36).—A solution of 400 mg of analytically pure diol acid **18** in 25 ml of acetone was oxidized at 0° with 0.6 ml of Jones reagent.[12] The reaction mixture was poured into 50 ml of saturated NaCl containing 1 ml of 10% aqueous $NaHSO_3$. The resulting two-phase solution was extracted once with ether and four times with methylene chloride. The extracts were combined, washed with brine, dried over $MgSO_4$, and evaporated to give 370 mg (93%)

(16) A. Hassner and C. H. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964).

of a slightly green solid, mp 151–154°. The analytical sample (mp 159.8–161.8°) was obtained after one recrystallization from benzene, sublimation at 115° (20 μ), one additional recrystallization from $CHCl_3$ (0.75% ethanol), and drying at 55° (20 μ). When impure diol acid **18** was used, ketol acid **36** with a satisfactory melting point could not be obtained: nmr (pyridine) δ 0.92 (angular methyl); ir (KBr) 3480, 3300–2500, 1720, and 1705 cm^{-1}.

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.72; H, 7.96. Found: C, 63.97; H, 7.69.

2′-Hydroxyethyl 4aβ-Methyl-8,8-ethylenedioxy-8aα-hydroxydecahydronaphth-2β-oate (37).—A rapidly stirred mixture of 2.00 g of ketol acid **36** (mp 149–158° with previous softening), 34 mg of *p*-toluenesulfonic acid monohydrate, 50 ml of benzene, and 10 ml of ethylene glycol was refluxed through a calcium hydride water separator[15] for exactly 2 hr under dry nitrogen. Heating was discontinued and the two-phase reaction mixture was poured into an aqueous solution composed of 5 ml of 10% KOH, 95 ml of H_2O, and 25 ml of saturated NaCl (to break emulsion). The resulting two-phase mixture was extracted thrice with ether and the combined extracts were dried ($MgSO_4$) and evaporated to give 2.07 g of solid material. Two recrystallizations from benzene–hexane gave 1.12 g (42%) of hydroxy ketal ester **37**, mp 108–112°. Several additional recrystallizations from the same solvent gave analytically pure material: mp 110.8–113.2°; nmr ($CDCl_3$ containing approximately 5% benzene) δ 1.10 (angular methyl), 3.6–4.3 (eight-proton multiplet, $-CH_2O-$); ir ($CHCl_3$) 3600, 3575, 3450, and 1725 cm^{-1}.

Anal. Calcd for $C_{16}H_{26}O_5$: C, 61.13; H, 8.34. Found: C, 61.12; H, 8.32.

If the ketalization is carried out under more vigorous conditions the sole product of the reaction is a compound whose nmr spectrum suggests the presence of three ethylene glycol moieties.

Methyl 4aβ-Methyl-8,8-ethylenedioxy-8aα-hydroxydecahydronaphth-2β-oate (35).—To 20 ml of "anhydrous" (0.017% H_2O) methanol was carefully added 5 ml of 1.5 *M* methyllithium in ether, followed by 300 μl of ethyl benzoate (water scavenger). After refluxing under nitrogen for 2 hr, the methanol solution was cooled and to it was added 910 mg of **37**. The reaction mixture was refluxed for 0.5 hr and partially neutralized with solid $NaHCO_3$. The resulting methanol solution was poured into brine and the resulting mixture was thrice extracted with ether. The combined ether extracts were thrice washed with brine, dried over $MgSO_4$, and evaporated to give 930 mg of methyl ester **35** containing approximately 30% methyl benzoate as estimated by nmr. An analytical sample was obtained by vpc (6 ft × 0.25 in. 15% SF-96 on Chromosorb W at 220°): nmr ($CDCl_3$) δ 1.11 (angular methyl), 3.63, and 3.81 (OCH_3, $-CH_2O-$); ir ($CHCl_3$) 3650, 3580, and 1725 cm^{-1}.

Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.38; H, 8.45. Found: C, 63.55; H, 8.50.

Conversion of Hydroxy Ketal Ester 35 into (±)-Norketoagarofuran (4).—To 20 ml of dry dioxane, under nitrogen, was added 4 ml of 1.5 *M* methyllithium in ether, followed by a slight excess (250 μl) of dry methanol. To remove any hydroxide ion present, 150 μl of ethyl benzoate was added, and the reaction mixture was refluxed for 3 hr, at which time the ir spectrum still showed carbonyl absorption. To this solution was added 680 mg of 70% pure (*vide supra*) hydroxy ketal methyl ester **35**. The reaction mixture was refluxed and the progress of the reaction was followed by ir. After 18 hr, no reaction appeared to have taken place and no lactone absorption was visible in the ir spectrum. The reaction was cooled and a small modified Soxhlet extractor[15] with a thimble containing calcium hydride was added to the system. The reaction mixture was then refluxed with the condensate passing through the CaH_2 on its return to the reaction flask. After 29 hr of reflux, the reaction had apparently stopped. An ir spectrum of the reaction mixture showed two carbonyl absorptions of similar intensity at 1780 and 1730 cm^{-1}.

The reaction mixture was allowed to cool overnight and 9 ml of 1.5 *M* methyllithium in ether was added. After the reaction mixture was stirred at room temperature for 1.75 hr, 25 ml of saturated NaCl was carefully added. The two-phase mixture was separated and the aqueous phase was extracted with ether (two 25-ml portions). The initial dioxane layer and the ether extracts were combined, washed with brine, dried over $MgSO_4$, and evaporated to give 750 mg of oil.

This oil was dissolved in 40 ml of acetone containing 4 ml of H_2O, and 8 drops of concentrated HCl was added. The acetone solution was stored at 0°. After 2.5 days, 0.5 g of solid K_2CO_3 was added and the acetone was removed below 25°. The residue was extracted into ether and this ether extract was dried over $MgSO_4$ and evaporated to give 540 mg of oil. An ir spectrum of this oil indicated that complete hydrolysis of the ketal had not occurred. The oil was dissolved in 30 ml of acetone containing 3 ml of H_2O, and 20 drops of concentrated HCl was added. The resulting solution was refluxed on a steam bath for 1.75 hr. After cooling, solid K_2CO_3 was added and the reaction mixture was poured into saturated NaCl. The resulting two-phase mixture was thrice extracted with ether. The ether extracts were combined, washed with saturated NaCl, dried over $MgSO_4$, and evaporated to give 330 mg of oil. This oil was chromatographed on 10 g of Merck alumina packed with benzene. Elution with 60 ml of benzene afforded 140 mg of oil. A vpc of this oil showed it to be a readily separable mixture of (±)-norketoagarofuran (**4**) (65%) and isopropenylbenzene (30%). An analytical sample of **4**, obtained by preparative vpc (6 ft × 0.25 in. 15% SF-96 on Chromosorb W at 170°) gave nmr and ir spectra identical with those published for the levorotatory antipode of **4**:[2] nmr (CCl_4) three singlets at δ 0.83, 1.07, and 1.35; ir (CCl_4) 1718, 1380, 1360, 1110, 1010, and 888 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.66; H, 10.02.

Registry No.—**4,** 35666-91-2; **14,** 35666-92-3; **17,** 35666-93-4; **18,** 35666-94-5; **19,** 35666-95-6; **20,** 35666-96-7; **25,** 35666-97-8; **29,** 35666-98-9; **31,** 35666-99-0; **34,** 35667-00-6; **35,** 35667-01-7; **36,** 35667-02-8; **37,** 35666-03-9; **43,** 35667-04-0.

Acknowledgments.—I would like to thank Professor Clayton H. Heathcock for several helpful discussions. The financial support of the Petroleum Research Fund, administered by the American Chemical Society (Grant 2381-A1 to C. H. Heathcock), is gratefully acknowledged.

Specific Chemical Synthesis of Ribonucleoside O-Benzyl Ethers[1a]

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Received May 12, 1972

A facile new method for the one-step synthesis of 2′- and 3′-*O*-benzyl ethers of adenosine, inosine, guanosine, cytidine, and uridine by reaction of the free nucleoside with phenyldiazomethane in the presence of a Lewis acid catalyst ($SnCl_2$) is reported. A unique and rapid method of isomer differentiation by uv spectrophotometry is described. An evaluation was made of the ease of removal of the benzyl group by catalytic hydrogenolysis. An unusual example of long-range proton coupling is reported.

A great deal of interest has been generated recently in the chemical and enzymatic synthesis of oligoribonucleotides of defined chemical structure.[2-4] One of the major difficulties in the synthesis of oligoribonucleotides lies in selectively blocking the 2′-hydroxyl group of the starting ribonucleoside so that the required 3′ → 5′ internucleotide linkage may be specifically formed. The ideal blocking group must meet the following criteria: it must not undergo facile 2′ → 3′ migration, it must be stable to the conditions required for oligonucleotide synthesis, and it must be readily removable under conditions which do not permit 3′ → 2′ phosphate migration.

A number of workers have recommended the benzyl group as a protecting function which meets each of the above criteria; it is stable, does not migrate readily, and is removed by mild catalytic hydrogenolysis.[5-9]

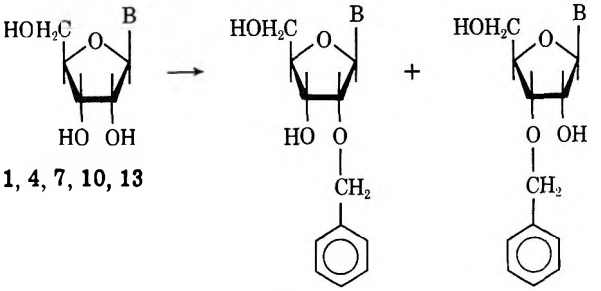
The first specific chemical synthesis of a 2′-*O*-methylribonucleoside was achieved by direct methylation of adenosine with diazomethane in a homogeneous 1,2-dimethoxyethane–water solution.[10] It has very recently been shown that this reaction is markedly catalyzed by Lewis acids such as $SnCl_2$.[11] Thus, adenosine was converted into a 99% total yield of 2′- and 3′-*O*-methyladenosine in a 1:2 ratio. In a similar reaction with cytidine the 2′:3′ ratio was 5:1.[11]

These results suggested that the Lewis acid catalyzed reaction of phenyldiazomethane with unprotected purine and pyrimidine ribonucleosides should lead directly to the desired 2′- and 3′-*O*-benzyl ethers. These syntheses, the development of a unique and facile method of structure assignment, and studies on the ease of reductive cleavage of the benzyl ethers form the basis of this report.

Results and Discussion

The presence of one and only one benzyl group in each of the benzylated nucleosides (Scheme I) was evident from elemental analysis. It was clear in all cases from examination of the uv spectra (Table I) that alkylation had occurred only on the sugar portion of the molecule. Therefore only the site of alkylation on the carbohydrate moiety remained to be determined.

SCHEME I



1–3, B = adenine
4–6, B = hypoxanthine
7–9, B = guanine
10–12, B = uracil
13–15, B = cytosine

TABLE I

UV DATA FOR SOME RIBONUCLEOSIDE *O*-BENZYL ETHERS

Compd	λ_{max}, nm ($\epsilon_{max} \times 10^{-3}$) pH 1	pH 7	pH 11
1	257 (15.1)	259 (15.1)	259 (15.3)
2	257 (12.7)	259 (13.0)	259 (12.7)
3	257 (15.6)	259 (15.8)	259 (15.5)
4	248 (12.4)	248 (12.9)	252 (13.7)
5	250 (10.6)	250 (10.6)	253 (11.5)
6	248 (13.7)	248 (13.1)	252 (14.2)
7	255 (12.3)	252 (13.5)	256 (11.3)
8	257 (10.2)	253 (11.3)	257 (9.50)
9	256 (12.7)	252 (13.9)	256 (11.7)
10	261 (10.5)	261 (10.6)	260 (7.90)
11	262 (8.90)	262 (8.70)	261 (6.65)
12	261 (10.6)	261 (10.6)	260 (7.95)
13	278 (12.9)	269 (9.05)	269 (8.95)
14	279 (11.4)	271 (7.60)	271 (7.60)
15	279 (13.7)	270 (9.50)	270 (9.40)

The two isomers obtained from the direct benzylation of uridine (**10**) were readily characterized by melting point comparisons with known compounds. Each of the three possible mono-*O*-benzyl ethers of uridine has been prepared by multistep procedures: 5′-*O*-benzyluridine reportedly melted at 162°,[12] 3′-*O*-benzyluridine (**12**) at 204–206°,[6] and 2′-*O*-benzyluridine (**11**) at 181–182°.[7,8] The 3′- and 2′-*O*-benzyluridines (**12** and **11**) reported above melted at 205–207 and 177–179°, respectively. The pmr data for **11** and **12**

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TABLE II

PMR SPECTRAL DATA FOR SOME RIBONUCLEOSIDE O-BENZYL ETHERS[a]

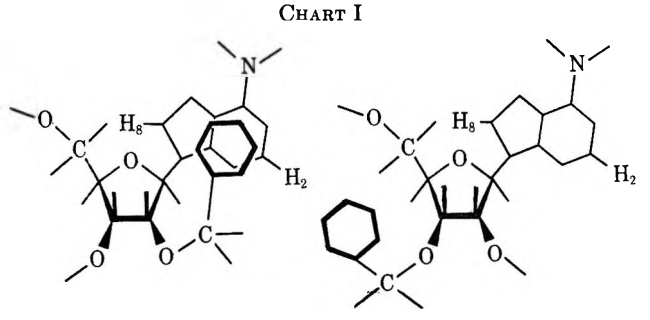
Compd	Chemical shift, δ					
	C-2 H	C-8 H	C-1′ H	C-5 H	C-6 H	Phenyl
2	7.92	8.15	5.98 (d, 5.8)			7.03
3	7.99	8.17	5.85 (d, 6.1)			7.23
5	7.88	8.13	5.97 (d, 5.1)			7.07
6	7.97	8.25	5.89 (d, 6.1)			7.29
8		7.73	5.79 (d, 4.8)			7.11
9		7.77	5.67 (d, 6.2)			7.21
11			5.83 (d, 4.4)	5.47 (d)	7.68 (d)	7.15
12			5.73 (d, 5.6)	5.55 (d)	7.68 (d)	7.20
14			5.88 (d, 3.2)	5.65 (d)	7.77 (d)	7.22
15			5.77 (d, 4.0)	5.67 (d)	7.72 (d)	7.24
1[b]	8.10	8.27	6.03 (d, 5.8)			
2[b]	7.92	7.98	5.84 (m)			6.93

[a] Unless otherwise indicated, solutions are about 6% in DMSO-d_6 with DSS (sodium 2,2-dimethyl-2-silapentane sulfonate) reference. Coupling constants in hertz are given in parentheses; d ≡ doublet, m ≡ multiplet. [b] Concentration 0.075 *M* in D_2O, DSS as internal reference.

(Table II) also correlated well with those reported earlier[13] for the two monobenzyluridines.

Assignment of the hitherto unknown 2′- and 3′-*O*-benzyl ethers of adenosine (**2** and **3**) was made using pmr and uv spectroscopy. The 5′ position was eliminated as a site of benzylation by the observation of a triplet at δ 5.37 in the pmr spectrum of **2** and a triplet at δ 5.50 in the pmr spectrum of **3** (dry DMSO-d_6 was the solvent). Both peaks disappeared rapidly upon addition of D_2O to the DMSO-d_6 solution. Such triplets have been shown to arise from the coupling of –OH (5′) to the methylene protons at C-5′.[14,15] The assignment of **2** and **3** as 2′- and 3′-*O*-benzyl isomers, respectively, was readily made using uv spectrophotometry. Examination of C-P-K molecular models reveals that a very favorable stacking interaction between the purine base and the benzene ring is possible with the 2′ isomer **2**, but impossible with the 3′ isomer **3**. A diagram of the probable conformation of each is given in Chart I. It is clear from extensive dinu-

CHART I



cleoside phosphate and model compound studies that parallel–planar overlap of "aromatic" bases results in marked hypochromicity when the bases are linked by three or more carbon atoms.[16] The finding of marked hypochromicity relative to the starting nucleoside of one of a pair of 2′(3′)-*O*-benzyl ribonucleosides would establish that isomer as 2′, since there is essentially no difference in the extinction coefficients between the 3′-*O*-benzyl nucleosides and the parent nucleosides (Table I). Table III shows clearly that this is

TABLE III

PER CENT HYPOCHROMICITY OF 2′-*O*-BENZYL NUCLEOSIDES RELATIVE TO PARENT NUCLEOSIDES

Compd	pH 1	pH 7	pH 11
2	16.0	14.0	17.2
5	14.5	17.8	16.0
8	17.1	16.3	16.0
11	15.2	17.9	17.1
14	11.6	16.0	15.1

the case for **2** and for each of the other 2′-*O*-benzyl nucleosides reported. This provides a unique and extremely facile means for determining the site of *O*-benzylation of ribonucleosides.

Each of the benzyl nucleoside pairs obeys the empirical rule of Reese and coworkers,[13] which states that the chemical shift will be at lower field and the coupling constant smaller for the anomeric proton of the 2′ isomer of a 2′(3′)-*O*-substituted pair of nucleosides. It should be noted, however, that in the case of adenosine both the chemical shift difference (δ 0.07) and the coupling constant difference (0.3 Hz) between the isomers are very small. Furthermore, *both* isomers are required before the Reese rule may be applied. The uv technique described above, however, appears to be completely general for benzyl ethers of ribonucleosides and can be utilized by comparing *either* isomer with starting material.

The demonstration of hypochromicity for 2′-*O*-benzyladenosine relative to adenosine suggested, as noted above, that stacking of the purine and the benzene ring probably occurs in aqueous solution. In order to support this concept a study of the pmr spectrum of 2′-*O*-benzyladenosine in D_2O was carried out. It is well known that intramolecular stacking in dinucleoside phosphates may be readily evaluated by pmr in D_2O solution;[17,18] the influence of the diamagnetic anisotropy of a neighboring base leads to upfield shifts of protons on an adjacent ring. Comparison of the data obtained for **2** and adenosine at equivalent con-

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centrations in D_2O (Table II) supports the intramolecular stacking illustrated in Chart I. The purine C-8 H and C-2 H protons of 2 appear 0.29 and 0.18 ppm, respectively, upfield from those of adenosine. The anomeric proton, C-1′ H, is also shielded by 0.19 ppm in 2 relative to adenosine. The pattern for the C-1′ H signal of 2 is completely unlike that of adenosine in either DMSO-d_6 or D_2O or that of 2 in DMSO-d_6. Instead of the usual doublet ($J_{1',2'} \cong 3$ Hz), the anomeric proton signal of 2 in D_2O resembles a pair of overlapping triplets containing apparent first-order coupling constants of 7.1 and 2.4 Hz. That this is a conformationally dependent long range coupling was established by recording the spectrum of 2 in D_2O at 70°; at this temperature the five-band multiplet collapsed cleanly into a doublet ($J_{1',2'} = 6.5$ Hz). The same pattern was observed in the case of 2′-*O*-benzylinosine (**5**). The spectrum of 2′-*O*-benzyluridine (**11**) in D_2O, on the other hand, shows an entirely normal doublet ($J_{1',2'} = 6.0$ Hz). The spectra of 2′-*O*-benzylguanosine (**8**) and 2′-*O*-benzylcytidine (**14**) could not be obtained because of limited solubility in D_2O. The difference between the purine nucleosides and the pyrimidine nucleoside is not surprising in view of the known conformational differences in the carbohydrate moieties of purine and pyrimidine nucleosides.[19] Decoupling experiments designed to elucidate the exact nature of the observed long-range coupling are presently in progress and will be reported elsewhere.

A very important feature of this general procedure for nucleoside O-benzylation is that little or no benzylation occurs on the purine or pyrimidine bases (as evaluated by tlc examination of the reaction mixtures), even though methylation with diazomethane of uridine[20] and inosine[21] leads in all cases to alkylation of the heterocyclic moiety. Only in the case of guanosine is the possibility of substantial N-benzylation confirmed by tlc; guanosine is quantitatively N-alkylated by diazomethane.[22] A detailed study of the reaction conditions required to optimize yields has not been undertaken, since the primary purpose of this work is to provide a *rapid* method for obtaining blocked nucleosides in reasonable yields.

Since the benzyl cation is relatively stable and N → N benzyl migration is well known in heterocyclic systems[23] it was of interest to ascertain whether O-2′(3′) → O-3′(2′) migration could occur either thermally or under the conditions used for the synthesis. When 2 and 3 were dissolved separately in methanol containing $SnCl_2 \cdot 2H_2O$ (1×10^{-3} *M*) and stirred for 6 days at room temperature, no interconversion was observed. Samples of 2 and 3 were heated above their melting points and maintained at that temperature for 2 hr. Although a small amount of decomposition occurred to give adenine, there was no isomerization detectable to tlc. Clearly isomerization will present no problem to the utilization of benzyl ethers in oligonucleotide synthesis.

As expected, hydrogenolysis under mild conditions (3 atm, room temperature) suffices to quantitatively debenzylate the *O*-benzyl purine nucleosides with no side reactions detectable by chromatography. 2′-*O*-Benzyluridine (**11**) as previously reported[7,8] may be cleanly hydrogenolyzed over palladium at 1 atm with no reduction of the ring. Contrary to a previous report,[8] in our hands hydrogenation of the ring of 2′-*O*-benzylcytidine does not proceed more rapidly than debenzylation; however, some reduction of the 5,6-double bond (10–25%) does occur by the time complete removal of the benzyl group is effected. Based upon these studies, it is clear that at least four of the five 2′-*O*-benzyl nucleosides reported herein are suitable candidates for oligonucleotide and polynucleotide synthesis.

Experimental Section

Proton magnetic resonance data were obtained using a Jeol C60H spectrometer. A Cary 15 spectrophotometer was used for the measurement of uv spectra. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo.

The synthesis of phenyldiazomethane was carried out as previously described.[24] Concentrations of phenyldiazomethane solutions were measured by quantitative reaction with *p*-nitrobenzoic acid and found to be about 0.125 mmol/ml of ether solution.

General Procedure for the O-Benzylation of Ribonucleosides.—To a solution of MeOH (100 ml/g of nucleoside) containing $SnCl_2 \cdot 2H_2O$ (1×10^{-3} *M*) was added the nucleoside to be benzylated (1 g of nucleoside is *ca.* 4 mmol). A phenyldiazomethane solution (~12.5 mmol in 50 ml of 1,2-dimethoxyethane prepared by evaporating the ether *in vacuo*[25] and dissolving the oil in 1,2-dimethoxyethane) was added slowly over about 8 hr to the stirred solution at room temperature. Completion of the reaction was ascertained by the absence of starting material as judged by tlc (SilicAR 7 GF, EtOAc:H_2O:*n*-PrOH, 4:2:1, upper phase). Silica gel (5 g) was added to the solution and the solvent was removed *in vacuo*. The silica gel containing the adsorbed nucleosides and various impurities (*i.e.*, benzyl alcohol) was placed on a silica gel column (50 g) and rapidly eluted as described below to obtain a mixture of isomers free from contaminants.

2′-*O*-Benzyladenosine (2) and 3′-*O*-Benzyladenosine (3).—Adenosine (23.0 g, 86.0 mmol) was benzylated as described above. The silica gel column was washed with $CHCl_3$ (2 l.), EtOAc:$CHCl_3$ (1:1, 6 l.), and EtOAc (16 l.) Elution with EtOAc:MeOH (95:5, 15 l.) gave two fractions; the first (fraction A) contained pure 2′ isomer 2 and the second (fraction B) a mixture of 2 and 3. Removal of the solvent *in vacuo* from fraction A followed by recrystallization from EtOH gave pure 2 (1.25 g). Evaporation *in vacuo* of the solvent from fraction B followed by fractional crystallization of the residue from MeOH gave pure 3 (11.88 g). Removal of the methanol from the filtrates followed by chromatography on Dowex-1 × 8 (OH^-, 200–400 mesh) using 20% aqueous methanol according to Dekker[26] gave, after removal of the solvent and recrystallization of the residue from acetone, 2 (7.18 g).

The total yield of 2 was 8.44 g (27%), mp 147–150° (after one recrystallization from EtOH).

Anal. Calcd for $C_{17}H_{19}N_5O_4$: C, 57.13; H, 5.36; N, 19.60. Found: C, 56.89; H, 5.48; N, 19.41.

The yield of 3 was 11.88 g (38.5%), mp 195–196°.

Anal. Calcd for $C_{17}H_{19}N_5O_4$: C, 57.13; H, 5.36; N, 19.60. Found: C, 57.03; H, 5.37; N, 19.95.

2′-*O*-Benzylinosine (5) and 3′-*O*-Benzylinosine (6).—The benzylation of inosine (2.0 g, 7.5 mmol) was carried out. The column was washed with $CHCl_3$ (1.5 l.) and EtOAc (2 l.). The isomeric mixture was eluted with EtOAc:MeOH (9:1). The solvent was removed *in vacuo*. The residue was dissolved in 1 *N* NH_4OH and applied to a column containing 500 g of DE-52 (Whatman DEAE cellulose) preequilibrated with 1 *N* NH_4OH. Elution with the same solvent gave two major bands. The pooled fractions containing the most rapidly eluted material

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were evaporated *in vacuo* and the residue was recrystallized from acetone to give **5** (572 mg, 21%), mp 218–220°.

Anal. Calcd for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06; N, 15.64. Found: C, 56.91; H, 5.07; N, 15.62.

The pooled fractions containing the slower moving band were also evaporated *in vacuo*. The residue was recrystallized from ethanol–water to give **6** (385 mg, 14%), mp 219–221°.

Anal. Calcd for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06; N, 15.64. Found: C, 57.17; H, 5.06; N, 15.48.

2′-*O*-Benzylguanosine (8) and 3′-*O*-Benzylguanosine (9).—Guanosine (1.0 g, 3.5 mmmol) was benzylated by the general method. The column was washed with $CHCl_3$ (1 l.) and EtOAc (2 l.). The benzylated nucleosides were eluted with EtOAc:MeOH (95:5). The solvent was removed *in vacuo* and the residue was dissolved in 1.5 *N* NH_4OH. The solution was applied to a column containing 500 g of DE-52 (Whatman DEAE cellulose) preequilibrated with 1.5 *N* NH_4OH. Elution with the same solvent gave two bands. The combined fractions corresponding to the first band were evaporated *in vacuo* and the residue was crystallized from ammonia–water to give **8** (207 mg, 16%), mp >310°, darkens at 270°.

Anal. Calcd for $C_{17}H_{19}N_5O_5$: C, 54.68; H, 5.13; N, 18.76. Found: C, 54.81; H, 5.24; N, 18.89.

The material from the second band was treated in the same manner to give **9** (233 mg, 18%), mp >310°, darkens above 260°.

Anal. Calcd for $C_{17}H_{19}N_5O_5$: C, 54.68; H, 5.13; N, 18.76. Found: C, 54.39; H, 5.16; N, 18.62.

2′-*O*-Benzyluridine (11) and 3′-*O*-Benzyluridine (12).—Uridine (5.0 g, 20.5 mmol) was benzylated. The column was washed with $CHCl_3$ (2 l.) and $CHCl_3$:EtOAc (1:3, 2 l.) and the isomers were eluted with EtOAc (4 l.). The solvent was removed *in vacuo* and the residue was crystallized from EtOAc:Me_2CO to give a mixture of **11** and **12** (4.17 g, 56%). Separation of the isomers was accomplished by fractional crystallization from EtOH. Isomeric purity of the fractions was evaluated using tlc (SilicAR 7 GF, 3% aqueous NH_4Cl). The total yield of **11** was 1.52 g (20.3%), mp 177–179°. Analytical samples were obtained by recrystallization from EtOH.

Anal. Calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.47; H, 5.47; N, 8.48.

The total yield of **12** was 1.08 g (14.5%), mp 205–207°.

Anal. Calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.47; H, 5.71; N, 8.46.

2′-*O*-Benzylcytidine (14) and 3′-*O*-Benzylcytidine (15).—Cytidine (**13**, 6.0 g, 24.7 mmol) was benzylated as described above. The column was washed with $CHCl_3$ (2 l.), EtOAc (3 l.), and EtOAc:MeOH (95:5, 3 l.). The isomeric mixture was eluted with EtCAc:MeOH (85:15). The solvent was removed *in vacuo* to give **14** and **15** as a solid foam (5.33 g, 65%).

The above mixture (1.0 g) was dissolved in a solution of MeOH (14 ml) and H_2O (28 ml). The solution was applied to a column containing Dowex 1 × 8 (OH^-) and eluted with 30% aqueous MeOH. The fractions corresponding to the first major band were combined and evaporated. The residue was recrystallized from H_2O to give **14** (530 mg, 34% from **13**), mp 160–161°.

Anal. Calcd for $C_{16}H_{19}N_3O_5$: C, 57.65; H, 5.74; N, 12.61. Found: C, 57.49; H, 5.94; N, 12.46.

The combined fractions corresponding to the second major band were evaporated to dryness *in vacuo*. The residue was dissolved in H_2O and lyophilized to give **15** (287 mg, 19% from **13**).

Anal. Calcd for $C_{16}H_{19}N_3O_5 \cdot 0.5H_2O$: C, 56.13; H, 5.89; N, 12.27. Found: C, 56.01; H, 5.86; N, 12.28.

Debenzylation Procedure for *O*-Benzyl Purine Ribonucleosides.—*O*-Benzyl nucleoside (50 mg) was dissolved in EtOH (25 ml) containing 1 *N* NaOH (0.5 ml). The solution was added to 5% Pd/C. The mixture was shaken under hydrogen (45 psi). After 3.5 hr, debenzylation was complete as judged by tlc (SilicAR 7 GF, EtOAc:H_2O:*n*-PrOH, 4:2:1 upper phase).

Debenzylation Procedure for *O*-Benzylpyrimidine Ribonucleosides.—2′-*O*-Benzyluridine (50 mg) was dissolved in EtOH (25 ml) containing H_2O (10 ml) and 1 *N* NaOH (2 ml). The solution was added to 10% Pd/C (25 mg) and stirred under hydrogen (1 atm). After 1 hr debenzylation was complete as judged by tlc (as above); quantitative uv evaluation showed better than 95% recovery of uridine.

Treatment of 2′-*O*-benzylcytidine (**14**) under these conditions led to complete debenzylation, but about 10–25% reduction to dihydrocytidine occurred.

Registry No.—**1**, 58-61-7; **2**, 35638-82-5; **3**, 35638-83-6; **4**, 58-63-9; **5**, 35638-84-7; **6**, 35638-85-8; **7**, 118-00-3; **8**, 35687-58-2; **9**, 35638-86-9; **10**, 58-96-8; **11**, 6554-02-5; **12**, 4710-74-1; **13**, 65-46-3; **14**, 22423-30-9; **15**, 35687-60-6.

An Unusual Spirane Synthesis

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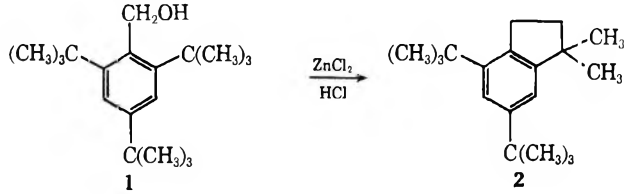
The structure of the spirane formed by the cyclodehydration of the alcohol 5-*tert*-butyl-5-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene (**3a**) has been established. The method used was to demonstrate the existence of a more stable isomer by lowering the barrier to ring inversion, and then to thermally isomerize the first to the second. The nmr spectra of the isomers are in agreement with the chemical results. Attempts to extend the cyclization reaction to five- and six-membered rings were unsuccessful. Two possible mechanisms for the cyclization are presented.

An unexpected cyclization is sometimes observed when a positive charge is formed near a crowded *tert*-butyl group. The positive carbon atom appears to insert itself into a carbon–hydrogen bond of one of the methyl groups of the *tert*-butyl substituent. The first example[1] of this reaction to be reported was the formation of indan **2** from alcohol **1**. Since no indan is formed when one of the ortho *tert*-butyl groups is replaced by methyl, some crowding is necessary for cyclization to occur. Other examples have subsequently appeared which include indans,[2] a benzocyclobutene,[3] and a cyclopropane.[4] We wish to report another example of this type of cyclization in which a three-membered ring is closed to form spirononatriene **4** in good yield (75%).



1 **2**

While attempting to prepare chloride **3b** for another problem, alcohol **3a** was synthesized by treating di-

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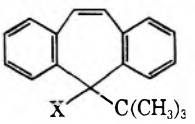
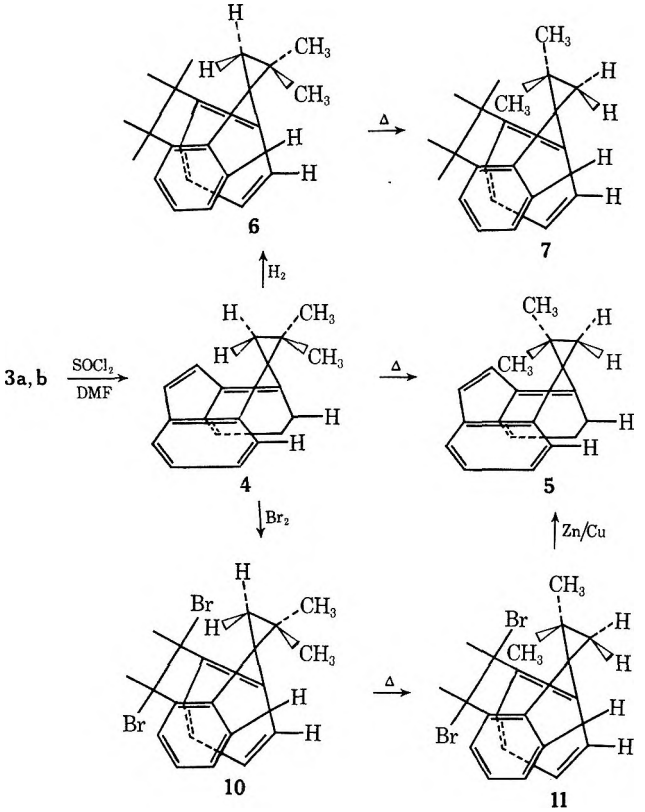


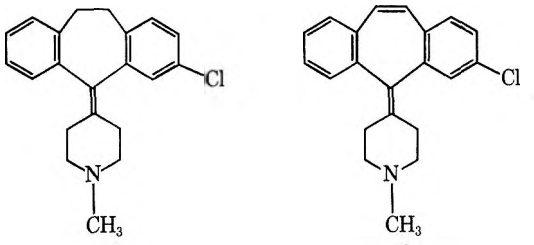
3a, X = OH
b, X = Cl

benzotropone with *tert*-butylmagnesium chloride. When the alcohol is treated with thionyl chloride and dimethylformamide (DMF), the only product isolated is a hydrocarbon, which differs from the starting alcohol by the loss of water. It no longer has a *tert*-butyl group (mass spectrum, nmr), but has a *gem*-dimethyl group (singlet, τ 8.69) and two cyclopropyl protons (singlet, τ 9.70). The most probable structures for this compound are **4** and **5**. Since its spectral properties do not allow a choice to be made between them, the chemical behavior of the spirane was examined.

Catalytic hydrogenation of the spirane occurs smoothly and, if care is taken to avoid heat, a thermally labile dihydrospirane is obtained. When this hydrocarbon is heated on a steam bath, it is isomerized to a new dihydrospirane. Based on the nmr spectra and molecular models of the two dihydrospiranes, structure **6** is assigned to the less stable and structure **7** to the more stable isomer. Isomerization causes the methyl groups to move out of the deshielding plane of the aromatic rings and away from the peri hydrogen atoms. The result is an upfield shift (τ 8.58 → 9.08) of the methyl signal. The cyclopropyl protons move into this deshielding area vacated by the methyl groups, and are shifted downfield (τ 8.91 → 8.71). Molecular models show that a steric interaction between the methyl groups and the peri hydrogen atoms is relieved by isomerization of **6** to **7**.



Our interpretation of these findings is that the spirane has the thermodynamically less stable structure **4**, in which there is a steric interaction identical with that proposed for dihydrospirane **6**. Isomerization to the more stable spirane **5** does not occur because of a high energy barrier to ring inversion. When the vinyl group is reduced, the less stable isomer **6** is formed, but the energy barrier has been lowered so that isomerization to the more stable form **7** can readily occur at 100°. The barrier to inversion is known to be significantly lower for the dihydro system. For example, the activation energy for the inversion[5] (racemization) of **8** is 9 kcal/mol lower than that of **9**. Models



show that dihydrospirane **6** undergoes ring inversion with only a slight twist of the ethano bridge and aromatic rings. Spirane **4** must turn itself inside out to effect isomerization.

If this interpretation is correct, isomerization of spirane **4** to **5** should be possible if the temperature is raised high enough. The expected isomerization does occur at 210°, and is complete after 5 days. It can also be effected in refluxing quinoline (bp 238°) in 13 hr. The more stable spirane **5** has also been prepared by an alternative method. Bromination of the less stable spirane **4** produces the thermally labile dibromospirane **10** which, upon heating at near 100°, readily isomerizes to **11**. Debromination of **11** with zinc–copper couple gives the more stable spirane **5**.

The behavior of 9-*tert*-butyl-9-hydroxyfluorene (**12a**) and 9-*tert*-butyl-9-hydroxyxanthene (**13a**) toward thionyl chloride and DMF was examined to see if spirane formation could be extended to the five- and six-membered rings. Both alcohols are converted to the corresponding chlorides, **12b** and **13b**, in high yield under these conditions.

12a, X = OH
b, X = Cl

13a, X = OH
b, X = Cl

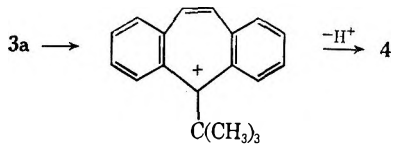
Alcohol **12a** has recently been found to undergo rearrangement when treated with strong acid,[6] but spirane formation was not observed. The difference in behavior between alcohol **3a** and alcohols **12a** and **13a** is probably due to the planarity of the central five- and six-membered rings. The boat-shaped seven-membered ring in **3a** causes a steric interaction between the equatorial substituent at carbon 5 and the peri hydrogen atoms. Relief of this interaction is probably the driving force for cyclization. Models show that the two substituents at carbon 9 in alcohols

(5) A. Ebnöther, E. Jucker, and A. Stoll, *Helv. Chim. Acta*, **48**, 1237 (1965).

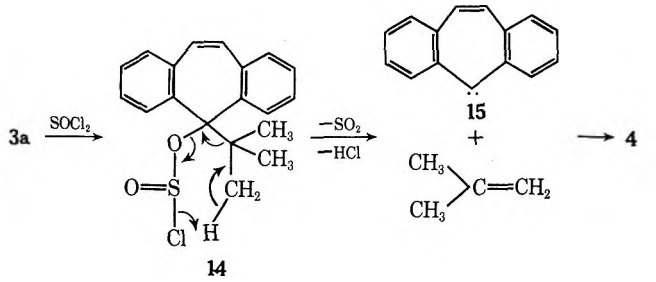
(6) H. Volz, G. Zimmermann, and B. Schelberger, *Tetrahedron Lett.*, 2429 (1970).

12a and **13a** occupy positions with nearly identical relationships to the rest of the molecule, and neither experiences any steric crowding.

Two mechanisms appear reasonable for the cyclization process. The first is the carbonium ion path suggested by Barclay and MacDonald,[1] which involves attack of the cation center by an sp^3 carbon orbital.



The second mechanism is the stepwise or concerted formation of carbene **15** and isobutylene from ester **14**.



Subsequent addition of the carbene to the olefin within the solvent cage would give spirane **4**. No evidence has been obtained which allows a distinction to be made between these two possibilities.

Experimental Section

5-*tert*-Butyl-5-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene (3a).—A Grignard reagent was prepared from 18.5 g (0.20 mol) of *tert*-butyl chloride, 4.8 g (0.20 g-atom) of magnesium, and 300 ml of anhydrous ether, and a solution of 25 g (0.12 mol) of 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one in 100 ml of dry benzene was added rapidly with stirring. After 2 hr the mixture was poured into excess saturated ammonium chloride solution, and the organic layer was separated, washed, dried, and concentrated. The residue was chromatographed on Florisil with 20% benzene in ligroin (bp 63–75°). The first fractions solidified and were recrystallized from ligroin to give alcohol **3a**: yield 6.5 g (20%); mp 145–146°; ir (KBr) 3500 cm^{-1} (OH); nmr ($DCCl_3$) τ 9.20 (s, 9, *tert*-butyl), 7.80 (s, 1, exchanges with D_2O, OH), 3.20 (s, 2, olefinic), 2.4–2.7 (m, 6, aromatic), 1.7–1.9 (m, 2, aromatic); mass spectrum *m/e* (rel intensity) 264 (0.4, parent), 249 (0.3), 207 (100), 179 (14), and 178 (26).

Anal. Calcd for $C_{19}H_{20}O$: C, 86.3; H, 7.6. Found: C, 86.1; H, 7.7.

The use of *tert*-butyllithium in place of the Grignard reagent gave the same yield of product.

Reaction of 5-*tert*-Butyl-5-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene (3a) with Thionyl Chloride and DMF.—A mixture of 2.0 g (0.0076 mol) of alcohol **3a**, 6 ml of thionyl chloride, and 4 drops of DMF was heated at reflux for 30 min. The solvent was distilled and the solid residue was washed with water and recrystallized from ethanol: yield 1.4 g (75%) of spirane **4**; mp 104–105°; nmr ($DCCl_3$) τ 9.79 (s, 2, cyclopropyl), 8.69 (s, 6, methyl), and 2.4–2.9 (m, 10, aromatic and vinyl); uv λ_{max} (EtOH) 282 nm (log ϵ 4.08); mass spectrum *m/e* (rel intensity) 246 (100, parent), 245 (77), 231 (61), 216 (30), 215 (36), and 189 (39).

Anal. Calcd for $C_{19}H_{18}$: C, 92.6; H, 7.4. Found: C, 92.4; H, 7.1.

Reduction of Spirane 4.—A mixture of 2.1 g (0.085 mol) of spirane **4**, 150 ml of ethanol, and 0.1 g of 10% palladium on charcoal was treated with hydrogen at 50 psi for 15 hr. The catalyst was removed by filtration and the solvent was distilled, care being taken not to heat the solution above room temperature. The product, dihydrospirane **6**, was recrystallized from methanol in such a manner as to minimize exposure to heat: yield 1.8 g (86%); mp 87–88°; nmr ($DCCl_3$) τ 8.91 (s, 2, cyclopropyl), 8.58 (s, 6, methyl), 6.1–7.4 (m, 4, benzyl), 2.95–3.03 (m, 6, aromatic), and 2.6–2.9 (m, 2, aromatic); mass spectrum *m/e* (rel intensity) 248 (79, parent), 247 (39), 283 (100), 191 (21), 189 (21), and 91 (16).

Anal. Calcd for $C_{19}H_{20}$: C, 91.9; H, 8.1. Found: C, 91.8; H, 8.1.

Isomerization of Dihydrospirane 6.—Heating 1.0 g of dihydrospirane **6** on a steam bath for 20 min caused it to isomerize to compound **7** quantitatively: mp 56–58° (recrystallized from methanol, mp 58–59°); nmr ($DCCl_3$) τ 9.08 (s, 6, methyl), 8.71 (s, 2, cyclopropyl), 6.3–7.5 (m, 4, benzyl), 3.10 (s, 8, aromatic); mass spectrum identical with that of isomer **6**.

Anal. Calcd for $C_{19}H_{20}$: C, 91.9; H, 8.1. Found: C, 91.7; H, 7.9.

Thermal Isomerization of Spirane 4.—A 0.050-g sample of spirane **4** was dissolved in 0.3 ml of hexachlorobutadiene and heated in an nmr tube at 206° for 26 hr. Nmr spectra were measured at intervals during this time and showed a decrease in the methyl (τ 8.69) and cyclopropyl (τ 9.79) peaks of spirane **4** and the appearance of the methyl (τ 9.32), cyclopropyl (τ 8.70), and vinyl (τ 2.97) peaks of spirane **5**. Integration showed that isomerization was 60% complete after 26 hr. When spirane **4** was sealed in an ampoule and heated at 210° for 5 days, the nmr spectrum of the product was that of spirane **5**.

A solution of 0.10 g of spirane **4** in 0.3 ml of quinoline was heated at 240° for 13 hr. The nmr spectrum showed complete isomerization to **5**. The solution was poured into dilute hydrochloric acid and the solid was collected and recrystallized from acetonitrile to give 0.060 g (60%) of spirane **5**: mp 97–98°; nmr ($DCCl_3$) τ 2.65 (m, 3, aromatic), 2.97 (s, 2, olefinic), 8.70 (s, 2, cyclopropyl), 9.32 (s, 6, methyls); mass spectrum is identical with that of spirane **4**.

Anal. Calcd for $C_{19}H_{18}$: C, 92.6; H, 7.4. Found: C, 92.6; H, 7.7.

Bromination of Spirane 4.—A mixture of 1.0 g (0.0040 mol) of spirane **4**, 0.65 g (0.0040 mol) of bromine, and 1 ml of carbon tetrachloride was wrapped in aluminum foil and left at room temperature for 15 hr. The solvent was removed and the solid was washed with 3 ml of ethanol to give 1.2 g (74%) of dibromide **10**: mp 143–144°; nmr ($DCCl_3$) τ 8.97, 8.90, 8.25, 8.18 (AB quartet, 2, cyclopropyl), 8.46 (s, 3, methyl), 8.60 (s, 3, methyl), 3.18, 3.33, 4.34, 4.48 (AB quartet, 2, benzylic), 2.6–3.0 (m, 7, aromatic), and 2.0–2.2 (m, 1, aromatic); mass spectrum *m/e* (rel intensity) 404 (0.3, parent), 325 (40), 269 (18), 246 (43), 245 (100), and 215 (32).

Anal. Calcd for $C_{19}H_{16}Br_2$: C, 56.2; H, 4.5; Br, 39.4. Found: C, 56.4; H, 4.4; Br, 39.4.

Isomerization of Dibromide 10.—A solution of 1.2 g of dibromide **10** in 10 ml of toluene was heated on a steam bath for 1 hr and the solvent was distilled. Recrystallization of the residue from methylcyclohexane gave 1.05 g (88%) of the isomeric dibromide **11**: mp 165–166°; nmr ($DCCl_3$) τ 8.92 (s, 3, methyl), 8.63 (s, 3, methyl), 8.37, 8.47, 8.70, 8.80 (AB quartet, 2, cyclopropyl), 3.55, 3.75, 4.27, 4.47 (AB quartet, 2, benzyl), 2.6–3.1 (m, 7, aromatic), and 1.9–2.1 (m, 1, aromatic); mass spectrum identical with that of dibromide **10**.

Anal. Calcd for $C_{19}H_{16}Br_2$: C, 56.2; H, 4.5; Br, 39.4. Found: C, 56.4; H, 4.4; Br, 39.1.

Debromination of Dibromospirane 11.—A mixture of 0.90 g (0.0022 mol) of dibromospirane **11**, 1 g of zinc–copper couple, 2 drops of DMF, and 20 ml of 1,2-dimethoxyethane was heated at reflux with stirring for 1 hr. The solid was separated and the filtrate was concentrated to a solid, which was dissolved in benzene and passed through a small amount of Florisil. The benzene was removed and the product was recrystallized from acetonitrile to give 0.49 g (90%) of spirane **5**, mp 97–98°.

Treatment of 9-*tert*-Butyl-9-hydroxyfluorene with Thionyl Chloride and DMF.—A mixture of 2.0 g (0.0084 mol) of alcohol **12a**,[7] 6 ml of thionyl chloride, and 1 drop of DMF was heated at reflux for 30 min. The solvent was removed, leaving 2.15 g (100%) of chloride **12b**: mp 101–103° (reported[8] mp 104–105°); nmr ($DCCl_3$) τ 2.26–2.83 (m, 8, aromatic) and 8.90 (s, 9, *tert*-butyl); mass spectrum *m/e* (rel intensity) 256 (24, parent), 241 (4), 221 (3), 206 (13), 200 (24), 199 (50), 165 (25), and 57 (100).

9-*tert*-Butyl-9-hydroxyxanthene (13a).—A Grignard reagent was prepared from 45 g (0.50 mol) of *tert*-butyl chloride, 12 g

(7) C. L. Arcus and E. A. Lucken, *J. Chem. Soc.*, 1634 (1955).

(8) R. C. Fuson, H. A. DeWald, and R. Gaertner, *J. Org. Chem.*, **16**, 21 (1951).

(0.50 g-atom) of magnesium, and 300 ml of anhydrous ether, and a solution of 39 g (0.20 mol) of xanthone in 500 ml of warm benzene was added to it as rapidly as possible. The mixture was stirred overnight, and was poured into an excess of ammonium chloride solution. The benzene layer was separated, washed, dried (Na_2SO_4), and concentrated. The residue was taken up in benzene and passed through 600 g of Florisil. The first benzene fractions contained the desired alcohol **13a**, which was recrystallized from methylcyclohexane to give 13 g (26%): mp 106–107°; nmr (CCl_4) τ 2.0–2.2 (m, 2, aromatic), 2.4–2.9 (m, 6, aromatic), 8.00 (s, 1, exchangeable with D_2O, hydroxyl), and 9.20 (s, 9, *tert*-butyl); mass spectrum *m/e* (rel intensity) 254 (0.3, parent), 239 (1), 197 (100), 168 (3), and 152 (6).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1. Found: C, 80.2; H, 7.2.

Treatment of 9-*tert*-Butyl-9-hydroxyxanthene with Thionyl Chloride and DMF.—A mixture of 1.0 g (0.0039 mol) of alcohol **13a**, 6 ml of thionyl chloride, and 2 drops of DMF was heated at reflux for 30 min. The solvent was removed and the residue was washed with acetonitrile to give 1.0 g (93%) of chloride **13b**, mp 86–88°. The nmr spectrum of the residue showed no other components. An analytical sample was prepared by recrystallization from acetonitrile: mp 88–89°; nmr (CCl_4) τ 1.8–2.0 (m, 2, aromatic), 2.4–2.9 (m, 6, aromatic), and 9.00 (s, 9, *tert*-butyl; mass spectrum *m/e* (rel intensity) 272 (1, parent), 257 (2), 237 (2), 215 (100), 197 (7), 181 (4), and 152 (6).

Anal. Calcd for $C_{17}H_{17}ClO$: C, 74.9; H, 6.3; Cl, 13.0. Found: C, 74.7; H, 6.4; Cl, 12.9.

Registry No.—**3a**, 35666-50-3; **4**, 35666-51-4; **5**, 35666-52-5; **6**, 35666-53-6; **7**, 35666-54-7; **10**, 35666-55-8; **12b**, 20685-15-8; **13a**, 35666-57-0; **13b**, 35666-58-1.

The 9-Fluorenylmethoxycarbonyl Amino-Protecting Group

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A new amino-protecting group, the 9-fluorenylmethyloxycarbonyl group (FMOC), which is stable toward acids and catalytic hydrogenation but readily cleaved under mildly basic, nonhydrolytic conditions, is reported. The FMOC group may be introduced by reaction of the amine with 9-fluorenylmethyl chloroformate. A number of protected amino acid derivatives were coupled with other amino acids or esters by use of the corresponding *N*-hydroxypiperidine esters. Deblocking of the FMOC group was carried out with liquid ammonia or at room temperature with piperidine, morpholine, ethanolamine, etc.

The amino-protecting groups which are most commonly used are those which are deblocked under various acidic conditions.[1] Heretofore no amide or urethane function has been available which could be rapidly cleaved under mild, alkaline, nonhydrolytic conditions, although several protective groups are known to be cleaved by basic reagents. The phthaloyl group[2] is removed by hydrazine in ethanol[2a] (or more recently by the use of aqueous methylamine[2b]), and the trifluoroacetyl group by dilute aqueous alkali.[3] Strong aqueous alkali or sodium ethoxide has been used to cleave the β-tosylethyloxycarbonyl group,[4] a cleavage process the nature of which anticipates to some extent the method described in the present paper. This work originated in the observation of Crowley[6] that the carbanilate **2** derived from 3,3,3-trichloro-1-nitro-2-propanol (**1**)[7] upon treatment with ammonia in benzene was converted to aniline in good yield. This result had been anticipated on the basis of Chattaway's work[8] on the base-induced reactions of simple esters of alcohol **1**, reactions which clearly involve β eliminations followed by conjugate addition to the intermediate α,β-unsaturated nitro compound **3**. Since this process might conceivably be the basis for a new type of amino-protective group, it has been further examined. The same idea was pursued independently by Wieland,[9] and the related β elimination involving the corresponding sulfone analogs has already been recommended by Stirling[4] as a deblocking procedure for the β-tosylethyloxycarbonyl group.

$$\begin{array}{l} CCl_3 \\ | \\ HOCHCH_2NO_2 \end{array}$$
1

$$\begin{array}{l} CCl_3 \\ | \\ C_6H_5NHCOOCHCH_2NO_2 \end{array}$$
2

$$CCl_3CH{=}CHNO_2$$
3

In our work it early became apparent that the simple β-nitroethyloxycarbonyl group could probably not be developed into a practical, generally useful protective group since the sensitivity toward cleavage by basic reagents is too high. We have used stability toward pyridine as a criterion, as we wished to achieve development of a group stable at least to such a mild base since pyridine represents a common solvent for a number of functional group transformations. For special purposes there may of course be need for a protective group cleavable by such a base or one even milder. Neither **2** nor **4a** was stable toward standing in

$$\begin{array}{l} R \\ | \\ C_6H_5NHCOOCH_2CHNO_2 \end{array}$$
4a, R = H
b, R = CH_3

(1) For reviews see (a) E. Schröder and K. Lübke, "The Peptides," Vol. 1, Academic Press, New York, N. Y., 1965, pp 3–51; (b) Y. Wolman in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968, Chapter 11.

(2) (a) D. A. Kidd and F. E. King, *Nature (London)*, **162**, 776 (1948); *J. Chem. Soc.*, 3315 (1949); J. C. Sheehan and V. S. Franck, *J. Amer. Chem. Soc.*, **71**, 1856 (1949); (b) S. Wolfe and S. K. Hasan, *Can. J. Chem.*, **48**, 3572 (1970).

(3) F. Weygand and E. Csendes, *Angew. Chem.*, **64**, 136 (1952). For an alkyl-type protective group which is cleaved by methanolic ammonia, see M. Rasmussen and N. J. Leonard, *J. Amer. Chem. Soc.*, **89**, 5439 (1967).

(4) A. T. Kader and C. J. M. Stirling, *J. Chem. Soc.*, 258 (1964). We have now found that the β-tosylethyloxycarbonyl group is also cleaved under the conditions described in the present paper (liquid ammonia, ethanolamine, etc.). In the case of liquid ammonia cleavage the by-product β-tosylethylamine[5] is easily separated from the desired amine by virtue of the insolubility of the former in ether.

(5) J. Madinaveita, A. R. Martin, F. L. Rose, and G. Swain, *Biochem. J.*, **39**, 85 (1945).

(6) P. J. Crowley, M. S. Thesis, University of Massachusetts, Amherst, 1958.

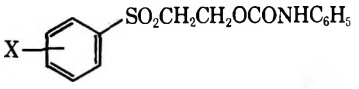
(7) F. D. Chattaway and P. Witherington, *J. Chem. Soc.*, 1178 (1935).

(8) F. D. Chattaway, *ibid.*, 355 (1936).

(9) T. Wieland, G. J. Schmitt, and P. Pfaender, *Justus Liebigs Ann. Chem.*, **694**, 38 (1966).

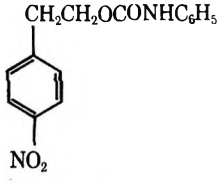
pyridine at room temperature for 4 hr. While the stability toward pyridine could be increased by substitution of a methyl group on the α carbon atom, *e.g.*, **4b** was stable in pyridine under the above conditions and was only partially cleaved after 24 hr, this system has the disadvantage of incorporating an asymmetric carbon, a possible disadvantage in the protection of optically active compounds.

Much less sensitive to basic reagents were the sulfone analogs, **5**. The *o*- and *p*-nitro derivatives (**5b**, **5c**) of Stirling's compounds did not appear to offer any advantages over the parent substance **5a**. All of these



5a, X = H
b, X = *o*-NO_2
c, X = *p*-NO_2

compounds were found to be cleaved to aniline by means of ethanolamine at room temperature. Other systems of potential interest which were examined but shown not to be cleaved by ethanolamine were the carbanilates **6–8**.



6

$Cl_2CHCH_2OCONHC_6H_5$

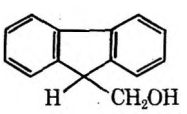
7

$Cl_2CHCH_2SCONHC_6H_5$

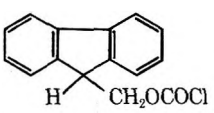
8

On the basis of some clues derived from a consideration of theoretical studies relating to β-elimination reactions of benzhydryl and 9-fluorenyl thiocyanates[10,11] we were led to investigate the 9-fluorenylmethyloxycarbonyl (FMOC) group. The results have proved the FMOC group to be eminently successful as a protective group for the purpose at hand. A preliminary report has outlined the results.[12] In the present paper we provide experimental details for the synthesis of key intermediates useful for introduction of the FMOC group, descriptions of acylation procedures, and examples of useful deblocking conditions. In addition it is shown that peptide coupling reactions and cleavages can be carried out with FMOC protection, thus demonstrating the potential utility of this blocking group in peptide synthesis.

9-Fluorenylmethanol **9**, which has been reported by Brown and Bluestein,[13] was used as the basis for the new protective system. Treatment of **9** with phosgene gave the chloroformate **10**, a stable compound which



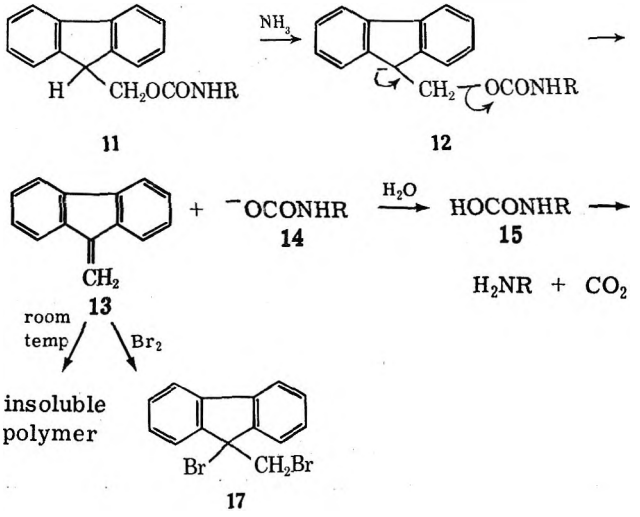
9



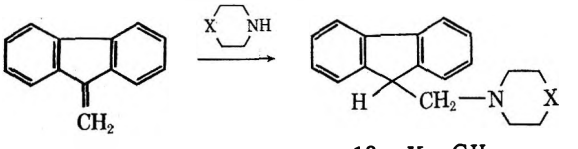
10

reacts normally with amino compounds to give the carbamates in yields of 88–97%.

A variety of basic, nonhydrolytic cleavage techniques for the FMOC group was examined, the mildest of which involves allowing a solution or suspension of the protected derivative to stand in contact with liquid ammonia for several hours. Work-up with water leads to the formation of the free amine without the necessity of acidification and rebasification.[4,14] Although no mechanistic studies were carried out, the reaction probably represents an ElcB-type elimination process activated by the aromaticity effect of the dibenzocyclopentadienyl anion. In contrast to the case of the β-tosylethyloxycarbonyl group, which on treatment with potassium hydroxide or sodium ethoxide gives the stable carbamate salt thereby requiring subsequent acidification to free the amine,[4] the present method leads to the direct formation of the free amino compound. This considerably simplifies the work-up technique. A by-product under these conditions is dibenzofulvene[15] (**13**), which can be isolated if desired.



In addition some dibenzofulvene polymer often accompanies the monomeric species. In fact, by choosing appropriate work-up conditions it is possible to effect complete conversion to the polymer, thus further simplifying the isolation technique. The polymer is insoluble in solvents which can be used to extract the desired amine. Ammonia shows no tendency to add to dibenzofulvene under the conditions of the reaction. On the other hand, if a secondary amine such as morpholine or piperidine is used as cleavage reagent, the amine subsequently adds to the initially formed dibenzofulvene to give adducts of type **18** in good yield. Authentic dibenzofulvene[15] was shown to react with piperidine and morpholine to give the same compounds. In many cases these adducts will have solubility and other properties which differ greatly from those of the



13

18a, X = CH_2
b, X = O

(10) (a) A. Ceccon, U. Miotti, U. Tonellato, and M. Padovan, *J. Chem. Soc. B*, 1084 (1969); (b) U. Miotti, A. Sinico, and A. Ceccon, *Chem. Commun.*, 724 (1968).

(11) *Cf.* (a) R. A. More O'Ferrall and S. Slae, *J. Chem. Soc. B*, 260 (1970); (b) R. A. More O'Ferrall, *ibid.*, 268, 274 (1970). See also T. A. Spencer, M. C. R. Kendall, and I. D. Reingold, *J. Amer. Chem. Soc.*, **94**, 1250 (1972).

(12) L. A. Carpino and G. Y. Han, *ibid.*, **92**, 5748 (1970).

(13) W. G. Brown and B. A. Bluestein, *ibid.*, **65**, 1082 (1943).

(14) Compare S. L. Johnson and D. L. Morrison, *ibid.*, **94**, 1323 (1972).

(15) A. Sieglitz and H. Jassoy, *Ber.*, **55**, 2032 (1922).

TABLE I
FMOC AMINO ACIDS AND ESTERS

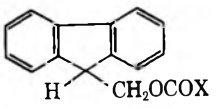
Compd	Registry no.	Mp, °C	Recrystn solvent	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	$\alpha^t D$ (t, c, solvent)
FMOC-DL-ala	35661-38-2	176–178	$MeNO_2$	88	69.45	5.47	4.50	69.44	5.67	4.48	
FMOC-L-ala	35661-39-3	144–145	EtOAc–Et_2O	94	69.45	5.47	4.50	69.40	5.40	4.38	−3.48 (28.6, 2.5, EtOAc)
FMOC-β-ala	35737-10-1	145–147	EtOAc	91	69.45	5.47	4.50	69.46	5.38	4.54	
FMOC-L-phe	35661-40-6	183–185	EtOAc	92	74.52	5.43	3.62	74.31	5.45	3.73	+11.6 (28.2, 1.2, EtOAc)
FMOC-gly-OEt	35661-41-7	109–110	Ligroin (bp 60–70°)	91	70.15	5.85	4.31	70.20	5.91	4.08	
FMOC-gly-OBu-t	35661-42-8	79–81	Et_2O–hexane	90	71.38	6.52	3.97	71.40	6.58	4.02	

desired amine. Curiously, diethylamine effected cleavage of **11** (R = C_6H_5) as shown by the isolation of aniline in good yield, but only dibenzofulvene and its polymer were observed as by-products rather than the diethyl analog of **18**. This may be due to the influence of steric effects in the addition to **13**. Ethanolamine was also routinely used to cleave the FMOC group and, in this case also, monomeric dibenzofulvene was the by-product formed, although the work-up procedure could undoubtedly be modified in such a way that the corresponding polymer would be the sole by-product (see above).

For a protective group to be most useful in the synthesis of multifunctional compounds it should be removable selectively under conditions which leave untouched other commonly used functions. Many of the common protective groups are cleaved by acidic reagents of various strengths.[1] Under such conditions, *e.g.*, treatment with trifluoroacetic acid or hydrogen bromide in acetic acid or nitromethane for periods of 1–2 days at room temperature, there was no attack on the FMOC group. In addition the FMOC derivative of ethyl glycinate could be hydrolyzed to FMOC-glycine in quantitative yield by refluxing the ester in a mixture of acetic and hydrochloric acids for 10 hr. Catalytic hydrogenation over a palladium catalyst in a Parr apparatus in methanol with a little added acetic acid for 24 hr led to complete recovery of starting material. The activity of the catalyst under these conditions was checked by hydrogenation of a 1:1 mixture of FMOC-aniline and benzyl carbanilate, whereby the latter was completely converted[1] to aniline whereas the former was recovered unchanged. With 85% hydrazine[1] in ethanol at room temperature for 12 hr or at 50° for 8 hr there was no observable cleavage, although after 5 hr at 65° aniline was liberated in over 80% yield. FMOC-aniline could be recovered, completely unaffected, from its solution in pyridine after 48 hr at room temperature.

Because of their potential special utility to the synthetic organonitrogen chemist,[16] we have synthesized and report here the properties of several hydrazine and related derivatives protected by the FMOC group. These include the carbazate (**19a**), azide (**19b**), and the hydrazo- (**20**) and azodiformates (**21**).

Introduction of the FMOC group onto the amino group of a simple amine such as benzylamine was carried out by slowly adding a solution of the amine to



19a, X = $NHNH_2$
b, X = N_3

FMOC—NHNH—FMOC
20

FMOC—N=N—FMOC
21

a cold solution of FMOC–Cl in benzene, ether, or other solvent. This order of addition avoids the presence of an excess of a basic amino compound, which might conceivably lead to premature degradation of the chloroformate or the desired FMOC derivative. In the case of amino acid derivatives a solution of FMOC-Cl in dioxane was added slowly to a solution of the amino acid in dilute sodium carbonate. For both techniques the yields were high (88–98%).

Using the protected amino acid derivatives, no difficulties were encountered in forming peptide linkages by the usual classical techniques involving active ester formation followed by condensation with another amino acid or amino acid ester. For convenience *N*-piperidyl esters[17] were chosen as active ester components. In one case the 8-hydroxyquinoline ester[18] was used successfully and presumably other active esters would serve as well. Since the main thrust of this work is not related to the synthesis of long-chain peptides, we leave this elaboration to others who may be interested in this area and see some value in our technique. Among the dipeptides synthesized as models were the FMOC derivatives of methyl glycyl-L-leucinate, ethyl L-alanylglycinate, ethyl L-leucylglycinate, and benzyl and *tert*-butyl L-tryptophylglycinate. In addition to studying the cleavage of FMOC-aniline, deblocking of the following models was carried out (yields 95–100%): FMOC-gly-gly-OH, by piperidine: FMOC-gly-OEt, FMOC-gly, FMOC-DL-ala, FMOC-gly-gly-OH, FMOC-L-Try-OH, and FMOC-L-phe-OH by liquid ammonia. In the last case the L-phenylalanine obtained after cleavage showed essentially the same optical rotation as the material from which the FMOC derivative was prepared. This suggests that neither introduction nor removal of the FMOC group leads to racemization. More refined techniques will have to be examined in order to detect whether minor amounts of racemization are taking place.[19] Amino acid derivatives not described in the Experimental Section are collected in Tables I–III.

(16) For related BOC derivatives see (a) L. A. Carpino, P. H. Terry, and P. J. Crowley, *J. Org. Chem.*, **26**, 4336 (1961); (b) L. A. Carpino, B. A. Carpino, P. J. Crowley, C. A. Giza, and P. H. Terry, *Org. Syn.*, **44**, 15 (1964); (c) L. A. Carpino, D. Collins, S. Göwecke, J. Mayo, S. D. Thatte, and F. Tibbetts, *ibid.*, **44**, 20 (1964).

(17) B. O. Handford, J. H. Jones, G. T. Young, and T. F. N. Johnson, *J. Chem. Soc.*, 6814 (1965).

(18) H.-D. Jakubke and A. Voight, *Ber.*, **99**, 2419 (1966).

(19) Compare D. S. Kemp, S. W. Wang, G. Busby, III, and G. Hugel, *J. Amer. Chem. Soc.*, **92**, 1043 (1970).

Table II
FMOC Amino Acid *N*-Piperidyl Esters[a]

Compd	Registry no.	Mp, °C	Recrystn solvent	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	$\alpha^{t}D$ (*t*, c, solvent)
FMOC-L-phe-ONC_5H_{10}	35737-11-2	60–62 dec	Et_2O	98	74.04	6.38	5.96	73.95	6.43	6.00	−2.68 (28.2, 2.5, EtOAc)
FMOC-L-ala-ONC_5H_{10}	35820-67-8	48–50	Et_2O–ligroin (bp 60–70°)	96	70.05	6.60	7.11	70.10	6.71	7.10	+4.65 (27.4, 2.5, EtOAc)
FMOC-L-leu-ONC_5H_{10}	35661-43-9	55–56 (dec)	Et_2O–ligroin (bp 60–70°)	91	71.56	7.34	6.42	71.27	7.66	6.12	−3.45 (27.8, 2.5, EtOAc)
FMOC-β-ala-ONC_5H_{10}	35661-44-0	111–113	EtOAc–Et_2O	87	70.05	6.60	7.11	70.10	6.67	7.15	
FMOC-L-Try-ONC_5H_{10}	35661-45-1	134–135 dec	EtOAc–Et_2O	99	73.08	6.09	8.25	72.90	6.31	8.24	+56.27 (25.4, 1.1, $CHCl_3$)

[a] The reaction time varied between 5 and 23 hr.

Table III
FMOC Dipeptides[a]

Compd	Registry no.	Mp, °C	Recrystn solvent	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	$\alpha^{t}D$ (*t*, c, solvent)
FMOC-gly-L-leu-OMe	35661-46-2	135–136.5 dec	EtOAc–ligroin (bp 60–70°)	100	67.92	6.60	6.60	67.84	6.69	6.44	+16.55 (2.5, $CHCl_3$)
FMOC-L-ala-gly-OEt	35737-12-3	153–155 dec	EtOAc–ligroin (bp 60–70°)	100	66.67	6.06	7.07	66.86	6.20	7.01	−20.84 (27.7, 2.5, $CHCl_3$)
FMOC-L-leu-gly-OEt	35661-47-3	138–140 dec	Et_2O	100	68.49	6.85	6.39	68.48	6.81	6.52	−59.8 (28.8, 2.5, 95% EtOH)
FMOC-L-Try-gly-$OCH_2C_6H_5$	35737-13-4	169.5–171 dec	EtOAc–ligroin (bp 60–70°)	100	73.30	5.41	7.33	73.04	5.47	7.24	+12.5 (29, 2, $CHCl_3$)

[a] The reaction time varied between 17 and 24 hr.

Experimental Section[20]

9-Fluorenylmethyl Chloroformate.—A solution of 7.12 g of phosgene in 75 ml of CH_2Cl_2 was cooled in an ice bath, and 12.8 g of 9-fluorenylmethanol[13] was added slowly with stirring. The solution was stirred for 1 hr in the ice bath and then let stand for 4 hr at ice-bath temperature. Removal of solvent and excess phosgene under reduced pressure gave an oil which crystallized after several hours to give 16 g (95%) of the crude chloroformate, mp 61.5–63°. Recrystallization twice from ether gave 14.5 g (86%) of the chloroformate as colorless crystals: mp 61.5–63°; ir ($CHCl_3$) 1770 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4–4.6 (m, 3, $CHCH_2$), 7.1–7.8 (m, 8, aryl).

Anal. Calcd for $C_{15}H_{11}ClO_2$: C, 69.63; H, 4.26. Found: C, 69.59; H, 4.26.

9-Fluorenylmethyl Azidoformate. A.—To an ice-cold, stirred solution of 0.52 g of NaN_3 in 2 ml of H_2O was added slowly a solution of 1.35 g of 9-fluorenylmethyl chloroformate in 2.5 ml of acetone. The mixture was stirred in the ice bath for 2 hr and at room temperature for 2 hr, and the solid was filtered, washed with water, and recrystallized from acetone to give 1.13 g (82%) of the azide as colorless crystals, mp 83–85°. The analytical sample, from hexane, had mp 89–90°: ir ($CHCl_3$) 2135 (N_3), 1730 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4–4.5 (m, 3, $CHCH_2$), 7.1–7.9 (m, 8, aryl).

Anal. Calcd for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.15; N, 15.85. Found: C, 67.87; H, 4.17; N, 15.80.

B.—Treatment of 9-fluorenylmethyl carbazate with $NaNO_2$ in HOAc–H_2O followed by the usual work-up and recrystallization from hexane gave the azidoformate, mp 89–90°, in 88% yield.

9-Fluorenylmethyl Carbazate.—To a mixture of 0.39 g of 95% N_2H_4 and 20 ml of ether was added slowly with stirring and ice-bath cooling a solution of 1 g of 9-fluorenylmethyl chloroformate in 20 ml of ether. The mixture was stirred at room temperature for 12 hr and evaporated to dryness, and 50 ml of H_2O was added. The residual solid was filtered and washed with H_2O to give 0.95 g (97%) of the crude carbazate, mp 170° dec. Recrystallization from nitromethane gave 0.94 g (96%) of the pure hydrazide: mp 171° dec; ir (KBr) 3310, 3202 (NH), 1686 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.87; H, 5.51; N, 11.02. Found: C, 70.67; H, 5.65; N, 11.00.

9-Fluorenylmethyl Hydrazodiformate.—To a solution of 1 g of 9-fluorenylmethyl chloroformate in 20 ml of benzene was added dropwise with stirring at ice bath temperatures 0.065 g of 95% N_2H_4. The mixture was stirred in the ice bath for 30 min and at room temperature for 10 min and then treated slowly with 5 ml of pyridine. The resulting clear solution was stirred at room temperature for 2 hr and poured into 200 ml of H_2O, and the organic layer was collected and washed with H_2O, 5% HCl, and H_2O again. Evaporation of the solvent left a solid which was recrystallized from nitromethane to give 0.91 g (99%) of the hydrazide: mp 202° dec; ir (KBr) 3307, 3290 (NH), 1720, 1710 cm^{-1} (C=O); nmr ($CDCl_3$–DMSO-d_6) δ 3.95–4.70 (m, 6, $CHCH_2$), 6.95–7.85 (m, 16, aryl), 7.90–8.40 (broad s, 2, NH).

Anal. Calcd for $C_{30}H_{24}N_2O_4$: C, 75.63; H, 5.04; N, 5.88. Found: C, 75.31; H, 5.08; N, 5.90.

9-Fluorenylmethyl Azodiformate.—A suspension of 2.0 g of 9-fluorenylmethyl hydrazodiformate and 0.332 g of pyridine in 200 ml of CH_2Cl_2 was treated slowly with 0.747 g of *N*-bromosuccinimide and the yellow solution was refluxed for 24 hr. The resulting solution was washed with H_2O, 10% Na_2CO_3, and again with H_2O and finally dried ($MgSO_4$) and evaporated to dryness. The residue was boiled with 200 ml of ether, the solution was filtered while hot to remove some unreacted hydrazo compound, and the filtrate was concentrated until orange crystals began to separate. Storage in a refrigerator overnight gave 1.85 g (94%) of the azo compound, mp 148–151° dec. Recrystallization from ether gave 1.83 g (93%): mp 149.5–151° dec; ir (KBr) 1770 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.0–4.8 (m, 6, $CHCH_2$), 6.95–7.85 (m, 16, aryl).

Anal. Calcd for $C_{30}H_{22}N_2O_4$: C, 75.95; H, 4.64; N, 5.91. Found: C, 76.11; H, 4.78; N, 5.80.

9-Fluorenylmethyl Carbanilate.—To a solution of 2 g of 9-fluorenylmethyl chloroformate in 10 ml of benzene was added dropwise with stirring in an ice bath 1.02 g of aniline. The mixture was stirred in an ice bath for 20 min and at room temperature for 1 hr, and 0.5 ml of H_2O was added. After the solution was stirred for 10 min, filtration gave 2.4 g (98%) of the crude carbanilate, mp 182–184°. Recrystallization from $CHCl_3$ gave 2.3 g (94%) of the pure ester, mp 188–190°. The same compound was obtained by treatment of 9-fluorenylmethanol with phenyl isocyanate in refluxing benzene: ir (KBr) 3335 (NH), 1700 cm^{-1} (C=O); nmr (DMSO-d_6–$CDCl_3$) δ 4.1–4.58 (m, 3, $CHCH_2$), 6.67–7.91 (m, 13, aryl), 9.55 (s, 1, NH).

(20) Melting and boiling points are uncorrected. Infrared spectra were obtained on a Beckman IR-10 instrument and nmr spectra on a Varian A-60 unit with TMS as internal standard. Elemental analyses were carried out by Charles Meade and associates, University of Massachusetts Microanalytical Laboratory and Galbraith Laboratories, Inc., Knoxville, Tenn.

Anal. Calcd for $C_{21}H_{17}NO_2$: C, 80.00; H, 5.40; N, 4.44. Found: C, 79.81; H, 5.63; N, 4.34.

9-Fluorenylmethyl *N*-Cyclohexylcarbamate.—A solution of 1 g of 9-fluorenylmethyl chloroformate in 200 ml of ether was cooled in an ice bath and 0.769 g of cyclohexylamine in 100 ml of ether was added slowly. The mixture was stirred in the ice bath for 20 min and at room temperature for 20 min. After filtration to remove the amine salt, the ether solution was washed with H_2O, dried ($MgSO_4$), and evaporated and the residue was recrystallized from ether to give 1.2 g (97%) of the carbamate, mp 158.5–161° dec. Further recrystallization from ether gave the pure ester as colorless needles: mp 165–167° dec; ir (KBr) 3330 (NH), 1679 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.7–2.2 (m, 11, cyclohexyl), 3.27–3.80 (broad s, 1, NH), 4.18–4.95 (m, 3, $CHCH_2$), 7.3–8.2 (m, 8, aryl).

Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.50; H, 7.17; N, 4.36. Found: C, 78.59; H, 7.24; N, 4.35.

9-Fluorenylmethoxycarbonyl-L-tryptophan.—To a solution of 1.58 g of L-tryptophan in 10 ml of dioxane and 20.5 ml of 10% Na_2CO_3 was added slowly with stirring and ice bath cooling a solution of 2 g of 9-fluorenylmethyl chloroformate in 20 ml of dioxane. The mixture was stirred in the ice bath for 4 hr and at room temperature for 8 hr, poured into 450 ml of H_2O, and extracted with ether. The aqueous layer was cooled in an ice bath, acidified with concentrated HCl to congo red paper, and stored in a refrigerator overnight. Filtration gave 3.1 g (94%) of the protected amino acid, mp 182–185° dec. Recrystallization from $MeNO_2$ followed by $CHCl_3$–hexane gave 3.0 g (91%) of the pure material, mp 185–187°, $[\alpha]^{23.8}D$ +6.4° (*c* 1, EtOAc).

Anal. Calcd for $C_{26}H_{22}N_2O_4$: C, 73.24; H, 5.16; N, 6.57. Found: C, 73.54; H, 5.22; N, 6.10.

9-Fluorenylmethoxycarbonylglycine. A. From FMOC-Cl.—To a solution of 0.57 g of glycine dissolved in 20.2 ml of 10% Na_2CO_3 was added with stirring and cooling in an ice bath a solution of 1.96 g of FMOC-Cl. The mixture was stirred at room temperature for 2 hr, poured into 400 ml of H_2O, and extracted twice with ether to remove small amounts of 9-fluorenylmethanol and the high-melting polymer of dibenzofulvene. The aqueous layer was cooled in an ice bath and acidified with concentrated HCl to congo red paper. The white precipitate was extracted with ethyl acetate, the extracts were washed with water, dried ($MgSO_4$), and evaporated, and the white residue, mp 173–176°, which amounted to 2 g (89%), was recrystallized from $MeNO_2$ to give 1.98 g (88%) of the pure acid: mp 174–175°; nmr (DMSO-d_6) δ 3.64–3.85 (d, 2, CH_2), 4.2–4.5 (m, 3, $CHCH_2$), 7.25–8.05 (m, 8, aryl).

B. From FMOC-N_3.—The reaction was carried out as described above except that the mixture was stirred for 64 hr at room temperature. The ether extracts yield some recovered FMOC-N_3 as well as the alcohol. Work-up as described gave 1.35 g (60%) of the protected derivative, mp 174–175°.

Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.69; H, 5.05; N, 4.71. Found: C, 68.45; H, 5.08; N, 4.85.

Hydrolysis of Ethyl 9-Fluorenylmethoxycarbonylglycinate.—A solution of 0.1 g of FMOC-gly-OEt in 10 ml of HOAc and 0.5 ml of concentrated HCl was refluxed for 10 hr and poured into 200 ml of H_2O, and the gelatinous precipitate was filtered, washed with H_2O, and dried in air to give 0.091 g (100%) of FMOC-gly-OH, mp 173–175°. The infrared spectrum was identical with that of an authentic sample and a mixture melting point showed no depression.

9-Fluorenylmethoxycarbonyl-L-leucine.—A solution of 0.993 g of L-leucine in 20.2 ml of 10% Na_2CO_3 and 10 ml of dioxane was treated as described for FMOC-gly with a solution of 1.96 g of FMOC-Cl in 15 ml of dioxane. Upon evaporation of the ethyl acetate extracts after acidification a syrup was obtained which solidified in a Dry Ice–acetone bath to give 2.4 g (90%) of colorless crystals, mp 155–156° dec after recrystallization from ether, $[\alpha]^{28.3}D$ −4.44 (*c* 2.5, EtOAc).

***N*-Piperidyl 9-Fluorenylmethoxycarbonylglycinate.**—To a solution of 0.5 g of FMOC-gly-OH and 0.187 g of *N*-hydroxypiperidine in 10 ml of anhydrous ethyl acetate was added 0.347 g of dicyclohexylcarbodiimide (DCCD). The mixture was stirred at room temperature for 1 hr and then for 5 min longer after the addition of a few drops of HOAc. The urea was removed by filtration and the filtrate was washed in order as follows: twice with 5% HCl, once with H_2O, twice with 5% Na_2CO_3, once with NaCl solution, and once with H_2O. After drying ($MgSO_4$), evaporation under reduced pressure and recrystallization from ether or ethyl acetate–ligroin (bp 60–70°) gave 0.55 g (86%) of the active ester: mp 123.5° dec; nmr ($CDCl_3$) δ 0.9–2.3 (m, 6, $CH_2CH_2CH_2$), 2.3–2.6 (m, 4, NCH_2CH_2), 3.9–4.2 (d, 2, $NHCH_2$), 4.2–4.7 (m, 3, $CHCH_2$), 5.6–6.0 (broad s, 1, NH), 7.0–8.3 (m, 8, aryl).

Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.47; H, 6.32; N, 7.37. Found: C, 69.44; H, 6.45; N, 7.35.

8-Quinolyl 9-Fluorenylmethoxycarbonylglycinate.—A solution of 1 g of FMOC-gly-OH and 0.538 g of 8-hydroxyquinoline in 125 ml of ethyl acetate was treated with 0.693 g of DCCD and the mixture was stirred at room temperature for 5 hr. After the addition of a few drops of HOAc and work-up as described for the corresponding *N*-piperidyl ester there was obtained 1.09 g (76%) of the active ester: mp 162–164° dec (acetone–ligroin); nmr ($CDCl_3$) δ 4.4–4.7 (m, 5, CH_2, $CHCH_2$), 5.7–6.1 (broad s, 1, NH), 7.4–8.2 (m, 14, aryl).

Anal. Calcd for $C_{26}H_{20}N_2O_4$: C, 73.58; H, 4.72; N, 6.00. Found: C, 73.55; H, 4.82; N, 6.58.

Ethyl 9-Fluorenylmethoxycarbonylglycylglycinate.—A mixture of 0.36 g of FMOC-gly-ONC_5H_{10}, 0.159 g of gly-OEt·HCl, 0.155 g of NaOAc·$3H_2O$, and 2 ml of dioxane was stirred at room temperature for 24 hr and poured into 100 ml of cold H_2O. The precipitated white solid was recrystallized from EtOAc–Et_2O to give 0.3 g (83%) of the dipeptide ester, mp 131.5–132.5°. By a similar technique the same compound was obtained in 77% yield from FMOC-gly-ONC_9H_6.

Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 65.97; H, 5.76; N, 7.33. Found: C, 65.94; H, 5.69; N, 7.34.

9-Fluorenylmethoxycarbonylglycylglycine.—To a solution of 2 g of FMOC-gly-ONC_5H_{10} in 25 ml of dioxane was added at room temperature a solution of 0.474 g of glycine in 6.31 ml of 1 *N* NaOH. The solution was stirred for 1 hr, 20 ml of H_2O was added, and stirring was continued for 1 hr. After pouring into 500 ml of H_2O and extraction with ethyl acetate the aqueous layer was cooled and acidified with concentrated HCl to congo red paper. The precipitate was dried in air and recrystallized from CH_3CN to give 1.44 g (77%) of the dipeptide, mp 176–177°. The same compound was obtained in 92% yield by acylation of gly-gly-OH by means of FMOC-Cl.

Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.41; H, 5.08; N, 7.91. Found: C, 64.47; H, 5.10; N, 7.67.

***tert*-Butyl 9-Fluorenylmethoxycarbonyl-L-tryptophylglycinate.**—To a solution of 2.2 g of FMOC-L-Try-ONC_5H_{10} in 55 ml of dioxane was added at room temperature a solution of 0.679 g of *tert*-butyl glycinate in 0.312 g of HOAc. After stirring for 24 hr the solution was poured into 1000 ml of H_2O and the mixture was cooled in an ice box for 2 hr. Filtration and recrystallization from ether–hexane gave 2.18 g (94%) of the ester, mp 146.5–148.5° dec, $[\alpha]^{23.2}D$ −18.9 (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{32}H_{33}N_3O_5$: C, 71.24; H, 6.12; N, 7.79. Found: C, 71.12; H, 6.17; N, 7.69.

Liquid Ammonia Cleavage of 9-Fluorenylmethyl Carbanilate.—A solution of 1 g of FMOC-NHC_6H_5 in 250 ml of liquid ammonia was stirred for 10 hr and evaporated to dryness and the residue was treated with 100 ml of ligroin. Filtration removed a small amount of dibenzofulvene polymer. The filtrate was concentrated to about 10 ml and cooled in a refrigerator, which caused the separation of dibenzofulvene as colorless needles. Evaporation of the filtrate, dissolution of the residue in benzene, and passage of HCl gas gave 0.33 g (80%) of aniline hydrochloride, mp 195–197°. The dibenzofulvene was characterized by treatment with bromine in ether solution. Recrystallization from ligroin gave 0.91 g (85%) of the dibromide, mp 139–141° dec (lit.[21] mp 143° dec).

Liquid Ammonia Cleavage of 9-Fluorenylmethoxycarbonyl-L-phenylalanine.—A solution of 1.55 g of FMOC-L-Phe-OH in 250 ml of liquid ammonia was stirred for 10 hr and evaporated to dryness, and 200 ml of ether was added to the residue. Dibenzofulvene could be isolated from the ether solution in 95% yield as the dibromide. The insoluble portion was filtered and dissolved in the minimum amount of H_2O. Filtration removed a trace amount of dibenzofulvene polymer and evaporation of the filtrate gave 0.66 g (100%) of L-phenylalanine, $[\alpha]^{27°}D$ −33.2 (1.992, H_2O), identified by comparison of its infrared spectrum with that of an authentic sample. The L-phenylalanine from which the above FMOC derivative was prepared had $[\alpha]^{26.7}D$ −33.24 (1.962, H_2O). By a similar method glycine (100%), DL-alanine (100%), glycylglycine (98%), and L-tryptophan [94%, $[\alpha]^{24.5}D$

(21) H. Wieland, F. Reindel, and J. Ferrer, *Ber.*, **55**, 3313 (1922).

−35.3 (c 1, H_2O)] were obtained from the corresponding FMOC derivatives.

Liquid Ammonia Cleavage of Ethyl 9-Fluorenylmethoxycarbonylglycinate. A.—A solution of 1 g of FMOC-gly-OEt in 150 ml of liquid ammonia was stirred for 6 hr and evaporated to dryness, and the residue was treated with 200 ml of ether. Ethyl glycinate was precipitated from the ether solution as the hydrochloride [0.39 g (90%), mp 135° dec] by treatment with dry HCl. The salt was identified by mixture melting point and comparison of infrared spectra with that of an authentic sample.

B.—The cleavage was repeated as above except that 0.1 g of the protected derivative was used and after evaporation of the liquid ammonia 250 ml of water was added and the mixture was stirred under ordinary diffuse daylight and incandescent room lighting for about 18 hr. After filtration of the dibenzofulvene polymer, extraction with ether and precipitation with HCl gave ethyl glycinate hydrochloride in 70–80% yield. Conversion of dibenzofulvene to its polymer under fluorescent room lighting appeared to require a considerably longer period.

Liquid Ammonia Cleavage of *tert*-Butyl 9-Fluorenylmethoxycarbonyl-L-tryptophylglycinate.—A solution of 1.0 g of FMOC-L-Try-gly-OBu-*t* in 150 ml of liquid ammonia was stirred for 10 hr and evaporated to dryness, and the yellow residue was extracted with six 50-ml portions of ligroin to remove dibenzofulvene. The insoluble residue was dissolved in 50 ml of warm ethyl acetate, the solution was filtered to remove a trace of dibenzofulvene polymer and evaporated, and the residue was recrystallized from ethyl acetate–ligroin. There was obtained 0.476 g (81%) of L-Try-gly-OBu-*t*, mp 95–97.5° (lit.[22] mp 94–97°), identified by comparison of the ir and nmr spectra with those of an authentic sample prepared by the hydrogenolysis of the carbobenzoxy derivative.[22]

Piperidine Cleavage of 9-Fluorenylmethyl Carbanilate.—A solution of 0.5 g of FMOC-NHC_6H_5 in 15 ml of piperidine was stirred at room temperature for 40 min and poured into 250 ml of cold H_2O. The precipitated solid was removed by filtration and the filtrate was extracted with ether. The dried ($MgSO_4$) ether extracts were evaporated, 2 ml of benzene added and the aniline derivatized by the addition of benzoyl chloride which gave 0.28 g (90%) of the benzamide derivative, mp 161–161.5°, after recrystallization from ethanol.

The solid (0.4 g, 96%, mp 117.5–119°) precipitated from the original solution by the addition of H_2O was recrystallized from ligroin to give 0.35 g (84%) of *N*-(**9-fluorenylmethyl**)**piperidine**: mp 116–117°; nmr ($CDCl_3$) δ 1.35–2.25 (m, 6, $CH_2CH_2CH_2$), 2.4–3.1 (m, 6, CH_2N), 3.84–4.18 (t, 1, $CHCH_2$), 7.12–8.06 (m, 8, aryl).

Anal. Calcd for $C_{19}H_{21}N$: C, 86.69; H, 7.98; N, 5.32. Found: C, 86.70; H, 7.92; N, 5.40.

N-(**9-Fluorenylmethyl**)**morpholine.**—Cleavage of FMOC-NH-C_6H_5 by means of morpholine (room temperature, 25 min) by a method analogous to that described for piperidine gave aniline in 96% yield (as the benzoyl derivative) and in 95% yield the adduct of dibenzofulvene and morpholine, mp 172.5–174° (95% ethanol).

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.51; H, 7.17; N, 5.28. Found: C, 81.79; H, 7.46; N, 5.13.

Dibenzofulvene.—A solution of 0.5 g of FMOC-NHC_6H_5 in 15 ml of β-methoxyethyl amine was stirred at room temperature for 30 min and poured into 250 ml of H_2O, and the turbid mixture was extracted with ether. The dried ($MgSO_4$) ether layer was evaporated and the residue was washed with ligroin to give 0.26 g (93%) of dibenzofulvene: mp 49–51° (lit.[15] mp 46–48°); nmr ($CDCl_3$) δ 5.82 (s, 2, CH_2), 7.0–7.8 (m, 8, aryl). The dibromide had mp 141° dec (lit.[21] mp 143°) and caused no depression of melting point of an authentic sample. On standing the dibenzofulvene was converted to a high melting polymer.[21,23]

From the orginal ligroin-soluble portion there was obtained aniline in 80% yield (as the benzoyl derivative).

Piperidine Cleavage of 9-Fluorenylmethoxycarbonylglycylglycine.—A solution of 1.3 g of FMOC-gly-gly-OH in 10 ml of piperidine was stirred at room temperature for 30 min and then poured into 200 ml of cold H_2O. The filtrate, after removal of 0.96 g (100%) of the piperidine–dibenzofulvene adduct, was evaporated by a current of air and the residue was recrystallized from ethanol–H_2O (10:1) to give 0.4 g (83%) of glycylglycine, mp >200°, identified by comparison of its infrared spectrum with that of an authentic sample.

2-(*o*-Nitrophenylsulfonyl)ethyl Carbanilate.—Treatment of the corresponding alcohol[24] with phenyl isocyanate in benzene in the presence of a few drops of triethylamine gave the urethane, mp 130–132°, after recrystallization from benzene.

Anal. Calcd for $C_{15}H_{14}N_2O_6S$: C, 51.42; H, 4.03; N, 8.00. Found: C, 51.52; H, 4.10; N, 8.00.

2-(*p*-Nitrophenylsulfonyl)ethyl carbanilate was prepared[25] as described for the corresponding ortho isomer and recrystallized from C_6H_6–nitroethane (1:1), mp 167–169° dec.

Anal. Calcd for $C_{15}H_{14}N_2O_6S$: C, 51.42; H, 4.03; N, 8.00. Found: C, 51.60; H, 4.17; N, 7.90.

2,2-Dichloroethyl carbanilate was prepared as described for the *o*- and *p*-nitrophenylsulfonylethyl derivatives and recrystallized from benzene–ligroin (1:1), mp 68–69°.

Anal. Calcd for $C_9H_9Cl_2NO_2$: C, 46.18; H, 3.87; N, 5.98. Found: C, 46.00; H, 3.66; N, 5.98.

***S*-(2,2-Dichloroethyl)thiocarbanilate** was prepared as described for the corresponding oxygen analog by substitution of 2,2-dichloroethanthiol for the alcohol and recrystallized from benzene–ligroin (bp 40–70°) (1:1), mp 86.5–87.5°.

Anal. Calcd for $C_9H_9Cl_2NOS$: C, 43.21; H, 3.63; N, 5.60. Found: C, 43.20; H, 3.56; N, 5.60.

Registry No.—**5b,** 35661-54-2; **5c,** 35661-55-3; **7,** 35661-56-4; **8,** 35661-57-5; **10,** 28920-43-6; **11** (R = Ph), 28991-69-7; **11** (R = cyclohexyl), 35661-50-8; **18a,** 35661-58-6; **18b,** 28991-70-0; **19a,** 35661-51-9; **19b,** 28920-44-7; **20,** 35737-14-5; **21,** 35661-53-1; 9-fluorenylmethoxycarbonyl-L-tryptophan, 35737-15-6; 9-fluorenylmethoxycarbonylglycine, 29022-11-5; 9-fluorenylmethoxycarbonyl-L-leucine, 35661-60-0; *N*-piperidyl 9-fluorenylmethoxycarbonylglycinate, 35661-61-1; 8-quinolyl 9-fluorenylmethoxycarbonylglycinate, 35661-62-2; ethyl 9-fluorenylmethoxycarbonylglycylglycinate, 35665-37-3; 9-fluorenylmethoxycarbonylglycylglycine, 35665-38-4; *tert*-butyl 9-fluorenylmethoxycarbonyl-L-tryptophenylglycinate, 35665-39-5.

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(22) C. H. Li, B. Gorup, D. Chung, and J. Ramachandran, *J. Org. Chem.*, **28**, 178 (1963).

(23) J. G. Burr, Jr., *J. Amer. Chem. Soc.*, **74**, 1717 (1952).

(24) B. A. Kent and S. Smiles, *J. Chem. Soc.*, 422 (1934).

(25) A. V. Sunthankar, B. D. Tilak, and K. Venkataraman, *Proc. Indian Acad. Sci.*, **38A**, 23 (1953); *Chem. Abstr.*, **49**, 8176*h* (1955).

Steric Effects in the Hydralumination, Carbalumination, and Oligomerization of *tert*-Butyl(phenyl)acetylene[1]

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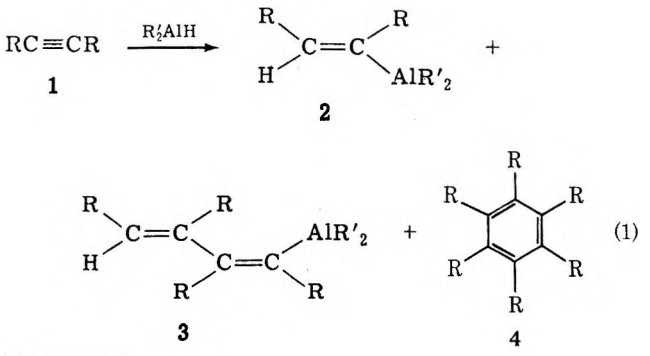
The hydralumination and subsequent reductive oligomerization of *tert*-butyl(phenyl)acetylene under the action of diisobutylaluminum hydride were examined. With a 1:1 equivalent ratio of reagents hydralumination proceeded (a) exclusively in a regiospecific cis fashion at 50°; (b) principally in a trans manner at 110°; and (c) preponderantly in a bis hydraluminating fashion at 140°. With a 2:1 ratio of alkyne:hydride and prolonged reaction time, the principal hydrolyzed product was *cis,cis*-1,4-di-*tert*-butyl-2,3-diphenyl-1,3-butadiene. Finally, by heating the alkyne with a small proportion of hydride, the reduced trimer, *cis,cis,cis*-1,3,6-tri-*tert*-butyl-2,4,5-triphenyl-1,3,5-hexatriene, was also obtained upon hydrolysis. The diene and triene were found to undergo conrotatory and, apparently, disrotatory ring closures, respectively. In addition, the clear-cut controlled hetero reductive dimerization of *tert*-butyl(phenyl)acetylene with a different alkyne, methyl(phenyl)acetylene, was achieved, leading to *cis,cis*-4-*tert*-butyl-2-methyl-1,3-diphenyl-1,3-butadiene. Finally, the carbalumination of *tert*-butyl(phenyl)acetylene by triphenylaluminum occurred regiospecifically to form 3,3-dimethyl-1,1-diphenyl-1-butene. The regiochemistry of the hydralumination observed here is shown to be consistent with a polar view, but that of the carbaluminations is seen to require a steric explanation. The nature of suitable activated complexes and the possible role of π-complex intermediates in the reductive oligomerization of alkynes are briefly considered.

The hydralumination of alkynes with dialkylaluminum hydrides is a valuable synthetic route to substituted vinylaluminum compounds. In a stereospecific fashion, the resulting adducts can, in turn, be (a) hydrolyzed to give cis alkenes[2,3] or trans alkenes;[3-5] (b) carbonated, with[6] or without[7] complexation with methyllithium, to yield substituted acrylic acids; (c) halogenated to provide vinylic halides;[4c,8,9] or (d) treated with various reagents, such as aldehydes[4b,6,8] or unsaturated hydrocarbons,[2,3,4b,10] to extend the carbon chain.[11] Competitive with the hydralumination of the alkyne are the reductive dimerization and the cyclotrimerization reactions,[2,3,12] which yield, upon hydrolytic work-up, *cis,cis*-1,3-alkadienes and hexasubstituted benzenes, respectively (eq 1). Although these reactions have been viewed[2] as simply consecutive steps in the concatenated pathway, **1** + RC≡CR → **2** → **3** → **4**, a survey of known interactions of organoaluminum compounds with alkynes has led to the alternative proposal of π-complex intermediates for such processes.[12]



The study of substituted acetylenes[3,5] has already demonstrated the importance of polar factors in the regioselectivity of hydralumination. Examination of sterically hindered acetylenes now appeared worthwhile for elucidating the pathways of the reductive dimerization and the cyclotrimerization reactions. To this end, we have examined the behavior of *tert*-butyl(phenyl)acetylene (**5**) toward diisobutylaluminum hydride (**6**). Through the presence of bulky R groups in **1**–**4** it was expected that the competing processes depicted in eq 1 might more readily be dissected and that certain previously undetected intermediates might be uncovered. Furthermore, the carbalumination of this same alkyne with triphenylaluminum also was of interest. From such a study we hoped to assess steric factors for a straightforward insertion analogous to the proposed process, **2** + RC≡CR → **3**.

Results

Hydralumination and Carbalumination of *tert*-Butyl(phenyl)acetylene.—Heating a 1:1 mixture of the acetylene **5** and the hydride **6** at 50° gave, upon hydrolysis, a 94% yield of *cis*-β-(*tert*-butyl)styrene (**7**) and a 6% yield of *cis,cis*-1,4-di-*tert*-butyl-2,3-diphenyl-1,3-butadiene (**8**). By hydrolysis of a similar reaction mixture with deuterium oxide, it was established from the nmr spectrum of **7** that only the olefinic hydrogen adjacent to the phenyl group was deuterated. Similarly it was found that only one of the two identical olefinic hydrogens in diene **8** was deuterated. The organoaluminum precursors (**9** and **10**) involved are, accordingly, those shown in eq 2. Even though the acetylene was already consumed after 24 hr, the ratio, 7:8, changed during the next 24 hr from 98:2 to 94:6. This indicates that **9** slowly dissociated into **5** and **6**,

(1) Part XXII of the series, "Organometallic Compounds of Group III," devoted to carbometalation and hydrometalation. Previous part: J. J. Eisch and S. G. Rhee, *J. Organometal. Chem.*, **42**, C73 (1972).

(2) G. Wilke and H. Müller, *Justus Liebigs Ann. Chem.*, **629**, 222 (1960).

(3) J. J. Eisch and W. C. Kaska, *J. Amer. Chem. Soc.*, **88**, 2213 (1966).

(4) For the principally trans hydralumination of alkynes with $LiAlH_4$ in THF, *cf.* (a) E. F. Magoon and L. H. Slaugh *Tetrahedron*, **23**, 4509 (1967), and (b) J. J. Eisch and M. W. Foxton, Abstracts, Third International Symposium on Organometallic Chemistry, 1967, p 340, and ref 5. For trans hydralumination of alkynes with $Li[Al(i\text{-}C_4H_9)_2(CH_3)H]$ in monoglyme, *cf.* (c) G. Zweifel and R. B. Steele, *J. Amer. Chem. Soc.*, **89**, 5085 (1967).

(5) J. J. Eisch and M. W. Foxton, *J. Organometal. Chem.*, **11**, P50 (1968); *J. Org. Chem.*, **36**, 3520 (1971).

(6) G. Zweifel and R. B. Steele, *J. Amer. Chem. Soc.*, **89**, 2754 (1967).

(7) J. J. Eisch and M. W. Foxton, *J. Organometal. Chem.*, **11**, P7 (1968).

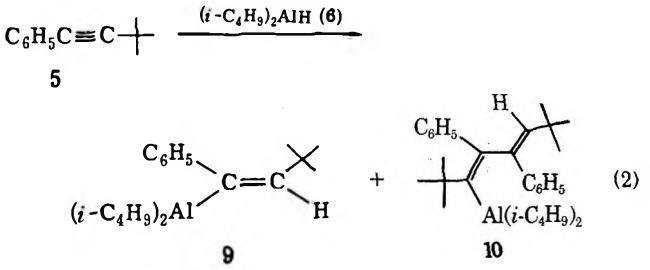
(8) G. Zweifel and C. C. Whitney, *J. Amer. Chem. Soc.*, **89**, 2753 (1967).

(9) *Cf.* J. J. Eisch and W. C. Kaska, *ibid.*, **88**, 2976 (1966), for the stereospecific iodinolysis of carbon–aluminum bonds.

(10) G. Zweifel, J. T. Snow, and C. C. Whitney, *ibid.*, **90**, 7139 (1968).

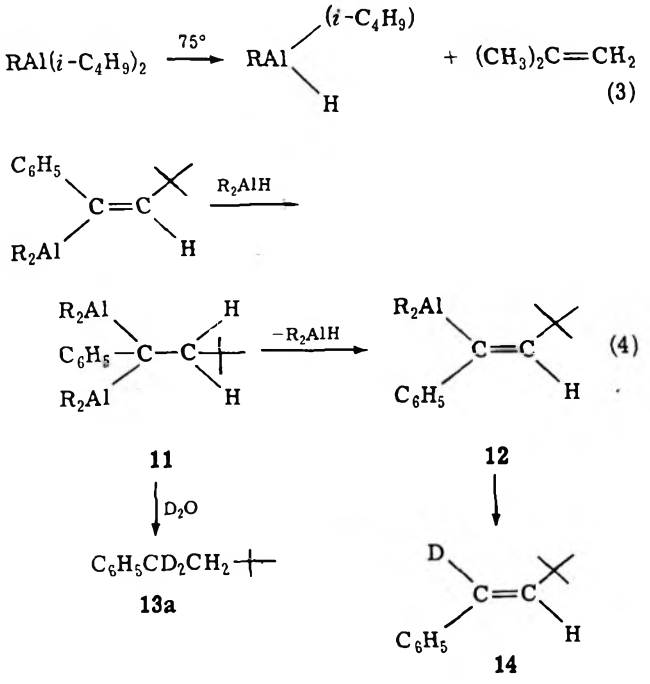
(11) H. Lehmkuhl, K. Ziegler, and H.-G. Gellert in "Houben-Weyl Methoden der Organischen Chemie," Vol. XIII/4, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1970, pp 204–258.

(12) J. J. Eisch, R. Amtmann, and M. W. Foxton, *J. Organometal. Chem.*, **16**, P55 (1969).

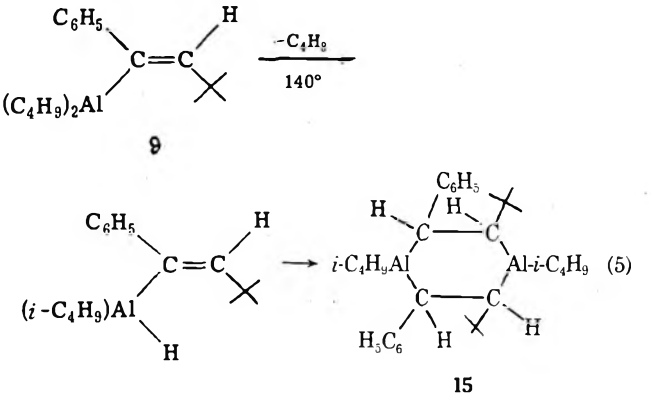


since the material balance of reactants and products did not reveal any new products.

A similar hydralumination reaction mixture as above was heated for 48 hr-periods at 75°, at 110°, and finally at 140°. Hydrolytic and deuterolytic work-up revealed changes in the nature of the products. At 75°, both bis hydralumination (16%) leading to **11** and isomerization (35%) leading to the trans isomer of **9** occurred. Since more bis hydralumination occurred than could be accounted for by the remaining 6% of **6**, some of the isobutyl groups in **9** and **10** clearly had been lost as isobutylene and additional Al–H bonds had been generated[13] (eq 3–4).



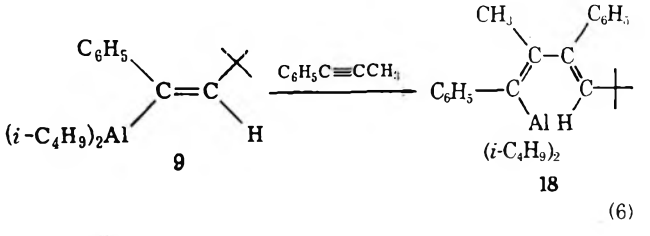
Previous work has offered strong evidence for the intermediacy of bis hydraluminated products like **11** in the cis,trans isomerization of vinylaluminum compounds.[3] The lability of adducts such as **11** was further revealed when the temperature was raised to 110°; the amount of **11** sank to 6%; and 68% of the product was now the trans adduct **12**. As a seeming contradiction to this finding, however, it was observed that heating for another 48 hr at 140° and then hydrolyzing led to the formation of 91.5% of the 3,3-dimethyl-1-phenylbutane (**13**). Only 2% of the cis olefin **7**, 6% of the trans olefin **14**, and 0.5% of the diene **8** remained. However, hydrolysis with deuterium oxide and nmr examination of **13b** showed that the deuterium was now distributed between the carbon α to the phenyl (61%) and the β carbon (39%). Since geminal adducts like **11** were apparently unstable at >100° and since the large amount of bis hydralumination revealed the importance of eq 3 at 140°, we propose that the increased amount of **13b** arose principally from a 1,4-dialuminacyclohexane intermediate (**15**) (eq 5).



Again, a 1:1 mixture of the acetylene **5** and hydride **6** were heated for 48 hr to yield a 94:6 mixture of **9** and **10**. Then 1 more equiv of acetylene **5** was introduced. After 16 hr at 50° the reaction mixture was hydrolyzed to give 33% of diene **8**, 38% of cis olefin **7**, and 29% of remaining acetylene **5**. Continued heating at 50–70° eventually gave >80% of diene **8**, and no other isomeric diene or oligomer could be detected.

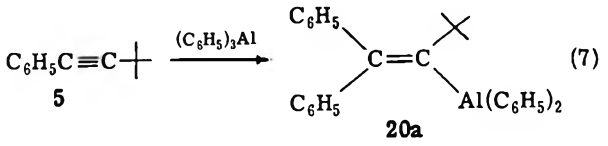
When 5:1 mixtures of the acetylene **5** and hydride **6** were maintained at 70–140°, again high yields of diene **8** were realized. However, when 7.5:1.0 mixtures were heated without solvent for 4 days at 140–160°, a new hydrocarbon, which proved to be *cis,cis,cis*-1,3,6-tri-*tert*-butyl-2,4,5-triphenyl-1,3,5-hexatriene (**16**), was also obtained.

Furthermore, it proved possible to achieve a controlled reductive heterodimerization of two different alkynes. Thus, after **9** was formed from a 1:1 mixture of *tert*-butyl(phenyl)acetylene (**5**) and hydride **6**, 1 equiv of methyl(phenyl)acetylene was introduced and the reaction mixture was heated at 50–60°. Upon hydrolysis, a 26% yield of *cis,cis*-4-*tert*-butyl-2-methyl-1,3-diphenyl-1,3-butadiene (**17**), uncontaminated by any other diene (except **8**, which was originally present), was isolated. By work-up of part of the reaction mixture with D_2O and nmr examination of **17**, it was revealed that deuteration occurred only at the 1 position of the butadiene. Hence, the aluminum precursor was **18**, as in eq 6.



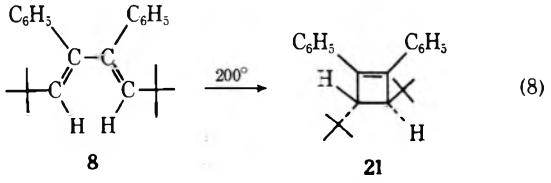
Finally, *tert*-butyl(phenyl)acetylene (**5**) was carbaluminated with triphenylaluminum (**19**) with difficulty, requiring prolonged heating at 90–110°. However, a single product, 3,3-dimethyl-1,1-diphenyl-1-butene (**20**), was isolated in good yield, showing that the reaction had formed **20a** regiospecifically (eq 7).

(13) K. Ziegler, H. Martin, and F. Krupp, *Justus Liebigs Ann. Chem.*, **629**, 14 (1960).



(7)

Structure Proofs of the Reaction Products.—The positions of the carbon–aluminum bonds in precursors **9**, **10**, **11**, **12**, **15**, and **18** could readily be ascertained by hydrolyzing with D_2O[3] and comparing the nmr spectra of the deuterated hydrocarbons with those of the hydrocarbons themselves. The stereochemical structure of the *cis,cis*-1,4-di-*tert*-butyl-2,3-diphenyl-1,3-butadiene (**8**) follows from (a) the two identical vinylic protons at 5.03 ppm (*cf.* nmr spectrum of **7**, where C_6H_5CH is at 6.38 and *t*-C_4H_9CH is 5.52 ppm); (b) the failure of **8** to be metalated by *n*-butyllithium in THF, thus ruling out that the protons at 5.03 ppm could be allylic; and (c) the facile thermal, conrotatory[14] ring closure of **8** to yield *trans*-3,4-di-*tert*-butyl-1,2-diphenylcyclobutene (**21**) (eq 8).



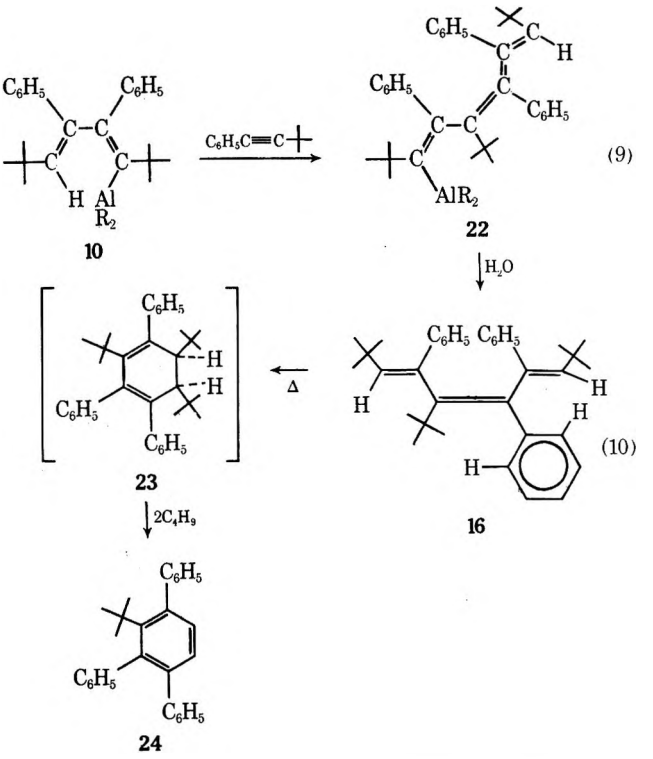
(8)

Isomeric with **8**, **21** had no nmr absorptions in the region 5.0–7.0 ppm, but instead displayed a two-proton singlet at 2.82 ppm. The ultraviolet spectrum of **21** displayed its long-wavelength maximum at 282 nm (*cf. cis*-stilbene, λ_{max} 280 nm), whereas the long-wavelength maximum in **8** was at 230 nm (*cf. cis*-β-*tert*-butylstyrene, λ_{max} 220 nm). The foregoing evidence, taken together with other spectral data for **8**, rules out the cis,trans and trans,trans forms as well as isomeric structures where the positions of the *tert*-butyl and phenyl groups would be different.

The assignment of the structure *cis,cis,cis*-1,3,6-tri-*tert*-butyl-2,4,5-triphenyl-1,3,5-hexatriene to the reductive trimer **16** follows from the following considerations: (a) the presence of dissimilar, unsplit vinyl protons at 5.41 and 5.51 ppm, respectively; (b) the occurrence of three distinct signals for the three *tert*-butyl groups; (c) the presence of two protons split into multiplets at 5.72–5.90 ppm and 13 protons at 6.5–7.05 ppm, suggesting that two aromatic protons were abnormally shielded; and (d) the fact that the vinyl protons at 5.41 and 5.51 ppm resembled the chemical shift of *t*-C_4H_9CH in **7** (5.52 ppm). Finally, the possible formation of **16** from organoaluminum precursor **10** (eq 9) and the pyrolysis of **16** to yield 3-*tert*-butyl-1,2,4-triphenylbenzene (**23**) (eq 10) are consistent with the structural assignment.

As shown in **16** (eq 10), the ortho protons of the 4-phenyl will tend to lie in the shielding cones of the flanking 2- and 5-phenyl groups. Also to be noted is that the transformation **16** → **24** can be viewed as a thermally allowed, disrotatory ring closure of a 1,3,5-hexatriene,[14] followed by aromatization through the thermolysis of two relatively labile allylic–*tert*-butyl, carbon–carbon bonds.

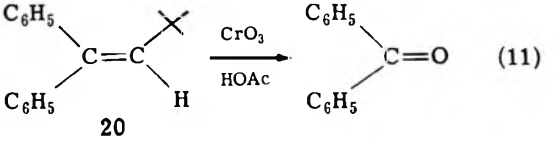
(14) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie, Weinheim, 1970, p 45.



(9)

(10)

The carbalumination of **5** by **19** was shown to yield only 3,3-dimethyl-1,1-diphenyl-1-butene (**20**) in the following manner: (a) gas chromatographic analysis of the reaction hydrolysate uncovered only **5** and **20**; (b) attempted acid-catalyzed isomerization of **20** was unsuccessful, whereas a 1,2-diphenylethylene would have yielded two isomers;[15,16] and (c) chromic acid oxidation of **20** yielded benzophenone (eq 11).



(11)

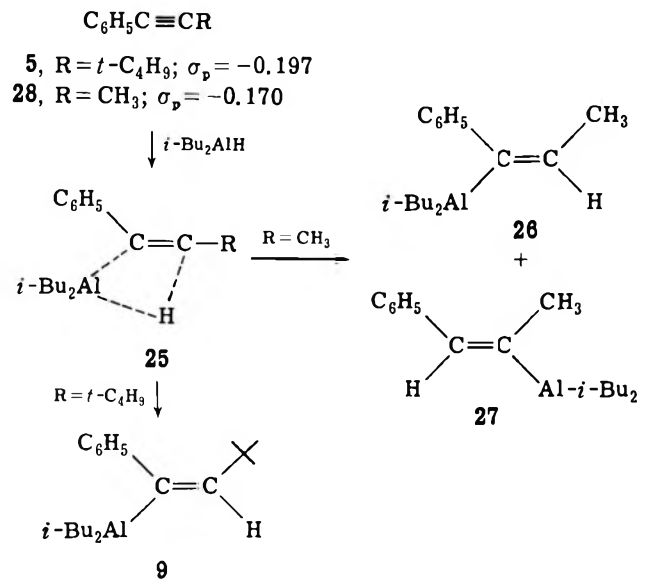
Finally, the sole diene obtained from the sequential reaction of hydride **6**, first with *tert*-butyl(phenyl)acetylene (**5**) and then with methyl(phenyl)acetylene, was shown to be *cis,cis*-4-*tert*-butyl-2-methyl-1,3-diphenyl-1,3-butadiene (**17**) as follows: (a) the unsplit vinyl proton at 5.88 ppm was assigned to *tert*-C_4H_9CH and the vinyl multiplet at 6.0 ppm to the C_6H_5CH (*cf.* **7**); (b) the methyl protons were split into a doublet (J = 1.0 Hz) and this fact excludes it from the 1 and 4 positions of the diene; and (c) all known homodimerizations of ordinary alkynes yield products of cis,cis configuration.

Discussion

The regiochemistry of hydraluminating triple bonds can readily be rationalized in terms of polar factors fostering electrophilic attack by the aluminum center (**25**), although, alternatively, an argument based on steric factors is possible. For the case of *tert*-butyl(phenyl)acetylene (**5**) the exclusive formation of **9**, compared with the 82:18 mixture of adducts **26** and **27** obtained from methyl(phenyl)acetylene (**28**), can be

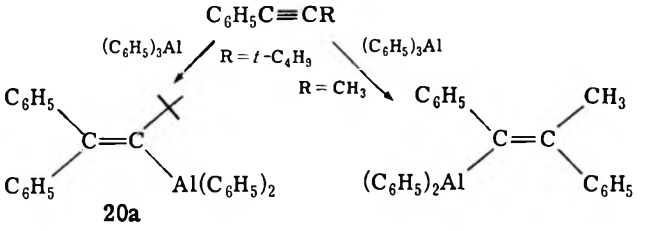
(15) J. J. Eisch and C. K. Hordis, *J. Amer. Chem. Soc.*, **93**, 2974 (1971).

(16) J. J. Eisch and J. M. Biedermann, *J. Organometal. Chem.*, **30**, 167 (1971).



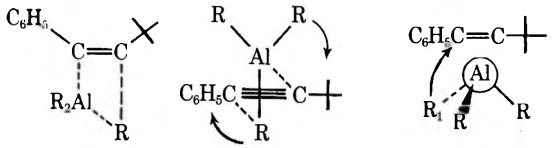
ascribed to the superior electron-releasing effect of the *tert*-butyl group, as mirrored in its σ_{para} value.

In contrast, this polar explanation cannot be extended to account for the carbalumination of **5**, either by triphenylaluminum or by **9**. Thus, the high regioselectivity in carbaluminating **28** (>95%) is just the reverse of that observed with **5**.



Since Stuart–Briegleb models of **5** and **19** show that the phenyl group behaves effectively as the larger group, in comparison with the splayed out diphenylalumino group, then the formation of **20** from **5** can be ascribed to steric factors operative in a four-center transition state similar to **25**. Such a steric explanation could be likewise invoked to rationalize the formation by an "insertion" process of **10** from **9**, of **18** from **9**, and of **22** from **9**. Possibly steric factors even intervene in the apparent dimerizing hydralumination, leading to the formation of **15**, a case where vicinal bis hydralumination of an alkyne becomes more significant than the usual geminal bis hydralumination.[2]

Although the importance of steric factors in the carbalumination and in the reductive oligomerization of *tert*-butyl(phenyl)acetylene is clear from these considerations, serious objections can be raised concerning the usual coplanar four-center transition state **29**. Examination of Stuart–Briegleb models shows that nonbonded interactions between C_6H_5 and R_2Al and between *tert*-C_4H_9 and R severely impede a close approach of the C≡C and Al—R bonds, when all these centers lie in a plane. On the other hand, when these bonds approach each other in a perpendicular orientation (**30**), nonbonded interactions are minimized and the four centers can easily be brought into appropriate contact. The direction of Al—R bond addition would then be determined by the torsional interactions in passing from **30** to the adduct. By slight modification of this view, the steric factor could be considered as operating through the preferential dissolution of a π-complex intermediate **31a**. Because of the Lewis acidity of unsolvated organoaluminum compounds, the Al covalent radius of 1.26 Å, and the C≡C bond length of 1.20 Å, structures **30** and **31a** are probably equally good models for the activated complex.



Finally, some remarks on the combined hydralumination and carbalumination reactions involved in eq 1 are in order. When *tert*-butyl(phenyl)acetylene (**5**) was subjected to these conditions, regiospecific hydralumination and reduction dimerization were likewise observed, but not the direct formation of a hexasubstituted benzene **4**. Instead, a reductive trimerization yielding **16** was found for the first time. Such products can be rationalized as arising from sequential insertions of alkynes into C—Al bonds,[2] *e.g.*, **2** → **3** or **9** → **10** → **22**, while the formation of **4** from **3** has been viewed as a Diels–Alder reaction or as an insertion, followed by dehydralumination.[2] Our finding of the open-chain reduced trimer **16**, considered together with the unlikelihood of dienes such as **3** and **10** assuming cisoid conformations, argues strongly against a Diels–Alder pathway to **4**. As to considering such alkyne oligomerizations as sequential insertions (**9** → **10** → **22**), it is true that the hetero reductive dimerization of two different alkynes occurs in accord with this view (eq 6). However, some reservations on the generality of this insertion mechanism should be entertained. Hydraluminated adducts, such as **2** and **9**, begin to dissociate into alkyne and R_2AlH in the temperature range (50–90°) where apparent insertion occurs. It is then possible that π-complex intermediates (**31b**) are the substrates actually responsible for the oligomerizations. The utility of the π-complex hypothesis in unifying many aspects of organoaluminum chemistry has already been discussed.[12] It is noteworthy that, contemporaneous with our report, Whitesides and Ehmann[17] published a masterly study of the cyclotrimerization of 2-butyne-*1,1,1-d*$_3$ by aluminum chloride (as well as by other catalysts). Their mass spectral analyses of the hexamethylbenzene obtained were consistent with the intervention of an intermediate of cyclobutadiene-like symmetry. Their results and our results on the oligomerization of alkynes by AlE_3 (E = Cl, H, or R) are consistent with a Lewis acid dimerization of alkynes, possibly *via* π complexes of the type **31b** or **31c**. This view is similar to that of Roberts and Sharts[18] for the chlorinative dimerization of 2-butyne (Smirnov–Zamkov reaction).

(17) G. M. Whitesides and W. J. Ehmann, *J. Amer. Chem. Soc.*, **91**, 3800 (1969).

(18) J. D. Roberts and C. M. Sharts in "Organic Reactions," Vol. 12, A. C. Cope, Ed., Wiley, New York, N. Y., 1962, p 17.

Experimental Section

The techniques necessary for the manipulations and reactions of organoaluminum compounds under an atmosphere of oxygen-free and dry nitrogen have been described previously.[3] Melting points were obtained with a Thomas-Hoover capillary melting point apparatus and are corrected. The following instrumentation for spectral measurements was employed: (a) infrared spectra in carbon tetrachloride solution or in a potassium bromide disc with a Perkin-Elmer Model 137 Infracord; (b) ultraviolet spectra with a Cary Model 15 spectrophotometer; (c) nmr spectra recorded with internal tetramethylsilane reference on the δ scale, with a Varian Model A-60 instrument; and (d) mass spectra with a Varian-MAT Model CH-5 spectrometer. Gas–liquid chromatographic analyses were performed with an F & M instrument, Model 720, with dual, 6-ft columns of 10% silicone rubber dispersed on Chromosorb.

The diisobutylaluminum hydride was obtained from Texas Alkyls Corp. and was fractionally redistilled before use. *tert*-Butyl(phenyl)acetylene,[5] methyl(phenyl)acetylene,[3] and triphenylaluminum[9] were prepared and purified as previously described.

Reactions of Diisobutylaluminum Hydride with *tert*-Butyl(phenyl)acetylene. A. Temperature of 50° and Equivalent Ratio of 1:1.—A solution of 14 mmol of diisobutylaluminum hydride and 14 mmol of *tert*-butyl(phenyl)acetylene (**5**) in 15 ml of dry hexane was maintained at 50° for 48 hr. Hydrolytic work-up and glc analysis showed the presence of 94% of *cis*-β-(*tert*-butyl)styrene (**7**) and 6% of *cis,cis*-1,4-di(*tert*-butyl)-2,3-diphenyl-1,3-butadiene (**8**). Distillation of **7** at 74–76° (15 mm) left a solid residue of **8**. The identity of **7** was established by comparing its refractive index, ultraviolet absorption, and nmr spectrum with published data[19] for **7**: nmr (CCl_4) δ 0.95 (s, 9 H, *t*-C_4H_9), 5.52 (center, d, $J_{\alpha\beta}$ = 12.5 Hz, β H), 6.38 (center, d, J = 12.5 Hz, α H to phenyl), 7.08 (s, 5 H, C_6H_5).

The reduced dimer **8** was recrystallized from methanol to yield colorless needles: mp 162–163° (repetition of melting giving lower melting range; *cf. infra*); uv λ_{max} (cyclohexane) 230 nm (sh, ϵ 20,680), 218 (24,300), 211 (sh, 21,980); nmr (CCl_4) δ 0.72 (s, 9 H), 5.03 (s, 1 H), 7.0–7.26 (m, 5 H).

Anal. Calcd for $C_{24}H_{30}$: C, 90.55; H, 9.45; mol wt, 318.5. Found: C, 90.37; H, 9.56; mol wt (osmometric in C_6H_6), 338; mol wt (mass spectrometric at 70 eV), 318 (P).

B. Temperature of 50° with a 1:1 Reactant Ratio Followed by Deuterium Oxide Work-Up.—As in part A, a run was maintained at 50° for 48 hr. One-half of the reaction mixture was treated with deuterium oxide (99.8%) and then worked up in the usual way. The nmr spectrum of the *cis*-β-(*tert*-butyl)styrene (**7**) showed no sign of the doublet centered at 6.38 ppm (vinyl H α to phenyl) and the signal of the β-vinyl H at 5.52 ppm was now a characteristic triplet (J = 2 cps). The ratio observed for the phenyl H:β-vinyl H signals of 5:1 gave the assurance that only α deuteration had taken place. The isolated dimer **8** was shown to be deuterated at one of its identical terminal vinyl positions (nmr signals of *tert*-butyl H:vinyl H, 18:1.

The remaining half of the reaction mixture was maintained for an additional 72 hr at 50°. Work-up with deuterium oxide revealed no change in the labeling of **7**, *i.e.*, no β-vinyl deuteration.

C. Reactants in a 1:1 Ratio at Higher Temperatures.—As in part A, the reactants were maintained at 50° for 48 hr, after which a glc analysis showed complete consumption of the acetylene. The reaction mixture was then heated for 48-hr periods at successively higher temperatures and then analyzed examining hydrolyzed samples by nmr and vpc: (1) 75°, 45% *cis*-β-(*tert*-butyl)styrene (**7**), 16% 3,3-dimethyl-1-phenylbutane (**13**), 35% *trans*-β-(*tert*-butyl)styrene (**14**), and 4% *cis,cis*-1,4-di(*tert*-butyl)-2,3-diphenyl-1,3-butadiene (**8**); (2) 110°, 26% **7**, 5% **13**, 68% **14**, and 1% **8**; (3) 140°, 2% **7**, 91.5% **13**, 6% **14**, and 0.5% **8**.

D. Reactants in a 1:2 Ratio of Diisobutylaluminum Hydride to tert-Butyl(phenyl)acetylene.—As in part A, the reactants were heated in a 1:1 ratio at 50° for 48 hr (complete consumption of acetylene). An additional 1 equiv of **5** was then introduced and the reaction mixture was maintained at 50° for another 16 hr. The ratio of products in a hydrolyzed aliquot was now 33% of dimer **8**, 38% of cis olefin **7**, and 29% of remaining acetylene **5**.

E. Reaction of *tert*-Butyl(phenyl)acetylene with a Small Amount of 6.—A mixture of 13 mmol of **6** and 91 mmol of **5** was heated at 50–60° without solvent for 2 hr and then at 175–180° (bath temperature) for a period of 6 days. During this time a yellow color developed, which persisted even after hydrolysis. Gas chromatographic analysis on a 4-ft Carbowax column showed the presence of the starting acetylene **5** and the cis olefin **7**. Analysis on a 2-ft silicon rubber column also revealed the presence of symmetrical diene **8** and a small amount of its cyclobutene relative **21** (column temperatures of 180 and 190°, respectively). Finally, at 260° a component was detected which proved to be the reductive trimer **16**, *cis,cis,cis*-1,3,6-tri-*tert*-butyl-2,4,5-triphenyl-1,3,5-hexatriene.

The crude reaction product was heated at 80° (0.5 mm) to remove residual **5** and **7** and the distillation residue then was fractionally crystallized from methanol to yield the symmetrical diene **8**. The methanolic mother liquor was freed of solvent and the residue was chromatographed on a neutral alumina–silver nitrate (4%) column (2.5 × 150 cm) with the rigorous exclusion of light from the column. Elution was successively conducted with 600 ml of hexane, 200 ml of hexane–benzene (9:1, v/v), 200 ml of hexane–benzene (3:1, v/v), and 200 ml of benzene. By mass spectrometry and nmr spectroscopy the fractions containing **16** were identified. (There is some evidence for the presence of a reductive tetramer as well.[20]) After 120 ml of eluate the fractions containing **16** began to be collected, and the next 400 ml yielded 1.1 g of crude **16**. Recrystallization from methanol gave 900 mg of **16**: mp 117–119°; uv λ_{max} (cyclohexane) 242 nm (sh, ϵ 16,000), 199 (52,000); ir (KBr) 1625 (m), 1585 (m), 1450 (s), 1360 (s), 1200 (s, br), 1075 (m), 1030 (m), 915 (s), 870 (s), 790 (s), 765 (s), and 695 cm^{-1} (s, br); nmr ($CDCl_3$) δ 0.78 (s, *t*-Bu), 0.94 (s, *t*-Bu), 1.1 (s, *t*-Bu), 5.41 (s, vinyl H), 5.51 (s, vinyl H), 5.72–5.90 (m, 2 H), and 6.5–7.05 (m, 13 H); mass spectrum (70 eV) *m/e* (rel intensity) 476 (P, 43), 420 (P − C_4H_8, 64), 421 (P − C_4H_9, 53), 362 (P − 114, 100), 307 (81), and 261 (55).

Anal. Calcd for $C_{36}H_{44}$: C, 90.71; H, 9.29; mol wt, 476.7. Found: C, 90.68; H, 9.30; mol wt (mass spectrometric at 70 eV), 476 (P).

Reaction of Triphenylaluminum with *tert*-Butyl(phenyl)acetylene.—A solution of 3.61 g (14 mmol) of triphenylaluminum and 2.21 g (14 mmol) of *t*-butyl(phenyl)acetylene in 25 ml of dry toluene was heated at 90° for 4 days and at the reflux temperature for another 24 hr. A glc analysis on a 6-ft, 5% silicone rubber on firebrick column of a hydrolyzed sample showed the presence of one major, new component (column temperature 255°) and a small amount of starting acetylene. Usual hydrolytic work-up yielded a viscous yellowish liquid. Distillation under reduced pressure provided 2.5 g (75%) of 3,3-dimethyl-1,1-diphenyl-1-butene (**20**) as a colorless liquid: bp 73–75° (0.5 mm); nmr (CCl_4) δ 0.96 (s, *t*-C_4H_9), 6.02 (s, vinyl H), 7.1 (s, C_6H_5), and 7.21 (br s, C_6H_5).

Anal. Calcd for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.44; H, 8.62.

Structure Proof of 3,3-Dimethyl-1,1-diphenyl-1-butene.—In order to distinguish between the 1,1-diphenyl and the 1,2-diphenyl (cis or trans) isomers for the above-mentioned product (**20**), a 1-ml sample was dissolved in 5 ml of glacial acetic acid containing one drop of concentrated sulfuric acid.[15,16] The solution was warmed at 70° for 8 hr. Usual basic work-up led to the recovered hydrocarbon, whose nmr spectrum was still identical with that of **20**. The absence of any acid-catalyzed isomerization rules against the presence of the 1,2-diphenyl isomer, which ought to have undergone cis,trans isomerization.

A 750-mg sample of **20** was treated with 600 mg of chromic anhydride dissolved in a mixture of 75 ml of glacial acetic acid and 25 ml of water. After 3 hr at 80° the mixture was diluted with water and extracted with ether. The ether extract was dried over anhydrous calcium sulfate and the solvent was then evaporated. The infrared spectrum of the crude residue showed all of the characteristic absorptions of benzophenone. Treatment with 2,4-dinitrophenylhydrazine gave a 65% yield of the benzophenone 2,4-dinitrophenylhydrazone, mp 236–237°, from glacial acetic acid (lit. mp 238°), which did not depress the melting point of an authentic sample.

Isomerization of *cis,cis*-1,4-Di(*tert*-butyl)-2,3-diphenyl-1,3-

(19) (a) D. Seyferth and G. Singh, *J. Amer. Chem. Soc.*, **87**, 4156 (1965); (b) H. Kristinsson and G. W. Griffin, *ibid.*, **88**, 379 (1966).

(20) Mr. Sue-Goo Rhee established a reliable procedure for the most difficult isolation of reductive trimer **16** and uncovered the first evidence for the reductive tetramer.

butadiene.[21]—Treatment of 1.6 g (5.3 mmol) of **8** with 6 mmol of *n*-butyllithium in 60 ml of anhydrous tetrahydrofuran for 6 hr at 0° did not lead to any development of color. Work-up with deuterium oxide and examination of the recovered **8** by nmr spectroscopy showed that the vinyl hydrogens at 5.03 ppm had not been metalated.

A 2.0-g sample of **8** was heated under nitrogen for 9 hr at 200 ± 5°.[22] The nmr spectrum of the product in CCl_4 showed new absorptions at δ 0.92 (s) and 2.82 (s). The ratio of these peaks, ascribable to **21**, to those of **8** at 0.72 and 5.03 was 5:2. Fractional recrystallization from methanol first yielded crops of recovered **8**, followed by rhombic crystals, **21**. Repeated crystallization provided a pure sample of *trans*-3,4-di-*tert*-butyl-1,2-diphenylcyclobutene (**21**): mp 88–88.5°; uv λ_{max} (cyclohexane) 282 nm (ε 14,620), 227 (23,850), and 208 (21,280); nmr (CCl_4) δ 0.92 (s, *t*-C_4H_9), 2.82 (s, cyclobuta H), and 7.32 (s, C_6H_5).

When the rhombic crystals, in turn, were heated at 200° for 3 hr, needles of **8** were found to sublime out of the melt.

Anal Calcd for $C_{24}H_{30}$: C, 90.55; H, 9.45; mol wt, 318.5. Found: C, 90.67; H, 9.50; mol wt (mass spectrometric at 70 eV), 318 (P).

Sequential Reaction of Diisobutylaluminum Hydride with *tert*-Butyl(phenyl)acetylene, Followed by the Addition of Methyl(phenyl)acetylene.—As in part A, a run was maintained at 50° for 48 hr, after which a glc analysis showed complete consumption of the acetylene. Then 14 mmol of freshly distilled methyl(phenyl)acetylene were added and the reaction mixture was maintained at 50–60° for 4 days. Thereupon the reaction mixture was divided into two parts, one part of which was hydrolyzed and the other part worked up with deuterium oxide (99.8%).

The hydrolyzed portion was analyzed by glc and nmr spectroscopy and was shown to contain 32% of *cis*-β-*tert*-butylstyrene (**7**), 32% of unreacted methyl(phenyl)acetylene (**28**), 10% of the symmetrical dimer **8**, and 26% of a new dimer **17**. No mono- or dimeric-reduced products of methyl(phenyl)acetylene alone were detectable. Distillation under reduced pressure gave a pale yellow, viscous liquid, bp 145–150° (0.50 mm), whose analytical data were consistent with its identity as *cis,cis*-4-*tert*-butyl-2-methyl-1,3-diphenyl-1,3-butadiene: nmr (CCl_4) δ 0.91 (s, *t*-C_4H_9), 2.01 (d, CH_3, J = 1.0 Hz), 5.88 (s, vinyl H), 6.0 (m, br, vinyl H), 7.13 (br s, C_6H_5), and 7.24 (m, C_6H_5).

Anal. Calcd for $C_{21}H_{24}$: C, 91.25; H, 8.75. Found: C, 90.98; H, 8.63.

The portion of the reaction mixture worked up with D_2O yielded a monodeuterated form of **17**, whose nmr spectrum showed no signal at 6.0 ppm and whose doublet at 2.01 ppm was now a sharp singlet. These data place the deuteron at the 1 position of **17**.

Pyrolysis of the Reductive Trimer 16 of *tert*-Butyl(phenyl)acetylene.—A sample of the reductive trimer **16** in a capillary tube was heated in an oil bath. Over 300° bubbling was observed to occur in the clear melt and over 400° the liquid residue evaporated.

Pyrolysis of 500 mg of **16** in an nmr tube for 45 min at 250–300°, dissolution of the product in $CDCl_3$, and recording of the spectrum uncovered multiplets at 2.7 and 5.4 ppm (ratio 3:1), in agreement with the presence of isobutylene. The crude yellow product (one sharp nmr peak at 0.99 ppm) was treated with charcoal and then recrystallized from a hexane–ethanol pair (1:1, v/v) to provide 300 mg of needles with a faint yellow cast, mp 146–148°, of 3-*tert*-butyl-1,2,4-triphenylbenzene (**24**): nmr ($CDCl_3$) δ 0.99 (s, 9 H), 6.75 (m, 12 H), and 7.04 (br s, 5 H); mass spectrum (70 eV) *m/e* (rel intensity) 362 (P, 84, 347 (P − CH_3, 100), and 306 (P − C_4H_8, 44); uv λ_{max} (cyclohexane) 230 nm (sh, ε 32,000) and 219 (ε 35,000).[23]

Anal Calcd for $C_{28}H_{26}$: C, 92.78; H, 7.23. Found: C, 92.60; H, 7.35.

Preparation of Authentic 3,3-Dimethyl-1-phenylbutane by Catalytic Reduction of *tert*-Butyl(phenyl)acetylene.—A solution of 4.75 g (30 mmol) of **5** in 25 ml of freshly distilled ethyl acetate was shaken with 500 mg of a 10% palladium-on-charcoal catalyst under an atmosphere of hydrogen at 45 psi. After a 2-hr treatment at 25° usual distillative work-up gave a 90% yield of **13**: bp 213–215°;[24] $n^{23}D$ 1.4822; nmr (neat) δ 0.89 (s, *t*-C_4H_9), 1.25–1.60 (m, CH_2-*t*-C_4H_9), 2.32–2.65 (m, $CH_2C_6H_5$), and 7.08 (s, C_6H_5).

Registry No.—**5**, 4250-82-2; **6**, 1191-15-7; **7**, 3740-05-4; **8**, 23764-10-5; **13**, 17341-92-0; **16**, 35323-92-3; **17**, 35323-93-4; **19**, 841-76-9; **20**, 23586-64-3; **21**, 23764-11-6; **24**, 35324-18-6.

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(21) *Cf.* H. H. Freedman, G. A. Doorakian, and V. R. Sandel, *J. Amer. Chem. Soc.*, **87**, 3019 (1965), for the metalation of *cis*-1,2,3,4-tetraphenylcyclobutene by *n*-butyllithium in tetrahydrofuran solution.

(22) G. A. Doorakian and H. H. Freedman, *ibid.*, **90**, 3582 (1968), have reported on the facile thermal cyclization of the sterically hindered diene, *trans*-1-bromo-*cis*-1,2,3,4-tetraphenylbutadiene.

(23) Mr. Csaba Kovacs made the initial observation of this interesting pyrolysis and Mr. Sue-Goo Rhee verified the course of the reaction.

(24) A. E. Bey and D. R. Weyenberg, *J. Org. Chem.*, **30**, 2436 (1965).

The Base-Catalyzed Fragmentation of 2-*tert*-Butylperoxy-2-methyl-1-propanol

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A kinetic and product study of the base-catalyzed fragmentation of 2-*tert*-butylperoxy-2-methyl-1-propanol (2) is reported. The products of the reaction in 40% aqueous methanol are *tert*-butyl alcohol, acetone, and formaldehyde. An ionic mechanism is proposed in this solvent, which is consistent with the product studies and the first-order dependence on both 2 and the base. The rate of decomposition of 2 in chlorobenzene at 100° was not found to be appreciably accelerated by triethylamine. These data allow comparisons to be made with the analogous base-catalyzed fragmentation reactions of 2-*tert*-butylperoxy-2-methylpropanoic acid and 3-chloro-2,2-dimethyl-1-propanol. The fragmentation of 2 was considered as a possible source of excited-state formaldehyde. However, the lack of light emission from an acceptor (fluorescein) added to the reaction mixture indicates that excited state formaldehyde is not produced. Calculations verify this observation.

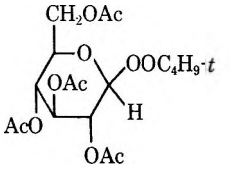
Although free-radical reactions of peroxides are well known, there is a growing body of reported ionic reactions of peroxides.[1] In this area we previously described the ionic fragmentation reaction of 2-*tert*-butylperoxy-2-methylpropanoic acid (1).[2] An anal-

$$(CH_3)_3COOC(CH_3)_2CO_2H$$
1

ogous fragmentation reaction was proposed more recently during the course of biological oxidations involving certain hydroxylases that require α-ketoglutarate as a cofactor.[3] We have now found that the alcohol (2) corresponding to 1 undergoes a simi-

$$(CH_3)_3COOC(CH_3)_2CH_2OH$$
2

lar base-catalyzed ionic fragmentation reaction. Although there are a number of proposed fragmentation reactions of peroxides,[4] with various electrofugal and nucleofugal groups,[5] to our knowledge the fragmentation reaction of an isolated hydroxy peroxide corresponding to 2 has not been reported. Such a fragmentation reaction may have occurred during the basic methanolysis of *tert*-butylperoxy 2,3,4,6-tetra-acetyl-β-D-glucoside (3);[4e] however, the fragmentation



3

may have proceeded *via* the tetrahedral alkoxide ion intermediate formed in the methanolysis of the ester.

Since 2 offers the opportunity of studying a fragmentation reaction of the simplest hydroxy peroxide, without complicating elimination reactions, we now report the products and kinetics of the base-catalyzed decomposition of this peroxide. Comparisons are made to other fragmentation and elimination reactions. The possibility of chemiluminescence from the fragmentation of 2 is also considered.

Results

Products.—In 40% aqueous methanol, the products for the basic (0.254 *M* sodium hydroxide) decomposition of 2 (4.13×10^{-2} *M*) at 30° are *tert*-butyl alcohol (100.6 ±1.8% yield) and acetone (64.2 ± 1.8% yield). The yields are based on eq 1 and result from an average of

$$2 \xrightarrow[40\%\text{ aq MeOH}]{OH^-} (CH_3)_3COH + CH_3COCH_3 + CH_2O \quad (1)$$

five measurements. The companion product is formaldehyde. Previously we have found that formaldehyde and acetone, under these basic conditions, undergo a condensation reaction.[6] Numerous products are reported from the base-catalyzed formaldehyde–acetone condensation reaction, where some products result from the condensation of more than one formaldehyde molecule per acetone.[7] Considering the quantitative yield of *tert*-butyl alcohol, the lower yield of acetone can be attributed to the formaldehyde–acetone condensation reactions. Furthermore, quantitative yields of both acetone and *tert*-butyl alcohol are produced in the base-catalyzed fragmentation of 1, where formaldehyde is not formed.[2]

Kinetic Data.—Typically kinetic measurements were made over 3 half-lives and acceptable first-order rate coefficients were obtained in individual measurements as indicated by the probable error. At constant base concentration (0.0821 *M*), the reaction is first order in 2 over a tenfold variation in the initial concentration of this reactant (Table I). First-order dependence upon base concentration is also observed, where constant second-order rate coefficients (k_2) are obtained from the ratio of the observed psuedo-first-order coefficient (k_{obsd}) to base concentration (Table II). The first-order dependence upon base concentration is further

(1) R. Curci and J. O. Edwards in "Organic Peroxides," Vol. I, D. Swern, Ed., Wiley-Interscience, New York, N. Y., 1970, p 199.

(2) (a) W. H. Richardson and R. S. Smith, *J. Amer. Chem. Soc.*, **89**, 2230 (1967); (b) *ibid.*, **91**, 3610 (1969).

(3) (a) B. Lindblad, G. Lindstedt, M. Tofft, and S. Lindstedt, *ibid.*, **91**, 4604 (1969); (b) C. K. Liu, P. M. Shaffer, R. S. Slaughter, R. P. McCroskey, and M. T. Abbott, *Biochemistry*, **11**, 2172 (1972), and references cited therein.

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Table I

Effect of Variation of the Initial Concentration of 2 in the Base-Catalyzed Fragmentation of 2 in 40% Aqueous Methanol at 30.00° [a]

$10^3[2]$, M	$10^4 k_{obsd}$,[b] sec^{-1}	$k_2 = (k_{obsd}/[NaOH])^c \times 10^3$, l. mol^{-1} sec^{-1}
0.311	3.66 ± 0.06	4.57
0.311	3.88 ± 0.04	4.84
1.24	3.68 ± 0.04	4.60
1.24	3.67 ± 0.07	4.57
3.11	3.61 ± 0.08	4.50
3.11	3.81 ± 0.08	4.74
	Av 3.72 ± 0.06	Av 4.79 ± 0.02

[a] 0.0821 M in sodium hydroxide. Ionic strength was maintained constant at 0.433 M with sodium perchloroate. [b] Observed first-order rate coefficient with probable error. [c] Second-order rate coefficient.

Table II

Effect of Base Concentration on the Rate of Fragmentation of 2 in 40% Aqueous Methanol at 30.00° [a]

[NaOH], M	$10^4 k_{obsd}$,[b] sec^{-1}	$k_2 = (k_{obsd}/[NaOH])^c \times 10^3$, l. mol^{-1} sec^{-1}
0.0260	1.12 ± 0.01	4.29
0.0260	1.19 ± 0.01	4.57
0.0800	3.68 ± 0.04	4.60
0.0800	3.67 ± 0.07	4.57
0.268	12.7 ± 0.2	4.75
0.268	12.7 ± 0.2	4.76
		Av 4.79 ± 0.02

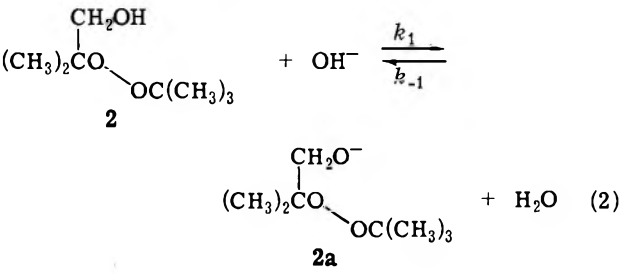
[a] Initial concentration of 2 is 1.24×10^{-2} M. Ionic strength is adjusted to a constant value of 0.433 M with sodium perchlorate. [b] Observed first-order rate coefficient with probable error. [c] Second-order rate coefficient.

confirmed by a least-squares treatment of a plot of log k_{obsd} *vs.* log $[OH^-]$, which yields a slope and thus the order in base as 1.029 ± 0.008. The effect of temperature and the resulting activation parameters for the base-catalyzed decomposition of 2 are given in Table III.

It was hoped that the base-catalyzed decomposition of 2 could be compared directly to the basic decomposition of the peroxy-substituted acid 1, which was studied in chlorobenzene with triethylamine. The rate of the latter reaction was conveniently measured at 25°. In contrast, the reaction of 2 with triethylamine in chlorobenzene was imperceptibly slow at 30° and so measurements were made at 100° in order to obtain measurable rates. Under these conditions, nonbase-catalyzed decomposition of 2 became important. As seen from Table IV, triethylamine does not appreciably accelerate the rate of decomposition of 2 compared to the decomposition of 2 in the absence of the base. Radical traps were employed in the decomposition of 2 in the absence of base in order to avoid possible induced decomposition of the peroxide. Since a radical trap was not used with triethylamine, the rate coefficient here is a maximum value.

Discussion

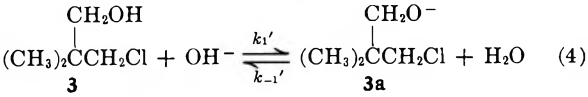
The mechanism of the base-catalyzed fragmentation of 2 in 40% aqueous methanol appears to be analogous to that of the base-catalyzed fragmentation of the peroxy-substituted acid 1.[2] The suggested mechanism for 2 is given by eq 2 and 3, where the base is



represented by OH^- for convenience. It was previously shown that the decomposition of 1 was concerted and presumably eq 3 is also concerted. Although radical mechanisms must be considered as a possibility when peroxides are involved, there is little doubt that the basic decomposition of 2 in 40% aqueous methanol is an ionic reaction. A primary clue to the ionic character of the reaction is seen in the quantitative yield of *tert*-butyl alcohol. A radical decomposition of 2 would undoubtedly generate *tert*-butoxy radicals, which would in part undergo fragmentation to produce acetone and methyl radicals in this polar protic solvent.[8,9] This result would be in conflict with the observed quantitative yield of *tert*-butyl alcohol. Simple homolytic decomposition of 2 at the temperatures used for the study in aqueous methanol is highly unlikely, considering that a temperature of 100° was required to produce appreciable rates for the decomposition of 2 in chlorobenzene in the absence of base (Table IV).

Fragmentation of 2a in eq 3 can be shown to be an extremely facile reaction. With reasonable approximations, the rate coefficient (k_f) for this step can be estimated. Using the steady-state approximation and the reasonable assumption that $k_{-1} \gg k_f$, which is typical in proton transfers between oxygen bases, the rate law derived from eq 2 and 3 is $-d[2]/dt = Kk_f \cdot [2][OH^-]$, where $K = k_1/k_{-1}$. The equilibrium constant K is given by $K = K_a(1/K_{auto})$, where K_a is the ionization constant of the peroxy alcohol 2 and K_{auto} is the autopyrolysis constant of 40% aqueous methanol. The value of the latter constant for this solvent was previously determined to be 10^{-14}.[10] The assumption that the ionization constant of 2 is similar to that of other primary alcohols[11] gives $K_a \cong 10^{-16}$, and thus $K = 10^{-16} \cdot 10^{14} = 10^{-2}$ M^{-1}. The rate coefficient for fragmentation of 2a is given by $k_f = k_2/K = 5 \times 10^{-3}$ M^{-1} $sec^{-1}/10^{-2}$ $M^{-1} = 0.5$ sec^{-1} at 30°, where k_2 is the observed second-order rate coefficient.

The fragmentation of 2 can be compared to the analogous fragmentation of the 1,3-chlorohydrin 3 (eq 4 and 5), which was previously studied in 40% aqueous



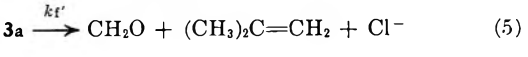


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TABLE III

ACTIVATION PARAMETERS FOR THE BASE-CATALYZED REACTION OF 2 IN 40% AQUEOUS METHANOL[a,b]

Temp, °C	$10^4 k_{obsd}$,[c] sec^{-1}	E_a, kcal/mol	Log A	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, eu
10.00	0.448 ± 0.007	18.5 ± 0.5	10.0	18.0 ± 0.5	−14.8 ± 2.0
20.00	1.42 ± 0.02				
30.00	3.51 ± 0.04				
40.00	11.8 ± 0.2				

[a] Initial concentration of 2 is 1.24×10^{-2} M and [NaOH] = 0.0762 M. Ionic strength is maintained constant at 0.433 M with sodium perchlorate. [b] Activation parameters are given with probable error. [c] Observed first-order rate coefficient with probable error.

TABLE IV

RATE OF DECOMPOSITION OF 2 IN CHLOROBENZENE AT 99.72°

[2], M	Additive	[Additive], M	$10^6 k_{obsd}$,[a] sec^{-1}
0.010	Triethylamine	0.200	6.1 ± 0.2
0.0713	Styrene	0.445	4.3
0.0578	2,6-Di-*tert*-butyl-*p*-cresol	5.22×10^{-3}	3.62 ± 0.08

[a] First-order rate coefficient with probable error.

methanol.[12] Here the middle fragment[5] possesses a π-carbon–carbon bond rather than a π-carbonyl bond as in the fragmentation of 2. Also, the nucleofugal fragment[5] is chloride in 3 as opposed to *tert*-butoxide in 2. The observed second-order rate coefficient ($k_{2'}$) for the base-catalyzed fragmentation of 3 is calculated to be 4×10^{-7} l. mol^{-1} sec^{-1} at 30° in 40% aqueous methanol from observed activation parameters.[12] With the approximations that were made previously, $k_{f'} = k_{2'}/K' = 4 \times 10^{-7}$ M^{-1} $sec^{-1}/10^{-2}$ $M^{-1} = 4 \times 10^{-5}$ sec^{-1} at 30°. Thus, the fragmentation step for 2a (eq 3) is 10^4-fold faster than the corresponding reaction for 3a (eq 5). The faster fragmentation rate of 2a as compared to 3a is no doubt related to the lower energy π-carbonyl system of the middle fragment, which results from 2a, *vs.* the π-olefinic middle fragment from 3a.[13] These energy differences between the two types of π bonds are reflected in the activated complexes in eq 3 and 5. If the same nucleofugal fragment was present in both 2 and 3, a rate enhancement considerably greater than 10^4 would be expected, since chloride is a much better leaving group than *tert*-butoxide.[16] The activation parameters for 2 and 3 reflect a composite of the fragmentation steps (eq 3 and 5) and the preequilibrium steps (eq 2 and 4). However, it is reasonable to assume that the contributions to the preequilibrium steps are similar in both reactions and that the differences in activation parameters result from differences in the fragmentation step. The effect of the two different types of middle fragments from 2 and 3 is clearly seen in the $\Delta H^{\pm}$ values (18.0 and 24.6 kcal/mol, respectively).

The entropy of activation is considerably more negative for the fragmentation of 2 ($\Delta S^{\pm} = -14.8$ eu) as compared to 3 ($\Delta S^{\pm} = -6.9$ eu). This may be explained by a greater dispersion of charge (*i.e.*, more bond breaking and making) at the transition for fragmentation of 2a relative to 3a, which is consistent with the lower $\Delta H^{\pm}$ value for 2. Solvent ordering may be greater in proceeding to the activated complex with increased charge dispersion, which would be consistent with the more negative $\Delta S^{\pm}$ for 2.. There is an additional contrasting feature between the fragmentation of 2a *vs.* 3a, namely, a more polar middle fragment is produced from 2a (acetone) as compared to 3a (isobutylene). This may result in more solvent ordering in proceeding to the transition state for the fragmentation of 2a *vs.* 3a and thus contribute to a more negative $\Delta S^{\pm}$ for 2.

A comparison of the overall rates of base-catalyzed fragmentation (preequilibrium plus the fragmentation steps) of the peroxy-substituted acid 1 and the peroxy-substituted alcohol 2 can be made in chlorobenzene with triethylamine as the base. From the observed activation parameters for this reaction with 1,[2b] a first-order rate coefficient of 10^{-1} sec^{-1} $\{[(C_2H_5)_3N] = 8.00 \times 10^{-2}$ $M\}$ is calculated at 100°. This may be compared to a maximum rate coefficient of 6.1×10^{-6} sec^{-1} $\{[(C_2H_5)_3N] = 0.200$ $M\}$ for 2 at 100°. This is a maximum value for 2, since nonbase-catalyzed decomposition is important under these conditions (*cf.* Table IV). Although the amine concentration differs in these two reactions, the order in amine for the fragmentation of 1 is only 0.23.[2b] This introduces a factor of only 1.2 in correcting the rate coefficient for 1 from 8.00×10^{-2} M to 0.200 M in amine. Thus, the peroxy-substituted acid 1 undergoes fragmentation (overall rate) at least 10^4 times faster than the peroxy-substituted alcohol 2. If the relative values of the equilibrium constants for 1 and 2 with triethylamine could be compared, it would be possible to determine the rates of the fragmentation steps. Unfortunately, the equilibria between acids and amines in nonpolar solvents is complex[17] and this estimate does not appear possible.

Previously, we reported a rate coefficient of 1.55×10^{-6} sec^{-1} for the triethylamine (0.200 M) catalyzed elimination reaction of *tert*-butyl isopropyl peroxide in chlorobenzene at 100°.[2b] This elimination reaction is then analogous to the triethylamine-catalyzed fragmentation of 2 in chlorobenzene $\{k_{max} = 6.1 \times 10^{-6}$ sec^{-1} at 100°, $[(C_2H_5)_3N] = 0.200$ $M\}$. For both of these reactions there is an appreciable amount of nonbase-catalyzed decomposition. Considering this, it does not appear that the fragmentation of 2 is appreciably more facile than the analogous elimination reaction.

In reactions where carbonyl compounds are produced, it is possible to generate these molecules in an excited state, providing that the sum of the activation energy and the heat of reaction is sufficiently large.[18] For example, with peroxides of sufficiently high energy,

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(15) Calculation from the data given in T. L. Cottrell, "The Strength of Chemical Bonds," Butterworths, London, 1954.

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(17) (a) S. Bruckenstein and D. F. Unterker, *J. Amer. Chem. Soc.*, **91**, 5741 (1969); (b) S. Bruckenstein and A. Saito, *ibid.*, **87**, 698 (1965).

(18) See (a) F. McCapra, *Quart. Rev., Chem. Soc.*, **20**, 485 (1966); (b) M. M. Rauhut, *Accounts Chem. Res.*, **2**, 80 (1969).

such as 1,2-dioxetanes, this criterion is met.[19] Since carbonyl compounds are produced from the fragmentation of 2, which is a molecule of reasonably high energy, the question of generating an excited state carbonyl species in this reaction was probed. This was done by determining if light emission resulted from an acceptor, which was added to the reaction mixture. This technique, with fluorescein as the acceptor, has been successful in detecting excited-state carbonyl molecules produced from the decomposition of 3,3-dimethyl-1,2-dioxetane.[6] No light emission was detected with or without fluorescein as an acceptor in the base-catalyzed decomposition of 2 in 40% aqueous methanol, which suggests that excited-state carbonyl molecules are not produced in this reaction. Calculations confirm the reasonableness of this observation, although the calculations are approximate, since they are for a gas-phase system. The maximum available enthalpy (ΔH_a) for producing an excited-state carbonyl species is given by $\Delta H_a = \Delta H^{\ddagger} - \Delta H_r$.[18,19] The value of $\Delta H^{\ddagger}$, obtained experimentally, is 18.0 kcal/mol for fragmentation of 2. The heat of reaction (ΔH_r) is given by $\Delta H_r = \Delta H^{\circ}_{f_P} - \Delta H^{\circ}_{f_R}$, where $\Delta H^{\circ}_{f_P}$ and $\Delta H^{\circ}_{f_R}$ are the heats of formation of the products (*tert*-butyl alcohol, acetone, and formaldehyde) and the reactant 2, respectively. The latter values are calculated to be −154.1 and −119.0 kcal/mol, respectively, so that $\Delta H_r = -35.1$ kcal/mol. The available enthalpy (ΔH_a) is then 53.1 kcal/mol. Of the two carbonyl molecules produced from 2, formaldehyde has the lowest singlet (81 kcal/mol)[20] and triplet (72 kcal/mol)[21] energies.[22] Thus, the calculations suggest that insufficient energy is available from the fragmentation of 2 to produce formaldehyde in the excited state, which is consistent with the results.

Experimental Section[25]

Materials.—The preparation and physical properties of 2-*tert*-butylperoxy-2-methyl-1-propanol (2) was reported previously by us.[26] The purity of 2 was estimated to be 98% by glc analysis. Anhydrous sodium perchlorate (G. F. Smith Co.) was prepared from the hydrated salt by heating at 110° for 48 hr under vacuum. Stock sodium hydroxide solutions were prepared from reagent grade pellets, starting from a 50% aqueous solution, which was filtered through a sintered glass frit to remove sodium carbonate. Vacuum sublimation [70° (0.1 mm)] was used to purify 2,6-di-*tert*-butyl-*p*-cresol (Matheson Coleman and Bell). Styrene (Matheson Coleman and Bell) was distilled immediately before use as a free-radical trap. The aqueous methanol solvent was prepared by volume (40 parts methanol/60 parts water) at 25° or by weight corresponding to the volumes. Methanol (Matheson Coleman and Bell, reagent) was purified by refluxing over magnesium turnings with a catalytic amount of iodine followed by distillation.[27]

Product Studies.—The reaction of 2 with sodium hydroxide in 40% aqueous methanol was carried out in sealed ampoules for 2.5 hr at 30° (ca. 10 half-lives). A 1.00-ml aliquot of a stock peroxide (2) solution was frozen in the ampoule at −78° and then 1.00 ml of a stock base solution was added. The contents of the ampoule were protected from moisture with a calcium chloride drying tube and sealed at −78°. Product analyses by glc were obtained with a 5 ft × 0.125 in. PAR-2 (Hewlett-Packard) column at 111° using a nitrogen flow rate of 29 ml/min. *n*-Butyl alcohol was used as an internal standard and the retention times for acetone, *tert*-butyl alcohol, and *n*-butyl alcohol were 6.6, 13, and 31 min, respectively. Areas of the chromatograms were integrated with a planimeter. Area ratios of products to the internal standard were compared to area ratios of a known mixture of compounds.

Kinetic Studies.—A solution of 2 with the internal standard (*n*-octyl alcohol) and a solution of sodium hydroxide with sodium perchlorate, to keep the ionic strength constant, in 40% aqueous methanol were allowed to thermally equilibrate separately for 30 min in a thermostated bath controlled to ±0.01°. After the thermal equilibration period, the solutions were mixed in a reaction vessel under a nitrogen atmosphere. Aliquots were withdrawn periodically and quenched with a cold 10% hydrochloric acid solution in 40% aqueous methanol. Twelve aliquots were usually removed over 3 half-lives. Analysis of the quenched samples were made by glc on a 7.5 ft × 0.125 in. 10% SF-96 on Varaport-30 column at 85° with a nitrogen flow rate of 24 ml/min. The retention times for 2 and *n*-octyl alcohol are 3.0 and 6.2 min, respectively. The ratio of the areas of 2/*n*-octyl alcohol from the glc analyses were processed by a first-order least-squares computer program.

The decomposition of 2 in chlorobenzene was carried out in sealed capillary tubes immersed in a thermostated bath at 100°. The rate of disappearance of 2 was followed by glc using a 15 ft × 0.125 in. 10% SF-96 on Varaport-30 column at 80° with a nitrogen flow rate of 24 ml/min. The retention times for chlorobenzene and 2 were 10 and 18 min, respectively. The ratio of the areas of 2/chlorobenzene were processed by a first-order least-squares computer program.

Registry No.—2, 35356-76-4.

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(20) J. C. D. Brand, *J. Chem. Soc.*, 858 (1956).

(21) G. W. Robinson and V. E. DiGiorgio, *Can. J. Chem.*, **36**, 31 (1958).

(22) The lowest singlet and triplet energies of acetone are 88.8[23] and 80 kcal/mol.[24]

(23) M. O'Sullivan and A. C. Testa, *J. Amer. Chem. Soc.*, **90**, 6245 (1968).

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(25) Temperatures of kinetic measurements are corrected. Gas–liquid chromatography (glc) measurements were performed on a Varian Aerograph Hy-Fi (FID) instrument.

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Mechanisms of Induced Decomposition. II. Reactivity of Di-*tert*-butylperoxy Phthalate[1]

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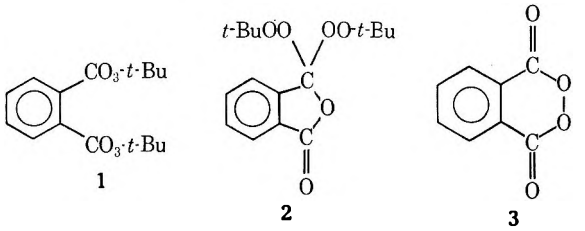
The reactivity of di-*tert*-butylperoxy phthalate (**1**) in cumene solution has been examined. The rate of disappearance of **1** ($k_1 = 4.68 \times 10^{-5}$ sec^{-1} at 115°) and the activation parameters for this process ($\Delta H^* = 33.6$ kcal/mol, $\Delta S^* = 7.8$ eu) are consistent with an initial one-bond cleavage at one of the peroxy groups and formation of the *o*-(carbo-*tert*-butylperoxy)benzoate radical (**11**). The products at 115° include CO_2, methane, acetone, *tert*-butyl alcohol, benzene, phthalic anhydride, phthalic acid, benzoic acid, bicumyl, *o*-cumylbenzoic acids **4**–**6**, and *o*-cumylbenzenes **7**–**9**. The potential reaction product *tert*-butylperoxy hydrogen phthalate (**12**) is thermally unstable at 80° and gives phthalic anhydride and *tert*-butyl hydroperoxide by a nonradical process. A mechanism for the reaction of **1** is proposed involving initial formation of **11**, which either abstracts hydrogen to form **12** or decarboxylates to form the *o*-(carbo-*tert*-butylperoxy)phenyl radical (**13**). The observed products are then formed by further reaction of **12** and **13**. *o*-Carbomethoxy-*o*′-isopropylbiphenyl (**10**), prepared by methylation of **4**, displays nonequivalent diastereotopic isopropyl methyl groups in the nmr owing to restricted rotation around the aryl–aryl bond at room temperature. This nonequivalence is greatly enhanced by the addition of tris-(dipivalomethanato)europium. The methyls remain nonequivalent below at least 105° in the noncomplexed case and 150° in the presence of the shift reagent.

Di-*tert*-butylperoxy phthalate (**1**) is a commerically available free-radical initiator with close structural similarities to 3,3-di-*tert*-butylperoxy phthalide (**2**)



1 2 3

and phthalyl peroxide (**3**). There has been great interest in the preparation and reactivity of **1**,[3a] **2**,[3] and **3**,[4] as well as other difunctional peresters and acyl peroxides, both cyclic[5] and noncyclic.[6] This investigation of **1** is part of a program in these laboratories to investigate intramolecular interactions between radicals and peroxides.[1]

There has been a brief report[7] on the kinetics of thermal decomposition of **1** in di-*n*-butyl phthalate solution measured by iodometric titration. We have measured the rate of reaction of **1** in cumene solution by observing the disappearance of the carbonyl band at 1770 cm^{-1} in the infrared. During the reaction new bands appear around 1790 (due to phthalic anhydride) and 1700 cm^{-1} (due to phthalic and benzoic acids) but satisfactory first-order kinetics for the disappearance of **1** were obtained using the absorption at 1770 cm^{-1} for up to one half-life. Rate constants and derived activation parameters obtained in this way are given in Table I, along with suitable data for comparison.[8,9]

Products for the decomposition of **1** in cumene were determined at 115° and are listed in Table II. After removal of gaseous and volatile products the residue was treated with KOH in ethanol and extracted with base, and the basic extract was acidified and treated with diazomethene. Analysis of the resulting material by vpc gave the yields of benzoic acid and the *o*-cumylbenzoic acids **4**–**6** (as their methyl esters), phthalic acid (as dimethyl phthalate), and phthalic anhydride (as methyl ethyl phthalate). The neutral residue from the base extraction was shown by vpc to consist of a number of minor products, of which the *o*-, *m*-, and *p*-cumylbenzenes (**7**–**9**) were identified.

o-Carbomethoxy-*o*′-isopropylbiphenyl (**10**), derived from methylation of the corresponding acid **4**, was identified by its unique nmr spectrum which shows nonequivalent isopropyl methyl groups at room temperature which coalesce near 110° (Figure 1). At 60 or 100 MHz methyl doublets ($J = 7.0$ Hz) appeared at δ 1.06 and 1.08; these methyl groups are rendered diastereotopic by the slow rotation around the aryl–aryl bond. However, the coalescence behavior of these peaks is somewhat anomalous, in that the signals appear to merge smoothly without prior line broadening. This may be due to the small chemical shift difference between signals causing the broadening to be imperceptible, or it may mean that the observed coalescence is an accidental equivalence caused by the temperature dependence of the solvation. The latter explanation is probably correct, because the observed coalescence temperature between 105 and 110° is

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TABLE I

RATE OF THERMAL DECOMPOSITION OF PERESTERS

Perester	Solvent	T, °C	k_1, sec^{-1} × 10^5	ΔH^*, kcal/mol	ΔS^*, eu	Ref
1	Cumene	130.1	26.0	33.6	7.8	
	Cumene	115.0	4.68			
	Cumene	99.9	0.834			
1	Di-*n*-butyl phthalate	130	48	37.0[a]	17.6[a]	7
		115	7.8			
		100	1.08			
XPhCO$_3$-*t*-Bu						
X = H	*p*-MePhCl	100	0.98[b]	33.6[b]	8.2[b]	8
X = *o*-*t*-Bu	PhCl	100	3.81	34.2	12.5	9

[a] Calculated from data in ref 7. [b] Calculated from data in ref 8.

TABLE II

PRODUCTS FROM THE THERMAL DECOMPOSITION OF DI-*tert*-BUTYLPEROXY PHTHALATE (1) AT 115° IN CUMENE

Product	Mole/mole of perester[a]
CO_2	1.15
CH_4	0.26
Acetone	0.27
t-BuOH	1.45
Benzene	0.26
Phthalic anhydride	0.11
Phthalic acid	0.03
Benzoic acid	0.04
Bicumyl	1.04
o-Cumylbenzoic acids 4–6	0.42[b]
o-Cumylbenzenes 7–9	~0.1[c]

[a] Yields of volatile products varied less than ±10% on duplicate runs, and other yields are estimated to be accurate to ±10%, except for the totals of 4–9, which may vary by ±0.1 mol/mol. [b] 35% ortho, 40% meta, 25% para. [c] 17% ortho, 57% meta, 26% para.

lower than what would be expected on the basis of the known coalescence temperatures of *o,o'*-di(acetoxymethyl)biphenyl (94–127°)[10] and *o,o'*-diisopropylbiphenyl (>200°).[11,12]

This interpretation received support from experiments using the shift reagent tris(divalomethanato)-europium [Eu(DPM)$_3$]. Addition of this reagent caused each of the methyl doublets to shift downfield, although the doublet originally at higher field was shifted more strongly and became the lower field absorption. At the highest concentration of Eu(DPM)$_3$ used, the pair of methyl doublets (J = 7 Hz) appeared at δ 1.72 and 2.15, respectively (Figure 2). When this solution of **10** and Eu(DPM)$_3$ was heated, the shift difference between the pair of doublets gradually decreased (analogous to the results of other studies of the temperature effect on lanthanide-induced chemical shifts).[13] However, above 100° the resolution obtainable rapidly deteriorated so that 150° was the highest temperature at which usable spectra could be obtained. At this temperature the pair of doublets had still not coalesced. This result indicates that the rotation around the aryl–aryl bond is still slow at this temperature, which is reasonable in view of the results cited above on analogous compounds.

(10) W. L. Meyer and R. B. Meyer, *J. Amer. Chem. Soc.*, **85**, 2170 (1963).
(11) H. Kessler, *Angew. Chem., Int. Ed. Eng.*, **9**, 219 (1970).
(12) We thank Professors M. Raban and T. H. Siddall, III, for helpful discussions regarding this point.
(13) (a) D. L. Rabenstein, *Anal. Chem.*, **43**, 1599 (1971); (b) R. R. Fraser, M. A. Petit, and J. K. Saunders, *Chem. Commun.*, 1450 (1971); (c) R. D. Bennett and R. E. Schuster, *Tetrahedron Lett.*, 673 (1972); (d) C. Beauté, S. Cornuel, D. Lelandais, N. Thoai, and Z. W. Wolkowski, *ibid.*, 1099 (1972).

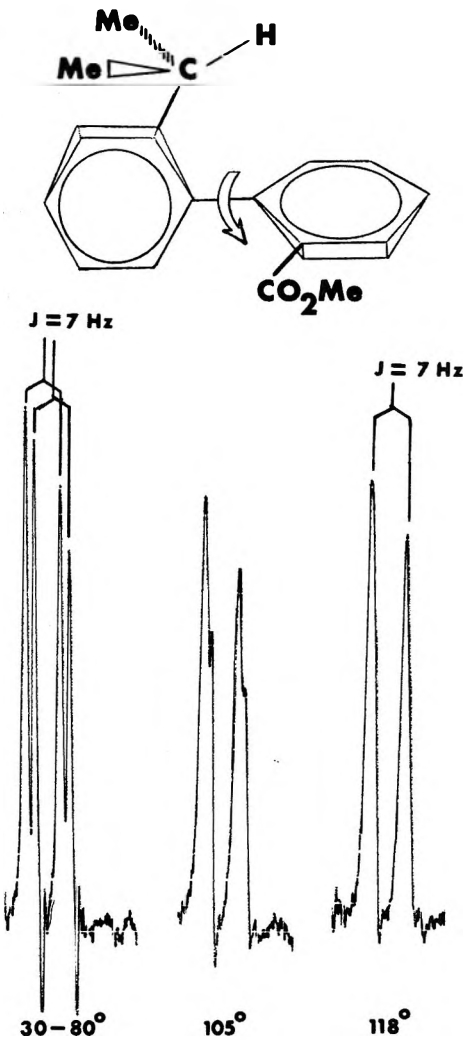


Figure 1.—Isopropyl portion of the nmr spectrum of *o*-carbomethoxy-*o'*-isopropylbiphenyl (**10**) at 60 MHz.

A mechanism to account for the rate data and the formation of the observed products is shown in Scheme I. The rate of disappearance of **1** is consistent with a normal one-bond homolysis leading to the *o*-(carbo-*tert*-butylperoxy)benzoate radical (**11**), without any rate acceleration due to participation by one perester grouping in the reaction of the other. Abstraction of hydrogen by **11** would lead to *tert*-butylperoxy hydrogen phthalate (**12**). This compound was shown in a separate experiment at 80° to undergo rapid transformation to the anhydride and *tert*-butyl hydroperoxide and would thus not be observed under the conditions used for the product study of **1**. Phthalic acid was

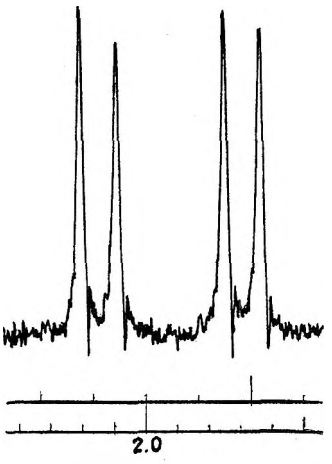
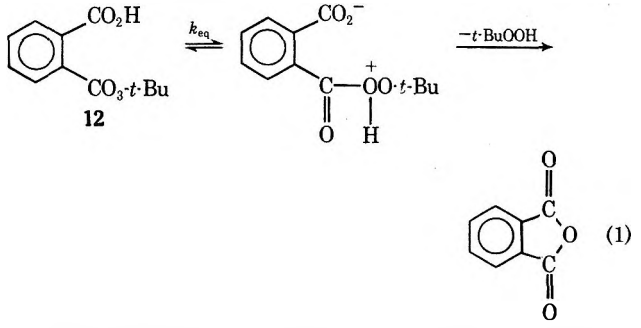


Figure 2.—Isopropyl portion of the nmr spectrum of *o*-carbomethoxy-*o'*-isopropylbiphenyl (10) with Eu(DPM)$_3$ at 60 MHz and 35°.

shown not to give formation of phthalic anhydride under the conditions of the product study. The formation of anhydride from the thermal reaction of **12** is consistent with the known thermal formation of phthalic anhydride from nonperoxidic half-esters of phthalic acid.[14] Several mechanisms have been considered for the latter process,[14] and a possible route for **12** is shown in eq 1.[15]



The product studies of the half-perester **12** at 80 and 115° (Table III) show the presence of small amounts

TABLE III

PRODUCTS FROM THE THERMAL DECOMPOSITION OF *tert*-BUTYLPEROXY HYDROGEN PHTHALATE (12) IN CUMENE

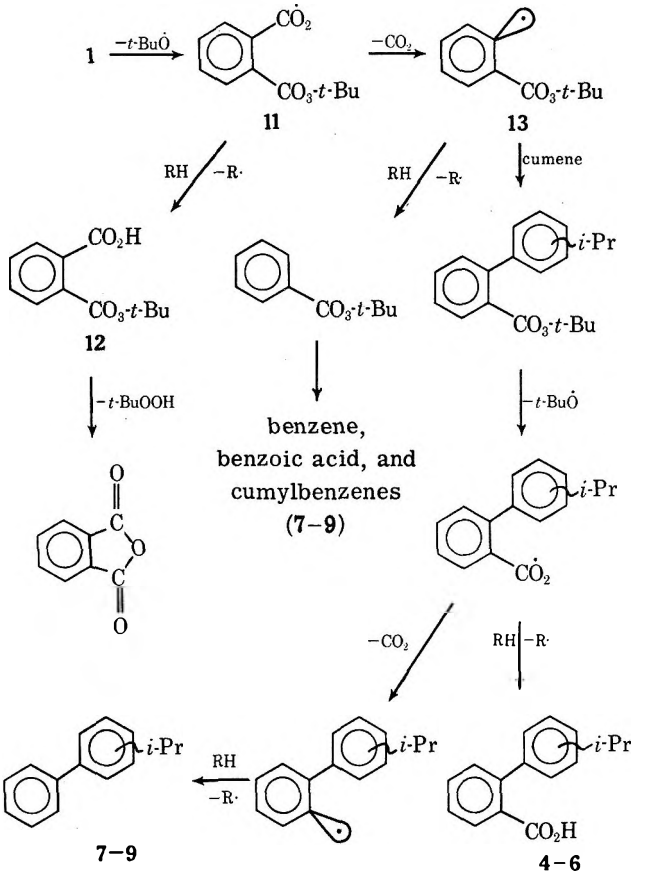
Product	Mole/mole of perester— 115°, 48 hr	80°, 4 hr
CO_2	0.02	0.01
CH_4	0.01	*a*
Acetone	Trace	*a*
t-BuOH	Trace	*a*
t-BuOOH	*a*	0.73
Phthalic anhydride	0.71	~1.0
Bicumyl	0.35	None
Phthalic acid	*b*	None

[a] Not examined. [b] Apparently present as shown by ir. All yields estimated ±10%.

of products derived from free-radical reactions. These products may indicate a small amount of homolytic dissociation of **12**, or may derive from an induced de-

SCHEME I

THERMAL DECOMPOSITION OF DI-*tert*-BUTYLPEROXY PHTHALATE (1)



composition route involving *tert*-butyl hydroperoxide. The latter compound undergoes slow reaction at 100°, and is itself subject to induced chain reaction.[16] The formation of phthalic acid from **12** at 115° indicates that **12** is the precursor of at least part of the phthalic acid observed in the reaction of **1**.

The formation of biphenyls in the reaction of **1** is in accord with results for the thermal decomposition of benzoyl peroxide in cumene. Two separate groups investigated the reactivity of phenyl radicals formed in this way. One group reported 60% abstraction and 40% ring substitution to give the isomeric isopropylbiphenyls in the ratio of 31% ortho, 42% meta, and 27% para,[17a] and the other group reported 47% abstraction with 53% ring substitution in the ratio 10% ortho, 60% meta, and 30% para.[17b] The difference between these analyses is presumably due to the inaccurate analytical techniques available at that time.

Other minor peaks were noticed in the gas chromatograms, and there are a variety of other products that could conceivably be formed in this reaction. Any of these products would constitute only a few per cent of the total, however.

Two conceivable SH2 displacement reactions of **11** are shown in eq 2, but neither is required to explain the observed results. Phthalyl peroxide (**3**) is known[18]

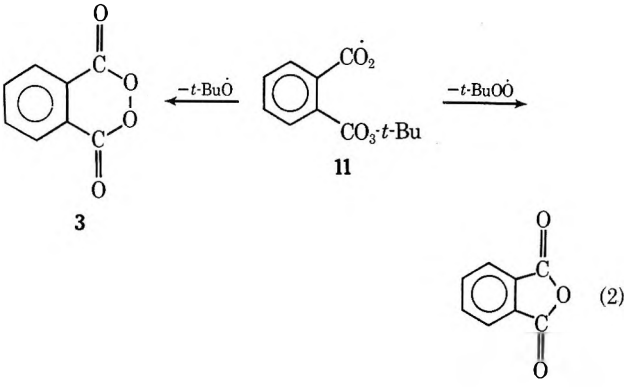
(14) J. W. Thanassi and T. C. Bruice, *J. Amer. Chem. Soc.*, **88**, 747 (1966).

(15) The formation of phthalic anhydride and *tert*-butyl hydroperoxide from **12** was discovered by T. D. Manly and D. R. Dixon and was cited by R. C. P. Cubbon, *Progr. React. Kinet.*, **5**, 29 (1970). We thank Dr. D. R. Dixon, ICI Ltd., Runcorn, Cheshire, for private communication of his results.

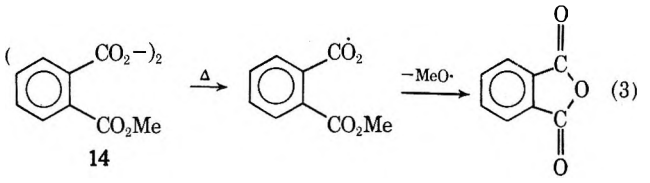
(16) R. Hiatt and K. C. Irwin, *J. Org. Chem.*, **33**, 1436 (1968).

(17) (a) D. H. Hey, B. W. Pengilly, and G. H. Williams, *J. Chem. Soc.*, 1463 (1956); (b) R. L. Dannley and B. Zaremsky, *J. Amer. Chem. Soc.*, **77**, 1588 (1955).

(18) (a) K. E. Russell, *ibid.*, **77**, 4814 (1955). (b) F. D. Greene, *ibid.*, **78**, 2246 (1956); **81**, 1503 (1959).



to be reactive under the conditions of our experiments and would probably not be detected even if it did occur. The SH2 reaction shown in eq 3 has been suggested[19] to occur in the reaction of *o,o'*-dicarbomethoxybenzoyl peroxide (**14**), but an alternative mechanism[19] involving



hydrogen abstraction and a nonradical cyclization to phthalic anhydride (analogous to eq 1) seems preferable.

Experimental Section

Di-*tert*-butylperoxy phthalate (1) (named in *Chemical Abstracts* as peroxyphthalic acid, di-*tert*-butyl ester) was prepared by the reaction of phthalyl chloride, potassium hydroxide, and *tert*-butyl hydroperoxide[20] and was purified by recrystallization from 2:1 pentane–ether at 0°, mp 48.5–49° (lit.[3b] mp 47–47.5°). The other crystal form,[3b] mp 57–57.5°, was also observed.

***tert*-Butylperoxy hydrogen phthalate** (12) was prepared by the reaction of phthalic anhydride, *tert*-butyl hydroperoxide, and pyridine[21] and was purified by recrystallization from 4:1 ether–pentane at 0°, mp 105–105.5° (lit.[21] mp 104–104.5°). The equivalent weight of the acid as determined by base titration was 236 (theory 238) and iodometric titration[22] indicated a purity of 96%.

Cumene was purified by washing with sulfuric acid until no further discoloration appeared, washing with water and sodium bicarbonate, drying over calcium chloride, and distillation under nitrogen from sodium at 148–148.5°.

Kinetic Method.—Rate runs were carried out by the ir method.[23] Sample tubes were washed first with nitric acid, then ammonium hydroxide and distilled water, and were thoroughly dried. In each tube was placed 0.5 ml of a 0.06 *M* solution of perester in cumene and the tubes were sealed without degassing. Tubes were placed in the constant-temperature bath and, after 5 min to equilibrate, were removed at intervals. The transmittance of each sample between 1900 and 1650 cm^{-1} was scanned using a Perkin-Elmer 621 spectrophotometer and 0.1-mm sodium chloride cells. Rate constants were calculated from the disappearance of the absorption at 1770 cm^{-1}. During the reaction other absorptions ascribed to phthalic anhydride and acids appeared, but good linear first-order rate plots were obtained during the period calculated to be the first half-life. At least two runs were made at each temperature, with a maximum deviation of ±3%.

Product Studies. I. Di-*tert*-butylperoxy Phthalate (1).—Product studies were carried out by the general procedure of Bartlett and Hiatt.[23] In a typical determination, 1.00 g (0.0034 mol) of perester was dissolved in 10 ml of purified cumene in a glass tube, degassed, and sealed. The sample was heated at 115° for 40 hr. (10 half-lives), cooled, and attached to a vacuum line. The tube was opened to the line *via* a break-seal and the carbon dioxide was absorbed on Ascarite. The amount of methane was determined from the residual pressure after the carbon dioxide had been absorbed. The identification was confirmed by mass spectrometry.

After determination of the gases, the material which was distillable at 25° (0.5 Torr) and trapped by a Dry Ice–isopropyl alcohol bath was removed. A weighed amount of cyclohexane was added as an internal standard, and the amounts of *tert*-butyl alcohol, acetone, and benzene were determined by vpc (10 ft × 1/8 in. 5% Carbowax 20M on 60/70 Chromosorb G). Identification was confirmed by isolation and spectral comparison with authentic samples.

The residual material was dissolved in hot absolute ethanol. On cooling bicumyl precipitated and was filtered, dried, and weighed. A 0.1 *N* solution of KOH in absolute ethanol was added to the filtrate and the solution was concentrated to a small volume *in vacuo;* water was added and the solution was extracted with chloroform.

The aqueous layer was acidified and extracted with ether (first by shaking and then by continuous extraction for 1 week). The combined ether fractions were dried ($MgSO_4$), concentrated, and treated with diazomethane in ether. A weighed amount of diethyl phthalate was added as an internal standard and the amounts of ethyl methyl phthalate (from phthalic anhydride) and dimethyl phthalate and methyl benzoate (from their respective acids) were determined by analytical vpc (10 ft × 1/8 in. 5% SE-30 on Chromosorb W). Identification was confirmed by isolation (preparative vpc on 10 ft × 1/8 n. 30% SE-30 on Chromosorb W) and spectral comparison with authentic samples. A control experiment with authentic phthalic anhydride gave a 95% conversion to ethyl methyl phthalate and 5% dimethyl phthalate.

Three other esters were also isolated from the reaction product and were identified as the three isomeric isopropyl-*o*-carbomethoxybiphenyls (from the corresponding acids 4–6) by their distinctive nmr spectra. The *o'*-isopropyl isomer (the first eluted) showed a pair of doublets for the diastereotopic isopropyl methyls resulting from slow rotation around the aryl–aryl bond. The yield of these isomers was taken as the difference in weight between the total weight of the acid residue and the combined weights of benzoic and phthalic acids and phthalic anhydride. The ratios of the separate isomers were determined by vpc integration.

The chloroform extract was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Preparative vpc (10 ft. × 3/8 in. 30% SE-30) gave numerous peaks, and the four major ones were isolated. The main fraction was shown to be bicumyl by comparison with authentic material. The three remaining components were identified as the isomeric cumylbenzenes (7–9) by their nmr spectra and comparison of their ir absorptions (ortho at 750, meta at 810, and para at 842 cm^{-1}) with those reported[17a] for these compounds.

The formation of phthalic anhydride was further confirmed by vpc isolation from material sublimed from the original solid reaction product and comparison with authentic material. Control experiments showed that the phthalic acid did not lead to phthalic anhydride under the reaction and work-up conditions.

II. *tert*-Butylperoxy Hydrogen Phthalate (12).—The volatile products [gases and material distillable at 25° (0.5 Torr)] from reaction at 115° were analyzed by the same procedure as the products of 1. Analysis of the residue by ir showed that phthalic anhydride was the major product, along with traces of acid and bicumyl. The residue was dissolved in warm chloroform and extracted with base. The chloroform layer was dried ($CaSO_4$) and concentrated *in vacuo* to afford a pale yellow solid. The major component of this solid (over 90%) was identified as bicumyl by vpc and spectral comparison with an authentic sample. The basic extract was acidified and extracted with ether. The ether fraction was dried ($CaSO_4$) and concentrated *in vacuo* to afford a white solid which was identified as phthalic acid by spectral comparison.

(19) G. I. Nikishin, E. K. Starostin, and B. A. Golovin, *Izv. Akad. Nauk SSSR, Ser. Khim.* 946 (1971), 327 (1972); *Chem. Abstr.*, **75**, 75902c (1971), **77**, 48104z (1972).

(20) N. A. Milas and D. M. Surgenor, *J. Amer. Chem. Soc.*, **68**, 642 (1946).

(21) A. G. Davies, R. V. Foster, and A. M. White, *J. Chem. Soc.*, 1541 (1952).

(22) L. S. Silbert and D. Swern, *Anal. Chem.*, **30**, 385 (1958).

(23) P. D. Bartlett and R. R. Hiatt, *J. Amer. Chem. Soc.*, **80**, 1398 (1958).

When the decomposition of **12** (0.512 g in 20 ml of cumene) was run at 80° for 4 hr, several modifications of the above procedure were used. The volatile liquids were distilled at 25° (0.5 Torr), collected in a Dry Ice–isopropyl alcohol trap, and made up to 25 ml with toluene. A 5-ml aliquot was subjected to iodometric titration. The peroxide content corresponded to a 73% yield of *tert*-butyl hydroperoxide. The solid residue from the distillation was shown by ir to be phthalic anhydride, with no detectable bicumyl or acids present.

Registry No.—**1**, 2155-71-7; **10**, 35356-77-5; **11**, 35356-78-6; **12**, 15042-77-0.

Ion Radicals. XXVI. Reaction of Perylene Perchlorate with Cyanide Ion[1]

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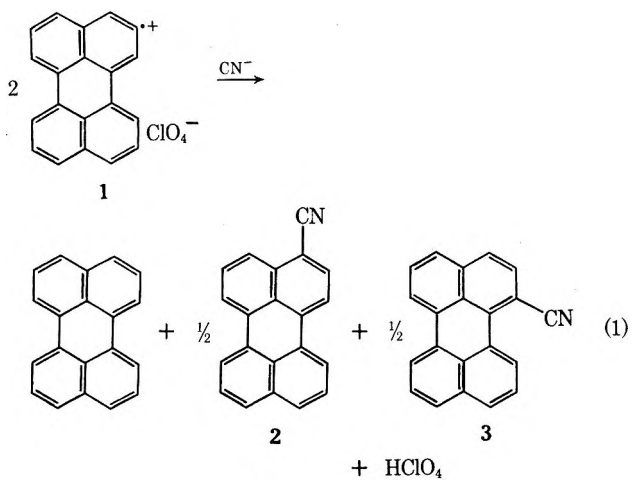
Received April 21, 1972

Reaction of perylene perchlorate (**1**) with potassium cyanide in acetonitrile gave both 3- (**2**) and 1-cyanoperylene (**3**), each in 13% yield. The structure of **3** was deduced from hydrolysis to the carboxylic acid and from reaction with $LiAlD_4$. Whereas reduction of **2** with $LiAlH_4$ led to 3-formylperylene, reaction of **3** with $LiAlD_4$ gave perylene-*1-d* (**4**) and 1′-aza-1,12-benzoperylene-*2′-d* (**5**). The reaction of **1** with cyanide ion is the first we have encountered of substitution in the 1 as well as 3 position of **1**. This is attributed to the high nucleophilicity, small size, and linearity of the cyanide ion.

In previous papers we have shown that perylene perchlorate (**1**) reacts with nucleophiles (NO_2^-, OAc^-, Bz^-, H_2O, pyridine) in the 3 position.[3,4] Charge densities in the perylene cation radical, according to the simple Hückel MO calculations,[5] are in accord with this, although one would anticipate that substitution in the 1 position (q = 0.084) might occur as well as in the 3 position (q = 0.110). This has now been achieved in reaction of **1** with cyanide ion. In addition to the anticipated perylene (eq 1) and 3-cyanoperylene (**2**),



a third product was formed which we deduce from its analysis, parent-peak mass number (277), and reactions to be 1-cyanoperylene (**3**). We believe the stoichiometry[3,4] of reaction to be as shown in eq 1, according to which the yields of **2** and **3** were each 26% of those anticipated, while the yield of perylene was greater than 100%, signifying that perylene was formed also by another reaction, *e.g.*, reduction by cyanide ion.

Compound **2** is known, having been made *via* the sequence perylene → 3-formylperylene → 3-formylperylene oxime → **2**.[6] We confirmed the structure of our **2** by hydrolysis to perylene-3-carboxylic acid,[6,7] by reduction with lithium aluminum hydride to 3-formylperylene,[6] and by oxidation of the 3-formylperylene to perylene-3-carboxylic acid, as well as by the direct synthesis of authentic **2**.[6]

As far as we are aware, compound **3** is new. Very few 1-substituted perylenes are known,[8-10] and we have deduced the structure in the following ways.

Hydrolysis of **3** gave a carboxylic acid, mp 395°. The only known perylenecarboxylic acids are perylene-3- (mp 335°) and perylene-2-carboxylic acid (mp 342°).[9] The acid with mp 395° had an ultraviolet spectrum similar to but not identical with the spectra of the known acids. The electronic spectra of perylene and its derivatives (alkyl,[10] acyl,[7] and carboxyl[7]) have numerous bands, and our acid, believed to be perylene-1-carboxylic acid, is no exception.

Zieger attempted to synthesize perylene-1-carboxylic acid by two routes starting with 1-bromohexahydroperylene, but was unsuccessful.[7] We also were unsuccessful in our attempts to prepare an authentic sample of the acid by oxidation of 1-methylperylene[8] with aqueous chromic acid, chromium trioxide in acetic acid, and potassium permanganate in acetone. We were unable to isolate products of oxidation, and it is perhaps possible that the perylene ring itself is too susceptible to oxidation to permit alkyl-group oxidation only. We were also unable to reduce **3** to 1-methylperylene by the technique of boiling with limonene over 5% palladium on charcoal.[11]

Further evidence for the structure of **3** was obtained by reduction with lithium aluminum deuteride ($LiAlD_4$). Reduction of **2** with $LiAlH_4$ led to 3-formylperylene easily. Reduction of **3** with $LiAlH_4$ gave perylene and another compound, isomeric with **3**, whose structure is discussed later. The course of reduction was discerned by use of $LiAlD_4$. This gave

(1) Part XXV: H. J. Shine, J. J. Silber, R. J. Bussey, and T. Okuyama, *J. Org. Chem.*, **37**, 2691 (1972). Supported by the National Science Foundation, Grant No. GP-25989X.

(2) Postdoctoral Fellow, 1970–1971, supported by a grant from Texas Tech University, no. 191-4719.

(3) C. V. Ristagno and H. J. Shine, *J. Amer. Chem. Soc.*, **93**, 1811 (1971).

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(5) C. A. Coulson and A. Streitwieser, Jr., "Dictionary of π-Electron Calculations," Pergamon Press, New York, N. Y., 1965.

(6) N. P. Buu-Hoi and C. T. Long, *Recl. Trav. Chim. Pays-Bas*, **75**, 1221 (1956).

(7) H. E. Zieger, Ph.D. Dissertation, Pennsylvania State University, 1961.

(8) H. E. Zieger and E. M. Laski, *Tetrahedron Lett.*, 3801 (1966).

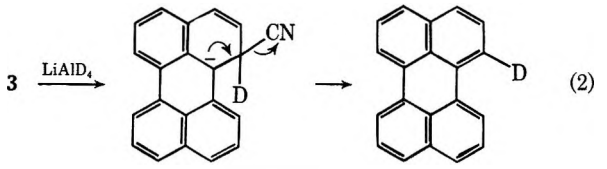
(9) H. E. Zieger, *J. Org. Chem.*, **21**, 2977 (1966).

(10) H. E. Zieger and J. E. Rosenkranz, *J. Org. Chem.*, **29**, 2469 (1964).

(11) K. Kindler and K. Luhrs, *Ber.*, **99**, 227 (1966).

perylene-*1-d* (**4**, 22% yield), whose identity was established by the nmr spectrum of its dianion.

The nmr spectrum of perylene-*1-d* itself was not clearly analyzable. Perylene dianion has a more clearly resolved spectrum,[12] and the effect of deuterium substitution should be more easily discernible in the dianion than in the parent hydrocarbon. This proved to be the case, as is shown in Figure 1. The splitting pattern for H-2 in the *1-d* dianion is no longer the triplet of the *1-h* dianion. Instead, a five-line pattern is observed, consisting of a triplet for H-2 (J = 8 Hz) and a doublet for H-2′ (J = 7 Hz). The multiplet for the H-1, H-2 protons is distorted in the spectrum of the *1-d* dianion, and integration of the spectrum gave, as anticipated, a ratio H(1,3,3′):H(2,2′) of 7:4. Integration of the undeuterated dianion spectrum gave the expected ratio 8:4. It is evident that attempted reduction of **3** ended in replacement of cyanide by deuteride ion (eq 2).



(2)

The second product (54% yield) from attempted reduction of **3** is believed to be a new compound, 1′-aza-1,12-benzoperylene-*2′-d* (**5**). This compound is like its carbocycle analog 1,12-benzoperylene (**6**).[13] Both compounds crystallize in yellow-green plates, and have similar ultraviolet spectra (Table I).

TABLE I

ULTRAVIOLET SPECTRA OF 1,12-BENZOPERYLENE (**6**)[a] AND 1′-AZA-1,12-BENZOPERYLENE-*2′-d* (**5**) IN ETHANOL

Compd	Spectrum, nm (log ε)[b]
5[c]	413 (3.93), 389 (3.87), 376 (4.02), 370 (4.03), 358 (3.96), 330 (3.61), 315 (3.55), 298 (4.40)
6[b]	407 (2.70), 388 (4.50), 367 (4.40), 348 (4.00), 331 (3.82), 303 (4.76), 292 (4.65)

[a] Reference 13. [b] Wavelengths have been rounded off to whole numbers. [c] We thank Mr. J. D. Cheng for recording the ultraviolet spectrum.

Further evidence in support of structure **5** was obtained from the change in ultraviolet spectrum on acidifying the solution (see Experimental Section). A shift to longer wavelengths occurred, which was reversed by neutralizing the acid. This behavior is characteristic of aza hydrocarbons of this type, *e.g.*, 9-azaphenanthrene.[14] In the case of **5** addition of acid also causes an increase in fine structure, and the spectrum had characteristics similar to those of a substituted perylene.

The parent-peak mass number of **5** was 278, as required by the proposed structure.

(12) C. V. Ristagno and R. G. Lawler, *J. Amer. Chem. Soc.*, **91**, 1534 (1969).

(13) E. Clar, "Polycyclic Hydrocarbons," Vol. 2, Academic Press, New York, N. Y., 1964, p 62.

(14) J. Nasielski and E. Vander Donckt, *Spectrochim. Acta*, **19**, 1989 (1963).

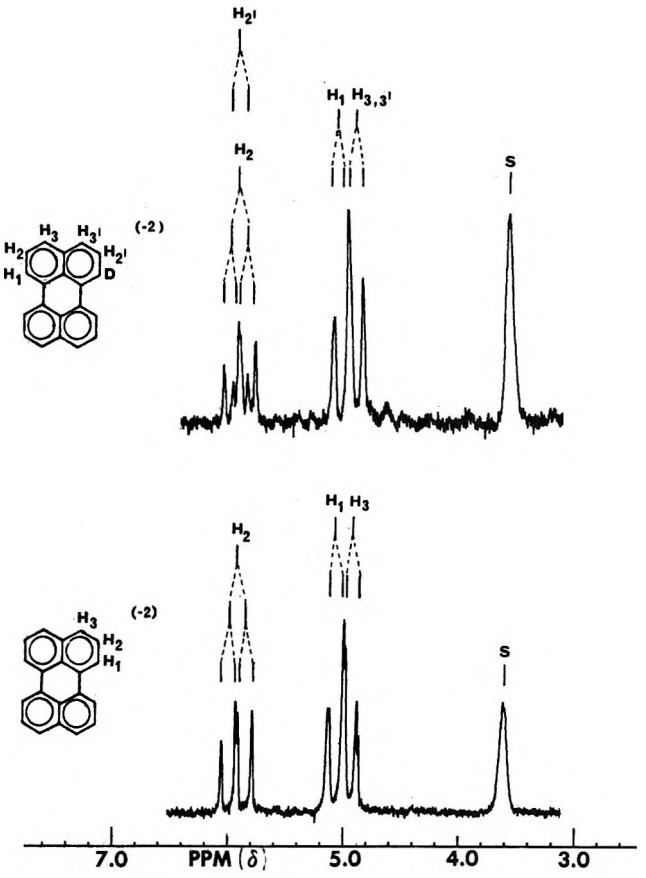
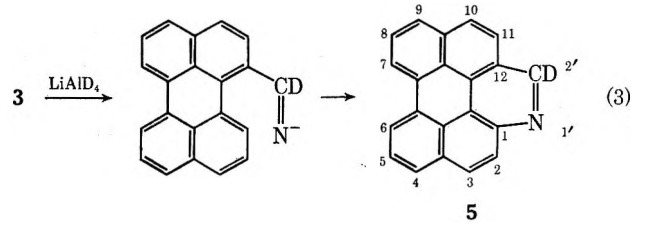


Figure 1.—60-MHz spectra of perylene dianion and perylene-*1-d* dianion in THF-d_8. The counterion is sodium. The peak (s) at 3.6 ppm arises from THF-d_7.

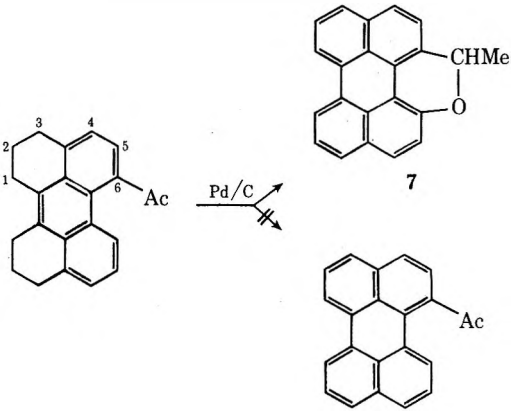
It appears that reaction of **3** with hydride (deuteride) ion results in cyclization (eq 3) as well as cyanide-ion



(3)

5

displacement. A similar reaction has been proposed for the attempted dehydrogenation of 6-acetylhexahydroperylene, which led instead to the cyclic ether **7**.[9]



In contrast, 5-acetylhexahydroperylene underwent the desired dehydrogenation. The situation is similar to our results with reduction of **2** and attempted reduction

of 3. That is, the groups in the 1 position of perylene seem not to behave like those in the 2 and 3 positions. We have not been able to find information in the literature on hydride reductions of compounds analogous to 3, *e.g.*, 4-cyanophenanthrene, and we have begun to study such compounds ourselves.

The reaction of 1 with cyanide ion constitutes, as far as we know, the most straightforward preparation of monocyanoperylenes. Anodic cyanation is a fairly well-known technique[15] but also, as far as we know, has not been applied to perylene.

The literature contains references to the formation of dicyanoperylenes by reaction of dihalogenoperylenes with cyanide ion.[16] Attempts to make a monocyanoperylene were unsuccessful until the work of Buu-Hoi with 2.[6]

The formation of 1-cyanoperylene from reaction of 1 with cyanide ion may be attributable to the linearity, small size, and high nucleophilicity of the cyanide ion. We have attempted a similar reaction with azide ion, but the reaction is much more complex than the cyanide-ion reaction and is still being pursued.

Experimental Section

Perylene perchlorate (1) was prepared electrochemically. Our earlier technique[4] was altered to give a mixture of 1 and perylene which contained 94% instead of 60–70% of 1. In place of the H cell, a copper cathode was placed in a Soxhlet thimble which contained electrolyte solution. The thimble was suspended within the cylindrical platinum gauze anode (Sargent-Welch, S-29672, diameter 40 mm, height 35 mm) held in a solution of electrolyte and perylene. Portions of perylene were added to the anode solution periodically during electrolysis, which proceeded for 1–2 hr at 1.2 V. The content of 1 in the solid which deposited on the anode was determined by iodimetry.[5]

Reaction of 1 with KCN.—A suspension of 65 mg (1.0 mmol) of KCN (previously crystallized from methanol and dried under vacuum) in 50 ml of acetonitrile (MeCN) was stirred under nitrogen in an erlenmeyer flask. To this was added 105 mg (0.28 effective mmol) of 1. The resulting purple mixture was stirred for 15 min, after which time it became yellow-brown, had a strong green fluorescence, and gave a negative starch–iodide test for cation radical. Unreacted KCN was filtered off and washed well with warm benzene. Tlc on both silica gel and alumina gave three spots. Column chromatography [4 × 50 cm, silica gel 70-325 mesh ASTM, E. Merck, 2:1 petroleum ether (bp 30–60°):benzene] gave two fractions. The first was perylene, 48 mg (0.19 mmol, 68%). The second consisted of 22 mg of orange solid, mp 160–167°, which gave two spots on tlc, and whose ir (KBr) had bands at 2212 and 2225 cm^{-1}. Column chromatography of the orange solid (4 × 50 cm, neutral alumina, Woelm, 2:1 petroleum ether:benzene) gave two 10-mg (0.036 mmol, 13%) fractions. Each was crystallized from ethanol. The first eluted compound was shown (see later) to be 1-cyanoperylene (3), mp 236–237°.

Anal. Calcd for $C_{21}H_{11}N$: C, 91.0; H, 3.97; N, 5.05. Found: C, 91.0; H, 4.19; N, 5.31.

Compound 3 had λ_{max} (methanol) at 452, 429, 288, and 261 nm, and ir $-C\equiv N$ at 2212 cm^{-1}. The mass spectrum showed a parent-peak mass number of 277.

The second eluted compound was shown (see below) to be 3-cyanoperylene (2), mp 231–232° (lit.[6] mp 228°).

Anal. Calcd for $C_{21}H_{11}N$: C, 91.0; H, 3.97; N, 5.05. Found: C, 91.2; H, 4.25; N, 5.21.

Compound 2 had λ_{max} (methanol) at 452, 429, 256, and 249 (sh) nm, and ir $-C\equiv N$ at 2225 cm^{-1}.

(15) N. L. Weinberg and H. R. Weinberg, *Chem. Rev.*, **68**, 449 (1968).
(16) A. Pongratz, *Monatsh. Chem.*, **48**, 639 (1927).

Synthesis of Authentic 3-Cyanoperylene.—A sample of 3-formylperylene, mp 233–234° (lit.[6] mp 236°), was prepared. This was converted into the oxime, mp 255°, and the oxime was dehydrated as described,[6] giving 3-cyanoperylene, mp 230–231° (ethanol), undepressed by mixture with 2.

Hydrolysis of 2 to Perylene-3-carboxylic Acid.—A solution of 20 mg (0.072 mmol) of 2 in 5 ml of ethanol and 5 ml of dioxane was boiled over solid NaOH for 72 hr. The solution was decanted, the solvent was removed under vacuum, and the yellow solid was washed with water and benzene. The solid was then stirred with 50 ml of 10% hydrochloric acid for 2 hr and collected, giving 20 mg (0.068 mmol, 94%) of orange solid. Crystallization from acetic acid gave perylene-3-carboxylic acid: mp 333° dec; λ_{max} (methanol) 441, 416, 393 (sh), and 247 (sh) nm; ir bands at 3200–2300 (br) and 1680 cm^{-1}.

Synthesis of Authentic Perylene-3-carboxylic Acid.—A solution of 12.5 mg (0.045 mmol) of 3-formylperylene in 10 ml of acetone was stirred at 50° with an excess of aqueous $KMnO_4$ solution for 3 hr. Precipitated MnO_2 was filtered and the solvent was removed under vacuum. Extraction of the residue with hot benzene gave 4 mg (0.014 mmol, 33%) of perylene-3-carboxylic acid, mp 332° dec (lit.[6] mp 334° from hydrolysis of 3-cyanoperylene).

Reduction of 2 with $LiAlH_4$ to 3-Formylperylene.—To a solution of 10 mg (0.036 mmol) of 2 in 25 ml of dry THF at 0° was added several milligrams of $LiAlH_4$. The mixture was stirred under nitrogen for 1 hr at 0°, poured onto ice-cold 10% hydrochloric acid, and extracted with benzene, giving 8 mg (0.028 mmol, 79%) of 3-formylperylene, mp 232–234°.

Hydrolysis of 3 to Perylene-1-carboxylic Acid.—The method was as described for the hydrolysis of 2, and gave 16 mg (0.054 mmol, 75%) of what we believe to be perylene-1-carboxylic acid: mp 395° (1:1 benzene:acetic acid); λ_{max} (methanol) 441, 417, 395, 371, 356, 284, and 274 nm; ir bands at 3200–2300 (br) and 1660 cm^{-1}.

Anal. Calcd for $C_{21}H_{12}O_2$: C, 85.1; H, 4.05. Found: C, 85.0; H, 4.15.

These characteristics do not correspond with those reported for perylene-3-[6,7] and perylene-2-carboxylic acid.[7]

Reaction of 3 with $LiAlD_4$.—Several attempts to reduce 3 with $LiAlH_4$ to 1-formylperylene failed and gave, in part, perylene instead. In order to diagnose the course of this reaction, $LiAlD_4$ (99% *d*, Merck Sharp, and Dohme) was used. To a cold (−5°) solution of 60 mg (0.22 mmol) of 3 in 30 ml of dry THF was added a cold solution of 20 mg (0.77 effective mmol) of $LiAlD_4$. The solution was stirred for 4 hr, decomposed by adding 5 ml of 15% aqueous NaOH, diluted with saturated aqueous NaCl, and extracted with benzene. The benzene extract was chromatographed on neutral alumina (Woelm). Elution with benzene gave 12 mg (0.05 mmol, 22%) of perylene-*1-d* (4). Elution with 10:1 benzene:ether gave 32 mg (0.12 mmol, 54%) of yellow-green solid, mp 307–308°, which we believe to have the structure 5.

Anal. Calcd for $C_{21}H_{10}DN$: C, 90.6; H, 4.34; N, 5.03. Found: C, 90.7, 90.9; H, 3.84, 4.08; N, 4.93.

The mass spectrum showed a parent-peak mass number of 278.

Addition of acid to the solid or its solution gave λ_{max} 445, 420, 377, 358, 300, 277, and 250 nm. This shift to longer wavelengths was reversed by adding base to the acidic solution.

Conversion of 4 to Perylene-*1-d* Dianion.—4 (12 mg) was placed in an nmr tube. A small piece of sodium was held in the top of the tube by a constriction, and the tube was sealed into a glass assembly attached to a reservoir containing dry THF-d_8. After the assembly was evacuated, *ca.* 0.5 ml of THF-d_8 was distilled into the nmr tube. Reduction of 4 was accomplished by bringing the solution in contact with the sodium over a period of several hours. The nmr spectrum was recorded on a Varian A-60A spectrometer and is given in Figure 1.

Registry No.—1, 12576-63-5; 2, 35426-74-5; 3, 35426-75-6; 5, 35426-76-7; 6, 191-24-2; perylene-3-carboxylic acid, 7350-88-1; 3-formylperylene, 35438-63-2; perylene-1-carboxylic acid, 35426-79-0; cyanide ion, 57-12-5.

The Hydrolysis of Salicylanilide Carbamates

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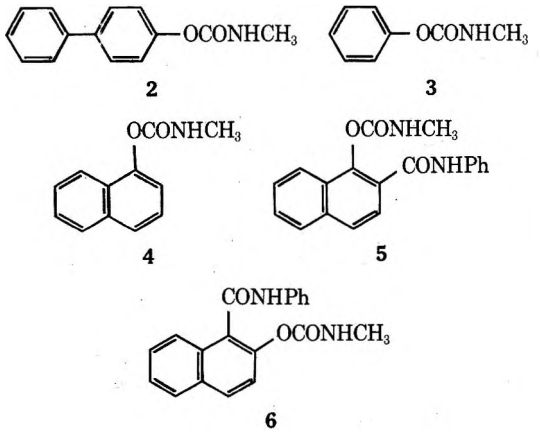
A series of substituted salicylanilide carbamates has been prepared and the rate of hydrolysis of these compounds investigated. The mechanism of the hydroxide ion catalyzed hydrolysis of the carbamates with neighboring-group participation is discussed.

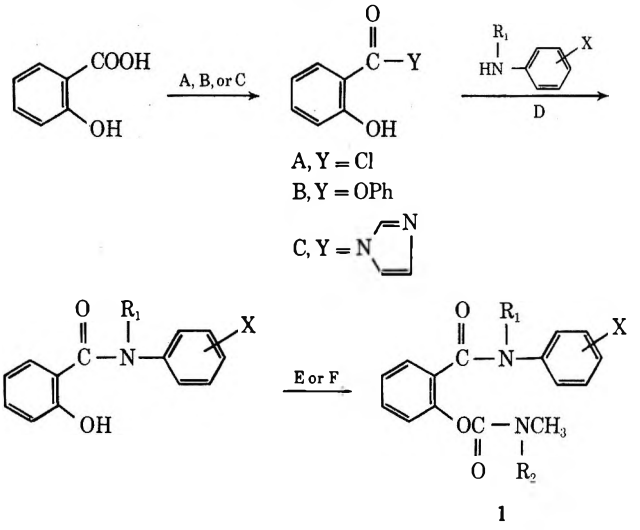
In the course of studying the biological activity of salicylanilide *N*-methylcarbamate (**1e**), we had occasion to determine the stability of this compound at various pH levels, particularly at pH 2 and pH 7.3 such as would be found in the stomach and blood serum. While **1e** is stable in strongly acidic media at 37°, it undergoes rapid hydrolysis at the phenol carbamate bond at or above pH 7.3. In contrast 4-biphenylyl *N*-methylcarbamate (**2**), phenyl *N*-methylcarbamate (**3**), and 1-naphthyl *N*-methylcarbamate (**4**) do not exhibit this susceptibility to alkaline hydrolysis. The facile removal of the carbamate group from **1e** appears to involve participation by the neighboring *o*-carboxanilide function. There are numerous literature examples[1] of participation by neighboring groups in the hydrolysis of esters and amides. This report describes the hydrolysis of a group of aryl carbamates with participation by a neighboring amide function.

Results and Discussion

Syntheses.—The interesting antiinflammatory activity of **1e** led us to search for analogs with greater stability toward hydrolysis and equal or greater biological activity. Compounds **1a–k** (see Table I) and **2–6** were synthesized for stability and activity evaluations as well as for studying the mechanism of this facile hydrolysis. The syntheses were carried out as shown in Scheme I. Salicylic acid was converted to its substituted anilides *via* its acid chloride, phenyl ester, or imidazolide. The anilides were then treated with either MeNCO or Me_2NCOCl to give the desired salicylanilide carbamates (**1**). Compounds **2–6** were



SCHEME I



also obtained in a similar manner by treating the appropriate phenols and naphthols with MeNCO. Table I lists the methods of preparation and melting points of these compounds.

TABLE I

PREPARATION OF ARYL CARBAMATES

Compd[b]	Structure (1) R1	R2	X	Method of prepn	Mp, °C[a]
1a	H	H	4-CN	A, D, E	163.5–164.5
1b	H	H	4-COMe	A, D, E	204–205.5
1c	H	H	4-CO_2Et	A, D, E	168.5–170
1d	H	H	4-Cl	B, D, E	159–161
1e[c]	H	H	H	E	160–161
1f	H	H	4-OMe	B, D, E	158–160
1g	H	H	4-OH	A, D, E[d]	174.5–176
1h	H	H	2,6-Di-Me	A, D, E	164–166
1i	Me	H	H	A, D, E	125–127
1j	Ph	H	H	A, D, E	162.5–164
1k	H	Me	H	F	110–111
5				C, D, E	181–182
6				C, D, E	177–179

[a] Melting points are uncorrected. [b] Satisfactory analytical data (±0.4% for C, N, H) were reported for all new compounds listed in the table: Ed. [c] Prepared by Dr. R. E. Strube. [d] Compound **1g** was obtained as its *o*-benzyl derivative by the indicated route of synthesis. The benzyl ether was then hydrogenolyzed in the presence of 10% Pd/C catalyst to give **1g**.

Hydrolysis Studies.—The hydrolytic reactions were followed by uv spectrophotometry in buffered 50% (v/v) H_2O–EtOH. Analytical wavelengths were selected so that, in each case, increasing absorbance (A_t) was measured at the maximum or prominent shoulder characteristic of the product in the reaction medium (Table II). Although in many cases the

(1) (a) M. S. Newman and S. Hishida, *J. Amer. Chem. Soc.*, **84**, 3582 (1962); (b) M. L. Bender and M. S. Silver, *ibid.*, **84**, 4589 (1962); (c) F. Ramierez, B. Hansen, and N. B. Desai, *ibid.*, **84**, 4588 (1962); (d) J. Zabicky, *Chem. Ind. (London)*, 236 (1964), and references therein; (e) G. L. Schmir and C. Zioudrou, *Biochemistry*, **2**, 1305 (1963); (f) T. Cohen and J. Lipowitz, *J. Amer. Chem. Soc.*, **83**, 4866 (1961); (g) J. A. Shafer and H. Morawetz, *J. Org. Chem.*, **28**, 1899 (1963); (h) M. T. Behme and E. H. Cordes, *ibid.*, **29**, 1255 (1964).

TABLE II

HYDROLYSIS OF ARYL CARBAMATES TO PHENOLS AT 37° IN BUFFERED AQUEOUS ALCOHOL

Compd	Molar concn	Wavelength,[a] nm	Apparent pH of reaction mixtures	k_{OH^-},[b] l. mol^{-1} min^{-1}	Relative stability[c]
1a	6.01×10^{-5}	308	5.4, 6.0, 6.6[d]	3.89×10^5	0.51
1b	8.01×10^{-5}	325	5.4, 6.0, 6.6[d]	3.07×10^5	0.64
1c	4.75×10^{-5}	308	5.4, 6.0, 6.6[d]	3.07×10^5	0.64
1d	6.25×10^{-5}	300	5.4, 6.0, 6.6[d]	2.37×10^5	0.84
1e	9.26×10^{-5}	300	5.4, 6.0, 6.6[d]	1.98×10^5	1.00
1f	7.10×10^{-5}	310	5.4, 6.0, 6.6[d]	1.52×10^5	1.30
1g	3.41×10^{-5}	305	5.4, 6.0, 6.6[d]	1.30×10^5	1.52
1h	6.87×10^{-5}	300	5.4, 6.0, 6.6[d]	1.10×10^5	1.80
1i	1.92×10^{-4}	285	7.4, 8.1, 8.6[e]	2.71×10^2	7.31×10^2
1j	1.04×10^{-4}	285	7.4, 8.0, 8.6[e]	2.60×10^2	7.62×10^2
1k	1.25×10^{-4}	337	10.1, 10.9[f]	5.93×10^{-2}	3.34×10^6
2	8.80×10^{-5}	275	10.0, 10.3, 10.6[f]	5.51×10^1	3.59×10^3
	6.06×10^{-5}		8.0, 8.6[e]	1.05×10^2	1.89×10^3
3	4.23×10^{-4}	277	9.9, 10.2, 10.6[f]	1.96×10^1	1.01×10^4
4	1.55×10^{-4}	308	9.8, 10.2, 10.6[f]	4.94×10^1	4.01×10^3
5	5.17×10^{-5}	346	5.3, 5.85, 6.4[d]	1.57×10^6	0.13
6	1.84×10^{-4}	332	7.4, 8.03, 8.55[e]	3.52×10^3	5.63×10^1

[a] At which reaction was followed. [b] Mean of data for the indicated buffer system. [c] Relative stability = k_{OH^-} of **1e**/k_{OH^-} of compound. [d] Acetate buffers. [e] Phosphate buffers. [f] Borate buffers.

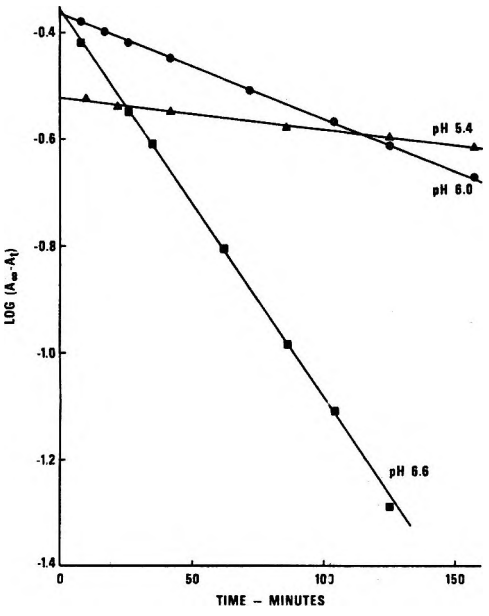


Figure 1.—First-order rate curves for hydrolysis of salicylanilide *N*-methylcarbamate (**1e**) as a function of pH at 37° in 50% EtOH–H_2O.

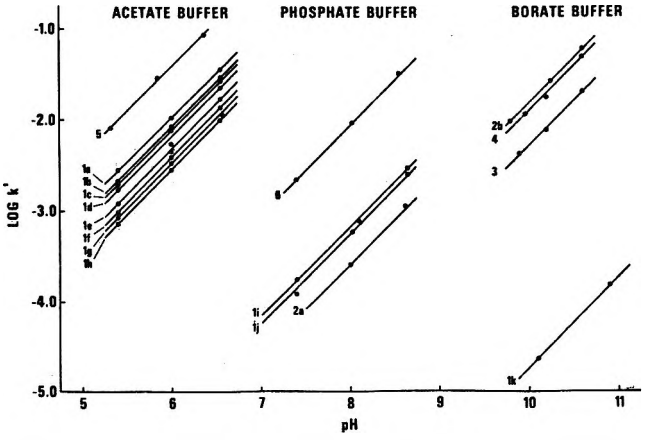


Figure 2.—Plot of log k' *vs.* pH for compounds **1a–k**, **2–6** at 37° in 50% EtOH–H_2O.

parent carbamate also absorbed at this wavelength, the difference in absorptivity for the carbamate and its respective salicylanilide (or phenol) was adequate for accurate determination of the reaction rate. To determine if carbamate hydrolysis was accompanied by significant simultaneous or subsequent hydrolysis of the anilide group, salicylanilide and several of its substituted analogs were examined spectrophotometrically under the reaction conditions. No evidence for anilide hydrolysis was observed. Moreover, in each rate study, hydrolysis of the parent carbamate gave a final uv spectrum which was stable, identical with that of the product anilide (or phenol), but different from that of a mixture of salicylic acid and $PhNH_2$ (or its appropriate analog). Therefore, the specificity of the method chosen for study of the carbamate hydrolysis was established.

Higuchi and Dittert[2] have shown that the hydrolysis of certain carbamates is first order in both hydroxide ion and carbamate. In the present studies a plot of log $(A_\infty - A_t)$ *vs.* time (t) at each pH for each carbamate, such as shown in Figure 1 for salicylanilide *N*-methylcarbamate (**1e**), was linear, confirming the first-order dependence on carbamate. Slopes of these plots provided pseudo-first-order constants, k'. For each carbamate studied, a plot of log k' *vs.* pH was linear with a slope of unity (Figure 2) establishing first-order dependence on hydroxide ion and permitting calculation of the specific reaction rate constants, k_{OH^-}, presented in Table II. Comparative hydrolytic stabilities, based on compound **1e** as a standard, are also shown in Table II.

The extremely low solubilities of the carbamates in H_2O dictated the use of H_2O–EtOH as solvent in these studies. Accordingly, pH values reported must be considered as apparent ones because of the liquid junction potential between the reference electrode and the solvent. The k_{OH^-} for compound **1e** with acetate buffer in H_2O–EtOH (Table II) is in good agreement with the value (1.30×10^5 l. mol^{-1} min^{-1}) reported for its

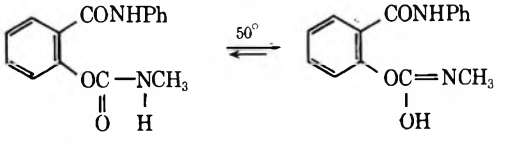
(2) T. Higuchi and L. W. Dittert, *J. Pharm. Sci.*, **52**, 852 (1963).

hydrolysis in a water–diglyme mixture with phosphate buffers, where the nonaqueous component was an inert solvent.[3] Thus, EtOH exerted a relatively minor effect on the hydrolysis rate of **1e**, even in the more basic medium.

In most cases (compounds **1a–h** and **5**), acetate buffers of constant ionic strength were employed. However, the slow rates of hydrolysis exhibited by the more stable compounds required use of more basic buffer systems, *e.g.*, phosphate and borate. The validity of comparing reaction rates obtained in two different buffer systems was examined for compound **2**. Observed k_{OH^-} values in phosphate and borate buffers (Table II and curves 2a and 2b, respectively, Figure 2) differed by less than a factor of two. In contrast, the smallest difference between hydrolysis rates of compounds studied in phosphate and borate buffers compared to those in the acetate system exceeded a factor of 30 (**6** *vs.* **1h**, Table II). Thus, although the use of different buffers affected the hydrolysis rates, these effects were small compared to the wide range of stability of the carbamates investigated. It is therefore felt that comparisons of rate data obtained in different buffer systems, *e.g.*, **1e** *vs.* **1i**, **1j**, **1k**, **2**, **3**, **4**, and **6**, were justified.

Mechanism of Hydrolysis.—The rate studies showed that the hydrolysis of the carbamates listed in Table II was first order with respect to both hydroxide ion and carbamate. Neighboring-group participation in the reaction was clearly demonstrated by the large difference between the hydrolysis rates of **1e** and **3** or **4** and **5**. Indeed all of the bifunctional compounds were hydrolyzed faster than the monofunctional ones by several orders of magnitude. In the three exceptional cases, either the anilide (**1i** and **1j**) or the carbamate (**1k**) nitrogen was disubstituted. Higuchi and Dittert[2] have shown that N,N-disubstituted aryl carbamates are 10^5 to 10^6 times as resistant toward hydrolysis as the corresponding monosubstituted compounds. N,N-Disubstituted amides likewise are known to hydrolyze with greater difficulty than monosubstituted ones. This stabilizing effect of full substitution on nitrogen can be reasonably expected to extend to the anchimerically assisted hydrolysis such as in **1i–k**.

Reasonable mechanisms for the alkaline hydrolysis of **1e** can be written with initial attack by hydroxide ion on either the anilide or the carbamate function. The latter is supported by nmr studies. The spectrum of **1e** in DMF-d_7 with Me_4Si as standard showed singlets at 630 (OH, structure **8**), 600 (anilide NH), and 182 Hz (CH_3, structure **8**), a doublet at 167 and 162 Hz (CH_3, structure **7**), as well as a complex aromatic hydrogen



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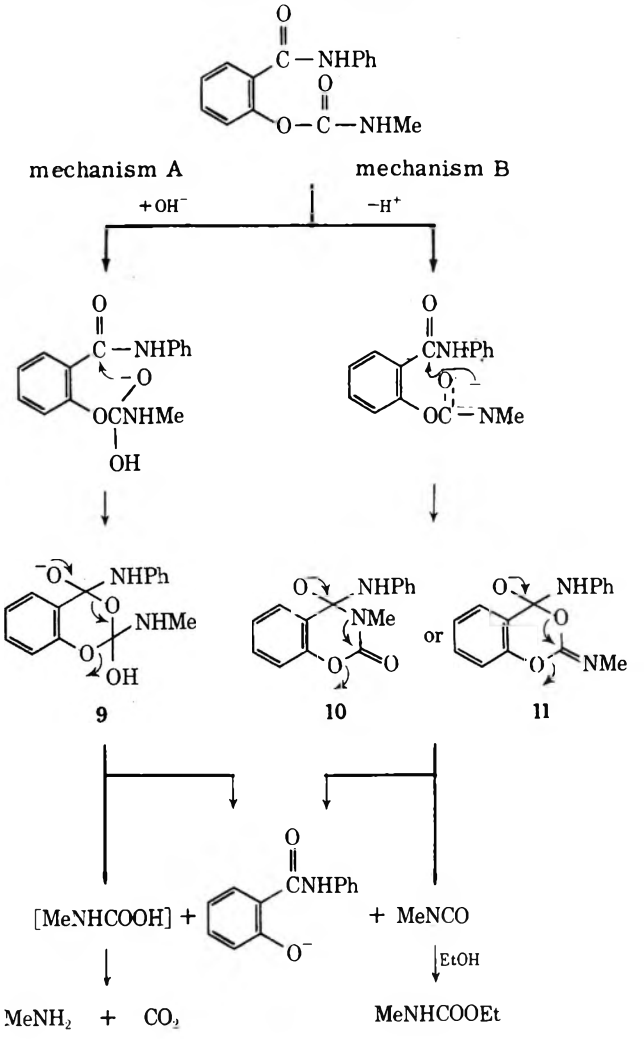
pattern at 480–420 Hz. When the solution was heated to 50°, the 630- and 182-Hz singlets increased in intensity while the doublet diminished. These changes were reversed on cooling the solution. Addition of D_2O erased the 630-Hz singlet and caused the doublet to collapse into a singlet at 165 Hz, while the singlet at 182 Hz remained unchanged. Throughout these studies the aromatic proton signals and the 600-Hz singlet were unaffected by D_2O or temperature changes. These findings clearly showed that the carbamate carbonyl was readily tautomerizable while the anilide carbonyl was not. The greater lability of the carbamate NH strongly suggests that attack by hydroxide ion on the carbamate group would be favored over attack on the anilide group.

The hydroxide ion may attack the carbamate by either addition to the carbonyl carbon (mechanism A, Scheme II) or proton extraction from the nitrogen

SCHEME II

PROPOSED MECHANISM FOR THE HYDROLYSIS OF SALICYLANILIDE *N*-METHYLCARBAMATE



(mechanism B). In either case intramolecular cyclization follows and the resulting intermediates **9** or **10** and/or **11**, on ring opening, would give salicylanilide. Glc analysis of a solution of **1e** in 50% H_2O–EtOH (pH 7.0), which had been kept at room temperature for 40 hr, showed presence of *N*-methylurethane, the expected by-product of mechanism B. No $MeNH_2$, the product of mechanism A, could be detected. Therefore, proton extraction appears to be the mechanism of choice.

The rate data in Table II also show that electron-withdrawing groups in the anilide phenyl ring (**1a–d**) enhance the hydrolysis rate of the carbamate while

(3) L. W. Brown and A. A. Forist, *J. Pharm. Sci.*, **61**, 858 (1972).

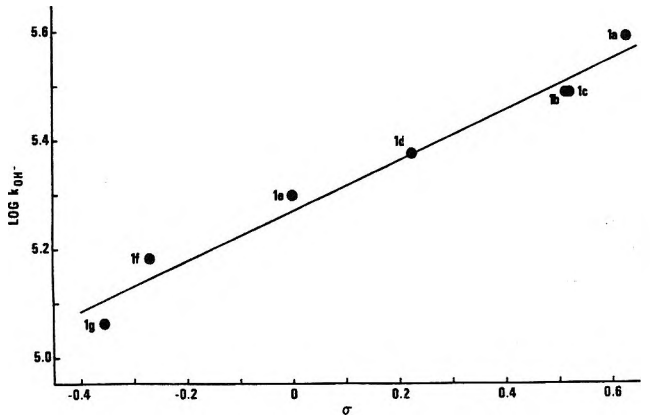
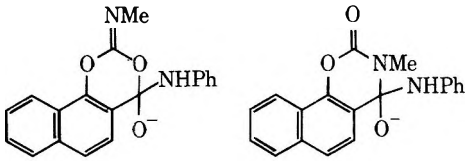


Figure 3.—Plot of log k_{OH^-} *vs.* σ constants for compounds 1a–g in 50% EtOH–H_2O at 37°.

electron-donating substitutions (**1f–h**) retard the rate. A plot of log k_{OH^-} *vs.* σ[4] for **1a–g** is shown in Figure 3. From the plot, which was fitted by the linear least-squares method, $\rho = 0.4627$ with correlation coefficient of 0.9859. The rate differences attributable to substitutions in the anilide phenyl ring are relatively small. By contrast, the stabilities of the isomeric **5** and **6** differed more than four-hundredfold. This large difference cannot be attributed to the electronic environment of the 1 and 2 positions of the naphthalene ring system as the pK_a's of 1- and 2-naphthols are virtually identical[5a] and the hydrolysis rates of ethyl 1- and 2-naphthoates differ only by a factor of three.[5b] The observed large rate difference between **5** and **6** could, however, be explained as a result of steric interference by the peri hydrogen atom with the formation of the tricyclic intermediates **14** or **15** from **6**. In intermediates **12** or **13** arising from **5**, there is less steric



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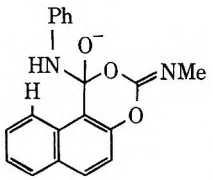

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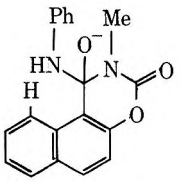

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hindrance, hence its more facile hydrolysis. The ability of these electronic and steric factors surrounding the anilide carbonyl to influence the hydrolysis rate of the carbamate strongly suggests that formation of a cyclic intermediate is the rate-controlling step in the process.

In summary, therefore, the facile anchimerically assisted alkaline hydrolysis of salicylanilide *N*-methylcarbamate appears to proceed with rapid proton extraction by the hydroxide ion from the carbamate nitrogen. A slow intramolecular cyclization follows and, on subsequent ring opening and fragmentation, the cyclic intermediate gives the product salicylanilide.

The great stability of **1k** is not unexpected and does not contradict the proposed mechanism for the hydrolysis of **1e**, because the absence of the carbamate NH in **1k** would force its hydrolysis to occur through some different mechanism. The stability of the N,N-disubstituted carbamate **1k** is 3×10^6 fold (Table II) that of the monosubstituted **1e**. In comparison, phenyl *N,N*-dimethylcarbamate has been reported[2] to be 3×10^4 fold as stable as phenyl *N*-methylcarbamate (**3**). Since **3** is 1×10^4 fold (Table II) as stable as **1e**, phenyl *N,N*-dimethylcarbamate is calculated to be 3×10^8 times as stable as **1e** or 1×10^2 times as stable as **1k**. The lower stability of **1k** in comparison with phenyl *N,N*-dimethylcarbamate suggests that the hydrolysis of **1k** also involves the anchimeric assistance by the neighboring *o*-carboxanilide group, though evidently to a lesser extent than in the case of **1e** in comparison to **3**, where the presence of the *o*-carboxanilide group increases the hydrolysis rate of the carbamate 10^4 fold.

Experimental Section

Salicylanilides from Salicyloyl Chloride. Method AD.—Salicyloyl chloride was prepared in 61–68% yield according to known procedure.[6] A solution of 0.15 mol of salicyloyl chloride in 20 ml of anhydrous THF was added dropwise in 15–30 min to a stirred solution of 0.30 mol of the appropriate aniline in 60 ml of THF. The mixture was stirred for 3–18 hr and evaporated at reduced pressure. The residue was mixed with 300–400 ml of H_2O. The insoluble crude product was recrystallized from benzene or a benzene–Skellysolve B mixture. The yield ranged from 72 to 91%.

Salicylanilides from Phenyl Salicylate. Method BD.—A mixture of phenyl salicylate (0.20 mol), the appropriate aniline (0.25 mol), and 60 ml of 1-methylnaphthalene was gently refluxed under N_2 for 2–3 hr. To the hot mixture was added 3.0 g of activated charcoal (Darco G-60) and 20 ml more of 1-methylnaphthalene. The mixture was heated to reflux with stirring and filtered while hot. The cooled filtrate usually solidified and was triturated with Skellysolve B and filtered. The crude product was recrystallized from EtOH, 86–94% yield.

Hydroxynaphthanilides from Hydroxynaphthoic Acids *via* Their Imidazolides. Method CD.—The appropriate hydroxynaphthoic acid was added in one portion to a stirred suspension of an equimolar amount of *N,N'*-carbonyldiimidazole in anhydrous THF (15 ml/g). The mixture was stirred under N_2 for 4 hr or until the evolution of CO_2 became very slow, whereupon an equimolar amount of $PhNH_2$ in anhydrous THF (5 ml/g) was added. The mixture was stirred at room temperature overnight, filtered, and concentrated at reduced pressure. The residual syrup was triturated with 1 *N* HCl and the resulting solids were filtered, washed with saturated $NaHCO_3$ solution, and dissolved in 1 *N* NaOH. Any insoluble material was filtered and the filtrate was acidified with 1 *N* HCl. The precipitates were recrystallized from benzene. In this manner, 1-hydroxy-2-naphthanilide was obtained in 74.4% yield, mp 154–155° (lit.[7] mp 154°), and 2-hydroxy-1-naphthanilide in 55% yield, mp 170–172° (lit.[8] mp 171.6–172.2°).

***N*-Methylcarbamates. Method E.**—To a 20% solution of the appropriate phenol in anhydrous THF was added 20% excess of a 50% solution of MeNCO in PhMe and a few drops of Et_3N. Crystallization of the product usually occurred within a few minutes. After 1–16 hr, the product was filtered, washed with Et_2O, and dried, ~90% yield, often analytically pure without further purification. If necessary the product was recrystallized from EtOH, benzene–Skellysolve B mixtures, or other solvents.

***N,N*-Dimethylcarbamates. Method F.**—A mixture of 0.10 mol of the appropriate phenol and 0.11 mol of Me_2NCOCl in 60

(4) σ values were obtained from H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(5) (a) R. T. Arnold and J. Sprung, *J. Amer. Chem. Soc.*, **60**, 1163 (1938); (b) M. Adam-Briers, P. J. C. Fierens, and R. H. Martin, *Helv. Chim. Acta*, **38**, 2021 (1955).

(6) R. Adams and L. H. Ulich, *J. Amer. Chem. Soc.*, **42**, 604 (1920).

(7) E. Schroeder, *Ann.*, **346**, 363 (1906).

(8) G. I. Gershzon, *J. Gen. Chem. USSR*, **13**, 82 (1943); *Chem. Abstr.*, **38**, 1220[9] (1944).

ml of anhydrous THF containing 15.4 ml (0.11 mol) of Et_3N was allowed to stand for 16 hr. The mixture was stirred with 500 ml of H_2O. The crystalline product was washed with Et_2O and recrystallized when necessary, ~70% yield.

Determination of Rate Constants.—The uv spectra of the 16 carbamates studied and their corresponding phenols were obtained on a Cary spectrophotometer. The characteristic shoulder or maximal wavelength for each phenol was used to follow the hydrolysis of the parent carbamate, which was carried out in a Beckman DU equipped with a constant-temperature cell. The wavelengths chosen for the individual compounds are listed in Table II.

A weighed sample of the carbamate was dissolved in 20 ml of 95% EtOH. Aliquots (5 ml) of the solution were diluted to 10 ml with the appropriate buffers. The resulting mixtures were shaken and introduced into previously warmed (37°) spectrometer cells. The absorbance was read at appropriate time intervals at 37° against a 1:1 H_2O–EtOH blank. The data thus obtained were treated as described in the discussion section. The results are summarized in Table II.

The ionic strengths of the acetate, phosphate, and borate buffers were 0.05, 0.08, and 0.07, respectively, before dilution with EtOH. The shifts in the pH values of the buffers upon addition of EtOH were determined with a pH meter and are given in Table III. The buffers were as follows: (1) acetate of pH 4.4, 25 ml of 1 *M* NaOAc plus 45 ml of 1 *M* HOAc diluted to 500 ml with deionized H_2O; (2) acetate of pH 5.0, 25 ml of 1 *M* NaOAc plus 12 ml of 1 *M* HOAc diluted to 500 ml with deionized H_2O; (3) acetate of pH 5.6, 25 ml of 1 *M* NaOAc plus 3.13 ml of 1 *M* HOAc diluted to 500 ml with deionized H_2O; (4) phosphate of pH 6.4, 50 ml of 0.1 *M* KH_2PO_4 plus 11.6 ml of 0.1 *M* NaOH diluted to 100 ml with deionized H_2O; (5) phosphate of pH 7.0, 50 ml of 0.1 *M* KH_2PO_4 plus 29.1 ml of 0.1 *M* NaOH diluted to 100 ml with deionized H_2O; (6) phosphate of pH 7.6, 50 ml of 0.1 *M* KH_2PO_4 plus 42.4 ml of 0.1 *M* NaOH diluted to 100 ml with deionized H_2O; (7) borate of pH 8.4, 50 ml of a mixture 0.1 *M* with respect to both KCl and H_3BO_3 plus 8.6 ml of 0.1 *M* NaOH diluted to 100 ml with deionized H_2O; (8) borate of pH 8.8, 50 ml of the above mixture (7) plus 15.8 ml of 0.1 *M* NaOH diluted to 100 ml with deionized H_2O; (9) borate of pH 9.2, 50 ml of the above mixture (7) plus 26.4 ml of 0.1 *M* NaOH diluted to 100 ml with deionized H_2O; (10) borate of pH 9.7, 50 ml of the above mixture (7) plus 40 ml of 0.1 *M* NaOH diluted to 100 ml with deionized H_2O.

Table III

Buffer	pH, H_2O	pH, H_2O–EtOH
Acetate	4.4	5.4
	5.0	6.0
	5.6	6.6
Phosphate	6.4	7.4
	7.0	8.0
	7.6	8.6
Borate	8.4	9.95
	8.8	10.25
	9.2	10.60
	9.7	10.90

Registry No.—**1a**, 16308-12-6; **1b**, 13499-87-1; **1c**, 18066-07-4; **1d**, 35410-11-8; **1e**, 5591-49-1; **1f**, 35410-13-0; **1g**, 35410-14-1; **1h**, 35410-15-2; **1i**, 35410-16-3; **1j**, 35410-17-4; **1k**, 35410-18-5; **2**, 5579-05-5; **3**, 1943-79-9; **4**, 63-25-2; **5**, 35410-20-9; **6**, 35410-21-0.

Acknowledgment.—We wish to thank our colleagues in the Physical and Analytical Chemistry Department for microanalyses, Dr. G. Slomp for interpretation of nmr spectra, and L. M. Reineke for gas chromatographic analyses.

Orientation in Electrophilic Addition Reactions to 2-Acetamidoacrylic Acid Derivatives[1]

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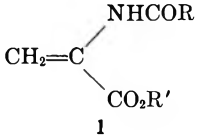
Department of Chemistry, Utah State University, Logan, Utah 84321

Received March 6, 1972

The mode of addition of selected electrophiles to 2-acetamidoacrylic acid and corresponding methyl ester has been investigated. The additions of hydrogen bromide and hydrogen chloride have been shown to yield 2-haloalanine derivatives as kinetically controlled products, while 3-haloalanine derivatives are the products resulting from conditions of thermodynamic control. The addition of thiocyanogen chloride and sulfur dichloride occurred in a similar manner; however, the products isolated were those resulting from subsequent elimination of hydrogen chloride to give the corresponding acetamidoacrylic acid derivatives substituted at the 3 position with a sulfur function.

2-Acylaminoacrylic acid derivatives (1) potentially can function as important precursors to a variety of novel α-amino acids. Cysteine derivatives have been prepared from **1** through radical additions.[2] Nucleophilic additions also have been reported[3] to yield substituted amino acids. Electrophilic additions of halogen[3a,4] and hydrogen halide[5] to 2-acylaminoacrylic acid derivatives are known. Knunyants and Shokina have reported[5] that 2-acylaminoacrylic acid derivatives undergo reaction with hydrogen bromide in acetic acid to yield 3-bromoalanine derivatives (2), which products likely result from a process of 1,4 addition or, as termed herein, Michael-type addition. Acrylic acid derivatives undergo similar Michael-type addition reactions with hydrogen bromide to give 3-bromopropanoic acid derivatives.[6]



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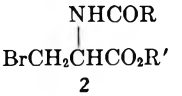

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We report herein results of studies pertaining to electrophilic addition reactions of selected reagents, *i.e.*, hydrogen bromide, hydrogen chloride, thiocyanogen

(1) Presented in part at the 26th Annual Northwest Regional Meeting of the American Chemical Society, Bozeman, Mont., June 1971.

(2) M. W. Farlow, *J. Biol. Chem.*, **176**, 71 (1948).

(3) (a) I. Z. Eiger and J. P. Greenstein, *Arch. Biochem.*, **19**, 467 (1948); (b) H. Behringer and E. Fackler, *Ann*, **564**, 73 (1948); (c) A. Schoberl and A. Wagner, *Chem. Ber.*, **80**, 379 (1947).

(4) O. V. Kil'disheva, L. P. Rasteikene, and I. L. Knunyants, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 231 (1955); *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 260 (1955).

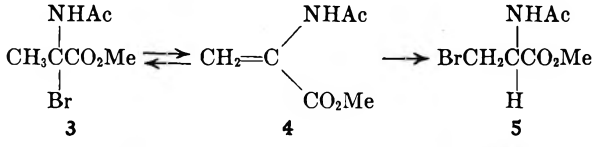
(5) I. L. Knunyants and V. V. Shokina, *J. Gen. Chem. USSR*, **25**, 1175 (1955); *Zh. Obshch. Khim.*, **25**, 1228 (1955).

(6) R. Monzingo and L. A. Patterson, "Organic Syntheses," Collect. Vol., III, Wiley, New York, N. Y., 1955, p 576.

chloride, and sulfur dichloride, to the 2-acetamidoacrylic acid system.

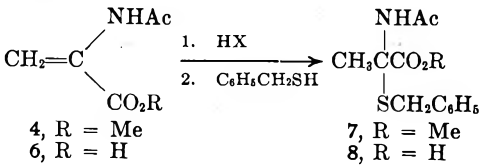
Hydrogen bromide in deuteriochloroform was allowed to react with methyl 2-acetamidoacrylate (**4**), and the course of the addition was followed by recording the nmr spectra of the reaction mixture at various time intervals. The nmr spectrum taken directly following the addition of hydrogen bromide showed the complete disappearance of vinyl proton signals of **4** at δ 6.5 and 5.8, while a singlet at 2.4, assigned to the β protons of the 2-bromo adduct **3**, appeared that was equal in intensity to the methyl ester and acetyl peaks at 3.9 and 2.8, respectively. The observed spectrum is consistent with the rapid, anti-Michael addition of hydrogen bromide to **4** to form methyl *N*-acetyl-2-bromo-DL-alaninate (**3**).

With the passage of time, the peaks at δ 2.8 and 2.4 diminished in intensity, while a singlet at 2.9, an apparent doublet imposed on the methyl ester peak at 3.9, and a quartet at 5.2 appeared. The observed changes in the nmr spectra are attributed to the formation of the 3-bromo adduct **5** and the corresponding decrease in the amount of the 2-bromo compound **3** present in the reaction mixture. After 3 days, the nmr spectrum showed mainly **5** to be present, and methyl *N*-acetyl-3-bromo-DL-alaninate (**5**) was isolated thereupon from the reaction mixture.



It is concluded, therefore, that the 2-bromoalanine **3** is the kinetically controlled addition product, while the product of Michael-type addition, the 3-bromoalanine **5**, is formed under thermodynamically controlled conditions; the latter results are consistent with those reported by Knunyants and Shokina.[5]

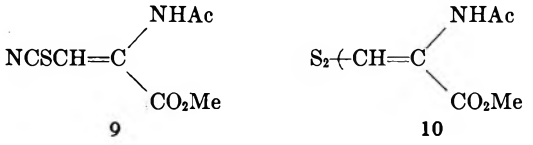
Further evidence for the intermediacy of the 2-bromoalanine **3** was obtained by isolation of the 2-benzylmercapto derivative **7** upon addition of benzyl mercaptan to a solution of **3** in chloroform. The sequence of reactions of **4** with hydrogen chloride and benzyl mercaptan in acetic acid also yielded **7**. In a similar manner, 2-acetamidoacrylic acid (**6**) was converted to the 2-benzylmercaptoalanine **8**. The reaction of alkyl mercaptans with α-haloalanine derivatives has been reported[7] to give the corresponding α-alkylmercaptoalanines.



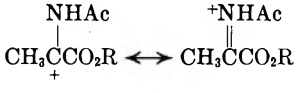
When the addition of hydrogen bromide to **4** in chloroform was allowed to proceed for 4 hr, followed by product isolation, the 3-bromoalanine **5** and methyl pyruvate were isolated. The latter product likely arises from hydrolysis, upon addition of water during work-up of the reaction, of the 2-bromo adduct **3** present. Hydrolysis of 2-bromoalanine derivatives to pyruvic acid derivatives has been reported.[4] If care was not taken to exclude small amounts of water from the reaction, a material thought to be acetamide hydrobromide could also be isolated as a solid that precipitated from the chloroform solution during the course of the reaction.

Methyl acrylate was treated with hydrogen bromide in deuteriochloroform and the reaction followed by nmr to determine if a similar phenomenon as with **4** was occurring. In comparison with **4**, the results were consistent for the initial rapid formation of the reported[6] Michael product, methyl 3-bromopropionate, and no further spectral changes were observed during the course of the reaction.

The addition of thiocyanogen chloride or sulfur dichloride to methyl 2-acetamidoacrylate (**4**) gave the acetamidoacrylic acid derivatives **9** and **10**, respectively. These products apparently result from anti-Michael addition, followed by dehydrochlorination of the 2-chloro compounds thus formed. Facile dehydrohalogenation of α-haloalanines has been observed.[4,8] The orientation in the addition of these sulfur electrophiles, therefore, appears to be the same as for the hydrogen halides discussed above.



These studies establish that the acetamido group in 2-acetamidoacrylic acid derivatives exercises a strong directive effect in the addition of electrophilic reagents to the double bond, as well as lending an enhanced reactivity to the α-halo group thus formed. A reasonable explanation for the orientation effect and reactivity observed is that the acetamido group functions to stabilize any positive charge generated at the α carbon during the course of the reaction, as represented by the resonance-stabilized carbonium ion **11**.



Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Ir spectra were recorded on a Beckman IR-20A spectrophotometer. Nmr data were obtained with a Varian A-60 nmr spectrometer at 60 MHz. Mass spectra were measured on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Evaporation *in vacuo* was carried out with a Buchler rotary evaporator.

Addition of Hydrogen Bromide to Methyl 2-Acetamidoacrylate (4).—To 1.0 ml of dry deuteriochloroform was added 0.2 g (1.4 mmol) of methyl 2-acetamidoacrylate[9] (**4**). Hydrogen bromide gas was passed over the solution for 2 min. The solution was then transferred to an nmr sample tube and spectra were recorded at intervals over 3 days. The initial spectrum showed the presence of only the 2-bromoalanine **3**: δ 3.9 (s, 3 H, methyl ester), 2.8 (s, 3 H, acetyl), 2.4 (s, 3 H, β protons). Subsequent spectral changes showed the gradual formation of the 3-bromoalanine **5** and the corresponding decrease in concentration of **3**.

(7) O. V. Kil'disheva, M. G. Lin'kova, V. M. Savosina, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1348 (1958).

(8). (a) O. V. Kil'disheva, L. P. Rasteikene, and I. L. Knunyants, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 251 (1955); *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 282 (1955). (b) R. Pfleger and M. V. Strandtmann, *Chem. Ber.*, **90**, 1455 (1957).

(9) T. Wieland, G. Ohnacker, and W. Ziegler, *ibid.*, **90**, 194 (1957).

The deuteriochloroform solution was added to 10 ml of chloroform, rinsed once with water, dried over magnesium sulfate, and evaporated *in vacuo* to leave 0.16 g of methyl *N*-acetyl-3-bromo-DL-alaninate (**5**, 51%): mp 91–93°; nmr ($CDCl_3$) δ 6.65 (s, 1 H, amide proton), 5.04 (m, 1 H, methine proton), 3.81 (s, 3 H, methyl ester), 3.80 (apparent d, 2 H, methylene protons), 2.07 (s, 3 H, acetyl methyl); *m/e* 225 (3.0), 223 (3.3) (molecular ions typical of mono bromo compounds).[10] When **5** was treated with triethylamine in chloroform, the acetamidoacrylate **4** was obtained in quantitative yield. An analytical sample of **5** was prepared by recrystallization from diethyl ether–ligroin (bp 60–90°), mp 90–91.5°.

Anal. Calcd for $C_6H_{10}BrNO_3$ (224.1): C, 32.2; H, 4.50; N, 6.25. Found: C, 31.8; H, 4.38; N, 5.81.

Methyl *N*-Acetyl-2-benzylmercapto-DL-alaninate (**7**).—To a solution of the acrylic acid methyl ester **4** (0.30 g, 2.1 mmol) in 8 ml of glacial acetic acid was added 0.52 ml (2.1 mmol) of 4 *N* hydrogen chloride in dioxane. After the mixture was stirred at room temperature for 5 min, benzyl mercaptan (0.28 g, 2.1 mmol) was added to the solution, following which the reaction mixture was stirred for 1 hr. The solvent was removed *in vacuo*, the oil obtained was taken up twice in ethyl acetate, and the solvent was removed *in vacuo* to yield a clear oil that slowly crystallized. Recrystallization from diethyl ether–ligroin (bp 60–90°) gave fine needles: mp 89–90°; nmr (trifluoroacetic acid) δ 1.47 and 1.49 (two s, 6 H, β-methyl and *N*-acetyl), 3.38 and 3.42 (two s, 5 H, methyl ester and benzyl), 6.88 (s, 5 H, phenyl), 7.08 (br s, 1 H, amide proton). This material was indistinguishable (tlc, nmr) from that obtained by the reaction of **4** with hydrogen bromide in chloroform followed by the addition of benzyl mercaptan.

Anal. Calcd for $C_{13}H_{17}NO_3S$ (267.3): C, 58.4; H, 6.40; N, 5.24. Found: C, 58.1; H, 6.26; N, 5.07.

***N*-Acetyl-2-benzylmercapto-DL-alanine** (**8**).—To a stirred solution of 2-acetamidoacrylic acid[9] (**6**, 0.20 g, 1.5 mmol) in 3 ml of trifluoroacetic acid and 7 ml of acetic acid was added 0.45 ml (1.85 meq) of 4.1 *N* hydrogen chloride in dioxane. The reaction mixture was stirred for 10 min, following which 0.19 g (1.5 mmol) of benzyl mercaptan in 2 ml of acetic acid was added in one portion, and the reaction mixture was stirred at room temperature for an additional 45 min. The solvent was removed *in vacuo* to give a white solid, which, after trituration with ethyl ether, gave 0.32 g (82%) of **8**: mp 150–153°; nmr (trifluoroacetic acid) δ 6.9 (s, 5 H, phenyl), 6.8 (s, 1 H, NH), 3.5 (s, 2 H, benzyl), 1.5 (s, 3 H, acetyl), and 1.4 (s, 3 H, β protons). An analytical sample was prepared by three recrystallizations from ethanol–ethyl acetate, mp 157.0–158.5°.

Anal. Calcd for $C_{12}H_{15}NO_3S$ (253.3): C, 57.0; H, 5.92; N, 5.52. Found: C, 56.9; H, 6.12; N, 5.39.

Identification of Methyl Pyruvate.—Hydrogen bromide was passed through a solution of 4.0 g (28 mmol) of methyl 2-acetamidoacrylate (**4**) in 50 ml of chloroform until the solution ceased to gain weight. After standing at room temperature for 4 hr, the solution was filtered to remove the white solid present and the filtrate was extracted with two 100-ml portions of water. The aqueous extracts were combined and evaporated under an air stream to leave 2.1 g of crude methyl pyruvate. The 3-bromo adduct **5** was isolated from the dried ($MgSO_4$) chloroform extract. The 2,4-dinitrophenylhydrazone of methyl pyruvate was prepared by a modification of an established method.[11] To a solution of 100 ml of water, 100 ml of methanol, and 10 ml of concentrated hydrochloric acid was added 1.0 g of the crude methyl pyruvate (9.8 mmol) and 3.0 g of 2,4-dinitrophenylhydrazine (15.1 mmol). The mixture was heated on a steam bath for 0.5 hr and slowly cooled to room temperature. The yellow 2,4-dinitrophenylhydrazone was removed by filtration and recrystallized twice from dioxane–methanol, mp 185–186° (lit.[11] 186.5–187.5°). The ir spectrum of this material was superimposable with the spectrum of an authentic sample of methyl pyruvate 2,4-dinitrophenylhydrazone.

The white solid obtained above was shown to be identical (ir, nmr) with the compound obtained[12] by treating acetamide with hydrogen bromide in chloroform: ir (KBr) 3230 (NH_2), 1678 cm^{-1} (C=O); *m/e* 82 (16.6, HBr), 80 (16.9, HBr), 59 (37.5, $AcNH_2$), 44 (100, $CONH_2$), 28 (37.5, CO); nmr (trifluoroacetic acid) δ 8.4 (s, 2 H, NH_2), 2.2 (s, 3 H, acetyl methyl protons). An aqueous solution of this material was acidic and treatment with silver nitrate solution immediately produced a precipitate.

Addition of Hydrogen Bromide to Methyl Acrylate.—Hydrogen bromide was passed over a solution of 0.20 g of methyl acrylate in 0.5 ml of deuteriochloroform for a period of 2 min. The sample was placed in an nmr tube and spectra were recorded at intervals over a 2-day period. The spectrum recorded immediately following the addition of hydrogen bromide was consistent for the formation of methyl 3-bromopropionate and no further changes were observed in subsequent spectra: nmr ($CDCl_3$) δ 3.90 (s, 3 H, methyl ester), 3.75 (t, 2 H, β-methylene), 3.00 (t, 2 H, α-methylene).

Methyl 2-Acetamido-3-thiocyanoacrylate (**9**).—To a solution of thiocyanogen chloride,[13] prepared from 1.5 g (21 mmol) of chlorine and 2.0 g (21 mmol) of potassium thiocyanate in 125 ml of dry acetic acid was added 2.0 g (14 mmol) of **4** and the reaction mixture was stirred at room temperature for 1.5 hr. The solution was concentrated *in vacuo* and solid material was removed by filtration. To the filtrate was added 200 ml of chloroform and the resulting solution was washed with three 300-ml portions of water, dried over magnesium sulfate, and evaporated *in vacuo* to yield 1.6 g (57%) of **9**. Two recrystallizations from chloroform afforded an analytically pure sample: mp 153°; ir (KBr) 3280 (NH), 2120 (SCN), 1677 and 1661 cm^{-1} (carbonyl); nmr ($CDCl_3$) δ 8.2 (s, 1 H, vinyl proton), 3.9 (s, 3 H, methyl ester), 2.2 (s, 3 H, acetyl); *m/e* 200 (9.4), 202 (0.57), 142 (81), 110 (100).

Anal. Calcd for $C_7H_8N_2O_3S$ (200.3): C, 42.0; H, 4.20; N, 14.0. Found: C, 42.1; H, 3.93; N, 13.8.

Bis(2-acetamido-2-carbomethoxyvinyl) Sulfide (**10**).—To a solution of 1.4 g (10 mmol) of **4** in 75 ml of chloroform was added 1.0 g (10 mmol) of sulfur dichloride, whereupon the solution was observed to refux spontaneously. The solution was cooled in a Dry Ice–acetone bath for 5 hr. An additional 1.4 g (10 mmol) of **4** was added and the solution was stirred at room temperature for 8 hr. The reaction mixture, after being cooled overnight in a refrigerator, was filtered to remove solid material and the filtrate was evaporated *in vacuo* to yield an oil. A solution of the oil in hot ethanol deposited, upon being chilled, 2.0 g (63%) of the sulfide **10**: mp 202.5–204 0°; nmr ($CDCl_3$) δ 7.96 (s, 1 H, amide), 7.59 (s, 1 H, vinyl), 3.48 (s, 3 H, methyl ester), 1.87 (s, 3 H, acetyl protons).

Anal. Calcd for $C_{12}H_{16}N_2O_6S$ (316.3): C, 45.6; H, 5.10; N, 8.86; S, 10.2. Found: C, 45.2; H, 5.28; N, 8.72; S, 10.2.

Registry No.—**4**, 35356-70-8; **5**, 35356-71-9; **7**, 35356-72-0; **8**, 30410-97-0; **9**, 35356-74-2; **10**, 35356-75-3.

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Determination of the Molecular Geometry of Eu(fod)$_3$ Complexes with Amides and Diamides and Its Conformational Significance

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Paramagnetic shifts, induced in the nmr spectra of some amides and diamides by Eu(fod)$_3$, have been used to assign configurational isomers in these compounds. The observed Eu-induced shifts agree well with values calculated on the basis that their origin is of pseudocontact nature, and have been used to determine the molecular geometries of the corresponding Eu(fod)$_3$–amide complexes. Remarkably, all the structures could be fitted by the same pseudocontact constant (eq 1, $K = 900 \pm 100$), Eu–O distance (3.0 Å), and average Eu–O–C angle (120°). The spatial location of the Eu ion in the complexes seems always to correspond with an orientation of amide molecule which has minimal intramolecular steric interaction with the other ligands. Consequently, the Eu–O–C–N dihedral angle (see Figure 4 in the text) varies appreciably in the amides studied. Finally, evidence is presented that, according to steric hindrance factors, diamides investigated form two distinct kind of complexes.

Convincing evidence has been recently presented[1-12] for a number of oxygenated compounds, that the shifts in the nmr signals induced by association of organic molecules with paramagnetic lanthanide chelates, are entirely or predominantly due to pseudocontact interaction according to eq 1[13] where χ is the O–Ld–H

$$\Delta\nu_{obsd} = K(3\cos^2\chi - 1)/r^3 \quad (1)$$

internuclear angle and r is the corresponding Ld–H distance. $\Delta\nu_{obsd}$ is usually taken as the slope in a plot of the induced chemical shifts *vs.* [Ld]/[S], where [Ld] and [S] are the respective molar concentrations of lanthanide and substrate.

Although nmr lanthanide shifts have been recently reported for two simple amides,[14] the geometry of the complexes and their pseudocontact constants (K in eq 1) were not investigated.

To explore this point, and its implications in the conformational analysis of more complex organic molecules containing amide groups, we have measured the Eu(fod)$_3$ induced shifts[15] for a series of amides and diamides reported in Table I.

These data, besides providing configurational assignments for the rotamers possessing a defined identity on the nmr time scale, have been used by us to determine the geometries of the complexes.

Remarkably, all the structures could be fitted by the same pseudocontact constant ($K = 900 \pm 100$), Eu–O distance (3.0 Å), and average Eu–O–C angle (120°). The latter two values appear to be in agreement with the most reliable values found for these parameters in a number of lanthanide complexes with alcohols[1-4,12] and ketones.[10]

The spatial location of the Eu ion in the complexes seems always to correspond with an orientation of amide molecule which has minimal intramolecular steric interactions with the other ligands. Finally, we have obtained evidence that, according to steric hindrance factors, diamides in Table I form two distinct kinds of complexes.

Experimental Section

Syntheses and characteristics of the amides used in this study were previously described.[16-18]

Induced Shift Measurements.—Eu(fod)$_3$ (Sievers reagent)[15] obtained from Alfa Inorganic (N. J.), was used without further purification. A concentrated (0.32 M) $CDCl_3$ solution of Eu(fod)$_3$ was used throughout this work. Spectra of 10% $CDCl_3$ solutions containing 0–0.50 mol of Eu(fod)$_3$/mol of amide were obtained at 60 MHz (Varian Associates A-60 and T-60 analytical spectrometers). In general, each signal could be followed in these spectra and the shift to lower field was for all signals directly proportional to the Eu(fod)$_3$:amide ratio present. An example is shown in Figure 1.

However, a marked upward curvature in the $\Delta\nu$ *vs.* [Ld]/[S] plot was observed for the methylene signals of the (conformationally mobile; see below) rotamer IIIc in Table I.

The Eu-induced shifts were found largely independent of the absolute concentration of amide, contrary to what was observed in the case of some alcohols[19a] and sulfoxides.[19b]

The population of the various amides rotamers was not found to vary appreciably with the Eu(fod)$_3$ concentration.[20]

Eu Location and Distance Measurements.—A Hewlett-Packard 9100 B computer was used to determine the optimal Eu-spatial location for monoamides I and II in Table I, and metal–hydrogen distances were analytically calculated from amide interatomic distances and bond angles deduced from pertinent literature data.[21]

For diamides IV–IX in Table I, the eq 1 parameters could be measured on Dreiding models, once R and φ were fixed at their optimal values (see text).

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(19) (a) I. Armitage, G. Dunsmore, L. D. Hall, and A. G. Marshall, *Chem. Commun.*, 1281 (1971); (b) K. K. Andersen and J. J. Uebel, *Tetrahedron Lett.*, 5253 (1970).
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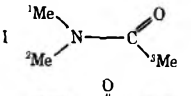
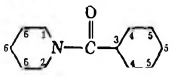
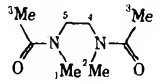
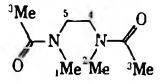
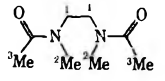
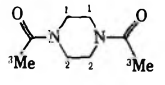
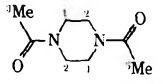
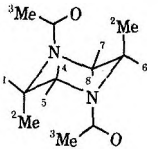
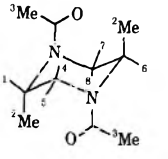
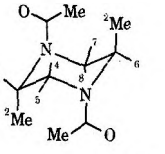
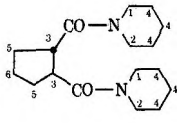
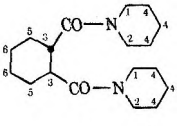
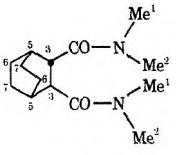
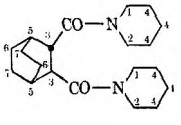
TABLE I

EFFECT OF Eu(fod)$_3$ ON THE 60-MHz NMR SPECTRA OF SOME AMIDES AND MOLECULAR GEOMETRY PARAMETERS OF THE CORRESPONDING COMPLEXES[a]

No.	Compd	1	2	3	4	5	6	7	8	R, Å	φ, deg	ω, deg	Eu–Eu, Å	K
I		*3.06* 8.1 (8.1)	*3.16* 3.8 (3.8)	*2.17* 9.2 (9.2)						3.0	110	80		890
II		*3.67* 8.4 (8.3)	*3.67* 4.3 (3.7)	2.47 6.2 (6.2)	1.67 5.9 (5.6)					3.0	110	90		910
IIIa		*3.14* 7.7	*3.14* 7.7	*2.17* 10.0	*3.67* 6.9	*3.67* 6.9								
IIIb		*3.14* 6.5	*3.14* 6.5	*3.67* 10.0	*3.67* 10.0	*3.67* 10.0								
IIIc		*3.67* *b*	*3.14* 4.2	*2.17* 6.5										
IVa		*3.70* 18.1 (17.4)	*3.70* 10.4 (7.3)	*2.30* 11.9 (11.8)						3.0	120	60	11.0	1040
IVb		*3.70* 13.8 (14.8)	*3.70* 7.7 (7.2)	*2.30* 13.5 (10.6)						3.0	120	60	11.3	940
Va[c]		*4.03* 5.2 (5.0)		*2.20* 6.5 (6.4)	*3.45* 5.8 (6.0)	*3.45* 5.8 (5.0)	*4.90* 12.5 (12.5)	*4.37* 12.8 (12.5)	*2.95* 5.8 (5.7)	3.0	120	50	11.0	850
Vb[d]		*4.03* 5.2 (4.9)		*2.20* 6.5 (5.9)	*3.05* 5.8 (5.8)	*4.23* 10.9 (10.9)	*4.03* 5.2 (5.7)	*4.23* 10.9 (10.8)	*3.05* 5.8 (6.0)	3.0	120	50	11.3	790
Vc[d]		*4.90* 12.5 (11.2)		*2.20* 6.5 (5.8)	*3.45* 5.8 (6.9)	*3.45* 5.8 (6.1)	*4.90* 12.5 (12.8)	*3.45* 5.8 (4.9)	*3.45* 5.8 (4.8)	3.0	120	50	11.0	860
VI		*3.66* 3.4 (2.5)	*3.66* 3.4 (2.5)	*3.66* 10.4 (10.2)		*1.90* 4.3 (3.9)	*1.90* 2.3 (1.9)			3.0	120	80	3.0	870
VII		*3.66* 2.0 (2.2)	*3.66* 2.0 (2.2)	3.22 6.2 (6.2)		*1.66* 2.5 (2.5)				3.0	120	80	0	940
VIII		*3.23* 2.5 (2.7)	*3.00* 2.5 (2.7)	3.77 12.3 (12.3)		*1.79* 4.6 (4.6)				3.0	120	80	3.0	1020
IX		*3.66* 1.8 (1.5)	*3.66* 1.8 (1.5)	*3.84* 11.2 (11.1)		*1.66* 4.4 (3.8)				3.0	120	80	3.0	850

[a] Only clearly detectable signals are reported; figures in the first row, in italics, indicate chemical shifts of the undoped spectra; figures in the second row indicate observed molar induced shifts; figures in the third row in parentheses indicate calculated molar induced shifts. [b] Deviates from linearity in the $\Delta\nu$ *vs.* [Ld]/[S] plot. [c] Both enantiomers contribute to the nmr spectrum. [d] This form has an inversion center.

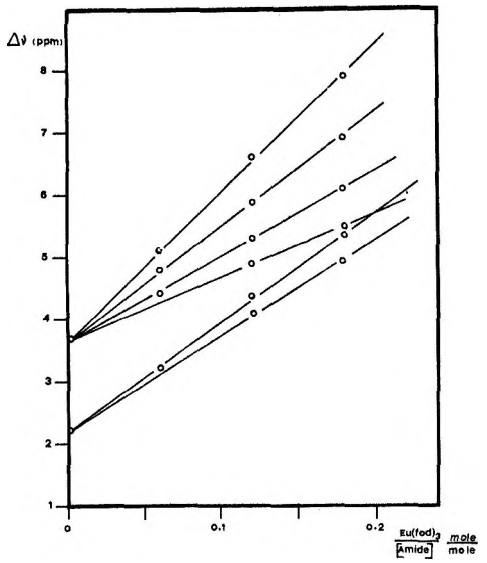


Figure 1.—Variation of induced shifts with molar ratio [Eu(fod)$_3$]/[substrate] for *N,N'*diacetylpiperazine, IV.

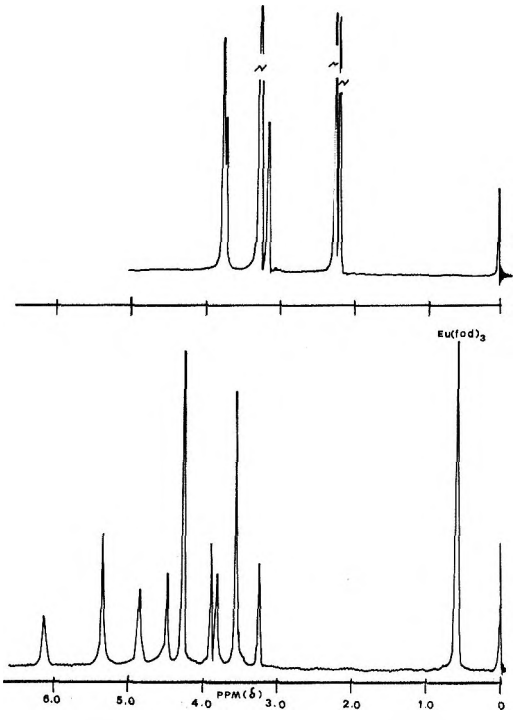


Figure 2.—60-MHz spectra ($CDCl_3$) of *N,N'*-diacetyldimethylethylenediamine, III: above, no Eu(fod)$_3$; below, [Eu(fod)$_3$]/[amide] = 0.12 mol/mol.

Results

General.—Kinetically restricted rotation around the C–N amide bonds does not produce nmr distinguishable rotamers for compounds I, II, VI–IX, in Table I. Previous work has shown[16] that in diamide V the piperazine conformational equilibrium is strongly biased towards forms containing diaxial methyl groups (nearly equipopulated mixture of the four rotamers possible), and has provided[16] the relative configurational assignments (see Table I).

On the other side, diamide III (Table I) is predicted[18] to exist as three isomers (cis–cis; cis–trans; trans–trans).

The Eu-induced shifts (Figure 2) allow, for the first time, direct detection of the three isomers and of their relative population (2:6:2). If the most populated rotamer (IIIb, Table I) is assigned to a cis–trans configuration, the ratio 2:6:2 speaks for the presence in equal amounts of cis and trans amide units in the mixture, indicating that the two amide moieties in diamide III behave as independent units.

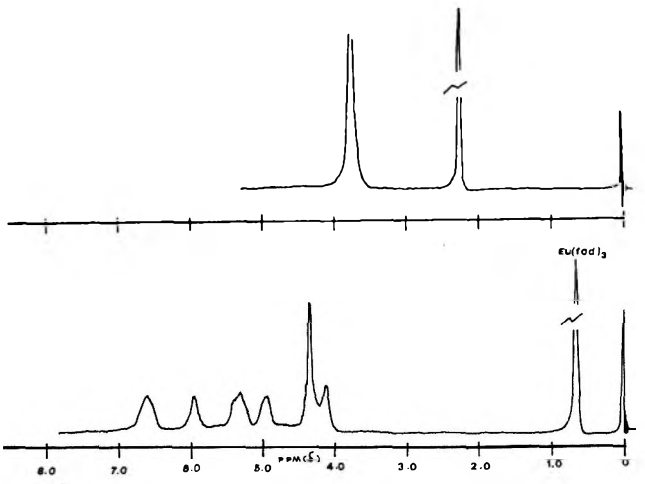


Figure 3.—60-MHz spectra ($CDCl_3$) of *N,N'*-diacetylpiperazine, IV: above, no Eu(fod)$_3$; below, [Eu(fod)$_3$]/amide] = 0.12 mol/mol.

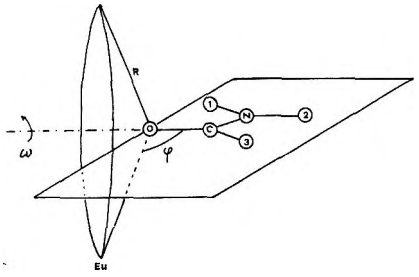


Figure 4.—Possible locations of the Eu ion in the space around the (planar) amide unit. R represents the Eu–O distance; φ is in the Eu–O–C internuclear angle; the dihedral angle Eu–O–C–N, ω, is 90° for the (perpendicular) configuration indicated in the figure. Varying R, φ, and ω, all the Eu possible spatial locations can be explored.

N,N'-Diacetylpiperazine IV (Table I) exists[18] in two forms (trans and cis). The Eu-induced shifts (Figure 3) allow, also in this case, the first direct detection of the two isomers and of their relative population (6:4).

Eu(fod)$_3$–Monoamide Complexes.—The molecular geometries of the Eu(fod)$_3$ complexes of monoamides I and II (Table I) were obtained determining the optimal location of the Eu ion in the space around the amide oxygen atom. A computer program was used to explore all the possible Eu spatial locations, defined in Figure 4 by polar coordinates R, φ, ω, where R is the Eu–O distance, φ is the Eu–O–C angle, and ω is the Eu–O–C–N dihedral angle. R was allowed to vary between 2.5 and 3.5 Å; φ was varied between 90 and 270° (values of φ between 0 and 90° are highly improbable); ω was varied over the entire 360° range. A reasonable agreement between the measured shifts (Table I) and $(3\cos^2\chi - 1)r^{-3}$, according to eq 1, was found only for a limited set of R, φ, and ω values centered in the space around $R = 2.8 \pm 0.4$ Å, $\varphi = 110° \pm 20$; $\omega = 80° \pm 10$. The set of R, φ, and ω values which gave the best correlation in the $\Delta\nu$ *vs.* $(3\cos^2\chi - 1)r^{-3}$

plot for both amides I and II (Figure 5), was selected to represent the optimal molecular geometry of these Eu(fod)$_3$ complexes.[22] Pertinent data are collected in Table I.

Eu(fod)$_3$–Diamide Complexes.—Lanthanide shift reagents have already been used with a number of bifunctional compounds,[23,24] but no diamides have been hitherto reported.

Eu-induced shifts for diamides III, IV, and V in Table I are considerably higher with respect to those of monoamides I and II. This seems to imply that two molecules of Eu(fod)$_3$ are involved in the complexes, each proton being subject to the deshielding effect of two Eu ions.

As far as diamide III is concerned the conformational mobility of its three isomers prevents any attempt to assess a reasonable average geometry for the corresponding Eu(fod)$_3$ complexes.[10,20]

Although both rotamers of diamide IV experience rapid chair–chair interconversion of the piperazine ring,[18] this conformational mobility does not prevent the determination of a reasonably accurate geometry for the Eu(fod)$_3$ complexes, if the piperazine ring is taken in the average planar position.[20]

In the case of diamide V, as discussed above the piperazine conformational equilibrium is strongly biased towards forms containing diaxial methyl groups,[16] so that the conformers detectable in the spectrum can be regarded as rigid structures on the nmr time scale.

According to these considerations, only the geometries of complexes corresponding to diamides IV and V have been investigated.

The method used to locate the Eu ions in the space around each amide unit is similar to that described in the case of monoamide complexes. However, to reduce the computing work involved, R and φ (Figure 4) were fixed at their optimal values determined in the case of monoamide complexes (Table I), and only ω was allowed to vary.[25]

The deshielding effects of the two Eu ions on each proton were computed for each pair of spatial locations of the Eu ions around the diamide molecule.

A reasonable agreement between the measured shifts and $(3\cos^2\chi - 1)r^{-3}$ was found only for a restricted number of cases in which the two Eu ions are in *identical spatial positions* with respect to each amide unit in the molecule. The optimal molecular geometry chosen for each complex (Table I) is the one which gave the best correlation of experimental and calculated shifts.

The pseudocontact constant (K, eq 1) was selected to allow direct comparison with observed shifts, and it is gratifying that the values found in this way come very close to the value obtained for the monoamides

(22) The cyclohexane ring in amide II was assumed biased in the chair conformation with the amide group in the equatorial position, and the tertiary atom placed in the most distant position with respect to the Eu ion (*i.e.*, the carbonyl bisects the cyclohexane ring).

(23) (a) H. Hart and G. M. Love, *Tetrahedron Lett.*, 625 (1971); (b) C. C. Hinekley, M. R. Klotz, and F. Patil, *J. Amer. Chem. Soc.*, **93**, 2417 (1971).

(24) (a) H. Van Brederode and W. C. B. Anysmans, *Tetrahedron Lett.*, 1695 (1971); (b) I. Fleming, S. W. Hanson, and J. K. M. Sanders, *ibid.*, 3733 (1971).

(25) The more rigorous analytical method used to determine the Eu location in monoamide complexes was not followed here because of the amount of computer work involved. Instead, simple Dreiding model measurements were used, which enabled us to assess tentative geometries for the complexes that could be later optimized to the degree of approximation needed.

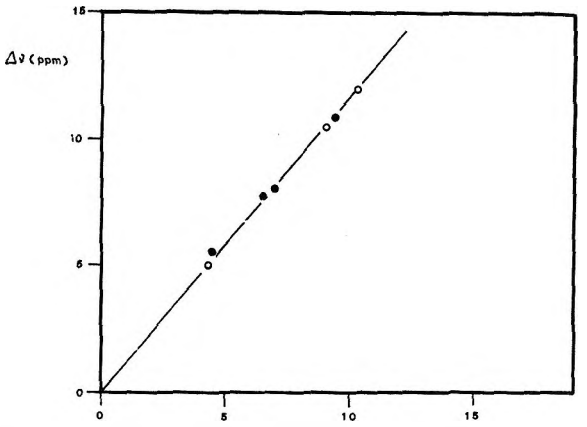


Figure 5.—Plot of measured shifts ($\Delta\nu$) against the pseudocontact geometric factor for N,N'-dimethylacetamide, I (open circles), and amide II (closed circles).

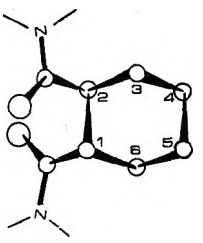


Figure 6.—Preferred conformation of diamide VII. The piperidine rings are omitted for clarity and only the cyclohexane ring is shown. The two C–O bonds are both almost eclipsed with respect to the C_1–C_2 bond.

(Table I). Recent work,[16,26] based on nmr data, dipole moments, and *priori* conformational energy estimates, has shown that diamides VI–IX (Table I) all exist in a preferred conformation, where the two diamide carbonyls lay close to each other, being almost eclipsed to the C_1–C_2 bond (Figure 6).

The Eu-induced shifts of the N-methylene protons for diamides VI–IX are *much lower* with respect to the corresponding shifts observed for the other diamides (Table I). Furthermore, they are *equally shifted* (contrary to all other cases in Table I), implying that the Eu(fod)$_3$ complexes are different from the cases hitherto considered. Inspection of molecular models shows that only one Eu(fod)$_3$ molecule can possibly come in contact with the two carbonyls, for diamides VI–IX in their preferred conformation (depicted in Figure 6 for diamide VII).

Assuming the same R and φ values used for the other diamides (Table I) and allowing only ω to vary, appropriate geometries for 2:1 Eu(fod)$_3$–diamide complexes could be obtained. In these complexes the Eu ion is considered *alternatively bound* to one oxygen atom, so that an average deshielding effect of the Eu ion on each proton has to be computed. In Figure 7 is shown, as an example, the spatial arrangement of this complex in the case of diamide VII.

The distance between the two Eu alternative locations (labeled Eu–Eu in Table I) is close to zero in this particular case; for diamides VI, VIII, and IX a finite value is found (3.0 Å).

A reasonable agreement exists between the measured shifts and those calculated for diamides VI–IX ac-

(26) C. G. Overberger, G. Montaudo, and P. Finocchiaro, *Macromolecules*, submitted for publication.

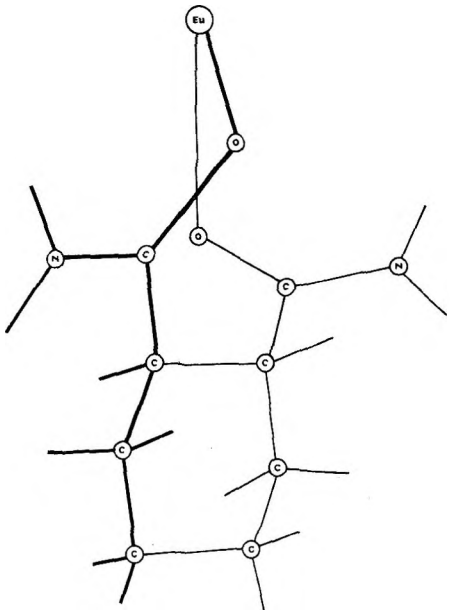


Figure 7.—Molecular geometry of the Eu(fod)$_3$–diamide VII complex. Diamide VII is represented in its preferred conformation (see also Figure 6). Only one Eu ion is involved in the formation of this complex (2:1 type).

cording to the molecular geometries defined by the R, φ, and ω parameters in Table I.[27] The pseudocontact constant (K), selected to allow direct comparison with observed shifts, was found also in this case very close to the value obtained for other amides in Table I.

Discussion

Although the molecular geometry of some lanthanide–substrate complexes has been already carefully investigated,[1-3] most of the work presented to date on the lanthanide shift reagents has been somewhat different in scope.

We have concerned ourselves with the determination of the molecular geometry of a series of Eu(fod)$_3$–amide complexes and it seems appropriate to discuss shortly the basis and limitations of the method, and the assumptions involved.

The exchange of lanthanide ions is a fast process on the nmr time scale and the shifted spectrum represents an averaged spectrum of free and complexed substrate.[1]

Accordingly, if there are several possible locations of the lanthanide in the complex, the observed shifts ($\Delta\nu_{obsd}$) are given by eq 2 where x_i is the mole fraction

$$\Delta\nu_{obsd} = \Sigma_i x_i \Delta\nu_i \qquad (2)$$

of the ith species of complexed substrate molecule and $\Delta\nu_i$ is the corresponding induced shift.

If this is the case, only an *averaged* molecular geometry can be found for these complexes and this geometry does not necessarily possess a physical identity.

On the other side, if it is assumed that there is *one* preferred lanthanide location in the complex (see below) eq 2 becomes eq 3 where x is the mole fraction of complexed substrate molecules and $\Delta\nu$ the corresponding induced shifts.

When this assumption is verified and it is possible to detect *one* preferred lanthanide location in the complex, eq 1 and 3 can be applied, and the best fit of the

$$\Delta\nu_{obsd} = x\Delta\nu \qquad (3)$$

experimental data can be approximately described as *the* molecular geometry of the complex.

At least two other conditions should be fulfilled in order to make the above analysis possible.

First, the substrate conformation should be rigid, or should remain unchanged by the lanthanide addition.[20] Second, if there are conformational isomers which owe their identity to a process slow on the nmr time-scale, their relative population should not vary appreciably with the lanthanide addition. Any failure under this respect should result in the deviation of the $\Delta\nu$ *vs.* [Ld]/[S] plots from linearity, so that it should be possible to verify experimentally if the above conditions are fulfilled.[20]

Diamide III is a conformationally mobile system in which some interconversions are fast compared to the nmr time scale (ethylene units) and some are not (amide units).

Accordingly, curved $\Delta\nu$ *vs.* [Ld]/[S] plots are expected, and found (Table I), for this compound. Linear plots are observed for other amides in Table I, enabling one to carry further the analysis of the data.

In general, our results support the idea that there is one preferential location of the Eu ion in the complex and, furthermore, seem to provide a common molecular model for the Eu(fod)$_3$–amide complexes. The optimal values found for the Eu–O distance (3.0 Å) and Eu–O–C angle (120°) in these complexes seem to correspond to chemical bond requirements, as ascertained by X-ray diffraction studies.[28,29] The Eu–O–C–N dihedral angle (Figure 4) is found to vary between 50 and 90° according to the steric requirements in each complex. Incidentally, it should be noted that the variation of the dihedral angle is an energetically favored process with respect to the variation of the Eu–O distance and Eu–O–C angle. This implies that the existence of one preferential Eu location in the complex is due to the minimum conformational energy requirements relative to the molecular architecture of each complex.

An important corollary of the common molecular model discussed above for the Eu(fod)$_3$–amide complexes is that the Eu ion binds itself to the amide units with a strength largely independent from the rest of the molecule to which the amide unit belongs. If this is true, the mole fraction of complexed substrate (eq 3) should remain roughly constant for this class of compounds. Our results strikingly confirm this expectation; K values in Table I are nearly constant for all the amides investigated.

A possible extention of the present work is in the structural and conformational analysis of complex organic molecules.

A long-range goal in our research is to apply this

(27) It should be stressed that there is no way to obtain agreement between measured shifts and those calculated on alternative hypotheses.

(28) P. A. Cunningham, D. E. Sands, W. F. Wagner, and M. F. Richardson, *Inorg. Chem.*, **8**, 22 (1969).

(29) S. Dahl and P. Groth, unpublished results quoted in ref 12.

technique to the study of the conformational properties and processes of appropriate macromolecules.

Registry No.—I, 127-19-5; I-Eu(fod)$_3$ complex, 35208-59-4; II, 7103-46-0; II-Eu(fod)$_3$ complex, 35208-60-7; III, 24768-60-3; IV, 18940-57-3; IV-Eu(fod)$_3$ complex, 35238-57-4; V, 35168-21-9; V-Eu(fod)$_3$ complex, 35208-61-8; VI, 35211-97-3; VI-Eu(fod)$_3$ complex, 35208-62-9; VII, 35168-20-8; VII-Eu(fod)$_3$ complex, 35208-63-0; VIII, 35212-03-4; VIII-Eu(fod)$_3$ complex, 35208-64-1; IX, 35212-04-5; IX-Eu(fod)$_3$ complex, 35238-58-5; Eu(fod)$_3$, 17631-68-4.

Acknowledgments.—Part of this work was carried out by G. M. at the Department of Chemistry, University of Michigan—Ann Arbor. The authors wish to express sincere thanks to Dr. C. G. Overberger who provided stimulating discussions and donated some of the samples used in the present work.

Intramolecular Oxygen–Nitrogen Benzoyl Migration of 6-Aroyloxyphenanthridines[1,2]

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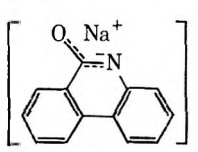
The sodium salt (1) of 6(5*H*)-phenanthridinone reacts with benzoyl chloride to give, under kinetically controlled conditions, the O-substituted product, 6-benzoyloxyphenanthridine (**2a**). When heated alone the *O*-benzoyl compound rearranges to the crystalline *N*-benzoyl isomer, *N*-benzoyl-6(5*H*)-phenanthridinone (**3a**), to the extent of at least 99%. This rearrangement also occurs in hexane or tetrahydrofuran solution but approaches an equilibrium with the ratio **3a**:**2a** of about 5:1. The approach to equilibrium in hexane is first order in **2a** or **3a** and is relatively insensitive to change in solvent polarity. The benzoylations with *p*-methoxybenzoyl chloride and with *p*-chlorobenzoyl chloride have been found to proceed in a similar fashion and the rate and equilibrium constants for reactions of the variously substituted compounds are compared. The effect of the crystalline state on the position of the equilibrium is discussed and other cases are reviewed where crystallization has been utilized to achieve isolation in the pure state of substances which are in mobile equilibrium in solution.

The ready 1,3 rearrangement of acyl groups between oxygen and/or nitrogen atoms[3] may be anticipated to have an important bearing on the chemistry of N- and O-acylated heterocyclic compounds. In a preliminary communication[4] the sodium salt (1) of 6(5*H*)-phenanthridinone was reported to undergo O-benzoylation in tetrahydrofuran to give 6-benzoyloxyphenanthridine (**2a**); when heated alone or in methylene chloride solution **2a** was found to rearrange to the *N*-benzoyl isomer **3a**. This paper presents a more detailed study



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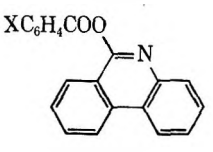
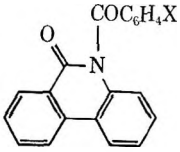


2a, X = H
b, X = CH_3O
c, X = Cl



3

of the equilibrium between **2a** and **3a** as well as rates of isomerization of **2a** and **3a** and their para-substituted analogs.

Experimental Section

Melting points were determined on a calibrated micro hot-stage melting point apparatus. Infrared spectra were determined with a Perkin-Elmer Model 521 spectrophotometer, uv spectra with a Cary Model 14 spectrophotometer, and nmr spectra by Mr. R. Thrift and his associates with a Varian Model A-56/60 and HA-100 spectrometer. Microanalyses were performed by Mr. J. Nemeth and his associates. Reproductions of the principal spectra are contained in the thesis[1] available from University Microfilms, Ann Arbor, Mich.

Unless otherwise indicated, solvents were purified as follows. Methylene chloride was spectral grade stored over molecular sieves. Pentane and petroleum ether (bp 90–120°) were treated with concentrated H_2SO_4, then with $NaHCO_3$ solution, dried with molecular sieves, and distilled from NaH. Tetrahydrofuran (THF) was freshly distilled from lithium aluminum hydride for each use. Benzene and toluene were reagent grade and were dried by passage through a column of molecular sieves. Glassware was dried in an oven at 120°.

Benzoylation of the Sodium Salt (1) of Phenanthridone. 6-Benzoyloxyphenanthridine (2a).—The sodium salt 1 was prepared from phenanthridinone (5.12 g) which had been purified by recrystallization from pyridine, washed with dilute HCl and water, and dried in a vacuum desiccator for 8 hr, by treatment in 200 ml of THF with 2.0 g of 57% NaH in mineral oil. After reaction the infrared maxima (THF solution) at 1678 and 1609 cm^{-1} had been replaced by absorptions at 1621, 1584, 1515, and 1474 cm^{-1}. The mixture was cooled in a Dry Ice bath and 3.66 g of benzoyl chloride was added. After several hours at −20° the mixture was filtered and the filtrate was evaporated to dryness. Extraction with pentane at −20° left an insoluble residue which was extracted with 250 ml of toluene at room temperature. Filtration of the toluene solution, evaporation at 0° under reduced pressure of the toluene solution to a volume of 100 ml, addition of 100 ml of pentane, and cooling to −20° gave 2.46 g (32% based on benzoyl chloride) of crude **3** as tan crystals. Three recrystallizations from toluene–pentane gave 0.55 g of white crystals: mp 119° (resolidified almost immediately and remelted at 189–193.5°); ir (CH_2Cl_2) 1743 (s), 1621 (m), 1593 (m), 1467 cm^{-1} (m); nmr ($CDCl_3$) δ 7.14–8.15 (m); uv (hexane–0.3% THF) λ_{max} 240 nm (ϵ 46,200), 249 (46,300).

Anal. Calcd for $C_{20}H_{13}NO_2$: C, 80.3; H, 4.4; N, 4.7. Found: C, 80.4; H, 4.3; N, 4.5.

A similar reaction mixture from which aliquots were withdrawn a few minutes after addition of the benzoyl chloride showed, in addition to the absorption at 1656 cm^{-1} attributed to unreacted phenanthridone, the development of the absorption at 1742 cm^{-1} of the benzoyloxyphenanthrene **2**. No absorption was observed at 1733 or 1656 cm^{-1} where the *N*-benzoyl isomer **3** absorbs.

***N*-Benzoyl-6(5*H*)-phenanthridinone (3). A. Room Temperature Benzoylation of the Sodium Salt 1.**—A reaction starting with 4.45 g of phenanthridinone, 1.70 g of 50% NaH, 200 ml of THF, and 6.0 g of benzoyl chloride carried out at room temperature for several minutes was completed by evaporation of the THF, extraction with pentane, and finally with boiling toluene. Filtration and partial evaporation of the toluene extracts gave upon

(1) Taken in part from the Ph.D. Thesis of J. H. E., University of Illinois, Urbana, Ill., 1969.

(2) We are very much indebted to the National Science Foundation for a grant which provided substantial support of this work.

(3) D. Y. Curtin and L. L. Miller, *J. Amer. Chem. Soc.*, **89**, 637 (1967).

(4) D. Y. Curtin and J. H. Engelmann, *Tetrahedron Lett.*, 3911 (1968).

TABLE I

KINETICS OF THE EQUILIBRATION OF THE *O*-AROYLPHENANTHRIDINES **2a–c** AND THE *N*-AROYL COMPOUNDS **3a–c**

Starting material	Substituent	Temp, °C	10^5k_e, sec^{-1}	St dev	K_e (3/2)	St dev	$10^5k_1 = [K_e/(K_e+1)]k_e$, sec^{-1}	$10^5k_{-1} = (k_e - k_1)$, sec^{-1}	$\Delta H^{\ddagger}$ kcal/mol Forward	$\Delta H^{\ddagger}$ kcal/mol Reverse	$\Delta G_1^{\ddagger}{}_{44.94°}$, kcal/mol	$\Delta S^{\ddagger}{}_{44.94°}$, cal/deg mol Forward	$\Delta S^{\ddagger}{}_{44.94°}$, cal/deg mol Reverse	$\Delta G_{44.94°}$ kcal/mol
2a	H	25					(0.70)[a]	(0.12)[a]						
		37.50	4.16	0.05[b]	5.38	0.09[b,c]	3.51	0.65						
		44.94	10.04	0.15[b]	5.25	0.21[b,d]	8.43	1.61	23.4	24.2	24.6	−4.7	−4.5	−1.0
		55.00	32.64	0.26[b]	4.91	0.04[b,e]	27.09	5.55						
2b	*p*-CH_3O	25.00					(0.364)[a]	(0.029)[a]						
		25.00	0.497	0.003[f]	16.18	0.28[f,g]	0.468	0.029						
		34.95	1.482	0.007[b]	11.27	0.14[b,h]	1.362	0.120						
		44.94	5.548	0.030[b]	10.00	0.58[b,g]	5.043	0.505	23.9	26.1	24.9	−3.2	−0.9	−1.5
		55.00	17.45	0.10[b]	9.01	0.15[b,i]	15.72	1.73						
2c	*p*-Cl	44.94	10.31	0.13[b]	11.17	0.47[b,i]	9.46	0.85						−1.5

[a] Obtained from extrapolation of data at higher temperatures. [b] In hexane solution. [c] Average of data from three equilibrations starting with **2a** and one with **3a**. [d] Average of two values. [e] Average of three values. [f] In tetrahydrofuran solvent. [g] Average of five values. [h] Average of six values. [i] Average of four values.

cooling 6.0 g (88%) of crystals, mp 189–192.5°. Four recrystallizations from toluene–petroleum ether gave 1.49 g of analytically pure **3**: mp 186–190°; ir (CH_2Cl_2) 1733 (s), 1656 (s), 1610 (m), 1600 (m), 1588 (m), 1450 (m), 1440 (m), 1424 cm^{-1} (m); nmr (HMPA) 7.2 (m); uv (hexane–0.3% THF) λ_{max} 236 nm (ϵ 50,400).

Anal. Calcd for $C_{20}H_{13}NO_2$: C, 80.3; H, 4.4; N, 4.7. Found: C, 80.1; H, 4.2; N, 4.6.

B. Rearrangement of 6-Benzoyloxyphenanthridine (2).—A sample of **2** heated under an argon atmosphere at 125° for several minutes melted and quickly resolidified. The product was shown by the uv analysis to be discussed to contain about 99% of the *N*-benzoyl compound **3**.

6-(4-Methoxybenzoyloxy)phenanthridine (2b).—4-Methoxybenzoyl chloride [6.08 g, bp 83° (0.3 mm)], was allowed to react for 10 hr at −20° with the sodium salt prepared from 7.58 g of phenanthridinone, 3.5 g of 57% NaH, and 200 ml of THF as above. After extraction with five 125-ml aliquots of toluene an equal volume of pentane was added to each of the toluene solutions at −20°; crystallization occurred. The material from the fourth and fifth extractions was recrystallized by solution in toluene at room temperature and addition of an equal volume of pentane. There was obtained 1 g (9% yield) of the *O*-methoxybenzoyl compound **2b**: mp 134° (with resolidification and remelting at 223–228°); ir (CH_2Cl_2) 1735 (s), 1625 (sh), 1605 (s), 1592 (sh), 1581 cm^{-1} (sh); nmr (pyridine-d_5) δ 7.24–8.69 (m, 12), 3.84 (s, 3); uv (hexane) λ_{max} 250 nm (ϵ 52,100), 256 (55,900).

Anal. Calcd for $C_{21}H_{15}NO_3$: C, 76.6; H, 4.6; N, 4.3. Found: C, 76.8; H, 4.8; N, 4.1.

***N*-(4-Methoxybenzoyl)-6(5*H*)-phenanthridinone (3b). A. By Benzoylation of the Salt 1.**—The first three fractions from the extraction procedure above gave material which was recrystallized three times from boiling toluene, filtered, and diluted with an equivalent volume of petroleum ether. There was obtained 1.0 g (8.5%) of white, crystalline **3b**: mp 226–229°; ir (CH_2Cl_2) 1721 (s), 1654 (s), 1602 (s), 1512 (m), 1335 cm^{-1} (m); nmr (pyridine-d_5) δ 6.98–8.67 (m, 12), 3.77 (s, 3); uv (hexane) λ_{max} 229 nm (ϵ 49,500).

Anal. Calcd for $C_{21}H_{15}NO_3$: C, 76.6; H, 4.6; N, 4.3. Found: C, 76.8; H, 4.8; N, 4.3.

B. By Rearrangement of the *O*-Methoxybenzoyl Isomer 2b.—When a sample of **2b** was heated to 150° under an argon atmosphere it melted and quickly recrystallized to give material shown by the uv analysis to be discussed below to be the *N*-benzoyl isomer **3b** in a purity of at least 99%.

6-(4-Chlorobenzoyloxy)phenanthridine (2c).—The reaction of the salt from 5 g of phenanthridinone and 1.5 g of NaH in 200 ml of THF with 4.3 g of *p*-chlorobenzoyl chloride was carried out for 5 hr at −20°, after which the mixture was warmed to room temperature and filtered. Evaporation of the filtrate to dryness and extraction with toluene at room temperature gave on addition of petroleum ether 2.55 g (42% based on unrecovered phenanthridinone) of **2b** as white crystals which were purified by further recrystallization from toluene–petroleum ether. [The toluene-insoluble fraction amounted to 2.55 g (42%) of unreacted phenanthridinone.] There was thus obtained 2.12 g of purified **2c**: mp 135° (resolidified and remelted at 195–200°); ir (CH_2Cl_2) 1742 (s), 1620 (w), 1592 cm^{-1} (m); nmr (pyridine-d_5) δ 7.17–8.67 (m); uv (hexane–0.3% THF) λ_{max} 248 nm (ϵ 61,270).

Anal. Calcd for $C_{20}H_{12}ClNO_2$: C, 72.0; H, 3.6; Cl, 10.6; N, 4.2. Found: C, 72.0; H, 3.7; Cl, 10.9; N, 4.3.

***N*-(4-Chlorobenzoyl)phenanthridinone (3c).**—A 1.0-g sample of analytically pure *p*-chlorobenzoylphenanthridine (**2c**) was recrystallized from boiling toluene to yield 0.82 g of analytically pure **3c**: mp 198–200°; ir (CH_2Cl_2) 1730 (s), 1655 (s), 1612 (m), 1590 cm^{-1} (m); nmr (pyridine-d_5) 7.08–8.67; uv (hexane–0.3% THF) λ_{max} 236 nm (ϵ 47,890).

Anal. Calcd for $C_{20}H_{12}ClNO_2$: C, 72.0; H, 3.6; Cl, 10.6; N, 4.2. Found: C, 72.0; H, 3.6; Cl, 10.8; N, 4.3.

Equilibration of 2a and 3a. A. Spectroscopic Analysis in Hexane Solution.—Solutions of **2a** in hexane were allowed to stand in a constant-temperature bath until no further change in the uv spectrum was observed. They were then analyzed with a least-squares curve-fitting method[5] which determined the concentrations of **2a** and **3a** from absorbancies of the mixture together with standard absorbancies of the pure components at 20 wavelengths with incremental steps from 211–215, 222–225, and 244–254 nm. Application of the method to known mixtures gave average deviations from the theoretical value of 1.3%. The equilibrium constants calculated from these data (K_e = **3a**/**2a**) are given in Table I. A solution of **3a** in hexane on long standing gave the same equilibrium spectrum as **2a**.

B. Analysis by Thin Layer Chromatography.—Qualitative confirmation of the uv results was obtained by dissolution of a sample of the more stable isomer **3a** in methylene chloride and heating the solution under reflux for 70 hr. Tlc on Eastman silica gel plates using 20% diethyl ether in benzene as eluent and with standard samples of **2a** and **3a** on the same plate showed the presence of two spots, one (the smaller) with the R_f corresponding to that of **2a** and the other with an R_f corresponding to that of **3a**.

Kinetics of the Rearrangements of the Benzoyloxyphenanthrenes 2a–c to the *N*-Benzoylphenanthridinones 3a–c.—Solutions 2×10^{-5}–10^{-4} *M* of **2a**, **b**, or **c** in spectral grade hexane were heated in a constant-temperature bath maintained at a temperature controlled to ±0.05°. Temperatures were measured with thermometers calibrated by the National Bureau of Standards. Aliquots were withdrawn after various times and analyzed by the uv method described in method A for the determination of the equilibrium between **2a** and **3a** above.[6] The per cent of starting material present at equilibrium, % C, was the average of several determinations in each case. Plots of ln (% C − % C_e) *vs.* time were linear to greater than 90% approach to equilibrium. Rate constants k_e are reported in Table I. Sample kinetic data are presented in Table II.

Reaction of 6-Benzoyloxyphenanthridine (2a) and *N*-Benzoylphenanthridinone (3a) with Piperidine.—Reaction of 176 mg of **2a** with 55 mg of piperidine in 5 ml of pentane for 24 hr at −20° gave, after removal of the pentane solution from the insoluble

(5) D. B. Pendergrass, Jr., Ph.D. Thesis, University of Illinois, Urbana, Ill., 1971, pp 148 ff.

(6) The analyses of mixtures from **2b** and **2c** were made from absorbancies at the even-numbered wavelengths from 222 to 260 nm (20 points) by an otherwise identical method. Average deviations from the correct values of known mixtures were 0.9% for **2b** and 0.67% for **2c**.

TABLE II

RATE OF EQUILIBRATION OF 2a AND 3a AT 44.94 ± 0.05

Time, min	2a, %	10^5k_e[a]
0	100	
30	85.27	10.70
70	71.04	10.05
110	60.52	9.61
140	51.26	10.32
180	42.53	10.65
192	41.34	10.38
240	35.02	10.29
280	30.13	10.58
300	28.53	10.54
340	26.15	10.32
361	24.85	10.35
415	22.26	10.38
420	22.54	10.08
510	20.16	9.76
600	18.31	9.88
600	18.58	9.58
660	18.10	9.21
690	16.98	10.54
780	16.81	9.70
	Average	10.15

[a] Value calculated by the method of least squares 10^5k_e 10.15. Per cent 2a at equilibrium, 15.91.

residue followed by extraction with water to remove the piperidine and evaporation to dryness, 74 mg (66% yield) of *N*-benzoylpiperidine, mp 48–49° (lit.[7] mp 48°), identified by comparison of the melting point, mixture melting point, and infrared spectrum with those of an authentic sample.[7] The pentane-insoluble fraction was 97 mg (84%) of phenanthridinone, mp 292–294°.

When 164 mg of **3a** was treated with 46 mg of piperidine and 10 ml of pentane at ambient temperature for 15 hr and then after addition of 40 ml of additional pentane under reflux for 5 hr, there was obtained after work-up as with the reaction of **2a** 24 mg (23%) of benzoylpiperidine, mp 47–49°, characterized by melting point, mixture melting point, and infrared spectrum. The pentane-insoluble residue yielded 123 mg (75%) of recovered **3a**.

Results and Discussion

The kinetically controlled aroylation of the sodium salt of phenanthridinone in THF (low temperatures and short reactions times) clearly shows a strong preference for attack at the oxygen atom. However, in hexane solution as well as THF the equilibration of *O*- and *N*-aroylphenanthridinones is readily obtained, the *N*-aroyl species being favored with an equilibrium constant of about 5 (Table I).[8] The solid-state equilibrium favors the *N*-aroyl isomer still more, at least 99% of the mixture being the N-substituted component.

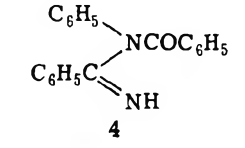
The evidence bearing on the mechanism of the acyl migration in solution can be summarized briefly. Linearity of first-order plots and the observation that a fourfold increase in concentration of starting material gave no change in the rate constant shows that the reactions interconverting **2a** and **3a** are first order. Since the observed rate constant k_e for the approach to equilibrium is the sum of forward and reverse rate constants k_1 and k_{-1}, it has been partitioned to give the values shown in Table I. Comparison of the rates of reaction of 2b and **3b** in tetrahydrofuran with their rates in hexane (Table I) shows that there is an increase of less than 30% in the more polar solvent.[9] The effects of substituents on the rate and equilibrium constants, shown in Table III, are small, the overall spread of any

TABLE III

RELATIVE VALUES OF THE RATE AND EQUILIBRIUM CONSTANTS FOR THE EQUILIBRATION OF THE N- AND O-PARA-SUBSTITUTED BENZOYLPHENANTHRIDINONES 2 AND 3 IN HEXANE AT 44.94°

Compd	Substituents	k_1 (rel)	k_{-1} (rel)	K_e (rel)
2b, 3b	*p*-CH_3O	0.60	0.31	1.90
2a, 3a	H	1.00	1.00	1.00
2c, 3c	*p*-Cl	1.12	0.53	2.12

set of constants being less than a factor of 4. Although the values of k_1 show a reasonable trend, *p*-methoxyl decreasing the rate and *p*-chloro increasing it, a plot of log k_1 *vs.* σ[11] is not linear. Calculation from pairs of rate constants using the Hammett equation gives values of ρ ranging from 0.22 to 0.88. One source of the nonlinearity is seen when the effect of substituents on the equilibrium constants K_e is considered. Both *p*-methoxy and *p*-chloro substituents increase the equilibrium constant and by amounts which are clearly outside experimental error and are comparable to the magnitudes of the effects on the rate constants. It seems unwise to attempt to draw conclusions about details of mechanism from such small substituent effects on the benzoyl phenanthridinone rearrangements without further data. However, the modest effect of substituents and solvent change on k_1 is reminiscent of the behavior of other 1,3-acyl migrations which are compared in Table IV. It may be noted also that a ρ of



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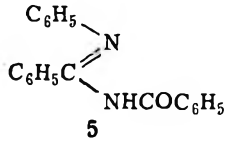

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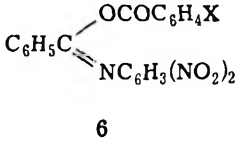

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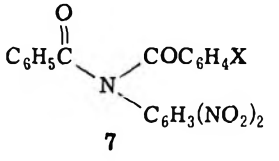

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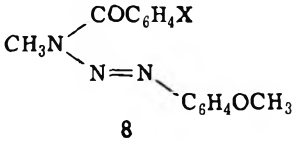

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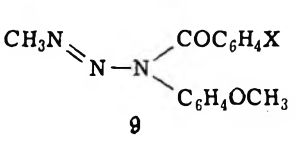

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+0.518 has been reported[12] for the reaction of meta- and para-substituted methyl benzoates with aniline in nitrobenzene to form benzanilides. In short, the interconversion of 2 and 3 seems to belong to a group of re-

(7) C. Schotten, *Ber.*, **17**, 2545 (1884); **21**, 2238 (1888).

(8) At the time of publication of the preliminary report[4] of this work the presence of a minor component of the solution equilibrium had not been recognized.

(9) If the assumption is made that the *Z* value for hexane is the same as that for isooctane [E. M. Kosower, *J. Amer. Chem. Soc.*, **80**, 3253 (1958)] and it is employed to calculate k_1 with eq 6 of Smith, Fainberg, and Winstein,[10] the rate constants for the reaction of **2b** in hexane and in tetrahydrofuran (Table I) lead with the Smith–Fainberg–Winstein equation (eq 7)[10] to an "*a*" value for the rearrangement of **2b** to **3b** of 0.17.

(10) S. G. Smith, A. H. Fainberg, and S. Winstein, *J. Amer. Chem. Soc.*, **83**, 618 (1961); S. G. Smith, *Tetrahedron Lett.*, 979 (1962).

(11) L. P. Hammett, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1970, pp 355 ff.

(12) N. T. Vartak, N. L. Phalnikar, and B. V. Bhide, *J. Indian Chem. Soc.*, **24**, 131A (1947).

Table IV

1,3-Acyl Migrations Between Nitrogen and/or Oxygen Atoms

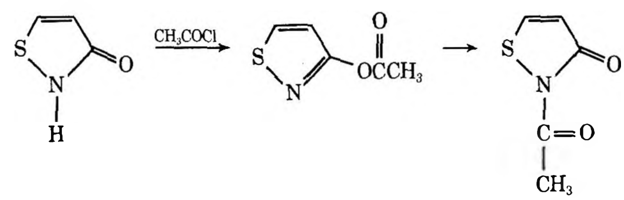
Reaction	Change	Solvent	Temp range studied, °C	Rate of compd (X = H) $10^6 k_1$, sec^{-1}	Temp, °C	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/mol deg	ρ
$4^a \rightarrow 5^a$	N → N	Toluene	45–80	1.3	45.00	20.2	−17	
$6^b \rightarrow 7^b$	N → O	Benzene	42–64	6.1	42.86	23.8	−2	0.6
$2a \rightarrow 3a^c$	O → N	Hexane	37–55	10.0	44.94	23.14	−5	0.6
$3a \rightarrow 2a^c$	N → O	Hexane	37–55	1.6	44.94	24.2	−5	0.0 ± 2
$8 \rightarrow 9^d$	N → N	Diphenyl ether	148–185	2×10^{-5}	43[e]	33.6	−3	0.6

[a] D. A. R. Thompson, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1970; H. L. Wheeler, T. B. Johnson, and D. F. McFarland, *J. Amer. Chem. Soc.*, **25**, 787 (1903); D. A. Peak, *J. Chem. Soc.*, 215 (1952). [b] Reference 4. [c] This paper. [d] C. L. Mampaey, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1968; see also D. Y. Curtin and J. D. Druliner, *J. Org. Chem.*, **32**, 1552 (1967). [e] Data extrapolated to this temperature.

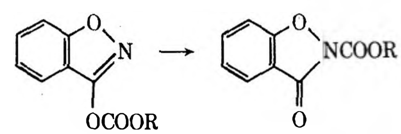
actions whose mechanism is essentially an intramolecular nucleophilic replacement at a carbonyl group, as discussed previously.[3] As is seen in Table IV, these proceed under mild conditions (with the exception of the rearrangement of the benzoyltriazene **8**) in nonpolar solvents in spite of the fact that a strained four-membered cyclic transition state is involved.

The interconversion of *N*- and *O*-acyl derivatives of heterocycles could be expected to be a general reaction and to proceed under mild conditions. The aroylation of the sodium salt of 2-pyridone suspended in benzene was shown in a preliminary study[13] to yield what appeared to be a mixture of *N*- and *O*-aroylpyridones, the N isomer disappearing on standing. Furthermore, acetylation of the thallous salt of 2-pyridone in chloroform at −40° has been reported[14] to produce a solution whose nmr spectrum strongly suggests that a mixture of *N*- and *O*-acetyl products is formed in a ratio (N:O) of 2:3, the *N*-acetyl compound being converted to O-acetyl on standing at room temperature. It is not certain just how far toward the *O*-acyl derivatives the equilibria lie in the case of the acylpyridones. It is somewhat surprising that an *N*-oxalyl derivative of 2-pyridone has been reported to show no tendency to rearrange to the O-substituted derivative.[15] The equilibria between hydroxy pyridine and pyridone isomers with proton transfer and with methyl transfer have been studied in considerable detail.[16] However, as was pointed out by Chan and Crow[17] in their study of the positions of equilibria of *N*- and *O*-acyl-3-hydroxyisothiazoles, acyl equilibria differ from equilibria involving proton or alkyl migration not only because of polar effects but also due to steric effects arising from the preference for a planar conformation of the ester and amide functional groups.

The study[17] of the acyl-3-hydroxyisoxazoles is of interest in another connection. Acylation of the parent isoxazole with acetyl chloride and triethylamine in benzene (the kinetically controlled reaction) favored the *O*-acetyl compound by a factor of at least 9:1. The O compound could be made subsequently to rearrange to the N-substituted isomer, but not by an intramolecular path. It seems likely that the intra-



molecular 1,3-acyl migration is slower in the case of five-membered heterocycles because of the increased N–C–O bond angle of the five-membered ring; a competing intermolecular reaction can then predominate. A reaction which may be related is the rearrangement of the *O*- to *N*-carbalkoxylbenzisoxazoles recently reported.[18]



As a further example of what seems to be an intermolecular rearrangement, 4-pyridone on acetylation gives the *N*-acetyl derivative as the stable crystalline product which on solution in methylene chloride rearranges to an equilibrium mixture of 4-acetoxypyridine and *N*-acetyl-4-pyridone in nearly equal amounts.[19] More information about the mechanism of this equilibration would be of interest.

The utilization of crystal forces to shift the equilibrium between **2** and **3** from one balanced in solution to an equilibrium essentially completely one-sided in the crystalline state deserves further emphasis. Numerous examples have been recently reported of the use of the great selectivity inherent in the crystallization process to obtain in pure form one or more isomeric species which are known to be in equilibrium in solution. These include crystallization of rotational conformers,[20] equilibrium asymmetric transformers,[21] cis–trans iso-

(13) Reference 3, footnote 23.

(14) A. McKillop, M. J. Zelesko, and E. C. Taylor, *Tetrahedron Lett.*, 4945 (1968).

(15) L. J. Bollyky, B. G. Roberts, R. H. Whitman, and J. E. Lancaster, *J. Org. Chem.*, **34**, 836 (1969).

(16) P. Beak, T. S. Woods, and D. S. Mueller, *Tetrahedron*, in press; A. R. Katritsky, *Chimia*, 134 (1970).

(17) A. W. K. Chan and W. D. Crow, *Aust. J. Chem.*, **21**, 2967 (1968).

(18) H. Böshagen and W. Geiger, *Chem. Ber.*, **103**, 123 (1970).

(19) I. Fleming and D. Philippides, *J. Chem. Soc. C*, 2426 (1970).

(20) S.-I. Mizushima, "Structure of Molecules and Internal Rotation," Academic Press, New York, N. Y., 1954; J. W. Barsch, *J. Chem. Phys.*, **43**, 3473 (1965); P. Klaeboe, *Acta Chem. Scand.*, **23**, 2641 (1969); F. R. Jensen and C. H. Bushweller, *J. Amer. Chem. Soc.*, **91**, 3223 (1969); T. Fujiyama, *Bull. Chem. Soc. Jap.*, **44**, 3317 (1971); T. Miyazawa, *ibid.*, **42**, 3021 (1969).

(21) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, pp 58–60, 63–65; R. E. Pincock and K. R. Wilson, *J. Amer. Chem. Soc.*, **93**, 1291 (1971); S. A. Chawdhury, A. Hargreaves, and R. A. L. Sullivan, *Acta Crystallogr., Sect. B*, **24**, 1222 (1968).

mer,[22] proton-transfer tautomers,[23] ring–chain tautomers,[24] and diastereoisomeric hemiacetals,[25] as well as the isomers related by 1,3-acyl migration discussed above. In many of the cases cited it is not clear whether the selectivity observed is due to preferential nucleation of one isomer or to a thermodynamic preference for one isomer in the crystalline state.

(22) I. R. Gault, W. D. Ollis, and I. O. Sutherland, *Chem. Commun.*, 269 (1970); N. A. Bailey and S. E. Hull, *ibid.*, 960 (1971); D. Y. Curtin and J. W. Hausser, *J. Amer. Chem. Soc.*, **83**, 3474 (1961); E. F. Schoenwaldt, R. B. Kinnel, and P. Davis, *J. Org. Chem.*, **33**, 4270 (1968); M. Raban and E. Carlson, *J. Amer. Chem. Soc.*, **93**, 685 (1971); A. G. Sanchez, A. M. Valle, and J. Bellanato, *J. Chem. Soc. B*, 2330 (1971); F. Sondheimer, *Accounts Chem. Res.*, **3**, 81 (1972); A. Rieker and H. Kessler, *Chem. Ber.*, **102**, 2147 (1969); A. J. Bellamy and R. D. Guthrie, *J. Chem. Soc. C*, 2090 (1968).

(23) B. H. Chase and J. Walker, *J. Chem. Soc.*, 3518 (1953); J. W. Schulenberg, *J. Amer. Chem. Soc.*, **90**, 1367 (1968); E. M. Peresleni, M. Y. Uritskaya, V. A. Loginova, Y. N. Sheinker, and L. I. Yakontov, *Dokl. Akad. Nauk SSSR*, **183**, 1102 (1968); G. A. Newman and P. J. S. Pauwels, *Tetrahedron*, **25**, 4605 (1969); E. Spinner and G. B. Yeh, *J. Chem. Soc. B*, 279 (1971); T. Shono, Y. Hayashi, and K. Shima, *Bull. Chem. Soc. Jap.*, **44**, 3179 (1971); D. Hadzi, *J. Chem. Soc.*, 2143 (1956); G. T'oth, I. T'oth, and L. Toldy, *Tetrahedron Lett.*, 5299 (1969); W. Walter and K. J. Reubke, *Chem. Ber.*, **102**, 2117 (1969).

(24) P. R. Jones and P. J. Desio, *J. Org. Chem.*, **30**, 4203 (1965); W. Flitsch, *Chem. Ber.*, **103**, 3205 (1970); A. F. McDonagh and H. E. Smith, *J. Org. Chem.*, **33**, 1 (1968); W. Schaefer and H. Schlude, *Tetrahedron Lett.*, 2161 (1968); H. Alper, E. C. Keung, and R. A. Partis, *J. Org. Chem.*, **36**, 1352 (1971), and earlier papers.

(25) M. C. Tanret, *Bull. Soc. Chim. Fr.*, **33**, 337 (1905); C. S. Hudson and E. Yanovsky, *J. Amer. Chem. Soc.*, **39**, 1013 (1917); R. W. King, C. F. Murphey, and W. C. Wildman, *ibid.*, **87**, 4912 (1965); J. Karle, J. A. Estlin, and I. L. Karle, *ibid.*, **89**, 6510 (1967).

Differential thermal analysis in which **2a** was heated at a rate of 10°/min showed an endotherm (partial melting) interrupted by an exotherm (heat of reaction and recrystallization of the **3a** which had been formed) and then a melting endotherm corresponding to the melting of the product **3a**.[26] From the areas of these peaks the thermal changes were estimated to be 4.7 kcal/mol for the first endotherm and −6.9 kcal/mol for the exotherm. At the end of those changes, if melting, reaction, and recrystallization had taken place, the net change for the process **2a** (solid) → **3a** (solid) was 4.7 + (−) 6.9 = 2.2 kcal/mol. These data are not of high accuracy but the result is reasonable. The final melting endotherm had an area which gave a value for the heat of fusion of 12 kcal/mol for the **3a** which had been formed. The value of the heat of fusion obtained with recrystallized **3a** was 9.3 kcal/mol. The reason for the greater stabilization of **3a** by crystal packing forces must await information about the crystal structures of these compounds.

Registry No.—**1**, 20178-62-5; **2a**, 20178-63-6; **2b**, 35454-86-5; **2c**, 35356-68-4; **3a**, 20178-64-7; **3b**, 35427-28-2; **3c**, 35356-69-5.

(26) We are indebted to Dr. S. R. Byrn for these results. The method employed has been described: D. Y. Curtin, S. R. Byrn, and D. B. Pendergrass, Jr., *J. Org. Chem.*, **34**, 3345 (1969).

Carbon-13 Nuclear Magnetic Resonance Spectroscopy. Conformational Analysis of Methyl-Substituted Cycloheptanes, Cycloheptanols, and Cycloheptanones[1]

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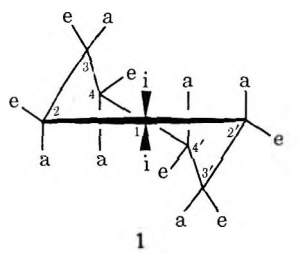
The ^{13}C chemical shifts were determined of the carbons in 12 cycloheptanes, 21 cycloheptanols, and 8 cycloheptanones. In some cycloheptanols and cycloheptanones, the assignments have been obtained unambiguously by the synthesis of deuterated derivatives and the use of paramagnetic-shift reagents. Substituent effects for the different types of groups have been calculated. The most informative data about the cycloheptane conformations were provided by the relatively well understood γ effects. The results are generally in good agreement with predictions based on the twist-chair form, which has been predicted by Hendrickson to be the most stable conformation. Pairs of cis–trans isomers are found to have rather characteristic differences in their ^{13}C spectra. This fact was used to assign the resonances found for cis–trans mixtures of methyl-substituted cycloheptanols to specific isomers.

In contrast to the many published studies of cyclohexane conformations, the results of relatively few experimental investigations of the cycloheptane conformations have been reported.[3] One reason is complexity. The twist-chair conformation (**1**) of cycloheptane is predicted to be most stable,[4] and this form has three different equatorial (e) and axial (a) positions besides two identical isoclinal (i) or axis positions. Substituents at the i and the various *e* positions are calculated to have pretty much the same conformational energy.[4d] To add to the complexities, and, in contrast to the rather rigid cyclohexane chair form, the cycloheptane twist form is quite flexible and an unsubstituted twist form can transform to another one by "pseudorotation" in which the axis of symmetry has moved by one carbon. The barrier to pseudorotation is estimated to be 1.4 kcal/mol[4e] and the highest point of energy along the interconversion pathway is the chair form **2**, which has a plane of symmetry.[4e] The twist-boat (**3**) and the boat (**4**) are other cycloheptane con-



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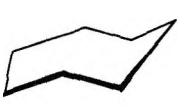

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(1) Supported by the National Science Foundation.

(2) Max Kade Foundation, Inc., Fellow, 1970–1971.

(3) For a review see W. Tochtermann, *Fortschr. Chem. Forsch.*, **15**, 378 (1970).

(4) (a) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **83**, 4537 (1961); (b) *ibid.*, **84**, 3355 (1962); (c) *ibid.*, **89**, 7036 (1967); (d) *ibid.*, **89**, 7043 (1967); (e) *ibid.*, **89**, 7047 (1967).

3 4

formations which are also relatively stable. They can also be intercoverted by pseudorotation, as for the chair forms. However, the calculated energies of **3** and **4** are higher by 2.4 and 2.7 kcal/mol than the twist-chair form.[4c] It is expected, therefore, for simple substituted cycloheptanes that the boat family of forms should not be populated to more than 1% at room temperature. The results of calculations by Bixon and Lifson[5] are similar to those of Hendrickson,[4] except that they obtained an energy difference between twist-chair and chair conformations of only 0.7 kcal/mol. The substantial flexibility of the cycloheptane ring has been demonstrated by the fluorine-labeling technique.[6] The low-temperature ^{19}F spectra were found to be different from spectra taken at room temperature only if substituents like *gem*-methyl groups[6a] or vicinal bromine atoms[6b] were present. Pseudorotation is clearly very rapid unless relatively large substituents are present. No evidence was found which was not in agreement with the twist-chair conformation being favored at equilibrium. Heteroatoms, such as sulfur, in a saturated seven-membered ring also seem to increase the barrier to pseudorotation.[7] X-Ray studies of 4-bromo-6,10-dimethylbicyclo[5.3.0]decan-3-one[8] and the "dimeric cycloheptanone peroxide"[9] show that the carbocyclic seven-membered rings in these compounds prefer the chair conformation in the solid state.

Carbon-13 nuclear magnetic resonance (^{13}C nmr) has been used quite successfully in conformational studies with cyclohexane,[10-12,13a] cyclopentane,[14] and cyclononane[13b] derivatives. Encouraged by these results, we have undertaken a ^{13}C nmr investigation of cycloheptane derivatives, the results of which we report here.

Results and Discussion

The ^{13}C chemical shifts were measured at about 40° and, of course, the rates of interconversion of the conformations are all exceedingly fast at this temperature. The shifts are therefore average values to which several conformations will contribute according to their populations as determined by the Boltzmann distribution. To assign the resonance lines to specific carbons, we used off-resonance proton decoupling and, whenever possible, specific proton decoupling.

A. Methylcycloheptanes.—The chemical shifts of methylcycloheptanes, kindly supplied by Professor James B. Hendrickson,[15] have been determined in carbon disulfide as solvent, with tetramethylsilane as internal reference. Some representative cycloheptanes were also run in dioxane as solvent, which also served as internal reference. In dioxane, the shifts were uniformly upfield by about 1 ppm, compared to carbon disulfide. The results are summarized in Table I, while Table II gives the substituent effects of the methyl groups which result by comparison of the chemical shifts of a particular methyl-substituted cycloheptane with a corresponding cycloheptane having one less methyl group. The substituent effects are classified as α, β, γ, δ, and ϵ effects[11a] and listed along with the previously determined methyl substituent effects for cyclohexanes.[10a] The α effect is that produced by a methyl on a carbon to which it is directly attached, the β effect is on the carbon next removed, and so on.[11a] Considerable difficulties will be encountered later in discussion of the shift changes by a need to distinguish between the numbering of positions for nomenclature purposes and the numbering of carbons in the twist-chair conformation where the isoclinal carbon will be taken as C-1. In order to clarify this, we will use C-1i, C-2e,a, etc., when we refer to the carbons of conformations, and omit the lower case letters otherwise.

In methylcycloheptane, the resonances of three methylene carbons can be readily distinguished. Compared to the unsubstituted cycloheptane, the resonance of C-2 at 155.0 ppm is shifted downfield by 9.3 ppm by the β effect of the methyl group. The position corresponding to C-3 is the result of a 1.3-ppm upfield γ effect, while the line for C-4 is 0.7 ppm downfield. The α and β effects have about the same magnitude as for methylcyclohexane.[10a] The γ effect, however, is increased by 0.8 ppm. Because the γ effect appears to arise from direct steric interactions between the groups under consideration, it is believed to be relatively well understood.[14] We assume here that the larger γ effect arises from a stronger average interaction between the methyl group and C-3 in methylcycloheptane than in methylcyclohexane. In this connection and in others to be discussed later, it is helpful to have Hendrickson's values for the steric interaction energies of a single methyl group with the other atoms of cycloheptane.[4d]

Position	Calcd energy, kcal/mol
1i	0.5
2e,2e′	0.4
2a,2a′	3.0
3e,3e′	0.3
3a,3a′	3.3
4e,4e′	0.4
4a,4a′	1.8

The most stable conformation of 1,1-dimethylcycloheptane should be **5**, which is a twist-chair form with both methyl groups in the favorable isoclinal positions.

(5) M. Bixon and S. Lifson, *Tetrahedron*, **23**, 769 (1967).

(6) (a) J. D. Roberts, *Chem. Brit.*, 529 (1966); (b) R. Knorr, C. Ganter, and J. D. Roberts, *Angew. Chem.*, **79**, 577 (1967); *Angew. Chem., Int. Ed. Engl.*, **6**, 556 (1967); (c) E. S. Glazer, R. Knorr, C. Ganter, and J. D. Roberts, *J. Amer. Chem. Soc.*, **94**, 6026 (1972).

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(8) T. Sato, H. Minato, M. Shiro, and H. Koyama, *Chem. Commun.*, 363 (1966).

(9) P. Groth, *Acta Chem. Scand.*, **21**, 2631 (1967).

(10) (a) D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, **89**, 6612 (1967); (b) D. K. Dalling, D. M. Grant, and L. F. Johnson, *ibid.*, **93**, 3678 (1971); (c) H. J. Schneider, R. Price, and T. Keller, *Angew. Chem.*, **83**, 759 (1971); *Angew. Chem., Int. Ed. Engl.*, **10**, 730 (1971).

(11) (a) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Amer. Chem. Soc.*, **92**, 1338 (1970); (b) H. J. Reich, M. Jautelat, M. T. Messe, F. J. Weigert, and J. D. Roberts, *ibid.*, **91**, 7445 (1969).

(12) G. W. Buchanan and J. B. Stothers, *Can. J. Chem.*, **47**, 3605 (1969).

(13) (a) F. A. L. Anet, C. H. Bradley, and G. W. Buchanan, *J. Amer. Chem. Soc.*, **93**, 258 (1971); (b) F. A. L. Anet and J. J. Wagner, *ibid.*, **93**, 5266 (1971).

(14) M. Christl, H. J. Reich, and J. D. Roberts, *ibid.*, **93**, 3463 (1971).

(15) J. B. Hendrickson and R. K. Boeckman, Jr., *J. Org. Chem.*, **36**, 2315 (1971).

TABLE I

^{13}C CHEMICAL SHIFTS (IN PPM) OF METHYLCYCLOHEPTANES RELATIVE TO CARBON DISULFIDE

Registry no.	Cycloheptane	C-1	C-2	C-3	C-4	C-5	C-6	C-7	CH_3	
291-64-5	Cycloheptane[a]	164.3								
4126-78-7	Methyl	157.6	155.0	165.6	163.6				168.1	
13151-49-0	1,1-Methyl	159.2	149.9	168.7	161.7				161.7	
13151-50-3	*trans*-1,2-Dimethyl	151.2		156.7	165.8	162.8			169.9	
13151-51-4	*cis*-1,2-Dimethyl	155.0		158.5	165.9	163.3			174.6	
13151-52-5	*trans*-1,3-Dimethyl	161.4	147.8		155.0	163.4			168.2	
13151-53-6	*cis*-1,3-Dimethyl	158.3	145.6		155.1	166.0			167.6	
13151-54-7	*trans*-1,4-Dimethyl	157.3	155.9[b]			155.7[b]	168.4		168.2	
14190-15-9	*cis*-1,4-Dimethyl	158.3	159.0			154.1	165.5		168.2	
35099-89-9	1,1,2-Trimethyl	156.9	149.3	160.1	162.8[b]	162.1[b]	169.7	148.6	*trans*-1-CH_3	162.8
									cis-1-CH_3	168.8
									2-CH_3	173.7
24162-71-3	1,1,3-Trimethyl	160.1	141.1	163.0	153.1	162.4	169.0	150.0	*trans*-1-CH_3	163.0
									cis-1-CH_3	160.1
									3-CH_3	166.8
2158-55-6	1,1,4-Trimethyl	159.2	151.9[b]	160.5	155.6	152.5[b]	170.0	149.9	*trans*-1-CH_3	161.3
									cis-1-CH_3	161.9
									4-CH_3	168.4

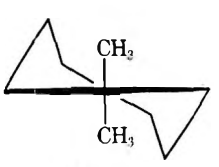
[a] J. J. Burke and P. C. Lauterbur, *J. Amer. Chem. Soc.*, 86, 1870 (1964). [b] Tentative assignments.

TABLE II

^{13}C CHEMICAL-SHIFT SUBSTITUENT EFFECTS (IN PPM) PRODUCED BY SUBSTITUTION OF A METHYL GROUP ON CYCLOHEPTANE (CYCLOHEXANE), METHYLCYCLOHEPTANE (METHYLCYCLOHEXANE), AND 1,1-DIMETHYLCYCLOHEPTANE (1,1-DIMETHYLCYCLOHEXANE)[a]

Cycloheptane (cyclohexane)	α Effect	β Effect	γ Effect	δ Effect	ϵ Effect
Methyl	−6.7	−9.3	1.3	−0.7	
	(−6.0)	(−8.7)	(0.5)	(0.7)	
1,1-Dimethyl	1.6	−5.1, −6.4[b]	3.1	−1.9	
	(3.1)	(−4.1, −6.1[b])	(4.0)	(−0.1)	
trans-1,2-Dimethyl	−3.8	−6.4, −8.9	2.2, 1.7, 1.8[b]	−0.8, 0.2	
	(−3.8)	(−6.5, −9.6)	(−0.3, −0.5, 2.5[b])	(−0.3)	
cis-1,2-Dimethyl	0.0	−2.6, −7.1	2.3, 3.5, 6.5[b]	−0.3, 0.3	
	(1.3)	(−1.4, −5.0)	(2.7, 4.3, 7.0[b])	(2.9)	
trans-1,3-Dimethyl	−4.2	−7.2, −8.6	3.8, −0.2	−2.2, 0.0, 0.1[b]	
	(−0.5)	(−5.7, −7.5)	(5.8, 6.0)	(1.9, 2.2[b])	
cis-1,3-Dimethyl	−7.3	−9.4, −8.5	0.7, 2.4	0.4, 0.1, −0.5[b]	
	(−6.3)	(−8.9, −9.0)	(−0.1, 0.2)	(0.4, −0.1[b])	
trans-1,4-Dimethyl	−6.3	−9.7, or −9.9	0.9 or 0.7	−0.3	0.1
		−7.9 or −7.7	2.8	0.7 or 0.9	
	(−6.2)	(−9.1)	(0.2)	(0.5)	(0.0)
cis-1,4-Dimethyl	−5.3	−6.6, −9.5	4.0, −0.1	0.7, −0.9	0.1
	(−3.7)	(−4.4)	(4.9)	(3.0)	(2.6)
1,1,2-Trimethyl[c]	−0.6	−2.3, −8.6	1.1, −1.3, 1.1,[b] 7.1[b]	0.4, 1.0	
	(−2.0)	(−2.9, −8.7)	(−0.1, −1.4, −1.7[b], 9.7[b])	(−0.2)	
1,1,3-Trimethyl[c]	−5.7	−8.8, −8.6	0.9, 0.7	0.3, 0.1, 1.3,[b] −1.6[b]	
	(−5.7)	(−9.5, −9.0)	(0.0, −0.8)	(0.3, −4.9,[b] 3.9[b])	
1,1,4-Trimethyl[c]	−6.1	−8.2, −9.2	2.0 or 2.6,	0.0, 0.0	−0.4, 0.2
		or −9.8	1.3		

[a] Parenthetical values are for cyclohexane derivatives. [b] Effect on the ^{13}C nmr shift of a methyl already present. [c] Substituent effects relative to 1,1-dimethylcycloheptane.



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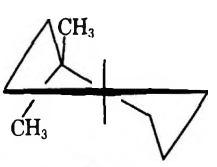

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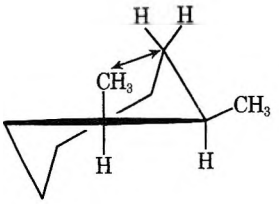
The γ effect of the second methyl group is 3.1 ppm, which is 0.9 ppm less than in 1,1-dimethylcyclohexane, which indicates less axial character. The same trend is found in the α and β effects, which are less positive and more negative, respectively, than for 1,1-dimethylcyclohexane. However, 3.1 ppm for the γ effect is more than twice as much as in methylcycloheptane. Conformation **6**, with the methyl groups in the 4e and 4a positions, should be only about 1.2 kcal/mol less stable than **5**, and may well be sufficiently populated to impose some average axial character to the methyl groups. The substituent effects seem to provide unambiguous assignments of the ^{13}C nmr resonances of the *cis*- and *trans*-1,2-dimethylcycloheptanes. The serious steric interaction between the methyl groups in the cis isomer produces a large upfield shift of the methyl carbons, as has been observed in other similar compounds.[10a,11a,14] The substituent effects in these isomers show the same regularities as in the 1,2-dimethylcyclohexanes. The α and β effects are more negative in the trans isomer, while the γ effects are larger in the cis isomer. In the most stable conformation of the latter, the methyl groups should occupy the

i and 2e or 2e′ positions of the twist-chair (**7**). All the other conformations should be more than 1 kcal/mol



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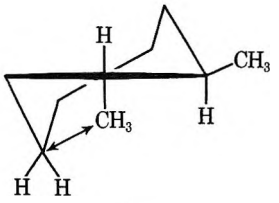


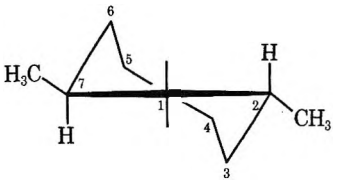
8

less stable but, because of their large number, they could well be considerably populated and, on the basis of Hendrickson's calculations,[4d] the axial character of the methyl groups can be estimated to be 10%. For the trans isomer **8**, a much larger number of favorable conformations is possible and the axial character of the methyl groups should be below 1%. As a consequence of the relatively small difference in the conformational character of the methyl groups, their substituent effects do not differ so much between the cis and trans cycloheptane isomer as for the corresponding cyclohexanes, where the difference in the axial character is 50%. The two γ-methyl effects on the ring carbons in the cis isomer are different, being 2.3 and 3.5 ppm. This can be explained by an important contribution of **7**, in which introduction of an isoclinal methyl group will give a greater interference with the ring carbon adjacent to the methyl already present, rather than the one on the unsubstituted side. With the trans isomer, the situation is just reversed for the analogous conformation, as can be seen from **8**. However, both the size of the effects and their difference is smaller for the trans isomer because **8** is not the most favorable form. Other favorable conformations with the methyl groups in the 2e,3e, 3e,4e, 4e,4e′, 4e′,3e′, and 3e′,2e′ positions should have smaller γ interactions, about the same magnitude as for methylcycloheptane itself. This is borne out by thermochemical data which show the enthalpy difference between the *cis*- and *trans*-1,2-dimethylcycloheptanes to be 0.7 kcal/mol[16] compared to 1.87 kcal/mol[17] between the corresponding cyclohexanes. The enthalpy differences between the *cis*- and *trans*-1,3- and -1,4-dimethylcycloheptanes are close to zero,[16] while 1.96 and 1.90 kcal/mol have been determined for the corresponding cyclohexanes.[17] These results follow from the average degree of axial character of the methyl groups which, from Hendrickson's[4d] conformational energies of methyl groups, are indicated to be only about 6% for the 1,3-dimethylcycloheptanes and 2% for the 1,4-dimethylcycloheptanes. Nonetheless, the ^{13}C nmr spectra seem sensitive to even the small differences for the 1,3 and 1,4 isomers. For the 1,2-dimethylcycloheptanes, the substituent effects resulting from introduction of the second methyl group are substantially different for the cis and trans isomers. With the 1,3-dimethylcycloheptanes, these differences decrease and become still smaller for the 1,4-dimethyl compounds.

(16) G. Mann, M. Mühlstädt, R. Müller, E. Kern, and W. Hadeball, *Tetrahedron*, **24**, 6941 (1968).

(17) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 53.

The γ effects are especially interesting. The *trans*-1,3-dimethylcycloheptane should only be favorably disposed as **9** and **10**, because in these conformations



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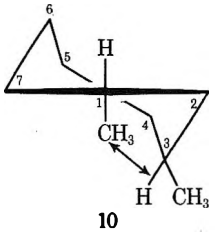

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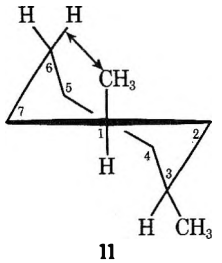

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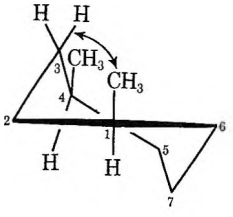
both methyl groups are placed in positions of minimum strain. The other trans conformations have at least one axial-type interaction. It is evident from **10** that an isoclinal methyl group should interact more strongly with C-3 than with C-6, which is reflected in the corresponding 3.8- and −0.5-ppm γ effects. The interaction with C-6 is the stronger one (2.4 ppm) in *cis*-1,3-dimethylcycloheptane, while the C-3 resonance is shifted upfield only by 0.7 ppm, both of which can be accounted for by **11**. The effects are smaller than in the trans compound, because for the cis compound there are two other conformations, 2e,4e and 3e,5e, which are quite favorable. This analysis is borne out by the shifts of the methyl carbons of the trans isomer, which appear at 0.6 ppm higher field than those of the cis isomer, in accord with greater average steric interactions of trans methyl groups. The methyl carbons of the *cis*- and *trans*-1,4-dimethylcycloheptanes have the same chemical shift. This is not surprising on the basis of the predicted difference in the interactions of the methyl groups in both the isomers. Again, the γ effects show a remarkable asymmetry. The C-3 interaction expected for conformation **12** of the cis isomer amounts to 4.0 ppm, which is close to the 4.9 ppm found for *cis*-1,4-dimethylcyclohexane. Practically no effect is found on the shift of C-7. Conformation **12**, one of



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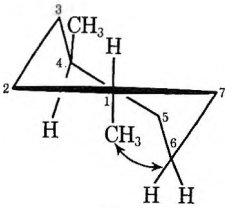
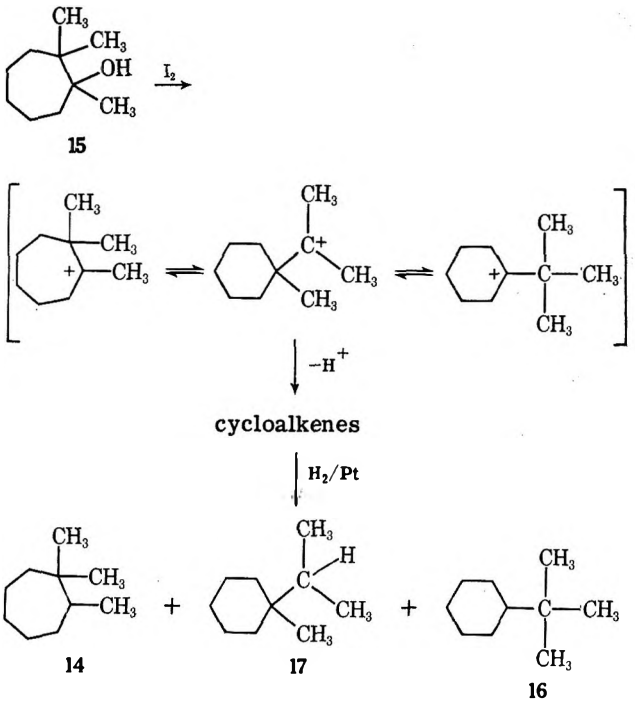


13

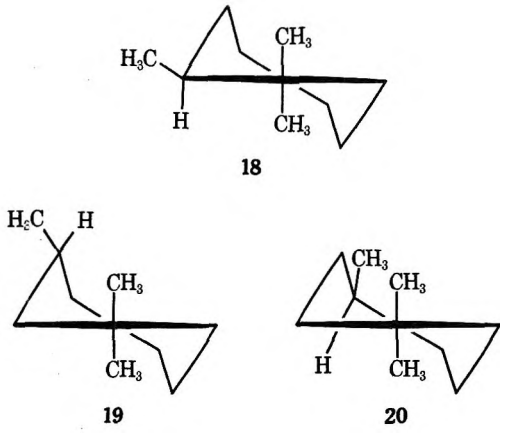
the favorable forms of the cis isomer, explains this well, while the interactions expected for **13** account for the reverse situation with the trans compound.

1,1,2-Trimethylcycloheptane (**14**) was not obtained pure. Dehydration of 1,2,2-trimethylcycloheptanol (**15**) yielded a mixture of cycloalkanes which, on hydrogenation, give a mixture of cycloalkanes. Gas chro-



matography of this mixture with two different columns showed it to be composed largely (88%) of two substances in equal amounts, one of which, from the ^{13}C nmr spectrum, was clearly *tert*-butylcyclohexane (**16**).[11a] Twelve other ^{13}C nmr resonances remained to be identified. Taking into account only tertiary carbonium ions in the dehydration of **15**, the reasonable other products appear to be 1-methyl-1-isopropylcyclohexane (**17**) or the desired 1,1,2-dimethylcycloheptane (**14**). One would expect **17** to exhibit seven ^{13}C nmr resonance lines, while **14** should have ten. Prediction of the line positions of **17** from related compounds[10a,18] gives a poor fit to the observed shifts, and the intensity ratios of the peaks are also incorrect. The most appropriate fit to the ten resonances expected for **14** are shown in Table I. Each of these assignments agrees with the off-resonance proton decoupled spectra. Two further resonances at 156.1 and 170.5 ppm were not assigned and were believed to arise from the 12% of remaining impurities. The substituent effects of the 2-methyl group (Table II) relative to 1,1-dimethylcycloheptane fit well in the general pattern of the substituent effects in methylcycloheptanes. 1,1,4-Trimethylcycloheptane was obtained by dehydration of 1,4,4-trimethylcycloheptanol and hydrogenation of the cycloalkene product. No rearrangement was detected.

It is evident from Table II that the γ effects of the 2-, 3-, and 4-methyl groups in 1,1,2-, 1,1,3-, and 1,1,4-trimethylcycloheptanes, respectively, are relatively small. If an additional methyl group is substituted on 1,1-dimethylcycloheptane, it can go to an equatorial position (**18**, **19**, and **20**) in which, at most, only a small γ interaction would be expected. In 1,1,2-dimethylcycloheptane, the assignment of the 1-methyl group, which is cis to the 2-methyl group, is facilitated by the direct steric interaction of these two groups, which produces a considerable differential between the shifts of the *gem*-methyl carbons (168.8 and 162.8 ppm). These γ effects of the 2-methyl are 1.1 and 7.1 ppm, slightly smaller than for *trans*-1,2-dimethyl- (1.8 ppm) and slightly larger than for *cis*-1,2-dimethylcycloheptane (6.5 ppm).



B. Methylcycloheptanols.—There have been several studies in recent years dealing with the conformations of substituted cycloheptanols.[19-22] In general, the results show the same kinds of regularities in spectra which are characteristic of the corresponding cyclohexanols, *i.e.*, that, in the *trans*-2-, *cis*-3-, and *trans*-4-methyl cycloheptanols, the hydroxyl group has more equatorial character than in the corresponding cis, trans, and cis isomers. However, the differences between cis–trans isomeric pairs are not usually so large as between the cyclohexanols. In the monomethylcycloheptanols, differences are greatest for the 2-methyl isomers. Borsdorf and coworkers[21] have used Hendrickson's conformational energies[4d] to calculate the differences in the axial character of the hydroxyl groups between cis–trans isomers for the 2-, 3-, and 4-methylcycloheptanols to be 23, 16, and 7%, respectively. With the corresponding methylcyclohexanols, the difference is expected to be about 70% for all three isomer pairs, if the conformational energy of a hydroxyl group is taken to be about one-half of that of a methyl group. For this kind of analysis, the proton spectra of dimethyl sulfoxide solutions are especially informative,[21] because they give the chemical shift of the hydroxyl proton, and with secondary alcohols, the coupling constant with the carbinyl proton. These parameters have been shown to depend systematically on the axial character of the hydroxyl group.[23,24] We have used this approach to characterize the secondary cycloheptanols used in this study, especially for mixtures, to determine which of the two isomers is the more abundant. It has also turned out that, for pairs of tertiary cycloheptanol isomers, the one with the more axial hydroxyl group has the more upfield hydroxyl proton chemical shift. The hydroxyl proton chemical shifts and coupling constants are collected in Table III.

All the cycloheptanols reported here were prepared be reduction of the corresponding ketones, which, in turn, were obtained by published procedures. Lithium aluminum hydride reduction of 3- and 4-methyl- and *cis*-3,5-dimethylcycloheptanone produced cis–trans mixtures of alcohols in ratios too close to 1:1 to permit

(18) D. M. Grant and E. G. Paul, *J. Amer. Chem. Soc.*, **86**, 2984 (1964).

(19) W. Hückel and J. Wächter, *Justus Liebigs Ann. Chem.*, **672**, 64 (1964).
(20) W. Hückel and O. Honecker, *ibid.*, **678**, 10 (1964).
(21) A. Zschunke, F.-J. Strüber, and R. Borsdorf, *Tetrahedron*, **24**, 4403 (1968).
(22) H. Baumann, H. Moehrle, and A. Dieffenbacher, *ibid.*, **25**, 135 (1969).
(23) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964).
(24) C. P. Rader, *ibid.*, **91**, 3248 (1969).

TABLE III

HYDROXYL PROTON CHEMICAL SHIFTS (IN PPM DOWNFIELD FROM EXTERNAL TETRAMETHYLSILANE[a]) AND H–C–OH COUPLING CONSTANTS (IN Hz) OF CYCLOHEPTANOLS IN DIMETHYL SULFOXIDE SOLUTION

Registry no.	Substituent	δ	J
502-41-0	None[b]	4.26	4.0
19790-05-7	*trans*-2-Methyl[c]	4.23	5.0
19790-04-6	*cis*-2-Methyl[c]	4.05	4.4
933-16-4	*trans*-3-Methyl[c]	4.13	3.8
933-15-3	*cis*-3-Methyl[c]	4.17	4.2
10126-52-0	*trans*-4-Methyl[c]	4.23	4.0
19790-06-8	*cis*-4-Methyl[c]	4.20	4.0
1194-32-7	2,2-Dimethyl	4.11	4.6
35099-83-3	3,3-Dimethyl	4.12	4.1
35099-84-4	4,4-Dimethyl	4.27	4.3
35099-37-7	*trans,trans*-3,5-Dimethyl	4.17	4.0
35099-38-8	*cis,cis*-3,5-Dimethyl	4.17	4.0
3761-94-2	1-Methyl	3.96	
35099-39-9	*trans*-1,2-Dimethyl	3.67	
35099-40-2	*cis*-1,3-Dimethyl	3.91	
35099-41-3	*trans*-1,3-Dimethyl	3.94	
35099-42-4	*trans*-1,4-Dimethyl	3.91	
35099-43-5	*cis*-1,4-Dimethyl	3.95	
35099-86-6	1,2,2-Trimethyl	3.63	
35099-87-7	1,3,3-Trimethyl	3.79	
35099-88-8	1,4,4-Trimethyl	3.93	

[a] The low-field ^{13}C satellite of the dimethyl sulfoxide protons at δ 3.68[23] was used as internal reference. [b] From ref 21. [c] Slightly different values are reported in ref 21.

assignment of the resonances to specific isomers on the basis of resonance intensities. In these cases, one of the two isomers was concentrated by chromatography on neutral alumina, or else a different ratio from 1:1 of alcohols was obtained by catalytic hydrogenation. The tertiary cycloheptanols were synthesized from the ketones and methyllithium. In these reactions, the isomers were not formed in the same amount.

The ^{13}C chemical shifts of 21 cycloheptanols and the substituent effects of the hydroxyl groups are shown in Table IV. Based on these parameters, the assignment of most of the resonance lines to specific carbons seems to be rather unambiguous. A few critical choices have been examined in detail, as by introduction of deuterium instead of hydrogen in specific locations, which causes almost complete loss of the signal of the directly attached carbon in the noise-decoupled spectra.[11b] Thus, investigation of *cis*- and *trans*-2-methylcycloheptanol-*2,7,7-d*$_3$ led to the unambiguous assignment of C-7 in these compounds. The ^{13}C nmr spectra of *cis*- and *trans*-3-methylcycloheptanol-*2,2,7,7-d*$_4$ and -*2,2,6,6-d*$_4$, as well as *cis*- and *trans*-4-methylcycloheptanol-*2,2,7,7-d*$_4$ and -*3,3,7,7-d*$_4$, permitted conclusive assignment of all of the carbons of the 3- and 4-methylcycloheptanols. Lanthanide shifts induced by europium tris(dipivaloylmethane), Eu(DPM)$_3$, and europium tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione), Eu(fod)$_3$, have been useful with our cycloheptanols. Downfield shifts of the resonances in the proton[25,26] and carbon-13 spectra[14,27] were observed and, because the effects normally (but by no means invariably) decrease with increasing distance of the nucleus under consideration from the europium atom, assignments can be made on the basis of the relative size of the pseudocontact shifts within a molecule. The measured shifts for benzene solutions of the alcohols are shown in Table V. In the absence of the lanthanide complexes, the ^{13}C nmr shifts differ only a few tenths of a part per million from those in Table IV, all of which were obtained for dioxane solutions. In contrast, the shifts of the methylcycloheptanes (Table I) are for carbon disulfide solutions, in which all resonances are shifted downfield by about 1 ppm, compared to dioxane. This should be kept in mind in discussion of the hydroxyl group substituent effects, which are calculated by subtraction of the chemical shifts of the corresponding cycloheptane from those of the cycloheptanol. Thus, the solvent influence makes all hydroxyl group substituent effects more positive by about 1 ppm.

The magnitudes of the hydroxyl group γ effects are sufficiently large for the monomethylcycloheptanols to make the uncertainties in them due to solvent effects unimportant. This should be no surprise after the discussion of the substituent effects in the dimethylcycloheptanes, where the axial character, if any, is divided between the two methyl groups. In the methylcycloheptanols, the methyl group, being the larger group, tends to occupy the equatorial positions, thus imposing axial character on the hydroxyl group which results in substantial γ interactions. For *trans*-2-, *cis*-3-, and *trans*-4-methylcycloheptanol, the sum of both the γ effects is smaller than in the corresponding cis, trans, and cis isomers, in accordance with expectations of the axial character of the hydroxyl groups in these compounds.[21] However, the γ effects in the former isomers are relatively large compared to those for corresponding cyclohexanols[11a] or for cycloheptanol itself. This may indicate some degree of population of conformations with axial hydroxyl groups or an increased γ effect of hydroxyl groups when forced into the isoclinal positions of the twist–chair (1) by having the methyl groups go equatorial.

The general pattern of the substituent effects in the cycloheptanols is very similar to that for the methylcycloheptanes. Cis–trans isomeric pairs display the same systematic differences in the α, β, and γ effects which decrease in going from the 2-methyl- to the 3-methyl- and finally to the 4-methylcycloheptanols. The asymmetry of the γ interactions discussed earlier is also observed. For *cis*-2-methylcycloheptanol, a large chemical-shift effect on the methyl carbon results from the direct steric interaction of the substituents, as has been observed also for *cis*-2-methylcyclohexanol[11a] and cyclopentanol.[14]

The γ effects of the hydroxyl groups in the geminal dimethylcycloheptanols are larger than expected because of the tendency of the hydroxyl group to be forced into axial positions. The difference between the chemical shifts of the two methyl carbons in 2,2-dimethylcycloheptanol is larger than between those of the methyl carbons in the two 2-methylcycloheptanols and, because of the direct steric interaction with the hydroxyl group, the resonance of the cis methyl group should be the one at the higher field.

In 4,4-dimethylcycloheptanol, the asymmetry introduced by the hydroxyl group is not sufficient to make

(25) J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, **93**, 641 (1971), and references cited therein.

(26) R. E. Rondeau and R. E. Sievers, *ibid.*, **93**, 1524 (1971).

(27) J. Briggs, F. A. Hart, G. P. Moss, and E. W. Randall, *Chem. Commun.*, 364 (1971).

TABLE IV

^{13}C CHEMICAL SHIFTS OF CYCLOHEPTANOLS[a]

Substituents	C-1	C-2	C-3	C-4	C-5	C-6	C-7	1-CH$_3$	2-, 3-, 4-, 5-CH$_3$		
None[b]	120.1	154.8	169.2	163.9							
	−44.2	−9.5	4.9	−0.4							
trans-2-Methyl	115.2	150.8	160.8	166.8	164.7	170.7	156.5		*trans*-2-CH$_3$	172.3	
	−39.8	−6.8	5.8	1.2	1.1	7.1	−9.1			4.2	
cis-2-Methyl	119.3	154.1	163.1	167.0	164.8	170.6	158.2		*cis*-2-CH$_3$	175.2	
	−35.7	−3.5	8.1	1.4	1.2	7.0	−7.4			7.1	
trans-3-Methyl	124.3	147.6	165.1	155.7	165.1	169.1	155.7		*trans*-3-CH$_3$	169.1	
	−41.3	−7.4	7.5	0.7	−0.5	5.5	−7.9			1.0	
cis-3-Methyl	121.9	146.0	162.9	156.3	166.9	170.4	155.3		*cis*-3-CH$_3$	168.9	
	−43.7	−9.0	5.3	1.3	1.3	6.8	−8.3			0.8	
trans-4-Methyl	121.0	157.1	161.1	158.6	156.4	172.3	155.7		*trans*-4-CH$_3$	169.3	
	−42.6	−8.5	6.1	1.0	1.4	6.7	−7.9			1.2	
cis-4-Methyl	121.9	158.7	163.1	159.0	155.4	170.4	155.1		*cis*-4-CH$_4$	169.3	
	−41.7	−6.9	8.1	1.4	0.4	4.8	−8.5			1.2	
2,2-Dimethyl	113.8	155.6	153.6	171.0	164.6	168.6	159.9		*trans*-2-CH$_3$	164.6,	*cis*-2-CH$_3$ 170.5
	−36.1	−3.6	3.7	1.3	2.9	6.9	−8.8			2.9	8.8
3,3-Dimethyl	124.9	141.2	162.0	150.7	170.1	166.8	153.5		*trans*-3-CH$_3$	163.7,	*cis*-3-CH$_3$ 161.0
	−43.8	−8.7	2.8	0.8	1.4	5.1	−8.2			2.0	−0.7
4,4-Dimethyl	120.6	161.2	153.4	160.3	150.8	174.0	157.6		*trans*-4-CH$_3$	162.4,	*cis*-4-CH$_3$ 162.4
	−41.1	−7.5	3.5	1.1	0.9	5.3	−4.1			0.7	0.7
trans,trans-3,5-Dimethyl	123.7	147.2	165.5	145.7	157.6	160.1	157.6		*trans*-3-CH$_3$	169.1,[c]	*trans*-5-CH$_3$ 168.5[c]
	−42.3	−7.9	7.2	0.1	−0.7	5.0	−8.4			*d*	*d*
cis,cis-3,5-Dimethyl	122.6	145.7	162.6	145.7	159.8	162.6	158.5		*cis*-3-CH$_3$	168.5,[c]	*cis*-5-CH$_3$ 169.1[c]
	−43.4	−9.4	4.3	0.1	1.5	7.5	−7.5			*d*	*d*
1-Methyl	120.3	150.1	170.5	163.3				162.0			
	−37.3	−4.9	4.9	−0.3				−6.1			
trans-1,2-Dimethyl[e]	120.1	149.3	162.0	165.0[c]	164.2[c]	171.1	149.9	163.8	*trans*[e]-2-CH$_3$	175.9	
	−31.1	−1.9	5.3	*f*	*g*	5.3	−6.8	−6.1		6.0	
cis-1,3-Dimethyl[e]	121.1	141.1	163.0	154.6	164.3	170.5	150.2	160.7	*cis*[e]-3-CH$_3$	168.1	
	−37.2	−4.2	4.7	−0.5	−1.7	4.5	−4.9	−6.9		0.5	
trans-1,3-Dimethyl[e]	120.7	141.1	165.4	154.0	163.6	170.5	149.8	163.0	*trans*[e]-3-CH$_3$	168.0	
	−40.7	−6.7	4.0	−1.0	0.2	7.1	−5.2	−5.2		−0.2	
trans-1,4-Dimethyl[e]	120.6	152.0	162.7	157.4	154.4	171.4	150.1	161.6	*trans*[e]-4-CH$_3$	169.3	
	−36.7	*h*	*i*	0.1	*j*	3.0	*k*	−6.6		1.1	
cis-1,4-Dimethyl[e]	120.4	152.7	161.8	157.2	154.0	171.6	149.7	162.2	*cis*[e]-4-CH$_3$	169.5	
	−37.9	−6.3	2.8	−1.1	−0.1	6.1	−4.4	−6.0		1.3	
1,2,2-Trimethyl	117.9	152.8	155.5	171.2	166.6	172.0	153.6	167.3	*trans*[e]-2-CH$_3$	168.0,[c]	*cis*[e]-2-CH$_3$ 168.2[c]
	−31.4	−4.1	6.9	1.5	*l*	*m*	−6.5	−6.4		*n*	*o*
1,3,3-Trimethyl	120.4	138.6	159.9	150.2	167.9	168.3	149.6	160.1	*trans*[e]-3-CH$_3$	162.3,	*cis*[e]-3-CH$_3$ 161.0
	−42.6	−2.5	−0.2	0.2	−1.1	5.9	−3.5	−6.7		−0.7	−0.1
1,4,4-Trimethyl	121.5	156.6	158.4	160.2	149.7	173.9	148.0	161.4	*trans*[e]-4-CH$_3$	162.6,	*cis*[e]-4-CH$_3$ 162.6
	−34.1	−3.9	*p*	1.0	−0.2	3.9	*q*	−7.0		1.3	0.7

[a] The upper numbers for each alcohol are the experimentally determined chemical shifts in parts per million upfield from carbon disulfide; the second values are substituent effects obtained by subtracting the chemical shifts in parts per million of cycloheptane or the corresponding methylcycloheptanes. [b] From ref 11a. [c] Tentative assignments. [d] 0.9 or 1.5 ppm. [e] Cis and trans refers to the 1-methyl group. [f] −0.8 or −1.6 ppm. [g] 1.4 or 2.2 ppm. [h] −3.9 or −3.7 ppm. [i] 6.8 or 7.0 ppm. [j] −1.3 or −1.5 ppm. [k] −5.6 or −5.8 ppm. [l] 4.5 or 3.8 ppm. [m] 9.2 or 9.9 ppm. [n] 5.2 or 5.4 ppm. [o] 0.6 or 0.8 ppm. [p] 6.5 or 5.9 ppm. [q] −4.5 or −3.9 ppm.

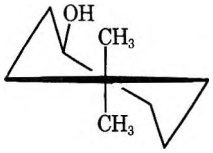
TABLE V

PSEUDOCONTACT SHIFTS OF ^{13}C RESONANCES IN SOME CYCLOHEPTANOLS (IN PPM)

Substituents	Molar ratio complex/cycloheptanols	C-1	C-2	C-3	C-4	C-5	C-6	C-7	1-CH$_3$	2-, 3-, 4-, 5-CH$_3$	
trans,trans-3,5-Dimethyl[a]	0.14	−6.9	−1.8	−1.0	−0.8	−0.8	−1.2	−2.2		3,5-CH$_3$	−0.4, −0.2
	0.22	−10.2	−3.0	−1.7	−1.3	−1.4	−1.6	−3.5			−0.6, −0.4
cis,cis-3,5-Dimethyl[a]	0.14	−8.0	−2.6	−1.1	−0.8	−0.9	−1.1	−2.2			−0.4, −0.2
	0.22	−12.8	−4.1	−1.8	−1.3	−1.3	−1.8	−3.5			−0.6, −0.4
1,2,2-Trimethyl[a]	0.24	*b*	−3.5	−2.6	−1.8	*c*	−2.8	−5.4	−6.8	2-CH$_3$	*c*
1,3,3-Trimethyl[d]	0.15	−6.2	−1.6	−0.6	−0.6	−0.5	−0.8	−1.3	−2.1	*trans*[e]-3-CH$_3$	−0.5
										cis[e]-3-CH$_3$	−0.2
1,4,4-Trimethyl[d]	0.10	*b*	−1.2	−0.7	−0.5	−0.6	−0.8	−1.0	−1.6	4-CH$_3$	−0.3

[a] Shift reagent Eu(DPM)$_3$. [b] Not observed. [c] Obscured by the *tert*-butyl methyl carbon resonance of Eu(DPM)$_3$ at 164.5 ppm. [d] Shift reagent Eu(fod)$_3$. [e] Cis and trans refer to the 1-methyl group.

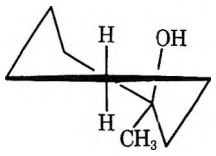
the methyl carbons nonequivalent. Presumably, there is a relatively small effect of the equatorial hydroxyl on the environment of the methyls in **21**, which is expected to be the most stable conformation for this substance.



21

The two isomeric 3,5-dimethylcycloheptanols which have the methyl groups cis to each other show characteristic differences in the ^{13}C nmr spectrum. The hydroxyl protons, however, have the same chemical shift and the same coupling constant as the carbinyl proton (Table III), indicating similar conformational positions for the hydroxyl groups. The pseudorotation itinerary of the twist–chair model, which contains 14 conformations, predicts a more equatorial hydroxyl group for the cis,cis isomer than for the trans,trans isomer. The substituent effects of the hydroxyl groups on the ^{13}C resonances reflect this trend. In one isomer, the α effect and the sum of the β effects are more negative, while the sum of the γ effects is less positive than for the other isomer, as would be expected for a higher equatorial character for the hydroxyl group of the former isomer which, therefore, should be the cis,cis structure.

The γ interaction of the hydroxyl group in 1-methylcycloheptanol, as reflected by the chemical shifts, is somewhat larger than the γ effect of a methyl group in 1,1-dimethylcycloheptane. This may indicate that **22**



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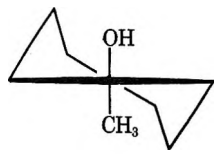
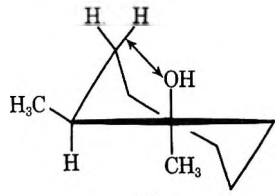


23

has some significant population relative to **23**. The principal product from 2-methylcycloheptanone and methyllithium appears to be the one with *trans*-methyl groups, because the chemical shift of the 1-methyl carbon is only 1.8 ppm upfield from the corresponding peak in 1-methylcycloheptanol. If the addition were to give *cis*-methyls, about a 6.5-ppm upfield shift would be expected (compare *cis*- and *trans*-1,2-dimethylcycloheptane). The γ effects of the hydroxyl in this compound are both 5.3 ppm, which appears to rule out **24** from being the only important conformation because it has only one strong γ interaction. Significant population of **25** and **26** would balance the γ effects of the hydroxyl, and these conformations are expected to be substantially more important than the corresponding ones for 1,1,2-trimethylcycloheptane because the relatively small hydroxyl group should not be so unfavorably situated in a 4a or 4a′ position of the twist–chair (**1**) as a methyl group.

The assignment of the two sets of lines of different intensities in the mixture of the 1,3-dimethylcycloheptanols to specific isomers has been made on the basis of the chemical shifts of the methyl carbons, the isomer with the low field 1-methyl being taken to have the methyl groups cis. With the exception of these and



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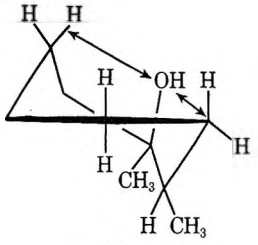

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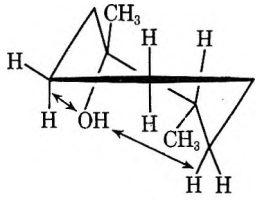
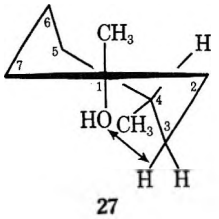


26

the resonances of C-3, all the chemical shifts are rather similar.

Still more similar in their ^{13}C nmr spectra are the two 1,4-dimethylcycloheptanols. The assignments followed those for the 1,3-dimethyl compounds except that now cis and trans were exchanged. The number of favorable conformers with both the methyl groups in equatorial or isoclinal positions are five for the trans and four for the cis. The similarity in the chemical shifts of the two isomers is therefore not surprising. The asymmetry of the γ interactions in these isomers can be explained by conformations **27** and **28**. The



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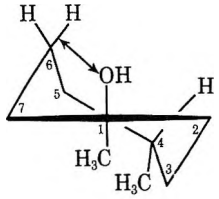

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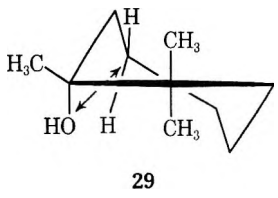
1,2,2-, 1,3,3-, and 1,4,4-trimethylcycloheptanols are rather highly substituted. Based on Hendrickson's conformational energies of the methyl group, and assuming half of these values for a hydroxyl group, one can calculate the energies of the possible conformations. The results suggest that, for all three cases, twist–chair forms should be more stable than other conformations by about 1 kcal/mol. The most favorable conformer of 1,2,2-trimethylcycloheptanol should be **29**, which



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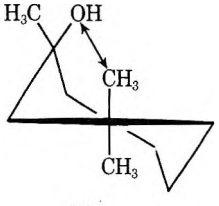

30

reflects the asymmetry of the γ effect of the hydroxyl group on the resonances of C-6 and C-3. The small chemical-shift difference between the two 2-methyl carbons allows only an arbitrary assignment, while the peak for the 1-methyl carbon was positively identified by specific proton decoupling.

TABLE VI

^{13}C CHEMICAL SHIFTS OF CYCLOHEPTANONES RELATIVE TO CARBON DISULFIDE (IN PPM)

Registry no.	Cycloheptanane	C-1	C-2	C-3	C-4	C-5	C-6	C-7	2-CH_3	3-CH_3	4-CH_3
502-42-1	Cycloheptanone[a]	−18.9	150.1	169.3	163.1						
932-56-9	2-Methyl	−19.9	147.2	159.9	164.5	163.3	168.8	150.9	176.1		
933-17-5	3-Methyl	−17.7	141.7	162.0	153.9	164.5	168.9	149.4		169.9	
5452-36-8	4-Methyl	−18.9	151.1	160.8	156.5	154.3	170.0	149.6			170.0
7228-52-6	2,2-Dimethyl	−21.7	146.1	154.0	168.2	162.5	166.7	153.5	167.6		
23438-70-2	3,3-Dimethyl	−16.9	137.5	160.8	148.4	168.9[b]	168.1[b]	149.5		163.9	
35099-49-1	4,4-Dimethyl	−18.6	154.1	156.9	159.9	149.8	173.3	149.8			164.6
24291-91-6	*cis*-3,5-Dimethyl	−18.0	141.2	162.2	144.6	157.0	160.4	150.4		168.9	168.9

[a] From ref 31. [b] Uncertain assignments.

TABLE VII

^{13}C CHEMICAL SHIFT SUBSTITUENT EFFECTS (IN PPM) ON CYCLOHEPTANE, METHYLCYCLOHEPTANE, AND 1,1-DIMETHYLCYCLOHEPTANE PRODUCED BY A KETONE GROUP

Cycloheptanone	α Effect	β Effect	γ Effect	δ Effect	Effect on the Methyl C[a]
Cycloheptanone	−183.2	−14.3	5.0	−1.2	
2-Methyl	−174.9	−10.4, −14.7	4.9, 5.2	−1.1, −0.3	8.0 (γ)
3-Methyl	−183.3	−13.3, −14.2	4.4, 5.3	−1.1, −1.1	1.8 (δ)
4-Methyl	−182.5	−14.5, −14.0	5.8, 4.4	−1.1, −0.7	1.9 (ϵ)
2,2-Dimethyl	−171.6	−13.1, −15.2	4.1, 5.0	−0.5, 0.8	5.9 (γ)
3,3-Dimethyl	−185.6	−12.4, −12.2	1.6, 6.4, or 5.7	−1.5, 0.2, or −0.5	2.2 (δ)
4,4-Dimethyl	−180.3	−14.6, −11.9	7.0, 4.6	0.7, −0.1	2.9 (ϵ)
cis-3,5-Dimethyl	−184.0	−13.9, −15.6	3.9, 5.3	−1.0, −1.3	1.3 (δ), 1.3 (ϵ)

[a] Type of interaction in parentheses.

The most stable conformation of 1,3,3-trimethylcycloheptanol should be **30**. The data in Table IV show that the C-3 shift is not influenced by the hydroxyl group. However, C-3 has no attached hydrogens and is likely to be less susceptible to a γ effect, as judged from other examples.[14] The hydroxyl group does interact with the 1-methyl group which is on the same side of the ring, and this one is therefore assigned the upfield resonance. Compared to other 1-methylcycloheptanols, the α-substituent effect of the hydroxyl group is quite high (−42.6 ppm). Apparently, as C-1 loses its directly attached hydrogen on introduction of the hydroxyl group, there is at least partial loss of the positive γ shift exerted by the 3-methyl groups. The result is a 8.5-ppm more negative shift than is found for the corresponding carbon of 1,4,4-trimethylcycloheptanol.

C. Methylcycloheptanones.—Studies of the conformational problems of cycloheptanones have been carried out with halogen[28] and alkyl derivatives.[29,30] It has been concluded from ir spectra that for *cis*-2,7-dichlorocycloheptanone the conformer with two equatorial chlorines is more stable by 1.1 kcal/mol than the diaxial one.[28] Allinger has reported the enthalpy difference between *cis*- and *trans*-3,5-dimethylcycloheptanone to be 0.8 kcal/mol, the cis isomer being the more stable.[29] Evidence for the twist–chair conformation of alkylcycloheptanones has been derived from benzene-induced shifts on the proton spectra.[30]

The chemical shifts obtained from the ^{13}C nmr spectra of some methylcycloheptanones in dioxane are given in Table VI. (See also Table VII.) The resonances of C-2 and C-7 have been identified by selective decoupling of the attached protons. Further assignments have been obtained unambiguously by comparison of the spectra of 3-methylcycloheptanone-*2,2,6,6-d*$_4$ and 4-methylcycloheptanone-*3,3,7,7-d*$_4$ with those of the corresponding nondeuterated ketones. Earlier[31] we did not properly characterize the resonances of C-3 and C-4 of the unsubstituted cycloheptanones. This has now been achieved with Eu(DPM)$_3$ in benzene solutions (in which the chemical shifts differ from those in dioxane by less than 1 ppm, in the absence of the paramagnetic chelate). At a molar ratio of ketone/complex of 3.0, the four different carbons moved downfield by 10.8, 3.4, 2.4, and 1.2 ppm, and we have assumed that the 1.2-ppm shift is that of C-4. For the 2-, 3-, and 4-methylcycloheptanones, the methine carbon resonances are easy to identify, and we have used these as references for the carbonyl substituent effects.[31] It is evident that the γ-shift effect of a carbonyl group in a cycloheptanone is much more positive than for cyclohexanones.[31] The small γ effects of carbonyl groups on cyclohexane resonances has been interpreted as evidence for flattening of the six-membered ring by the sp^2 hybridized carbonyl carbon.[31] The large γ carbonyl effects in cycloheptanones suggest that a sp^2 center does not critically affect the geometry of the cycloheptane ring. This could be a consequence of the relatively large bond angles in cycloheptane, which are, on the average, about 3° larger than in cyclohexane, according to the predictions of Hendrickson[4c] and the experiments of Groth.[9] It is noteworthy that the carbonyl carbon resonances are relatively invariant as respects methyl substitution on the ring. This was also observed for alkylcyclohexanones.[31]

Experimental Section

2-Methyl-,[32] 3-methyl-,[20,33] 4-methyl-,[33] 2,2-dimethyl-,[32] 3,3-dimethyl-,[34] 4,4-dimethyl-,[6c] and *cis*-3,5-dimethylcyclohepta-

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TABLE VIII

YIELDS, BOILING POINTS, AND ^1H CHEMICAL SHIFTS[a] (IN PPM DOWNFIELD FROM TETRAMETHYLSILANE) OF SOME CYCLOHEPTANOLS

Substituents	Yield, %	Bp, °C (Torr)	1-H	2 H–7 H	1-CH_3	2-, 3-, 4-, 5-CH_3
cis-cis-3,5-Dimethyl *trans-trans*-3,5-Dimethyl	80	84–86 (8)	3.88	1.1–2.0		~0.9
2,2-Dimethyl	80	92–94 (12)	3.41	1.0–2.1		0.89, 0.97
3,3-Dimethyl	75	92–94 (9)	3.75	1.2–1.9		0.91, 0.97
4,4-Dimethyl	79	97–99 (9)	3.76	1.1–2.1		0.88, 0.91
trans-1,2-Dimethyl	81	83–86 (8)		1.1–2.0		0.97
cis-1,3-Dimethyl[b] *trans*-1,3-Dimethyl[b]	80	70–74 (4)		1.1–2.0	1.23 1.26	0.95
trans-1,4-Dimethyl[c] *cis*-1,4-Dimethyl[c]	88	79–82 (6)		1.1–2.0	1.21	0.90
1,2,2-Trimethyl	93	86–90 (6)		1.1–2.1	1.15	0.90, 0.95
1,3,3-Trimethyl	86	83–87 (8)		1.3–1.9	1.22	0.92, 1.02
1,4,4-Trimethyl	85	89–91 (10)		1.0–1.9	1.22	0.89, 0.91

[a] Taken in $CDCl_3$ as solvent. [b] Cis:trans ratio, 60:40. [c] Trans:cis ratio, 55:45.

none[16] were prepared as described in the literature. 2-Methylcycloheptanone-*2,7,7-d*$_3$ and 3-methyl- and 4-methylcycloheptanone-*2,2,7,7-d*$_4$ were obtained from the nondeuterated ketones by means of sodium carbonate and deuterium oxide as described for other cyclic ketones.[35] 3-Methylcyclohexanone-*2,2,6,6-d*$_4$, obtained by exchange[35] with diazomethane,[33] gave a mixture of 3-methylcycloheptanone-*2,2,6,6-d*$_4$ and 4-methyl cycloheptanone-*3,3,7,7-d*$_4$ which was separated on our efficient spinning-band column.

Reduction of 2-methylcycloheptanone with H_2/Pt or Na/C_2H_5OH resulted in mixtures of the 2-methylcycloheptanols in which one or the other of the two isomers was in excess.[19,36] The 3-methylcycloheptanols were obtained as 1:1 mixture of cis–trans isomers by $LiAlH_4$ reduction of the corresponding ketone.[19] Chromatography of 1 g of this mixture on 50 g of neutral Al_2O_3 (Woelm, activity III) was assayed with pentane and pentane–ether as solvents. The first eight 100-ml portions eluted with pentane contained no alcohol. With pentane–ether, the ninth fraction contained 130 mg of the practically pure *trans* isomer, while in fractions 12 and 13 (200 mg) the cis–trans ratio was 2:1. Reduction of 4-methylcycloheptanone with lithium aluminum hydride resulted in a 1:1 mixture of cis–trans isomers. However, hydrogenation, as described for 2-methylcycloheptanone,[19,36] produced a mixture in which the cis compound was the more abundant component (about 60%). Reduction of *cis*-3,5-dimethylcycloheptanone with lithium aluminum hydride also gave a 1:1 mixture of two isomers which, by chromatography on neutral Al_2O_3 as above, led to enrichment of the cis,cis isomer to about 60% in the last fraction. A mixture of about the same ratio was obtained by reduction of the ketone with H_2/Pt. The deuterated cycloheptanones were all reduced by lithium aluminum hydride and the ^{13}C nmr spectra were examined without further attempts at separation. The 2,2-3,3- and 4,4-dimethylcycloheptanols were obtained by lithium aluminum hydride reduction of the corresponding ketones. Table VIII summarizes the properties of some secondary and tertiary cycloheptanols prepared in this work. The latter alcohols were obtained in addition of 30 mmol of methyllithium (about 15 cc of a commercial 2.1 *M* solution in ether) to 15 mmol of the appropriate cycloheptanone, dissolved in 10 cc of anhydrous ether. The mixture was heated gently under reflux for 15 hr, then hydrolyzed by addition of water. The ether phase was separated, dried over anhydrous sodium sulfate, and distilled. The products were found to be free of major impurities from their proton and ^{13}C nmr spectra. The isomer ratios of the cycloheptanol mixtures were estimated either from the hydroxyl proton intensities in the spectra in dimethyl sulfoxide or from the ^{13}C nmr spectra.

1-Methylcycloheptanol, Eu(DPM)$_3$, Eu(fod)$_3$, and methylcycloheptane were commercial materials used without further purification. The samples of the dimethyl- and 1,1,3-trimethylcycloheptanes were provided by Professor J. B. Hendrickson.

1,1,4-Trimethylcycloheptane.—1,4,4-Trimethylcycloheptanol (2.9 g) and 1 g of iodine were mixed and heated to 80–100° under a pressure of about 1 Torr. The volatile products were collected at −75°, taken up in ether, washed with aqueous sodium bisulfite solution to remove some iodine, dried over sodium sulfate, and distilled. After removal of the ether, a fraction of 900 mg was obtained, bp 71–75° (30 Torr). The vpc on Carbowax 20M showed two peaks of equal intensity. The distillate in 10 ml of acetic acid took up 275 ml of hydrogen in the presence of 150 mg of PtO_2 over 2 hr. The catalyst was removed by filtration, the filtrate was neutralized with potassium hydroxide solution and extracted with ether, and the extract was dried over sodium sulfate. Distillation gave a fraction of bp 72–75° (30 Torr), amounting to 700 mg (27%) which, in the vpc (Carbowax 20M), showed only one peak. The proton spectrum (neat + TMS) showed 2 H–7 H at δ 0.98–2.03 and CH_3 at δ 0.88. The same procedure, starting with 1,2,2-trimethylcycloheptanol, gave a 39% yield of a mixture of $C_{10}H_{20}$ hydrocarbons which, by vpc on two different columns (UCC/W98, silicon oil SE-30), showed two major products, each abundant to the extent of about 44%. The carbon-13 spectrum showed one of these substances to be *tert*-butylcyclohexane.[11a] The other product was assumed to be 1,1,2-trimethylcycloheptane (see text).

Nmr Spectra.—The ^{13}C spectra of the cycloheptanols and cycloheptanones were taken on dioxane solutions. The measurements of the pseudocontact shifts, however, were made on benzene solutions. The cycloheptanes were run in carbon disulfide with 20–30% (v/v) of tetramethylsilane, as required. The resonances of the carbons of the solvents were used as internal references. The chemical shifts reported here have all been corrected to carbon disulfide as external reference by the relationship $\delta_C = \delta_C^{dioxane} + 126.2$ ppm, $\delta_C = \delta_C^{benzene} + 64.55$ ppm, and $\delta_C = \delta_C^{tetramethylsilane} + 192.5$ ppm, and were reproducible to ±0.1 ppm. Most of the spectra were taken with a digital frequency sweep spectrometer, operating at 15.08 MHz, with its associated proton decoupler equipped with a narrow-band pseudorandom noise generator.[11a] The proton signals of the solvents provided a proton-field frequency lock. Some of the spectra were obtained with a Varian HR-220 spectrometer, operating at 55.34 MHz, and equipped with a proton decoupler and a pseudorandom noise generator. This instrument was used in the continuous-wave or the Fourier-transform mode. For the latter purpose, a Varian 620i computer was interfaced with the spectrometer.

Acknowledgment.—We are deeply indebted to Professor James B. Hendrickson of Brandeis University for the loan of samples of the dimethyl- and 1,1,3-trimethylcycloheptanes studied in this research.

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A Nuclear Magnetic Resonance Study of the Formaldehyde-Induced Exchange of Methylol Groups in Tetrakis(hydroxymethyl)phosphonium Chloride and Tris(hydroxymethyl)phosphine[1]

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^{1}H nmr spectra of solutions of tetrakis(hydroxymethyl)phosphonium chloride (1) to which less than 1 mol of NaOD was added exhibited signals due to the phosphonium salt and tris(hydroxymethyl)phosphine (2). At higher temperatures the separate signals coalesced to one singlet in a reversible manner. ^{31}P nmr spectra indicated at least one other major phosphorus-containing species to be formed in addition to 2. At elevated temperature all ^{31}P signals reversibly broadened. Upon removal of solvent and formaldehyde from fully neutralized solutions of the salt, the phosphine and a trace of the corresponding oxide (3) were isolated. The nmr results are interpreted as involving chemical exchange of methylol groups between the phosphonium salt and the phosphine, accomplished by reversible attack of the phosphine phosphorus on formaldehyde. A second pathway, equilibration of the phosphine with its O-methylolated adduct, is invoked to account for the second phosphorus-containing product, present in solution, but not isolated.

Neutralization of tetrakis(hydroxymethyl)phosphonium chloride (1) with aqueous sodium hydroxide to furnish tris(hydroxymethyl)phosphine (2)[3] has become

$$\underset{1}{(HOCH_2)_4\overset{+}{P}Cl^-} + OH^- \longrightarrow \underset{2}{(HOCH_2)_3P} + CH_2O + H_2O + Cl^-$$

important as the basis for several useful flame retardants[4] and the related reaction of 1 with fluorinated amines has been suggested[5] as a way to impart oil repellency to textile fabrics. Because of these practical applications, the reaction of 1 and base has been the subject of an extensive scrutiny by ^{1}H and ^{31}P nmr spectroscopy in these laboratories as a means to a better understanding of the role played by the various components of solutions of neutralized 1. During the course of our investigations, Vullo[6a] interpreted ^{1}H and ^{31}P nmr data obtained upon neutralization of 1 as indicative of reversible reaction of the product formaldehyde both with the phosphine 2 and the corresponding by-product[3] phosphine oxide 3 to yield mono-, di-, and trihemiformals of 2 and 3[6b] (Scheme I). While our early data were, for the most part, in agreement with that of Vullo, the nmr study of the system 1 + NaOH has been extended significantly. Evidence is now reported for what may be interpreted as a temperature-dependent chemical exchange of methylol groups between 1 and 2, brought about by reversible attack of the phosphorus in 2 on the carbon of formaldehyde.[7] Although a somewhat analogous case of averaging in which reversibly formed P–P bonds are involved has been recently reported,[8] reorganizations involving P–C bonds at quadruply bound phosphorus are apparently rare.[9] The present nmr study also leads to a better understanding of the part played by formaldehyde in certain reactions of the phosphine 2.

SCHEME I

$$\underset{2}{} + \underset{3}{(HOCH_2)_3PO} \overset{CH_2O}{\rightleftharpoons} \underset{\substack{4,\ n=1\\ 5,\ n=2}}{(HOCH_2)_{3-n}P(CH_2OCH_2OH)_n} + \underset{6,\ n=1}{(HOCH_2)_{3-n}\overset{O}{\overset{\|}{P}}(CH_2OCH_2OH)_n}$$

Results

Evidence of a reversible, temperature-dependent process involving the methylol groups of 2 developed during synthesis of the phosphine by a novel method which averted certain difficulties encountered in Gordon's procedure.[10] Fairly pure 2 was obtained in good yield by the simple expedient of adding Dowex-1 anion-exchange resin in the OH form to a nitrogen-blanketed aqueous or methanolic solution of the salt 1 until the equivalence point (pH 8.3[11] in water, apparent pH 7.3[11a] in methanol) was reached, followed by removal of solvent and formaldehyde *in vacuo* at 50–70°. An excess of the resin resulted, instead, in the formation of the oxide 3 in good yield, together with a copious evolution of hydrogen. Only the oxide could be recrystallized; the phosphine was used as the waxy solid obtained after cooling the syrupy product to −30°. Elemental analyses for both compounds were quite satisfactory, and peaks in their mass spectra above

(1) Presented in part at the Southeast–Southwest Regional ACS Meeting, New Orleans, La., Dec. 2–4, 1970.

(2) One of the Laboratories of the Southern Marketing and Nutrition Research Division, Agricultural Research Service, U. S. Department of Agriculture.

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(6) (a) W. J. Vullo, *J. Org. Chem.*, **33**, 3665 (1968). (b) Other evidence for the reversible nature of the reaction of 2 and formaldehyde was recently reported by R. H. Carlson, Abstracts of Papers, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 13–17, 1971.

(7) A report of less extensive evidence of averaging of the CH_2OH environmemts of 1 and 2 in pyridine or triethylamine has appeared: S. E. Ellzey, Jr., W. J. Connick, Jr., and G. J. Boudreaux, *Can. J. Chem.*, **49**, 3581 (1971).

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(11) (a) Values obtained from titration of 1 with NaOH in the respective solvents. (b) L. M. Fodor, Ph.D. Thesis, Cornell University, Ithaca, N. Y., 1963.

TABLE I

^{1}H NMR DATA FOR SOLUTIONS OF $(HOCH_2)_4P^+Cl^-$ (1) AND NaOD IN D_2O

Mol of NaOD/mol of 1	Temp, °C	δ, ppm (J, Hz) vs. DSS					
				1–2 composite			
		1	2	Found	Calcd[a]	3	Other
0.25	−13	4.77 (1.5)	4.14 (5.5)			*b*	4.85, 4.91
0.25	80			4.65	4.65	4.18 (3.0)	4.83
0.5	−7	4.80	4.15 (5.0)			*c*	*d*
0.5	65			4.52	4.50	4.22 (3.0)	4.87
0.85	−10	*d*	4.16 (5.4)			*c*	*d*
0.85	60			4.31	4.27	*c*	4.87
1.0	3		4.14 (5.5)			*b*	4.81, 4.83, 4.90
1.0	37			4.15	4.15	*c*	4.82

[a] Position of the composite singlet calculated from the relation $\delta = 4.77p_1 + 4.15p_2$, where p_1 and p_2 are the fractional CH_2 populations in 1 and 2, respectively. [b] One line under 2. [c] Not seen, under 2. [d] Under HOD.

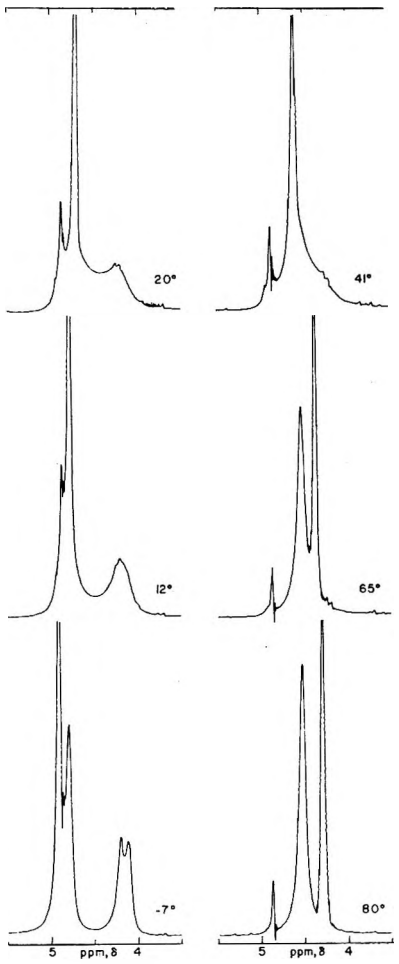

Figure 1.—Variable temperature ^{1}H nmr spectra for solution of 1 + 0.5 mol of NaOD in D_2O (DSS reference). The tallest peak is due to HOD.

those of the molecular ions were of insignificant intensity. When the 60-MHz ^{1}H nmr spectrum of the initially isolated phosphine 2 was run as the neat supercooled liquid at ambient temperature, the CH_2 protons gave a very broad signal (almost a singlet) at 4.38 ppm (TMS = 0 ppm). Examination at elevated temperature resulted in a sharpened *singlet* and not the doublet expected from coupling to phosphorus. In acetone-d_6 the CH_2 signal was a doublet at 4.24 ppm, J = 6.3 Hz, and impurity peaks occurred at 4.80 (singlet) and near 4.12 ppm (possibly a doublet), in good agreement with Vullo.[6a] In D_2O a "filled-in" doublet was at 4.15 ppm, J = 5.5 Hz (DSS as reference), at room temperature and reversibly became a singlet at higher temperatures.

Operation of a temperature-dependent process is strikingly illustrated by the nmr spectra of a solution of the salt 1 in D_2O to which 0.5 mol of NaOD was added (Figure 1). At the lowest temperature of observation, −27°, the broad singlet at 4.81 ppm,[12] due to 1, nearly obliterates signals due to OCH_2O near 4.9 ppm, although a broad doublet due to phosphine CH_2 is seen at 4.17 ppm, J = 5.5 Hz. As the temperature is raised to about 5°, the HOD signal moves upfield to cover the signals near 4.8–4.9 ppm, and the PCH_2 signal at 4.17 ppm is no longer a doublet. With a further temperature increase the signal due to 1 is broadened (under HOD) and the broadened signal at 4.17 ppm is surmounted by the small doublet at 4.22 ppm, J = 3.0 Hz, due to the oxide 3 (or a related structure). Between 20 and 40°, the signals due to 1 and 2 merge, and at 65° there results a sharper *singlet* ($w_{1/2} \sim 6$ Hz) at 4.52 ppm. (In a solution to which only 0.25 mol of NaOD was added, the *doublets* due to 1 and 2 may still be seen at 3°.) *The effects observed with varying ratios of NaOD to* 1 *are reversible with temperature changes.* From Table I it may be seen that the positions of the *composite* PCH_2 *singlet* at four different ratios of NaOD to 1 agree quite well with values (δ) calculated by weight averaging the *eight* protons of 1 with the *six* of 2, according to the relation $\delta = p_1\delta_1 + p_2\delta_2$, where p_1 and p_2 are the fractional CH_2 populations in the 1 and 2 environments.[13]

In a solution of a synthetic mixture (1:1 molar) of 1 and 2 at slightly below ambient temperature, *doublets* for the CH_2 signals of the phosphonium salt and the phosphine were at their normal positions, but at 70° these were already *reversibly coalesced to a broad singlet* at an averaged chemical shift, 4.57 ppm (calcd 4.50 ppm).

In a solution of 2 and an equimolar amount of formaldehyde (from thermal depolymerization of paraformaldehyde) in D_2O at 20° or below, the phosphine *doublet* was seen at 4.13 ppm, but, when observed at 60°, the doublet had been *reversibly coalesced into a singlet* at 4.18 ppm.

Information on the composition of solutions of neutralized 1 not obtainable from the ^{1}H spectra, and further evidence to support chemical exchange averaging of CH_2OH groups was given by variable temperature ^{31}P spectra obtained at 40.5 MHz on several of these solutions. The chemical shifts observed at room temperature are summarized in Table II. In many

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(13) E. D. Becker, "High Resolution NMR," Academic Press, New York, N. Y., 1969, p 219.

TABLE II
^{31}P NMR CHEMICAL SHIFTS FOR SOLUTIONS OF $(HOCH_2)_4P^+Cl^-$ (1) AND BASE

Solution (D_2O)	δ (^{31}P), ppm, *vs.* external 85% H_3PO_4
1[a]	−25.8[b]
1 + 0.5 mol of NaOD	−26.6, +24.8, +29.1[c]
1 + 0.85 mol of NaOD	−48.7, −47.9, −27.5, +24.3, +28.4, +33.0
1 + 1.0 mol of NaOH[d]	+24.6,[e] +28.8
2	−49.0,[f] +24.5[g]
2 + 1.0 mol of CH_2O	−49.3, −48.6, −47.7, +24.9, +29.1, +33.6
3[a]	−48.7

[a] Solvent H_2O. [b] Seven of the expected nine lines seen, $J \sim 2$ Hz. [c] In another sample observed at 24.3 MHz, an additional weak signal was seen at +32.9 ppm. Its presence or absence may depend on the age of the solution. [d] Solvent 80:20 MeOH-H_2O. [e] The value of $J \sim 5$ Hz could be easily determined from the low-field signal, but the high-field signal was rather broad and its splitting pattern was not evident. The latter comprised ~20% of the mixture. [f] Trace. [g] Five of the expected seven lines seen, $J \sim 5$ Hz.

cases the noise levels precluded observation of spin coupling patterns and electronic integration. For the solution of 85% neutralized 1 the estimated (planimeter) relative areas of the three signals at positive field were 46:42:12 (low to high field). An interesting feature of this solution was that in the temperature range 5–35° *all ^{31}P signals* (except the H_3PO_4 lock) *were sharper at low temperature and broadened reversibly with increasing temperature* (at 35° the weakest signals at −47.9, −48.7, and +33.0 ppm were lost in the noise), although the relative areas of the three highest field signals appeared to be rather temperature independent. Reversible broadening of all signals at elevated temperatures was also characteristic of solutions of half-neutralized 1 and a mixture of 2 and formaldehyde. The operation of such reversible temperature dependence in both the ^{1}H and ^{31}P nmr spectra is indicative of an exchange process involving CH_2OH groups attached to phosphorus.

Although the role played in the exchange process by the various phosphorus compounds is subject to some speculation, it seems apparent that formaldehyde is involved in the exchange of CH_2OH groups between the phosphonium salt 1 and the phosphine 2, and also plays a part in the temperature-dependent coalescence of the PCH_2 doublet of 2 either in fully neutralized solutions of 1 or in solutions of 2 and formaldehyde. Comparison of the integrals of the room temperature ^{1}H spectra of 2 in D_2O before and after heating the dry solid at 70° *in vacuo* (the odor of formaldehyde was noted in the pump exhaust) revealed a decrease in the impurity peak near 4.80 ppm as the CH_2 doublet at 4.15 ppm, $J = 5.5$ Hz, became sharper. The report[14] that singlets for the hydrates of the monomer and dimer of formaldehyde appear near 4.8 ppm in D_2O renders plausible the possible presence of these compounds in solutions of either 1 treated with base or of 2 prepared from 1. A sample of 2 in D_2O was treated overnight with dimedone (to remove formaldehyde as the water-insoluble dimethone derivative) and filtered; its nmr spectrum contained no signal at 4.8 ppm and the CH_2 *doublet* of 2 persisted even at 84° (other signals were present, apparently due to reaction between 2 and dimedone). A sample of the phosphine 2 (kindly supplied by Dr. A. W. Frank of SRRL) prepared from formaldehyde and *excess* PH_3[15] gave the expected *doublet* even at 80° in D_2O, but addition of 1 drop of formaldehyde solution caused almost complete coalescence at this temperature. Similarly, treatment with dimedone of an equimolar mixture of 1 and 2 effectively prevented coalescence and the separate CH_2 *doublets* for the salt 1 and phosphine 2 were seen at their normal positions at elevated temperature.

(14) J. Hine and F. C. Kokesh, *J. Amer. Chem. Soc.*, **92**, 4383 (1970).

Discussion

Methylol Group Exchange.—Based on the ^{1}H nmr data, it is feasible to explain the temperature-dependent coalescence of the doublets of 1 and 2 during neutralization of 1 as involving the exchange of CH_2OH groups between the salt and the phosphine, through the zwitterion 7 as an intermediate or transition state, as in Scheme II. The salt 1 yields water in its irreversible,

SCHEME II

$$1 \underset{H^+}{\overset{OH^-}{\rightleftharpoons}} \underset{7}{[(HOCH_2)_3\overset{+}{P}CH_2O^-]} + H_2O \rightleftharpoons 2 + CH_2O$$

$$1^* + [7] \rightleftharpoons [7^*] + 1$$

$$2 + \overset{*}{C}H_2O \rightleftharpoons [7^*] \rightleftharpoons 2^* + CH_2O$$

complete neutralization to 2 and formaldehyde through 7. As long as some 1 is present, an exchange of CH_2OH groups between 1 and 2 may take place by means of the virtual reactions between 1 and 7, and between 2 and formaldehyde. Thus, as the rate of P–C bond making or breaking (in times/second) in the $1 \rightleftarrows 2 + CH_2O$ exchange exceeds the value of J_{PCH} (in hertz) for one of the components, splitting in this signal will be lost and a *singlet* will result for that component. As the rate increases beyond the separation (in hertz) of the separate signals for the two components, the two singlets will coalesce into *one singlet* at a weighted-average position determined by the relative numbers of protons in the two environments. It should be noted that, if the exchange process took place somehow without breaking all P–C bonds, then the resulting averaged signal would be expected to be a *doublet* with a J_{PCH} which is the weighted average of the J values for 1 and 2. Arguments similar to the above based on the virtual reaction of 2 and formaldehyde through 7 may be used to explain absence of splitting in the CH_2 signal in solutions of the phosphine and formaldehyde.

The above discussion has apparently neglected the possibility of coalescence of the CH_2 signals from formaldehyde since these protons are also exchanging with those of 1 and 2. Whereas it is CH_2O which is involved in the reaction with 2, it is the signals for the hydrates of the monomer and dimer of formaldehyde which are actually observed in the nmr spectra.[14] If, *e.g.*, the dehydration of formaldehyde hydrate is the rate determining step in the reversible sequence of events by which the CH_2 protons of 1, 2, and formaldehyde hydrate exchange, then it is within the realm of possibility

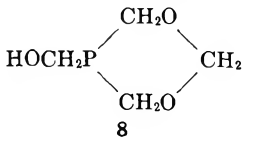
$$CH_2O + H_2O \rightleftharpoons CH_2(OH)_2$$

(15) M. Reuter and L. Orthner, German Patent 1,035,135 (1958); *Chem. Abstr.*, **54**, 14124 (1960).

that, although the reactions relating **1** and **2** (Scheme I) may proceed at a rate exceeding that required for coalescence of the CH_2 signals of **1** and **2** ($\Delta\nu$ = 37 Hz), the dehydration may proceed at a rate inferior to that required for coalescence of the three signals and the signal for formaldehyde hydrate will therefore persist.[14,16] Calculations show that the positions found for the **1**–**2** composite (Table I) agree better with values based on **1** and **2** only than with those based on **1**, **2**, and formaldehyde hydrate, particularly for the higher degrees of neutralization.

Still to be reconciled is the fact that the ^{31}P nmr spectra of solutions of **1** and base indicate the presence of a significant amount (equal to that of **2**) of a compound with a ^{31}P shift of +28.4 ppm and a lesser amount of a compound with a peak at +33.0 ppm, but neither is indicated *per se* by the ^1H spectra in D_2O at any temperature.[17] It is highly possible that these compounds have PCH_2 proton signals very close to that of **2**. Furthermore, in view of the good agreement between the values found for the PCH_2 composite and those calculated on the basis of the exchange of the eight protons of **1** with the six of **2**, it is also reasonable that the two compounds having high-field ^{31}P shifts may, like **2**, have three (magnetically similar) CH_2 groups about phosphorus. Reasonable structures for these two compounds are **4** and **5**, the mono- and dihemiformals of **2** postulated by Vullo mainly on the reasonableness of the observed ^{31}P chemical shifts. Intuitively one might expect **4** to be present in larger quantity. Of the two reactions of **2** and formaldehyde shown in Schemes I and II, that giving rise to **4** and **5** does not involve making and breaking of C–P bonds, and averaging of the PCH_2 protons of **2**, **4**, and **5** should lead to a composite *doublet* having an averaged chemical shift and J_{PCH}, with the OCH_2O protons giving rise to a signal near that of formaldehyde hydrate. As the rate of the virtual reaction of **2** and formaldehyde increases with increasing temperature, the making and breaking of C–P bonds will be the important reaction observed in the ^1H spectra but the ^{31}P spectra demonstrate the continued presence of the other phosphorus species.

The observation that the addition of excess base to a fully neutralized solution of **1** in methanol-water caused disappearance of the two high-field ^{31}P signals and appearance of one at −48.7 ppm (**3**) makes it appear unlikely that structures such as **8** or **9** are responsible for



8

$[(HOCH_2)_2PCH_2O]_2CH_2$

9

the signal at +28.8 ppm, since such structures might be expected to be more stable to base.

Of the remaining ^{31}P signals (those clustered near −48 ppm), it is likely that they are due to hemiformals related to the oxide **3**, such as **6** and higher homologs. The ^1H and ^{31}P nmr data are compatible with averaging of the PCH_2 groups in the oxides, but in a process distinct from that involving the phosphines. Since averaging in the oxides occurs among compounds formed by attack of formaldehyde at hydroxyl oxygen (without C–P bond involvement), it should result in a composite *doublet* for the CH_2 groups on phosphorus. This is borne out in the case of solutions of **1** and base at temperatures above the coalescence point for the phosphine *doublet;* a composite doublet due to **3** and the other oxides is readily seen near the position of the signal for pure **3** (there is some indication of a slight change in both chemical shift and J_{PCH} of the CH_2 groups in **3** upon addition of formaldehyde).

These observations, as well as those of Vullo,[6a] apparently rule out the presence of tetrakis(hydroxymethyl)phosphonium hydroxide (THPOH) in solutions of **1** neutralized with base.

The Role of Formaldehyde in Some Reactions of 2.— No compelling evidence for the existence of significant quantities of the zwitterion **7** has been obtained,[18] although it seems reasonable as a transition state in the exchange reaction involving **1** and **2** and in the virtual reaction of **2** and formaldehyde. Although Grayson[3] favored the zwitterion as an intermediate in the conversion of **1** to **3** with excess base, Fodor[11] felt that kinetic evidence favored, instead, the attack of base on hydrated **2**. Evidence has now been obtained that, even in the presence of dimedone, **2** is rapidly converted to its oxide **3** (with evolution of hydrogen) by 10% NaOD in D_2O.[20] Even in the presence of dimedone, the reverse transformation of **2** to **1** took place upon reaction with HCl, apparently by way of a disproportionation, since phosphine (PH_3) was identified (ir spectrum) among the several products.

In the presence of an equimolar amount of formaldehyde in D_2O, **2** was incompletely converted to its oxide (or formaldehyde adducts of the latter) during 3 months under argon at room temperature. After addition of HCl to the solution, ^1H nmr signals for **1** and the oxide **3** were observed. In a control experiment in which a sample of **2** was in D_2O in the presence of dimedone for 2 months, the final amount of **3** was about the same as initially present in the phosphine, although the amount of the phosphine was reduced, apparently by reaction with dimedone.[21] Weak singlets at 3.67 and 3.73 ppm in a D_2O solution of **1** and 1 mol of NaOD are apparently due, respectively, to ethylene glycol and a product resulting from the latter and formaldehyde (but not 1,3-dioxolane, which absorbs at 3.92 ppm in this solution). Addition of ethylene glycol to the solution caused an increase in the signals at 3.67 and 3.73 ppm. The glycol could result from ethylene oxide, formed from **2** and formaldehyde by a sequence analogous to that reported by Mark.[19]

Even in the presence of dimedone, the phosphine **2** in D_2O reacted rapidly with morpholine, resulting in a complex mixture, the ^1H nmr spectrum of which suggested the presence of the known tris(morpholino-

(16) For a discussion of the rate of dehydration of the hydrate see N. Landqvist, *Acta Chem. Scand.*, **9**, 867 (1955).

(17) Examination at 100 MHz (JEOL Model MH-100) of a solution of **1** and 1 mol of NaOD in D_2O did not reveal any new signals in the PCH_2 region that were not seen at 60 MHz.

(18) Indeed, Mark[19] has reported ^{31}P chemical shifts of about −30 ppm for various compounds of the type $(Me_2N)_3P^+CH(R)O^-$.

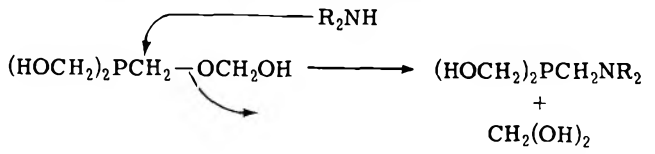
(19) V. Mark, *J. Amer. Chem. Soc.*, **85**, 1884 (1963).

(20) S. M. Bloom, S. A. Buckler, R. F. Lambert, and E. V. Merry, *Chem. Commun.*, 870 (1970), have recently reported the formation of phosphine oxides and hydrogen upon reaction of water-soluble tertiary phosphines with aqueous sodium hydroxide.

(21) The transformation of **2** to **3** under pressure at elevated temperature using a catalytic amount of formaldehyde has been reported recently: H. Haas, German Patent 1,930,521 (1970); *Chem. Abstr.*, **74**, 53987 (1971).

methyl)phosphine.[22] The complete absence of the phosphine 2 in the reaction mixture was readily ascertained from the spectrum; a weak doublet for the oxide 3, originally present in the phosphine, was the only signal present at this position.

Thus, it may be seen that reactions of 2 with base, with HCl, and with morpholine, known to occur in the presence of formaldehyde, also occur under formaldehyde-free conditions. In the case of reactions of secondary amines and the phosphine 2 in the presence of formaldehyde, it is possible that the product trisubstituted aminomethylphosphines may result directly from 2, as well as from one or all of the phosphorus species having ^{31}P chemical shifts in the +28–33-ppm region. On the assumption that relative ability to act as a leaving group is inversely related to base strength, and comparing the pK_a of $CH_2(OH)_2$ (13.27[23]) with that of water (15.7[24]), it is entirely feasible that the product aminomethylphosphines could arise from hemiformals of 2 by loss of formaldehyde hydrate.



Experimental Section[25]

Ir spectra were obtained from KBr disks, aqueous solutions between Irtran-2 plates, or a 10-cm gas cell on a Perkin-Elmer Model 137B spectrophotometer (NaCl optics).

Mass spectra of 2 and 3 were obtained at 70 eV from solid samples on a Perkin-Elmer Model 270 mass spectrometer.

All nmr spectra were obtained on samples (~20%) under nitrogen or argon. Variable temperature ^1H spectra were run on a Varian A-60A spectrometer at 60 MHz, with internal TMS or DSS at 0 ppm. The variable temperature ^{31}P spectra (external 85% H_3PO_4 reference) were run on a Varian HA-100 at 40.5 MHz on portions of the same solutions; a few room temperature ^{31}P spectra were run on a Varian HR-60-IL. Because of the many signals in most of the 40.5-MHz phosphorus spectra it was often necessary to use a CAT.

Tetrakis(hydroxymethyl)phosphonium chloride (1) was obtained from Hooker Chemical Corp. and was recrystallized from absolute ethanol: ^1H nmr (D_2O) CH_2 at 4.77 ppm (J_{PCH} = 1.7 Hz, $J_{^{13}CH}$ ~ 153 Hz). There appeared to be little, if any, temperature (ambient–80°) or concentration effect (20–40%) on the chemical shift or couplings.

Tris(hydroxymethyl)phosphine (2).—To a solution of 25.0 g (0.131 mol) of 1 in 100 ml of distilled water contained in a flask fitted with a mechanical stirrer, nitrogen flush, and a combination pH electrode was added over ~45 min ~150 ml (0.21 equiv) of 20–50 mesh Dowex-1 × 8 resin in the OH^- form until the pH was ~8.3–8.5. After the resin was filtered, the solution was washed portionwise with 150 ml of distilled water. The filtrate was concentrated on a rotary evaporator at 65–70° under aspirator vacuum and finally under high vacuum for ~30 min. The supercooled liquid weighed 13.0 g (80%), $n^{20}D$ 1.5497. Its neat ir spectrum between salt plates showed no bands at 1052 (1)[26] or 1043 or 1135 cm^{-1} (3),[26] but had intense, broad absorption at 1010 cm^{-1}.[26] On further evacuation and cooling at −30°, the viscous liquid solidified to a waxy solid: ^1H nmr (D_2O) CH_2 at 4.15 ppm (J_{PCH} = 5.5 Hz, $J_{^{13}CH}$ ~ 148 Hz), impurity peaks at 3.67 and 4.83 ppm. The CH_2 chemical shift was little affected by temperature or concentration.

Anal. Calcd for $C_3H_9O_3P$: C, 29.04; H, 7.31; P, 24.96; mol wt, 124. Found: C, 28.92; H, 7.46; P, 24.79; mol wt, 130 (ethanol).

A sample of 2 prepared by addition of the resin to a methanol solution of 1 to an apparent pH of 7.3 gave essentially the same proton spectrum.

Tris(hydroxymethyl)phosphine Oxide (3).—Slow addition of about a 130% excess (over an equimolar amount) of the resin to an aqueous solution of 25.0 g of 1 led to vigorous evolution of hydrogen. After the mixture stood overnight and was concentrated on a rotary evaporator, 16.1 g (88%) of the oxide was obtained. Recrystallization from absolute ethanol gave 11.9 g of hygroscopic product: mp 50–52° (lit.[26] mp 54–55°); ir (water) strong bands at 1043 and 1134 cm^{-1};[26] ^1H nmr (D_2O) CH_2 at 4.20 ppm (J_{PCH} = 3.1 Hz; $J_{^{13}CH}$ ~146 Hz).

Anal. Calcd for $C_3H_9O_4P$: C, 25.72; H, 6.48; P, 22.11; mol wt, 140. Found: C, 25.62; H, 6.52; P, 22.13, mol wt, 150 (ethanol).

Formaldehyde solution was prepared by bubbling the gas from thermally depolymerized paraformaldehyde into D_2O until ~24–30% was absorbed: ^1H nmr CH_2 ($HOCH_2OH$) at 4.83 ppm ($J_{^{13}CH}$ ~ 164 Hz), CH_2 ($HOCH_2OCH_2OH$) at 4.90 ppm ($J_{^{13}CH}$ ~ 166 Hz).

Solutions of 1 treated with various amounts of NaOD were prepard by addition of the calculated amount of 40% NaOD in D_2O to a solution of 1 in D_2O under nitrogen or argon with good stirring.

Registry No.—1, 124-64-1; 2, 2767-80-8; 3, 1067-12-5.

(22) H. Coates and P. A. T. Hoye, British Patent 842,593 (1960); *Chem. Abstr.*, **55**, 4363 (1961).

(23) R. P. Bell and D. P. Onwood, *Trans. Faraday Soc.*, **58**, 1557 (1962).

(24) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen and Co. Ltd., London, 1962, p 151.

(25) Analyses and osmometric molecular weights were by Galbraith Laboratories, Inc., Knoxville, Tenn. ^{31}P nmr spectra at 24.3 MHz were kindly furnished by Dr. R. H. Dinius of Auburn University, Auburn, Ala. Mass spectra were run by Dr. W. E. Franklin of SRRL. Use of the name of a company or product is not to be construed as an endorsement by the Departments of Agriculture or the Army.

(26) M. Anteunis, M. Verzele, and G. Dacremont, *Bull. Soc. Chim. Belg.*, **74**, 622 (1965).

Carbon-13 Nuclear Magnetic Resonance of Organophosphorus Compounds. III. Phosphorus Heterocycles

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^{13}C Chemical shifts and ^{13}C–^{31}P nuclear spin coupling constants have been determined for different patterns of ring methyl substitution in 32 phosphetane oxides, 3 phosphetane sulfides, 12 phosphetanium salts, a phospholane oxide, 3 phospholene oxides, and a phosphorianane oxide, as well as for trimethyl- and triethylphosphine oxides. The data are consistent with fixed, puckered conformations for four of the phosphetane ring substitution patterns and rapidly interconverting puckered forms for the single symmetrically substituted phosphetane. Variations of shifts and couplings as a function of ring substitution for several exocyclic phosphorus substituent pairs generally follow one another, but there are sizable deviations from this overall additivity. Seventeen cis–trans pairs of isomers are present in the above compounds. Strong stereospecificities in shift and coupling are apparent in the phosphetanes, especially for the one-bond coupling to carbon in phosphorus substituents and the three-bond coupling to the β-bound methyl carbon. These stereospecificities are useful in determining cis–trans isomer ratios in mixtures.

In spite of its low natural abundance (1%) and its much lower sensitivity, ^{13}C nmr holds promise of great value in the study of organophosphorus chemistry. ^{31}P spectra for most organophosphorus compounds provide only one chemical shift parameter, while the couplings to ^{13}C, and often those to ^{1}H, can be more easily and accurately determined from their respective spectra. A significant amount of experimental and theoretical work has been done in recent years, mainly concerning ^{13}C–^{31}P nuclear spin couplings.[2-18] Now with the development of more powerful techniques, ^{13}C nmr spectra can be obtained in natural abundance for molecules very much larger than those previously studied. In part I[2] a systematic inquiry was made into the effects of substitution on a carbon bound to phosphorus in a series of organophosphonates. Now we extend the inquiry into a class of compounds where different substitution patterns are allowed for carbon and phosphorus. Interesting compounds for this purpose are phosphorus heterocycles. The simplest available rigid systems are the four-membered ring compounds, the phosphetanes.

One of the earliest studies in phosphetane chemistry was that of Jungermann.[19] Useful synthetic extensions were developed by Cremer,[20] and in the last few years a great number of investigations have been centered on the stereochemistry of nucleophilic displacement reactions and the general chemistry of phosphetanes.[21] In addition, X-ray investigations have established the structures and stereochemistry of several phosphetane compounds.[22] These, coupled with the prodigious amount of work on stereoselective reactions,[21a,e-i,k-n,p-x] enable stereochemical assignments of most of the compounds treated in this work.

Results

The carbon chemical shifts (Tables I–VIII) are most easily assigned in the symmetrical 2,2,3,4,4-pentamethylphosphetanes in Table I. The large ^{13}C–^{31}P coupling and high shift (low shielding), as well as the twofold intensity, allow C-2 and C-4 to be identified. The high shift of C-3 is characteristic of a tertiary carbon. C-7 gives a shift normal for a free methyl bound to a carbon atom and has unit intensity. The remaining two doublets belong to the methyls bound to C-2

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(2) Part I: G. A. Gray, *J. Amer. Chem. Soc.*, **93**, 2132 (1971).

(3) Part II: G. A. Gray and S. E. Cremer, *Tetrahedron Lett.*, 3061 (1971).

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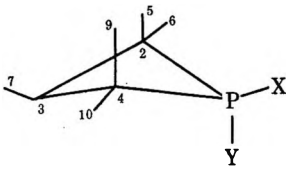
TABLE I

ALIPHATIC ^{13}C CHEMICAL SHIFTS AND ^{13}C–^{31}P NUCLEAR SPIN COUPLING CONSTANTS FOR 1-X, 1-Y 2,2,3,4,4-PENTAMETHYLPHOSPHETANE OXIDES, SULFIDES, AND SALTS[a]

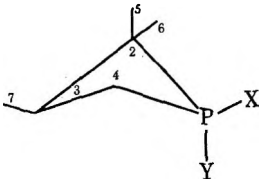


Compd	X	Y	C-2,4	C-3	C-5,9	C-6,10	C-7	X	Y
			Chemical shifts						
1	O	OH	48.77	42.90	18.18	24.03	6.96		
2	O	OCH_3	44.43	37.10	18.11	23.83	6.86		
3	OCH_3	O	44.23	37.65	18.28	24.49	8.15		
4	O	CH_3	45.41	42.61	17.28	24.71	7.31		9.79
5	CH_3	O	44.05	46.89	19.83	24.66	9.71	11.47	
6	O	Ph	46.68	44.88	18.90	24.00	7.33		
6a	O	*p*-C_6H_4F	47.23	45.33	19.01	24.35	7.50		
7	Ph	O	46.45	48.03	20.41	24.81	8.69		
8	O	Cl	57.35	42.79	18.27	26.09	7.37		
9	Cl	O	57.05	46.20	20.74	24.50	9.38		
10	O	Bz	46.96	43.80	18.06	25.40	7.18		31.90
11	Bz	O	46.96	47.39	19.71	24.20	8.64	33.05	
12	O	*t*-Bu	47.50	45.71	20.49	25.61	7.20		35.83 26.58
13	*t*-Bu	O	47.50	47.68	20.37	24.51	7.42	38.64 26.49	
14	S	Ph	46.62	51.06	22.52	25.48	9.55		
15	Ph	S	45.79	48.73	21.70	26.09	8.23		
16	CH_3	CH_3	38.07	51.42	18.96	24.43	8.75	4.94	4.15
17	CH_3	Ph	41.41	53.49	20.57	25.43	9.69	5.93	
17a	CH_3	*p*-C_6H_4F	41.98	53.44	21.04	26.03	9.67	8.01	
18	Ph	CH_3	42.11	50.43	20.17	24.94	8.08		6.90
19	CH_3	Bz	39.82	51.94	19.90	25.54	9.37	3.49	25.99
20	Bz	CH_3	40.40	50.93	19.50	24.66	8.69	26.65	2.15
21	Bz	Bz	42.28	50.82	19.76	25.02	8.06	26.20	25.05
			Coupling constants						
1	O	OH	76.6	11.7	3.2	5.3	21.9		
2	O	OCH_3	74.2	10.9	2.9	6.6	23.8		
3	OCH_3	O	73.5	10.4	5.5	3.7	18.5		
4	O	CH_3	59.4	6.3	4.6	3.6	23.0		40.9
5	CH_3	O	59.4	10.0	2.2	4.4	12.6	36.9	
6	O	Ph	58.7	6.2	4.6	3.5	23.1		
6a	O	*p*-C_6H_4F	58.3	6.2	4.7	3.9	23.4		
7	Ph	O	58.4	11.2	1.3	4.6	16.9		
8	O	Cl	56.8	1.6	3.8	6.8	30.1		
9	Cl	O	55.4	1.8	5.4	5.3	20.5		
10	O	Bz	56.9	5.7	4.6	3.8	22.9		34.8
11	Bz	O	56.9	11.8	2.0	5.6	15.5	30.7	
12	O	*t*-Bu	51.0	5.2	4.8	3.2	21.2		35.9 1.0
13	*t*-Bu	O	51.0	12.5	1.1	4.4	16.6	31.2 0.7	
14	S	Ph	47.9	5.4	1.7	4.2	20.9		
15	Ph	S	47.3	6.9	2.5	2.2	21.5		
16	CH_3	CH_3	45.2	11.2	2.5	3.7	18.1	29.1	34.7
17	CH_3	Ph	45.2	10.2	2.1	3.7	17.6	31.1	
17a	CH_3	*p*-C_6H_4F	45.8	9.5	1.9	4.0	18.9	30.6	
18	Ph	CH_3	45.3	10.5	3.1	3.4	22.2		35.9
19	CH_3	Bz	44.0	10.2	3.1	3.1	16.8	28.2	21.9
20	Bz	CH_3	44.3	10.2	2.8	4.2	19.1	18.6	34.3
21	Bz	Bz	41.0	9.1	2.5	4.0	19.4	17.8	23.4

[a] Chemical shifts, in parts per million, were determined to ±0.01 ppm from 60% enriched $^{13}CH_3I$ present in the lock capillary. The shifts were subsequently placed on the tetramethylsilane-^{13}C scale by subtracting 20.97 ppm, a value found for the shift of TMS-^{13}C, from the same lock capillary, in a 2:2:1 25:$CHCl_3$:TMS solution. The TMS was at natural abundance in ^{13}C. A positive value for the chemical shift represents a higher frequency shift, or deshielding of the carbon atom. Bz = benzyl, CH_2Ph; Ph = phenyl; *t*-Bu = *tert*-butyl.

TABLE II

ALIPHATIC ^{13}C CHEMICAL SHIFTS AND ^{13}C–^{31}P NUCLEAR SPIN COUPLING CONSTANTS FOR 1-X, 1-Y 2,2,3-TRIMETHYLPHOSPHETANE OXIDES AND SALTS[a]

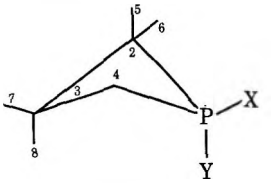


Compd	X	Y	C-2	C-4	C-3	C-5	C-6	C-7	PCH$_3$
			Chemical shifts						
22	O	OH	52.20	40.74	30.62	17.42	23.15	15.19	
23	O	OCH_3	52.93	39.71	30.27	16.65	22.05	14.12	
24	OCH_3	O	52.93	39.71	30.27	17.27	20.71	15.82	
25	O	Ph	49.96	37.42	30.97	16.89	23.67	14.75	
26	Ph	O	48.41	34.56	34.47	19.40	23.52	15.97	
27	CH_3	Ph	45.53	25.35	40.49	18.13	23.94	15.87	9.43
28	Ph	CH_3	44.91	24.86	38.72	17.75	23.31	15.92	6.29
			Coupling constants						
22	O	OH	81.8	67.7	18.1	4.2	4.9	23.4	
23	O	OCH_3	79.3	65.8	18.3	2.6	7.4	27.8	
24	OCH_3	O	79.3	65.8	18.3	6.1	2.	12.1	
25	O	Ph	63.3	52.5	11.9	4.4	3.2	28.3	
26	Ph	O	63.1	52.3	16.0	2.6	4.5	16.5	
27	CH_3	Ph	48.6	47.7	17.1	1	3.7	21.2	31.5
28	Ph	CH_3	48.5	46.1	15.9	1	3.9	23.7	37.3

[a] See footnote *a*, Table I.

TABLE III

ALIPHATIC ^{13}C CHEMICAL SHIFTS AND ^{13}C–^{31}P NUCLEAR SPIN COUPLING CONSTANTS FOR 1-X, 1-Y 2,2,3,3-TETRAMETHYLPHOSPHETANE OXIDES, SULFIDE, AND SALT[a]



Compd	X	Y	C-2	C-4	C-3	C-5	C-6	C-7[b]	C-8[b]	P-CH$_3$
			Chemical shifts							
29	OH	O	53.34	48.19	32.17	20.02	20.02	26.11	26.11	
30	OCH_3	O	54.47	47.86	31.97	19.48	20.45	26.73	26.24	
31	Ph	O	50.81	41.46	35.04	19.16	21.55	26.30	27.19	
32	Ph	CH_3	46.82	30.88	44.00	20.78	21.00	26.75	27.03	10.04
33	Ph	S	49.33	42.74	39.19	21.38	22.91	26.80	28.19	
			Coupling constants							
29	OH	O	81.8	67.7	14.6	4.8	4.8	15.3	15.3	
30	OCH_3	O	78.2	64.4	13.8	6.9	4.0	9.2	0.9	
31	Ph	O	62.8	52.0	11.9	4	2	11.3	13.6	
32	Ph	CH_3	47.2	46.0	14.0	3.0	4.4	14.2	8.0	34.2
33	Ph	S	49.7	44.8	10.5	1.9	3.1	9.4	13.9	

[a] See footnote *a*, Table I. [b] Tentative assignment.

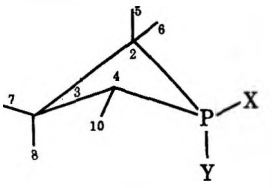
and C-4. The shift difference between them is primarily due to different methyl–methyl steric interactions and ring puckering rather than the cis or trans orientation with respect to the phosphorus substituents. This is evident in **1**, where rapid proton exchange renders the substituents on phosphorus identical, or in **16**, where they are in fact identical. In view of the generally smaller shift experienced by sterically crowded (as opposed to uncrowded) carbon,[23] as well as the small shift experienced by axial methyl carbons,[24] the methyl carbons of smaller shift are assigned to the pseudoaxial C-5 and C-9. Our calculations[25] based on reported X-ray fractional coordinates of 1-chloro-2,2,3,4,4-pentamethylphosphetane oxide,[22c] 1-phenyl-2,2,3,4,4-pentamethylphosphetane oxide,[22d] and 1-phenyl-1,2,2,3,4,4-hexamethylphosphetanium bromide[22b] show that the neighbor heavy atom interatomic contact distances for C-5 and C-9 are significantly shorter than those for C-6 and C-10. With this basic assignment the remaining exocyclic carbon shifts are easily assigned to the basis of

(23) D. M. Grant and B. V. Cheney, *J. Amer. Chem. Soc.*, **89**, 5315 (1967).
(24) D. K. Dalling and D. M. Grant, *ibid.*, **89**, 6612 (1967).

(25) Calculations of heavy atom interatomic distances were done using data from ref 22b–d using the molecular geometry program MGEOM, J. S. Wood, 1964. We thank Dr. Roger Eiss (OGC) for assistance in performing these calculations.

TABLE IV

ALIPHATIC ^{13}C CHEMICAL SHIFTS AND ^{13}C–^{31}P NUCLEAR SPIN COUPLING CONSTANTS FOR 1-X, 1-Y 2,2,3,3,4-PENTAMETHYLPHOSPHETANE OXIDES AND SALT[a]

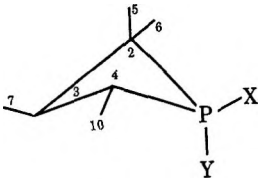


Compd	X	Y	C-2	C-4	C-3	C-5	C-6	C-7[b]	C-8[b]	C-10	PCH$_3$
			Chemical shifts								
34	OH	O	52.57	51.02	35.57	21.33	18.36	24.57	20.61	7.38	
35	O	OCH_3	53.00	50.13	35.64	20.13	18.28	23.73	20.58	7.34	
36	OCH_3	O	53.14	51.72	33.97	20.13	17.63	23.86	20.58	6.81	
37	Ph	O	49.20	43.10	41.74	22.92	17.66	24.38	22.11	6.56	
38	Ph	CH_3	46.24	36.33	46.95	22.17	19.67	26.54	22.17	8.41	5.98
39	O	Cl	60.54	58.75	40.69	23.08	17.99	24.40	20.49	7.14	
40	Cl	O	60.04	57.74	35.54	20.72	19.96	25.24	20.49	8.70	
			Coupling constants								
34	OH	O	78.9	72.8	10.6	3.1	6.2	28.9	1.8	7.5	
35	O	OCH_3	74.7	69.7	10.1	4.8	5.3	26.5	5.2	6.9	
36	OCH_3	O	74.2	67.8	10.1	2.6	6.8	30.3	1.8	7.6	
37	Ph	O	61.2	58.4	15.1	0.8	4.4	24.9	1.6	5.9	
38	Ph	CH_3	45.8	44.7	9.7	2.8	3.4	22.1	2.8	6.4	33.3
39	O	Cl	58.6	53.5	6.2	4.1	6.6	33.1	1.9	9.0	
40	Cl	O	57.8	51.7	2.9	3.8	6.8	35.1	1.9	9.5	

[a] See footnote *a*, Table I. [b] Tentative assignment.

TABLE V

ALIPHATIC ^{13}C CHEMICAL SHIFTS AND ^{13}C–^{31}P NUCLEAR SPIN COUPLING CONSTANTS FOR 1-X, 1-Y 2,2,3,4-TETRAMETHYLPHOSPHETANE OXIDES AND SALT[a,b]



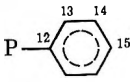
Compd	X	Y	C-2	C-4	C-3	C-5	C-6	C-7	C-10	PCH$_3$
			Chemical shifts							
41	OH	O	49.52	47.74	39.88	17.51	22.32	12.50	11.52	
42	OCH_3	O	50.18	48.17	38.84	16.70	21.72	11.63	11.06	
43	Ph	O	48.68	38.38	36.02	18.14	24.71	9.32	8.38	
44	Ph	CH_3	43.77	29.48	43.91	20.48	25.99	11.97	10.75	8.22
			Coupling constants							
41	OH	O	80.1	73.4	14.0	2.8	6.5	31.9	8.0	
42	OCH_3	O	76.1	70.4	13.8	2	6.7	31.8	8.1	
43	Ph	O	60.4	56.2	12.5	4.8	2.8	17.5	6.2	
44	Ph	CH_3	46.7	46.5	13.7	2.8	2.5	11.9	5.5	30.5

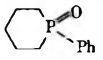
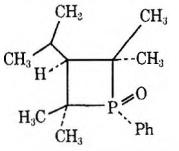
[a] See footnote *a*, Table I. [b] Pseudoequatorial C-10 trans to pseudoequatorial X assumed as conformation.

intensity, ^{13}C–^{31}P coupling, and nature of the exocyclic phosphorus substituents. The phosphorus-bound methyls in **16** were assigned using material in which one of the exocyclic CH_3 groups had been stereospecifically replaced by CD_3 (see Materials section). The resonances in Table II were assigned in much the same manner except that C-2 and C-4 possess different shifts. The general effect of replacing hydrogen on an aliphatic carbon with methyls is to increase the shift of the carbon atom.[24] Hence, the more shifted carbon is assigned C-2. The compounds listed in Table III reflect the placement of an equal number of methyls above and below the four-membered ring. Proton exchange in **29** makes C-5 and C-6 identical as well as C-7 and C-8. The small chemical shift difference in Table III between C-5 and C-6, also C-7 and C-8, reflects, in part, the difference in cis or trans orientation relative to the phosphorus substituents. This is largest when the atoms bound to phosphorus are different, as in **31**. Although there is uncertainty in assignment of the methyl shifts, the coupling constants provide some help, at least for C-5 and C-6 when compared with similar couplings in Tables I, II, and IV. The shifts and couplings for C-7 and C-8 in **30**, **31**, **32**, and **33** are so similar that the assignment may be the reverse of that shown. Assignments for C-2, C-4, and C-3 follow from the reasoning for compounds in Table II. All of the compounds in Table IV have a doublet with a moderately large coupling to phosphorus in the region of 24 ppm, an area characteristic of the pseudoequatorial C-6 or C-10 in

TABLE VI

AROMATIC ^{13}C CHEMICAL SHIFTS AND ^{13}C–^{31}P NUCLEAR SPIN COUPLING CONSTANTS FOR PHENYL-SUBSTITUTED OXIDES SULFIDES, AND SALTS[a,b]



Compd	X	Y	C-12 δ	C-12 $^1J_{CP}$	C-13[c] δ	C-13[c] $^2J_{CP}$	C-14[c] δ	C-14[c] $^3J_{CP}$	C-15 δ	C-15 $^4J_{CP}$
6	O	Ph	129.94	59.5	133.32	9.0	128.85	9.7	132.33	2.9
6a	O	*p*-C_6H_4F	124.58	62.6	135.06	9.4	115.50	11.0	165.15	3.2
7	Ph	O	131.88	54.5	132.65	8.8	129.12	10.1	132.37	2.7
14	S	Ph	129.45	46.4	134.75	9.4	128.89	11.1	132.34	2.2
15	Ph	S	132.23	58.3	131.38	8.8	128.86	10.7	135.13	0.0
17	CH_3	Ph	119.15	54.9	135.01	8.5	131.28	11.7	135.79	0.0
17a	CH_3	*p*-C_6H_4F	113.62	59.6	137.03	9.7	117.43	12.8	166.09	3.6
18	Ph	CH_3	120.68	48.9	133.81	8.5	131.55	11.3	135.65	0.0
25	O	Ph	131.40	72.3	131.02	9.7	128.99	10.6	132.11	2.9
26	Ph	O	133.06	57.6	131.02	9.7	128.85	11.9	132.11	2.9
27	CH_3	Ph	119.36	64.7	133.90	10.7	131.37	11.7	135.97	5.0
28	Ph	CH_3	120.52	58.4	133.90	10.7	131.26	11.5	135.85	4.7
31	Ph	O	133.78	67.8	131.56	9.7	129.18	10.8	132.34	2.9
32	Ph	CH_3	121.79	62.2	134.24	10.2	131.27	12.0	135.62	2.5
33	Ph	S	134.40	54.6	131.11	10.3	128.95	11.3	131.62	2.9
37	Ph	O	133.10	63.1	131.51	9.3	129.30	10.9	132.47	3.1
38	Ph	CH_3	120.85	58.4	132.92	10.2	131.22	11.7	135.63	7.4
43	Ph	O	134.49	64.6	130.80	8.0	128.67	10.5	131.82	4.6
44	Ph	CH_3	118.90	59.9	133.70	9.4	130.67	11.8	135.38	3.5
45			136.66	86.6	131.01	9.4	129.43	11.1	132.13	2.5
46			135.31	95.4	130.87	10.0	129.15	11.6	132.01	2.3
49			134.29	92.6	130.89	9.2	129.58	11.2	132.60	2.6
52			128.69	62.4	133.16	8.7	128.42	10.2	132.04	2.8

[a] See footnote *a*, Table I. [b] ^{13}C–^{19}F couplings—for 6a: C-15, 253.2 H; C-14, 21.0 Hz; C-13, 9.4 Hz; and C-12, 2.6 Hz. For 17a: C-15, 258.1 Hz; C-14, 21.8 Hz; C-13, 9.7 Hz; and C-12, 3.4 Hz. [c] Assignments for C-13 and C-14 made by noting 6 → 6a and 17 → 17a shifts and comparing with the analogous benzene → fluorobenzene changes as reported by H. Spieseke and W. G. Schneider, *J. Chem. Phys.*, **35**, 731 (1961).

Table I. C-7 in Table IV is similar to these in that it is bound to a tertiary carbon. X-Ray studies[22f] of **37** show a stable puckered ring with C-10 in the lower energy pseudoequatorial position. Since C-8 is present, C-6 should have a smaller shift than that in Tables I and II due to the additional methyl–methyl interaction. Also, C-5 should have a greater shift than C-5 in Tables I and II, since the C-5–C-9 steric interaction is missing. The couplings for C-5 and C-6 in **34** are similar to those in **1** if the order of shift is reversed from that in Tables I and II. It may be that the above two factors combine sufficiently to reverse the shift order of C-5 and C-6 in **34** with respect to **1**. The magnitude of the C-6 coupling in **34** is close to that of C-10, as indicated above. Upon considering **37** the same reasoning holds. C-6 has a coupling of 4.6 Hz in **7** and 4.4 Hz in **37**. Reversing the chemical shift order of C-5 and C-6 in going from **2** to **36** predicts the carbon having the smaller shift to have a larger coupling, in agreement with the experimental results. The insensitivity of C-8 coupling in all cases in Table IV (except for **35**) as well as the variability of C-5 coupling with substituent allowed a tentative assignment of these carbons to be made.

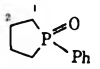
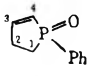
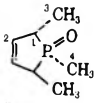
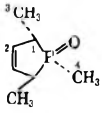
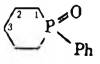
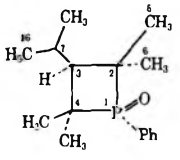
Table VII lists the aliphatic carbon shifts and ^{13}C–^{31}P couplings for compounds of interest in analyzing the data for the four-membered ring compounds.

Discussion

The overall chemical shifts in the pentamethylphosphetane systems in Table I are understandable in terms of an increased shift to be expected for C-2 and C-4 for α- and β- methyl substitution and a major shift of C-3 arising from the addition of one α-methyl and four β-methyls. The C-2 and C-4 shifts seem to be approximately related to the electronegativity of the exocyclic phosphorus substituents. The most shifted C-2 and C-4 carbons are in **1**, where both exocyclic phosphorus-bound atoms are oxygen, while the least shifted are in **16**, where both groups are methyls. The range of C-3 shifts is greater than that of any carbon in Table I, even

TABLE VII

ALIPHATIC AND OLEFINIC ^{13}C CHEMICAL SHIFTS AND ^{13}C–^{31}P NUCLEAR SPIN COUPLING CONSTANTS FOR SEVERAL ACYCLIC AND CYCLIC OXIDES[a]

Compd			C-1	C-2	C-3	C-4
45		δ	30.30	25.72		
		J	66.8	7.9		
46		δ	25.85	30.35	153.14	126.92
		J	71.0	10.4	24.0	92.0
47		δ	36.89	133.83	14.86	16.02
		J	65.4	13.4	4.0	59.7
48		δ	39.02	133.51	14.05	7.58
		J	64.9	14.3	3.7	58.8
49		δ	28.73	22.54	26.98	
		J	65.2	6.0	6.8	
50	$(CH_3)_3P{=}O$	δ	18.58			
		J	68.3			
51	$(CH_3CH_2)_3P{=}O$	δ	20.72	6.15		
		J	65.6	4.9		
52		δ		47.18	58.98	
		J		57.8	7.1	
			C-5	C-6	C-7	C-16
		δ	18.70	26.68	27.88	23.06
		J	5.4	4.3	26.4	0.0

[a] See footnote *a*, Table I.

TABLE VIII

CHANGES IN ^{13}C CHEMICAL SHIFT

Transition	Ring	Y	Isomer	ΔC-2	ΔC-4	ΔC-Y	ΔC-3	ΔC-5	ΔC-6	ΔC-7
4 → 16		CH_3	trans	7.3	7.3	5.6	−8.8	−1.7	0.3	−1.4
5 → 16		CH_3	cis	6.0	6.0	6.5	−4.5	0.9	0.2	1.0
6 → 17		Ph	trans	5.3	5.3	10.8	−8.6	−1.7	−1.4	−2.4
7 → 18		Ph	cis	4.3	4.3	10.2	−2.4	0.1	−1.1	0.6
10 → 19		Bz	trans	7.1	7.1	6.2	−7.7	−1.4	0.5	−1.8
11 → 20		Bz	cis	6.6	6.6	6.4	−3.5	0.2	−0.5	−0.0
25 → 27		Ph	trans	4.4	12.1	12.0	−9.5	−1.2	−0.3	−1.1
26 → 28		Ph	cis	3.5	9.7	12.5	−4.2	−1.6	0.2	0.0
31 → 32		Ph		4.0	8.7	12.0	−8.9	−1.7	0.6	−0.6
37 → 38		Ph	cis	3.0	6.8	12.2	−5.2	0.8	−2.0	−1.2
43 → 44		Ph	cis	4.9	8.9	15.6	−7.9	−2.3	−1.3	−2.6

though it is three bonds removed from the substituent. Its trend with electronegativity is opposite to that of the C-2 and C-4 carbons. On the whole, C-3 shows more sensitivity to exocyclic phosphorus substituent than C-2 or C-4. It is difficult to rationalize these C-3 shifts on the basis of either attenuated inductive effect (wrong direction) or direct steric effects (too far away).

The C-2, C-4, and C-3 methyls in Table I are also three and four bonds away from the phosphorus substituents but are much less affected by changes in these substituents than C-3. C-7 is less shifted than an isolated equatorial methyl.[24] The decreased shift is adequately predicted using shift parameters for methyl–methyl interactions in methylcyclohexanes.[24] Taking the shift of an isolated equatorial methyl carbon as 24 ppm and adding the effect of two axial C-2 and C-4 methyls (−12 ppm) and two equatorial C-2 and C-4 methyls (−4 ppm), we calculate a shift of 8 ppm for C-7, agreeing well with the observed C-7 shifts in Table I.

The chemical shifts in Table II reflect the less crowded situation when the C-9 and C-10 methyls are replaced by hydrogens. C-4 is affected more dramatically and, interestingly, to a different degree in the

oxides and salts. For example, C-4 decreased in shift by 9 ppm in going from **6** to **25** but 16 ppm in going from **17** to **27**. The C-3 shifts are affected similarly, however, in the above cases, showing a decreased shift of ~13–14 ppm upon removal of the two β-methyl groups. C-7 is also increased in shift by 6 to 8 ppm in both oxide and salt as the steric crowding of the two β-methyl groups is removed. If we were considering the analogously substituted cyclobutane we would expect concomitant shift increase of the pseudoequatorial methyl on C-1. However, in the structurally similar **27**, the phosphorus-bound methyl carbon is increased in shift by only half of the 6-ppm change experienced by C-7. This lower sensitivity in shift probably results from the larger P–C bonds, which cut down on the methyl–methyl steric perturbations. Note that the pseudoaxial phosphorus exocyclic methyl in **28** is only shifted −0.6 ppm in going from **18** to **28**.

In going to Table III we introduce the effect of another methyl group at C-3. This has primary effect on C-7, which is strongly shifted by ~11 ppm. The absence of the unique ring carbon methyl group makes C-5 and C-6 much more alike in terms of steric interactions and thus shifts.

In Tables I and IV we see that chlorine as an exocyclic phosphorus substituent produces a severe shift of C-2 and C-4. The effect is not propagated too far, since all the other carbons have shifts similar to those in compounds having carbon or oxygen as exocyclic phosphorus substituents.

An accurate set of substituent parameters should be able to describe the variation of shift with ring structure for different sets of exocyclic phosphorus substituents. There does seem to be some consistency in overall pattern to within a few parts per million. However, some complete reversals of significant size are apparent and no accurate set of substituent parameters can be extracted from the data.

Aromatic carbon chemical shifts are given in Table VI. C-12 is not very sensitive to phosphetane ring substitution in at least this one type of oxide.

In comparing pairs of oxides and salts in which the only difference is the replacement of oxide by methyl, we may assess the uniformity of shift differences and note any dependence on phosphetane ring structure. C-3 shows highly sensitive behavior in the transition oxide → salt. This is documented in Table VIII, where differences in shifts are noted for compounds in which the oxide oxygen is replaced by methyl: in the *trans*-2,2,3,4,4-pentamethylphosphetane case ΔC-2 is smaller in magnitude than ΔC-3. The reverse is true for the corresponding cis isomer. C-4 is more severely affected than C-2 for cases in which C-4 has less than two attached methyl groups. Note that putting two methyl groups on C-3 does not lower ΔC-3 to the same level as ΔC-2. C-5 and C-6 are barely affected by the transition, even though they are, as is C-3, three bonds away from the substituents. Exocyclic phosphorus substituents are shifted in the same direction as C-2 and C-4. Methyl and benzyl give Δ values close to those for C-2 and C-4, but Δ values for phenyl (C-12) are 2–4 times those for C-2 or C-4.

^{13}C–^{31}P Coupling Constants.—The phosphetane oxides and salts provide significant new data concerning the sensitivity of ^{13}C–^{31}P couplings to substituent and structural effects. Several compounds in Table VII can serve as unstrained acyclic and cyclic reference compounds. The one-bond ^{13}C–^{31}P coupling in $(CH_3)_3$-P=O is decreased slightly in going to **51**, where methyl is replaced by ethyl. Conversion to the six-membered ring compound **49** does not affect the coupling significantly. There is a slight increase in coupling in contracting the ring to **45**, but the smaller C-4 coupling to phosphorus in **25** is evidence that contraction to a four-membered ring structure results in a sizable decrease in the corresponding coupling.

The phosphetane backbone can contribute a number of coupling constants for assessing the effect of exocyclic phosphorus substituent variation on ^{13}C–^{31}P couplings. There appears to be a loose relationship between substituent electronegativity and C-2 (C-4) couplings in Table I. The sensitivity of the C-4 coupling to methyl substitution on C-4 is fairly small in the salts (*e.g.*, a change of only 1–2 Hz for **17** or **18** → **27** or **28**) in contrast to some of the oxides, where changes up to 10 Hz occur. Interestingly, the number of hydrogens on the phosphorus-bound exocyclic carbon influences the C-2 (C-4) couplings to a higher degree than those of the exocyclic carbons themselves, *i.e.*, 59.4 (**4**), 56.9 (**10**), and 51.0 Hz (**12**). Note that the C-2 and C-4 couplings in the oxides are much more sensitive to change in phosphorus substituent than those in the salts. The small values for C-5, C-6, C-9, and C-10 couplings in Table I are not a consequence of unusual or strained geometry, since the analogous coupling to the *tert*-butyl methyl carbons in **12** is also small (1.0 Hz). The couplings to C-3 in Table I are typically larger and more variable, even though it is again a two-bond coupling. One surprising aspect is the magnitude of the three-bond couplings to C-7 in Table I. In fact, in **20** this coupling is larger than the one-bond coupling to the benzyl carbon. The magnitude of this coupling is not especially sensitive to the exocyclic phosphorus substituent for a series of cis or series of trans isomers (except for chloro), although it is generally lower when the oxide is converted into the corresponding salt. Chlorine bound to phosphorus has some interesting effects. Even though chlorine is more electronegative than carbon, the C-2 and C-4 couplings are greater for phenyl or methyl as phosphorus substituents as opposed to chloro. The major effect is felt in the C-3 coupling, which is reduced, and the C-7 coupling, which is enhanced.

The coupling for C-7 seems most sensitive to ring structure. The drop in coupling in going to the 2,2,-3,3-tetramethyl is not a result of placing another methyl on C-3, since similar values are found for rings in Tables II and IV. Rather, this must result from one or the other of two dynamical possibilities. Either the ring geometry is changed or the puckered form is undergoing rapid interconversion. A static puckered form is difficult to accept because of the similarity in the C-5/C-6 shifts and also the C-7/C-8 shifts. The results in Tables I, II, IV, and V are very consistent in showing a large three-bond coupling for C-7. Since these rings are puckered[22] to relieve steric interactions, the C-7 coupling is an indicator of coupling to be expected for a pseudoequatorial methyl carbon bound to C-3. Hence, static puckered rings corresponding to compounds in Table III should show C-7 and C-8 cou-

plings similar to compounds in Table IV. The choice then is between possibly a flattened ring and interconverting puckered forms. The differences in C-7 and C-8 couplings should then be composed of two factors: (1) the portion of time spent in each conformer, and (2) the cis–trans nature with respect to the substituents. It is conceivable that both structural possibilities are in effect with some ring flattening present, affecting the expected magnitude of the C-7 and C-8 couplings. It is very difficult to draw on other four-membered ring systems for analogies, since both puckered[26a-f] and flat[26g-j] examples have been found for rings symmetrically substituted on the carbon skeleton. However, since *all* the carbon-bound substituents on the ring are methyls, a flat molecule would be expected to be a fairly high energy conformer, since all the methyls would be eclipsed with each other. Thus, on the basis of couplings and conformer energetics, rapidly interconverting conformers are favored. It is difficult to estimate the fraction of each conformer, since the larger P–C bonds in the ring remove, to some extent, the degree of steric interaction associated with the exocyclic phosphorus substituents.

The C-12 coupling is sensitive to phosphetane ring substitution. The sensitivity of aromatic carbon coupling to phosphetane ring substitution virtually disappears in going to the ortho, meta, and para carbons in the oxides. A similar situation prevails in the salts, except that the para coupling is much more variable, ranging over 7.4 Hz. Replacing oxide by sulfide results in decreases in C-12 and C-2/C-4 couplings. This effect is also apparent in going from trimethylphosphine oxide (68.3 Hz) to trimethylphosphine sulfide (56.1 Hz[6]). The effect is not promulgated over more than one bond, since the remaining couplings are unaffected. In fact, since the shifts of the remaining carbons are also unaffected, the primary perturbation in going from oxide to sulfide seems to be felt only at the phosphorus.

^{13}C Shifts and ^{13}C–^{31}P Couplings in Cis–Trans Isomers.—In those compounds with unsymmetrical methyl substitution, cis and trans isomers are possible. X-ray studies[22] of several of the compounds in Table I, on both cis and trans isomers, have shown that C-7 is in a pseudoequatorial position and that the ring backbone is essentially independent of the stereochemistry of particular compounds. A trans oxide will be defined as having the oxide oxygen in a cis configuration with respect to C-7. Therefore, **6** is a trans oxide and **7** a cis oxide. Likewise, **17** is a trans salt (1-phenyl and 3-methyl trans) and **18** is a cis salt (1-phenyl and 3-methyl cis). It is also convenient to assign **20** as a cis salt (1-benzyl and 3-methyl are cis) and **19** as a trans salt. The availability of cis and trans isomers allows examination of changes in shifts and couplings in the cases where only the exocyclic phosphorus substituents are modified, in this case merely switched. This switch can possibly have steric implication and reflect more subtle influences on shifts and couplings. There does not appear to be any isomeric dependence for the C-2 and C-4 carbon shifts or couplings other than a slight shift increase in the trans oxides and in salts **17** (*vs.* **18**) and **19** (*vs.* **20**). C-3 is uniformly more shifted in the cis oxide and, in the cases where the phosphorus substituents are carbon and oxide, the C-3 coupling is typically about 1.5–2.5 times greater in the cis isomer than in the trans. Essentially no stereospecificity is observed for the C-3 coupling in the salts except for the ΔC-3/ΔC-2 ratio in Table VIII. The only instances in which the C-5, C-6, C-9, and C-10 carbons show significant stereospecific shift behavior are in the oxides **4** and **5**. We have previously reported the stereospecific nature of the C-7 and one-bond exocyclic carbon couplings in some of the compounds in Tables I and II.[3] The difference between one-bond couplings of the same phosphorus-bound exocyclic carbon in cis and trans pairs is substantial, uniform in direction, and fairly unrelated to the other exocyclic phosphorus substituent in both aromatic and aliphatic cases. This last fact indicates that the size of the exocyclic group bound to phosphorus is probably not too important in causing this difference in coupling. The three-bond C-7 coupling is unusually stereospecific (up to 15.7 Hz for **23** and **24**) in that the relative orientation of the coupled atoms *remains fixed* while groups α to one of the coupled atoms interchange positions (this is also the situation for the C-3 couplings discussed above). Normally, stereospecific ^{31}P–^{1}H long-range couplings result from sensitivity of the coupling to relative orientation of the coupled atoms.[27] The degree of difference of exocyclic phosphorus substituents is directly related to the magnitude of the stereospecificity. It does seem unlikely that through-space steric or electronic effects are directly responsible, since C-7 and the phosphorus exocyclic group cis to it are well separated (4.8 Å in **26**).[25] C-7 is uniformly increased in shift in the cis oxides with respect to the trans oxides and decreased in shift in the cis salt (*e.g.*, **18**) with respect to trans salt (*e.g.*, **17**). The phosphorus-bound methyl carbons exhibit orientation-dependent chemical shift, as seen in **4** *vs.* **18**, **19**, *vs.* **20**, and **27** *vs.* **28**. In all cases except **17** *vs.* **18** the trans methyl is of smaller shift than the cis methyl in the same isomer pair. The couplings are all consistently stereospecific, however. Phenyl, benzyl, and *tert*-butyl behave similarly in stereospecificity. Stereospecific C-12 shifts are shown in **6** *vs.* **7**, **17** *vs.* **18**, **25** *vs.* **26**, and **27** *vs.* **28**, where C-12 in trans phenyl has a

(26) (a) Cyclobutane, S. Meiboom and L. C. Snyder, *J. Amer. Chem. Soc.*, **89**, 1038 (1967); (b) octafluorocyclobutane, H. P. Lemaire and R. L. Livingston, *ibid.*, **74**, 5732 (1952); (c) *cis-* and *trans*-1,2-dibromo-1,2-dicarbomethoxycyclobutane, I. L. Karle, J. Karle, and K. Bitts, *ibid.*, **88**, 2918 (1966); (d) *cis*-1,3-cyclobutanedicarboxylic acid, E. Adman and T. N. Margulis, *Chem. Commun.*, 641 (1967); *J. Amer. Chem. Soc.*, **90**, 4517 (1968); (e) *N*-methyl-*N*-*tert*-butyl-3-hydroxyazetidinium methanesulfonate, E. L. McGandy, H. M. Berman, J. W. Burgner, II, and R. L. Van Etten, *ibid.*, **91**, 6173 (1969); (f) L-azetidine-2-carboxylic acid, H. M. Berman, E. L. McGandy, J. W. Burgner, II, and R. L. Van Etten, *ibid.*, **91**, 6177 (1969); (g) octahydroxycyclobutane, C. M. Bock, *ibid.*, **90**, 2748 (1968); (g) tetraphenylcyclobutane, J. D. Dunitz, *Acta Crystallogr.*, **2**, 1 (1949); (i) *trans*-1,3-cyclobutanedicarboxylic acid, T. N. Margulis and M. S. Fischer, *J. Amer. Chem. Soc.*, **89**, 223 (1967); (j) 1,1-debenzyl-3,3-dimethylazetidinium bromide, R. L. Snyder, E. L. McGandy, R. L. Van Etten, L. M. Trefonas, and R. L. Towns, *ibid.*, **91**, 6187 (1969).

(27) (a) L. D. Hall and R. B. Malcomb, *Chem. Ind.* (*London*), 92 (1968); (b) J. P. Albrand, D. Gagnaire, J. Martin, and J. B. Robert, *Chem. Commun.*, 1469 (1968); (c) J. P. Albrand, D. Gagnaire, J. Martin, and J. B. Robert, *Bull. Soc. Chim. Fr.*, 40 (1969); (d) J. Nelson, R. Spratt, and B. J. Walker, *Chem. Commun.*, 1509 (1970); (e) J. G. Verkade and R. W. King, *Inorg. Chem.*, **1**, 948 (1962); (f) E. J. Boros, K. J. Coskran, R. W. King, and J. G. Verkade, *J. Amer Chem. Soc.*, **88**, 1140 (1966); (g) D. W. White and J. G. Verkade, *J. Magn. Resonance*, **3**, 111 (1970); (h) D. W. White, R. D. Bertrand, G. K. McEwen, and J. G. Verkade, *J. Amer. Chem. Soc.*, **92**, 7125 (1970); (i) W. G. Bertrand and J. H. Hargis, *ibid.*, **92**, 7136 (1970); (j) L. D. Quin and T. P. Barket, *J. Amer. Chem. Soc.*, **92**, 4303 (1970); see also J. P. Albrand, D. Gagnaire, M. Picard, and J. B. Robert, *Tetrahedron Lett.*, 4593 (1970).

smaller shift than C-12 in cis phenyl. The five-membered ring isomers **47** and **48** show minor differences in coupling but significant differences in α carbon and exocyclic phosphorus methyl shifts, reflecting the dissymmetry above and below the plane of the ring.

Assuming that C-10 is pseudoequatorial in all compounds in Table IV, as shown in **37**,[22f] the stereospecificity of C-7 coupling is reversed from that in compounds of Tables I and II for two sets of isomers and also reduced in magnitude. Since just addition of another methyl to C-3 or C-4 produces this effect, isolation and characterization of isomers of the compounds in Table V may help to clear up the function of ring substitution on stereospecificity of C-7 coupling.

Theoretical Analysis.—Although the complexity and number of the compounds used here makes detailed calculation impractical, some of the ideas developed in theoretical studies of ^{13}C chemical shifts and nuclear spin couplings might prove useful in developing an understanding of the experimental results.

^{13}C chemical shifts have been the subject of much theoretical investigation,[28-37] usually starting from Ramsey's formulation[38] and employing approximations of varying severity.

Since no calculations have been done on the phosphetanes, we are restricted to only qualitative estimates of the origin of the observed shifts. In cases where the phosphetane backbone remains fixed for various substituents on phosphorus, all the phosphetane carbon shifts are for carbons at least two bonds away from the substituent. Carbon charge density variation may be the controlling factor in determining these carbon shifts. For a given ring configuration the observed range of shifts for different phosphorus substituents would then be primarily due to differences in charge densities resulting from the range of electronegativities of the substituents. At first glance, the full positive charge present on phosphorus in the salts would lead to a prediction of a large C-2/C-4 shift, since this would represent a type of very powerful inductive withdrawal of charge. However, C-2 and C-4 have smaller shifts in the salts than in the oxides. It could be that the oxides are better represented as P(IV) rather than "P(V)," *i.e.*, P^+-O^- instead of P=O.

If charge density polarization is the dominant mechanism for changes in the paramagnetic contribution to the chemical shift, some definite reversals are to be noted in the expected order of shifts. Note that C-2 and C-4 have a *higher* shift in **4** or **6** than in **2**. In fact, with the exception of chloro as a substituent, the C-2/C-4 shift in Table I is fairly insensitive to phosphorus substituent. When chloro is omitted the range of C-2/C-4 shifts is only 4.4 ppm, as opposed to 12.4 ppm for analogous $^{13}CH_3CH_2X$ shifts.[39] Carbons three bonds away from substituents in 1-substituted bicyclo[2.2.2]octanes have been reported to have shifts in the same direction as carbons two bonds away, but are significantly more attenuated.[39] The compounds in Table I show that the trend in C-3 is opposite that of C-2/C-4 and is actually more sensitive to the character of the substituent. This is difficult to explain on the basis of attenuated inductive effect and may be the result of alternating positive and negative charge densities around the phosphetane ring.

Theoretical analysis of $^{13}C-^{31}P$ nuclear spin couplings has been hampered by the until recent paucity of experimental data and the difficulty of doing detailed calculations involving a second-row element. The only available theoretical treatments of $^{13}C-^{31}P$ couplings have been by Cowley and White,[15] who calculated $^{13}C-^{31}P$ couplings in CH_3PH_2, CF_3PH_2, and $CH_3PH_3^+$ by a parameterized LCAO-SCF-MO theory in the Pople–Santry[16] approximation, Jameson and Gutowsky,[17,18] who developed a general qualitative model of spin coupling based on the contact contribution and core polarization, and Gray (part I),[2] who used the finite perturbation INDO-SCF-MO theory of Pople, McIver, and Ostlund[40] to calculate $^{13}C-^{31}P$ couplings in a series of phosphonates. In this last investigation the relationship between "s character" and $^{13}C-^{31}P$ coupling was examined. The coupling followed the calculated bond order but varied about twice as fast. In the phosphetanes, substituents are varied on phosphorus, whereas in the phosphonates the site of variable substitution was on the phosphonate carbon. The relationship between one-bond coupling to phosphorus and $C_{2s}-P_{3s}$ bond order in this different kind of bonding situation is a subject for further theoretical analysis, but treatments of spin coupling involving carbon[2,40,41] offer good promise that changes in couplings involving carbon, especially for carbons not undergoing substitution, reflect to a degree changes in the valence s-orbital bond order between the coupled atoms.

The C-2 and C-4 couplings in Table I cover a range of over 35 Hz (25 Hz in the oxides alone). Even if the $C_{2s}-P_{3s}$ bond order does not proportionately follow the observed couplings, the range of couplings in the oxides must point toward sizable differences in $C_{2s}-P_{3s}$ bond order throughout the oxides. Since the substituent variation is on phosphorus, it is likely that the main contribution to a change in bond order is from changes in the P_{3s} orbital contribution to the bonding orbital. There does not appear to be a drastic change in the observed couplings in proceeding to the salts. If this can be interpreted as resulting from a small change in the bond order for the coupled atoms, then prediction of sizable P(IV) character for the oxides is reinforced.

The smaller values for coupling to exocyclic alkyl carbons on phosphorus relative to the C-2 and C-4 carbons are interesting, especially in view of the frequently assumed correlation of bond angle with carbon hybridization. The $C_3-C_{2,4}-P$ angles in the phos-

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(31) T. Tokuhiro, N. K. Wilson, and G. Fraenkel, *ibid.*, **90**, 3622 (1968).
(32) W. Adam, A. Grimison, and G. Rodriguez, *J. Chem. Phys.*, **50**, 645 (1969).
(33) T. Tokuhiro and G. Fraenkel, *J. Amer. Chem. Soc.*, **91**, 5005 (1969).
(34) H. Spiesecke and W. G. Schneider, *Tetrahedron Lett.*, 468 (1961).
(35) M. Karplus and J. A. Pople, *J. Chem. Phys.*, **38**, 2803 (1963).
(36) J. Mason, *J. Chem. Soc. A*, 1038 (1971).
(37) R. Ditchfield, D. P. Miller, and J. A. Pople, *J Chem. Phys.*, **54**, 4186 (1971).
(38) N. F. Ramsey, *Phys. Rev.*, **78**, 699 (1950); **83**, (1951); **86**, 243 (1952).
(39) G. E. Maciel and H. C. Dorn, *J. Amer. Chem. Soc.*, **93**, 1268 (1971).
(40) (a) J. A. Pople, J. W. McIver, Jr., and N. S. Ostland, *Chem. Phys. Lett.*, **1**, 456 (1967); (b) *J. Chem. Phys.*, **49**, 2960, 2965 (1968); N. S. Ostlund, M. D. Newton, J. W. McIver, Jr., and J. A. Pople, *J. Magn. Resonance*, **1**, 185 (1969).
(41) (a) G. E. Maciel, J. W. McIver, Jr., N. S. Ostlund, and J. A. Pople, *J. Amer. Chem. Soc.*, **92**, 1, 11, 4151, 4497, 4506 (1970); (b) P. D. Ellis and G. E. Maciel, *ibid.*, **92**, 5829 (1970).

phetanes are 84–88°,[21] considerably distorted from normal tetrahedral values. The C_2–P–C_4 angles are also distorted (82–86°).[21] These values are suggestive of angles for hybrids of considerable p character, arguing for small one-bond couplings. There is a small reduction in the one-bond coupling for the α-ring carbon in going from the larger five- and six-membered rings to an analogous four-membered ring coupling like the C-4 coupling in **25** or **26**. However, this reduction amounts to only a few hertz, nothing like a reduction based on hybridization arguments for C-2 and C-4. Note that the C-12 coupling in this same trend goes from 92.6 Hz in **49** to 86.6 Hz in **45** to 55–75 Hz in the various phosphetanes, pointing toward reduced P_{3s} orbital contribution to this coupling in this bond as the ring contracts.

Since the stereospecificity in exocyclic one-bond coupling is somewhat insensitive to the size of the group containing the coupled carbon or its electronic nature, it seems that the effect must arise from differences in the phosphorus bonding orbitals directed toward the substituents. Analogous stereospecificities have been noted for ^{13}C–^{1}H couplings in bicyclobutane[42] and 3-phenyl-1-azabicyclo[1.1.0]butane,[43] as well as ^{13}C–^{19}F couplings in some methyl-substituted 2,2-difluoronorbornanes.[44] Approximate MO methods based on the Fermi contact contribution have proved successful in calculation of ^{13}C–^{13}C and ^{13}C–^{1}H couplings[41] and have been able to account for the stereospecificity of the ^{13}C–^{1}H coupling in bicyclobutane.[41b] A notable property of these calculations is that the ^{13}C–^{13}C and ^{13}C–^{1}H couplings closely parallel the calculated s-orbital bond order for *structural* rather than *substituent* changes. If this pattern holds for the ^{13}C–^{31}P couplings in the structurally different cis and trans isomers here, the greater exocyclic coupling for the pseudoaxial bond predicts a corresponding greater s-orbital bond order for this bond than the pseudoequatorial bond.

Experimental Section

^{13}C spectra were obtained on a Varian HA-100 spectrometer operating at 25.14 MHz in a field–frequency locked mode. The instrument was controlled by a Varian 620-i 8K computer, which also served for time averaging. A Varian V-3512-1 provided a noise-modulated proton decoupling rf field which eliminated C–H splittings in the ^{13}C spectra. The V-4335-1 probe accommodated spinning 8-mm tubes and was double-tuned for 25 and 100 MHz. The field–frequency lock signal was derived from the resonance of 60% enriched $^{13}CH_3I$ contained in a sealed 2-mm-o.d. capillary tube supported by Teflon collars which could be inserted in the sample tube. Chemical shifts and coupling constants were taken from computer readouts of from usually 10 to 100 spectral accumulations for signal enhancement and accurate peak placement. The line positions were determined to ±0.1 Hz by direct frequency counting of peaks in scans usually 25–50 Hz in width. Scanning rates were normally 1 Hz/sec.

Most of the data were taken using a modification of the standard Varian equipment. In these situations the ^{13}C center band was derived from a 251-MHz signal, digitally divided by ten and amplified, which replaced the crystal-generated rf frequency in the V-4311 rf unit. The analytical frequency sweep was also replaced by a computer-driven Wavetek voltage-controlled oscillator. Using this option, the Varian 620-i computer generated a digital voltage ramp which, under software control, is keyed to the memory locations. The Wavetek oscillator was stable to ±0.1 Hz over a period of hours.

The oxides were run as saturated solutions (1–2 *M*) in $CHCl_3$ except for those which are liquid at room temperature. The salts were examined as saturated solutions in water except for **44**, which was run in $CHCl_3$, and **21**, for which glacial acetic acid was used. The ambient probe temperature under proton decoupling was not measured but was usually significantly higher than room temperature. The chemical shifts in Tables I–VI are with respect to tetramethylsilane-^{13}C. In practice all shifts are recorded with respect to the $^{13}CH_3I$ in the lock capillary and are accurate to ±0.01 ppm for comparisons of shifts for the particular compound studied. For comparison with other compounds they have been corrected to the TMS scale by the shift (20.97 ppm) of TMS-^{13}C from $^{13}CH_3I$ (lock capillary), determined in a 1:2:2 TMS:$CHCl_3$:**25** solution. Even though all the solutions in this work (except for **4** and **21**) were approximately 1:1 oxide:$CHCl_3$ or salt:H_2O, some change in bulk susceptibility is to be expected in going from one sample to another with the largest change expected for changing from $CHCl_3$ to H_2O.

Materials.—Compound **1** was prepared according to the procedure of Jungermann and coworkers.[19e] The phosphinic esters **2** and **3** were made by a previously described method;[21g] likewise, the materials **4**, **6**, **7**, **16–18**, **20**, **25–28**, **31**, and **32** were synthesized by reported routes.[20] The synthesis of derivatives **10**, **37**, **45**, **46**, and **49** has recently appeared.[21a] The phospholene 1-oxides **47** and **48** were obtained by following the procedure of Quin.[27j] The phosphine oxides **50** and **51** are commercially available (*e.g.*, K and K Laboratories, Plainview, N. Y.). The phosphinic acid chlorides **8** and **9** were prepared by reported, general procedures.[19e,21g]

The ^{1}H nmr given below were recorded on a Varian A-60 spectrometer with TMS as an internal standard. Microanalyses were carried out by Alfred Bernhardt, Elbach, West Germany. All melting and boiling points are uncorrected. All of the reactions were carried out under a nitrogen atmosphere and were stirred mechanically or with a magnetic stirring bar.

1,2,2,3,4,4-Hexamethylphosphetane 1-Oxide (5).—The preparation of the cis isomer **5** followed that for the trans isomer **4** except for the mode of quenching of the reaction intermediate with water.[20] If the anhydrous intermediate (namely, the 1-chloro-1,2,2,3,4,4-hexamethylphosphetanium tetrachloroaluminate salt) in methylene chloride was added dropwise to an excess of rapidly stirred ice–water, a *ca.* 7:3 ratio of **5**:**4** was formed. This is in contrast to previously reported results;[20] more careful experimental work using methylphosphonous dichloride (Ethyl Corp.) gave a 90% yield of product (previously, 23%). The pure cis isomer **5** has a melting point of 99–101° (sealed capillary tube).

Anal. Calcd for $C_9H_{19}OP$: C, 62.05; H, 11.00. Found: C, 61.99; H, 10.94.

1-*tert*-Butyl-2,2,3,4,4-pentamethylphosphetane 1-Oxide (12).—To 90 g (0.46 mol) of 1-chloro-2,2,3,4,4-pentamethylphosphetane 1-oxide[19e] in 1 l. of dry ether cooled to −40°, 440 ml (0.55 mol) of 1.24 *M* *tert*-butyllithium in pentane was added dropwise over 1.5 hr. The reaction mixture was allowed to warm to room temperature, stirred for several hours, and cooled again to −30°. A saturated solution of sodium sulfate in water (50 ml) was added followed by sufficient anhydrous magnesium sulfate to pick up excess water. The reaction was warmed to 25° and the inorganic salts were filtered and washed with additional dry ether. Evaporation of the ether gave the crude solid. Additional material was obtained by trituration of the inorganic salts with methylene chloride. The crude product was recrystallized from cyclohexane to give 56 g (56% yield) of white needles, mp 147–149°. The analytical sample was recrystallized from cyclohexane and then sublimed at 100° (0.1 mm).

Anal. Calcd for $C_{12}H_{25}PO$: C, 66.63; H, 11.65; P, 14.32. Found: C, 66.51; H, 11.45; P, 14.52.

From the method of its synthesis this compound is presumed to be the trans isomer (1-*tert*-butyl and 3-methyl). The ^{1}H nmr showed only one isomer to be present. Treatment of a mixture of the isomeric acid chlorides **8** and **9** with *tert*-butyllithium by this same procedure gave a mixture of **12** and **13**, mp 94–120° from petroleum ether (bp 30–60°). An nmr (methylene chloride) showed all of the characteristic peaks expected for both isomeric oxides.

1-Benzyl-2,2,3,4,4-pentamethylphosphetane 1-Oxide (10 and 11).—An isomeric mixture of **10** and **11** was prepared in a manner

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identical[21a] with that of the pure trans isomer **10** by treatment of a mixture of **8** and **9** with benzylmagnesium chloride. The isomeric oxides were recrystallized from cyclohexane. An nmr (pyridine) showed the presence of two isomers; the benzyl protons for **10** appeared at τ 6.57 (2 H, d, J_{PCH} = 11 Hz) and those for **11** at τ 6.61 (2 H, d, J_{PCH} = 11 Hz).

1-Phenyl-2,2,3,4,4-pentamethylphosphetane 1-Sulfide (**14**).—Treatment of a predominance of the trans phosphetane[20] precursor in refluxing benzene with 1 equiv of molecular sulfur gave a precipitate which was recrystallized from cyclohexane to give white needles, mp 96–100°, in good yield. Fractional recrystallization from cyclohexane gave the pure trans isomer, mp 100.5–102°. The product is presumed (by its mode of synthesis) to be the trans isomer (1-phenyl and 3-methyl). The nmr ($CDCl_3$) indicated one major isomer to be present: τ 1.6–2.7 (5 H, m), 7.4 (1 H, dq, J_{HCCH} = 7 Hz, J_{PCCH} = 2 Hz), 8.62 (6 H, d, J_{PCCH} = 20.0 Hz), 8.92 (6 H, d, J_{PCCH} = 19.0 Hz), 9.00 (3 H, dd, J_{HCCH} = 7, J_{PCCCH} = 1.2 Hz).

Likewise, the cis sulfide **15** was made by treatment of a predominance of the cis phosphetane with sulfur in benzene to give a 60% yield of product. Recrystallization from cyclohexane gave needles, mp 85–90°. Several recrystallizations from petroleum ether gave nearly pure cis isomer, mp 91–93°. The nmr ($CDCl_3$) showed absorption at τ 2.05–2.72 (5 H, m), 7.28–8.0 (1 H, dq), 8.54 (6 H, d, J_{PCCH} = 20 Hz), 8.66 (6 H, d, J_{PCCH} = 18 Hz), 9.05 (3 H, dd, J_{HCCH} = 7.5, J_{PCCCH} = 1.2 Hz).

1-Trideuteriomethyl-1,2,2,3,4,4-hexamethylphosphetanium Bromide (**16**).—About 2 g of the trans isomer **4** was dissolved in 35 ml of 3 *M* sodium deuteroxide solution and heated on a steam bath for 4 days. The solution was acidified and extracted repeatedly with chloroform. The chloroform was dried and evaporated to give a quantitative yield of **4** with a CD_3 substituent on phosphorus trans to the 3-CH_3 group. Reduction and quaternization following previous methods[20] gave the salt **16** (1-CD_3 and 3-CH_3 trans). The position of the label was consistent with the result of a previous study, which indicated that the cis 1-methyl of **16** (note that the word trans in ref 21f must be changed to cis and vice versa because of subsequent stereochemical revision; see ref 21h) underwent H–D exchange more rapidly than the trans 1-methyl in **16**.

1-Benzyl-1,2,2,3,4,4-hexamethylphosphetanium Bromide (**19**).—The corresponding *trans*-1-benzyl-2,2,3,4,4-pentamethylphosphetane[21a] was treated with methyl bromide in benzene–ether to give an 80% yield of the phosphetanium salt. Recrystallization from acetonitrile gave needles, mp 212–218°. The nmr ($CDCl_3$) showed absorption at τ 5.25 (2 H, d, J_{PCH} = 15 Hz), 6.8–7.2 (1 H, m), 7.82 (3 H, d, J_{PCH} = 13.5 Hz), 8.31 (6 H, d, J_{PCCH} = 19 Hz), 8.60 (6 H, d, J_{PCCH} = 19 Hz), 8.98 (3 H, dd, J_{HCCH} = 7.5, J_{PCCCH} ≈ 1 Hz). The elemental analysis was previously performed on a mixture of isomers (**19** plus **20**).[20]

1-Methoxy-2,2,3,3-tetramethylphosphetane 1-Oxide (**30**) and the Corresponding Acid **29**.—To a mixture of 67 g (0.5 mol) of anhydrous aluminum chloride and 69 g (0.5 mol) of phosphorus trichloride in 200 ml of methylene chloride at 0–5°, 49 g (0.5 mol) of 2,3,3-trimethyl-1-butene in 500 ml of methylene chloride was added dropwise with stirring over 3 hr. The mixture was stirred overnight at room temperature and then quenched by pouring it over 400 g of ice. The two layers were quickly separated and the methylene chloride was dried over anhydrous sodium sulfate. Evaporation of the solvent gave 83 g of crude, viscous liquid. Direct hydrolysis of the crude liquid with 4 *M* sodium hydroxide solution gave the phosphinic acid **29** in 60% yield; isolation of the acid was achieved by acidification of the basic, aqueous layer with hydrochloric acid followed by extraction of the product with methylene chloride. The white, crystalline acid **29** was purified by sublimation at 145° (0.1 mm) to give material with mp 186–188°.

The above crude, viscous liquid (phosphinic acid chloride) in 300 ml of benzene was treated with 45 g of triethylamine followed by dropwise addition of 15.3 g of methanol in 125 ml of benzene over 1 hr. The mixture was then brought to reflux for 2 hr. Evaporation of the benzene followed by distillation of the residue gave 40.1 g of solid, platelike material, mp 50–52° (23% overall yield). The ester **30** was recrystallized from petroleum ether and sublimed at room temperature under vacuum (0.2 mm) to give the purified sample, mp 52–55°. The nmr (benzene) showed peaks at τ 6.45 (3 H, d, J_{POCH} = 11 Hz), 9.00 (3 H, d, J_{PCCH} = 19.0 Hz), 8.82 (3 H, d, J_{PCCH} = 19.5 Hz), 9.02 (3 H, s), 9.03 (3 H, s), 7.68–7.98 (2 H, four peaks observed).

Anal. Calcd for $C_8H_{17}O_2P$: C, 54.53; H, 9.73; P, 17.58. Found: C, 54.59; H, 10.02; P, 17.56.

1-Methoxy-2,2,3,3,4-pentamethylphosphetane 1-Oxide (**35**) and **36** and Associated Derivatives **34**, **40**, and **39**.—To a mixture of 13 g (0.1 mol) of anhydrous aluminum chloride and 14 g (0.1 mol) of phosphorus trichloride in 100 ml of methylene chloride, 11.2 g (0.1 mol) of 3,4,4-trimethyl-2-pentene in 100 ml of methylene chloride was added dropwise over 1.5 hr; the mixture was cooled to 0° and stirred during the addition. The mixture was poured over 200 g of ice and the layers were quickly separated. The organic layer was dried and evaporated to give 18.5 g of brown semisolid. Recrystallization from cyclohexane gave 9.8 g (50% yield) of the acid chloride **40**, mp 112–115°. The nmr ($CDCl_3$) showed absorption at τ 6.75 (1 H, dq, J_{HCCH} = 7.5, J_{PCH} ≈ 14.5 Hz), 8.50 (3 H, d, J_{PCCH} = 22.5 Hz), 8.69 (3 H, d, J_{PCCH} ≈ 23 Hz), 8.72 (3 H, dd, J_{HCCH} = 7.5, J_{PCCH} = 26 Hz), 8.90 (6 H, broad singlet).

A mixture of 1 g of **40** and 10 ml of 1 *N* sodium hydroxide was stirred for 12 hr. The mixture was extracted with benzene and the benzene extracts were discarded. The aqueous layer was then acidified with concentrated hydrochloric acid and extracted with methylene chloride. The methylene chloride was dried and evaporated to give 0.8 g of yellow oil which solidified on standing. This material was sublimed several times at 100° (0.1 mm) to give a pure sample of **34**, mp 104–105°.

Anal. Calcd for $C_8H_{17}O_2P$: C, 54.53; H, 9.72. Found: C, 54.29; H, 9.60.

The ester **36** was prepared from **40** using the following procedure. To 0.1 mol of sodium methoxide in 100 ml of dry methanol, 19.5 g (0.1 mol) of **40** in 100 ml of methanol was added over 1 hr. The temperature was maintained at 20° by external cooling. The reaction was stirred overnight, the solvent was evaporated, and the residue was extracted with three 150-ml portions of methylene chloride. Evaporation gave a crude liquid, which was distilled to render 18.5 g of liquid which solidified on standing. This material was recrystallized from petroleum ether to give the hygroscopic, crystalline ester **36**, mp 105–107°. The nmr (benzene) showed peaks at τ 6.32 (3 H, d, J_{POCH} = 10 Hz), 8.77 (3 H, d, J_{PCCH} = 19 Hz), 9.08 (3 H, d, J_{PCCH} ≈ 19 Hz), 9.11 (3 H, dd, J_{HCCH} = 7.5, J_{PCCH} = 21 Hz), 9.2 (6 H, broad peak), 7.4 (1, H, six peaks, J_{HCCH} = 7.5, J_{PCH} ≈ 14.5 Hz).

The stereochemistry of the acid chloride **40** is assumed (by synthetic analogy) to be trans (1-chloro and 4-methyl groups). The formation of the ester **36** from **40** is assumed to go with retention of configuration.

The isomeric acid chloride **39**, present in a mixture with **40**, was prepared by slow, dropwise addition of the acid **34** in benzene to a tenfold excess (mole) of thionyl chloride in benzene at 50–55°. The product was formed in high yield; the nmr showed the presence of both isomers, **40** and **39**. The mixture was dissolved in dry benzene and treated with 1 equiv of triethylamine and methanol at room temperature followed by heating at reflux temperature. The product was distilled, bp 62–65° (0.15 mm); the nmr (benzene) showed two isomeric esters, **35** and **36**, to be present in a 7:3 ratio, respectively. The ester **35** gave a characteristic doublet at τ 6.39 (3 H, d, J_{POCH} = 10.5 Hz) which was upfield from the corresponding doublet of **36** (τ 6.32).

1-Phenyl-1,2,2,3,3,4-hexamethylphosphetanium Bromide (**38**).—The corresponding trans (1-phenyl and 4-methyl) phosphetane[21a] was treated with methyl bromide in benzene–ether solution to give the phosphetanium salt in high yield, mp 198–200°. The ^1H nmr and ^{31}P–^1H decoupled nmr were consistent with the structure and showed only one isomeric compound to be present.

Anal. Calcd for $C_{15}H_{24}BrP$: C, 57.15; H, 7.28; P, 9.84. Found: C, 57.04; H, 7.39; P, 9.79.

The quaternization is assumed[20] to go with retention of configuration to give the trans salt **38** (1-phenyl and 4-methyl are trans).

1-Hydroxy-2,2,3,4-tetramethylphosphetane 1-Oxide (**41**) and Ester (**42**).—The acid chloride precursor to **41** was prepared by the standard, general procedure;[19e,21a] it was obtained in 56% yield by addition of 4,4-dimethyl-2-pentene to phosphorus trichloride and aluminum chloride in methylene chloride. The nmr (benzene solution) indicated that most of the product consisted of a single isomer. The acid chloride, 1.0 g, was treated with 10 ml of 10% sodium hydroxide solution overnight. The reaction mixture was extracted with benzene and the aqueous layer was acidified with concentrated hydrochloric acid. The solution was extracted with methylene chloride. Evaporation of

the solvent gave an oil which solidified on standing. Recrystallization from cyclohexane gave 0.75 g (83%) of the acid **41**, mp 71–74°. The nmr ($CDCl_3$) gave peaks at τ −1.7 (1 H, s), 7.3–8.0 (1 H, m), ~8.8 (3 H, d, J_{PCCH} = 19 Hz), 8.87 (3 H, d, J_{PCCH} = 20 Hz), 8.81 (3 H, dd, $J_{HCCH} \approx 7$, $J_{PCCH} \cong 21$ Hz), ~9.0 (3 H, dd, $J_{HCCH} \cong 7$ Hz), ~8.3–8.9 (1 H, m, partially obscured by overlap).

Anal. Calcd for $C_7H_{15}O_2P$: C, 51.84; H, 9.32. Found: C, 51.96; H, 9.00.

The phosphinic acid chloride was treated with 1 equiv of sodium methoxide solution in methanol; the temperature was kept at 20°. An 85% yield of the ester **42** was obtained, bp 62–63° (0.1 mm). The nmr (benzene) showed the product to be a single isomer: τ 6.35 (3 H, d, J_{POCH} = 10 Hz), 7.28–8.05 (1 H, m), 8.88 (3 H, d, J_{PCCH} = 19 Hz), 8.93 (3 H, d, J_{PCCH} = 18.5 Hz), 8.95 (3 H, dd, J_{PCCH} = 20, J_{HCCH} = 7 Hz), 9.20 (3 H, broad d, J_{HCCH} = 7 Hz). An additional hydrogen was obscured by the upfield methyl signals.

1-Phenyl-2,2,3,4-tetramethylphosphetane 1-Oxide (43) and 1-Phenyl-1,2,2,3,4-pentamethylphosphetanium Iodide (44).—These compounds were prepared by analogous and standard procedures.[20,21a] The oxide was obtained as a viscous liquid in 22% yield by treatment of phenylphosphonous dichloride and aluminum chloride with 4,4-dimethyl-2-pentene in methylene chloride. The nmr (CCl_4) showed peaks at τ 1.9–2.6 (5 H, m), 9.14 (3 H, d, J_{PCCH} = 19.5 Hz), 8.71 (3 H, d, J_{PCCH} = 17 Hz), 8.68 (3 H, dd, J_{PCCH} = 19, J_{HCCH} = 8 Hz), 8.97 (3 H, broad d, $J_{HCCH} \cong 7$ Hz), ~6.3–7.2 (1 H, m), ~7.3–8.1 (1 H, m).

The phosphetane oxide **43** was reduced with trichlorosilane–pyridine in 60% yield and then treated with methyl iodide to give the pure salt **44** in 55% yield. The iodide salt was recrystallized from acetonitrile–ethyl acetate to give pale yellow needles, mp 209–213° dec. The nmr ($CDCl_3$) showed peaks at τ 7.35 (3 H, d, J_{PCH} = 13.5 Hz), 8.37 (3 H, d, J_{PCCH} = 21.0 Hz), 8.74 (3 H, d, $J_{PCCH} \cong 22$ Hz), 8.81 (3 H, dd, J_{HCCH} = 7.5, J_{PCCCH} = 1.3 Hz), 8.44 (3 H, dd, J_{PCCH} = 22, J_{HCCH} = 7.0 Hz), 5.5–6.3 (1 H, m), 6.5–7.3 (1 H, m), 1.5–2.5 (5 H, m, aromatic).

Anal. Calcd for $C_{14}H_{22}IP$: C, 48.29; H, 6.37; I, 36.45. Found: C, 48.36; H, 6.51; I, 36.30.

1-Phenyl-2,2,3,3-tetramethylphosphetane 1-Sulfide (33).—The phosphetane precursor[20] was treated with an excess of sulfur in refluxing benzene for 5 hr. The solution was filtered and the solvent was evaporated to give a residue which was recrystallized from cyclohexane. The purified product (50% yield) had mp 118.5–120.5° after several recrystallizations from petroleum ether. The nmr ($CDCl_3$) gave peaks at τ 1.93–2.8 (5 H, m), 6.6–7.9 (2 H, m), 8.62 (3 H, s), 8.98 (3 H, s), 8.63 (3 H, d, J_{PCCH} = 21.5 Hz), 9.03 (3 H, d, J_{PCCH} = 20.5 Hz).

1-Hydroxy-2,2,3-trimethylphosphetane 1-Oxide (22) and the Corresponding Isomeric Esters 23 and 24.—The acid chloride precursor to **22** was prepared using the generally described procedure;[19e,21a] 3,3-dimethyl-1-butene was employed as the olefin. The acid chloride was quite sensitive to hydrolysis and was obtained as a mixture with the acid **22**. The crude mixture was stirred with saturated sodium carbonate solution overnight; it was then filtered; and the filtrate was acidified with concentrated hydrochloric acid. Extraction with methylene chloride followed by evaporation of the solvent gave **22** as a viscous liquid. The nmr (CH_2Cl_2) was consistent with the expected product: τ −1.9 (1 H, s), 7.02–8.48 (3 H, m), 8.80 (3 H, d, J_{PCCH} = 19 Hz), 8.89 (3 H, d, J_{PCCH} = 20 Hz), 8.97 (3 H, d, J_{HCCH} = 7 Hz).

The acid was treated with thionyl chloride in benzene at 50° and the resultant mixture was converted to a mixture of isomeric esters [bp 40–41° (0.1 mm)] **23** and **24** by the methanol–triethylamine method.[21g] The nmr was in accord with these structures.

Anal. Calcd for $C_7H_{15}O_2P$: C, 51.84; H, 9.32. Found: C, 52.16; H, 9.10.

1,1-Dibenzyl-2,2,3,4,4,4-pentamethylphosphetanium Bromide (21).—The phosphetane precursor was treated with benzyl bromide in ether–benzene to give a 56% yield of the phosphonium **21**, mp 219.5–222.5°, from acetonitrile. The nmr was consistent with the expected structure.

Anal. Calcd for $C_{22}H_{30}BrP$: Br, 19.71. Found: Br, 19.66.

1-Phenyl-3-isopropyl-2,2,4,4-tetramethylphosphetane 1-Oxide (52).—The requisite olefin, 2,4-dimethyl-3-isopropyl-2-pentene, for the synthesis of **52**, was prepared by dehydration of triisopropylcarbinol. The alcohol was made by the slow addition of diisopropyl ketone in dry petroleum ether to isopropyllithium (Alpha Inorganics, Inc.) in pentane at 0–5°. After the addition was complete the solution was treated with saturated ammonium chloride solution. Fractional distillation gave a 50% yield of the desired alcohol, bp 193.5–196°, $n^{22}D$ 1.4475.[45] Dehydration was carried out with anhydrous copper sulfate; the alcohol was heated to 110–120° under vacuum (120 mm) to give a mixture of olefins, bp 148–151°.[23] Glpc analysis (6 ft × 0.25 in. column at 70°, 30% SE-30/Chromosorb) showed two major components. The component (40%) with the longer retention time (7.3 min) was collected. The nmr (neat) was consistent with the desired olefin: τ 7.1–7.6 (2 H, m), 8.32 (6 H, s), 8.98 (12 H, d, J_{HCCH} = 7 Hz).

Anal. Calcd for $C_{10}H_{20}$: C, 85.62; H, 14.38. Found: C, 85.63; H, 14.36.

For the synthesis of **52** the crude mixtures of olefins (directly from the dehydration) was used. This was treated with phenylphosphonous dichloride–aluminum chloride in the usual way;[20] water was added dropwise to the reaction to quench it. The initial product was a viscous liquid; treatment with petroleum ether followed by recrystallization (five times) from this solvent gave the phosphetane oxide **52**, mp 140–142°. The nmr ($CDCl_3$) showed peaks at τ 1.58–2.65 (5 H, m), 8.5 (6 H, d, J_{PCCH} = 16.0 Hz), 8.76 (6 H, d, 19.5 Hz), 9.0 (6 H, d, J_{HCCH} = 6 Hz).

Anal. Calcd for $C_{16}H_{25}OP$: C, 72.69; H, 9.53. Found: C, 72.73; H, 9.40.

It is assumed that the 1-phenyl and 3-isopropyl groups are trans. Quenching the reaction by adding it dropwise to water gave the cis isomer, mp 113–115°.

Registry No.—**1**, 35210-25-4; **2**, 26490-21-1; **3**, 26490-22-2; **4**, 33530-51-7; **5**, 28672-43-7; **6**, 16083-91-3; **6a**, 35624-12-5; **7**, 20047-46-5; **8**, 26674-18-0; **9**, 25145-33-9; **10**, 33530-55-1; **11**, 35624-07-8; **12**, 35624-08-9; **13**, 35624-09-0; **14**, 30664-59-6; **15**, 30664-60-9; **16**, 16084-01-8; **17**, 24436-07-5; **17a**, 35623-38-2; **18**, 35623-39-3; **19**, 35623-40-6; **20**, 35623-41-7; **21**, 31120-05-5; **22**, 35623-43-9; **23**, 34136-12-4; **24**, 34136-11-3; **25**, 34136-10-2; **26**, 34136-09-9; **27**, 35589-66-3; **28**, 35589-67-4; **29**, 35623-47-3; **30**, 35623-48-4; **31**, 16083-92-4; **32**, 16083-99-1; **33**, 35623-51-9; **34**, 35623-52-0; **35**, 35623-53-1; **36**, 35623-54-2; **37**, 35623-55-3; **38**, 35623-56-4; **39**, 35623-57-5; **40**, 35623-58-6; **41**, 35623-59-7; **42**, 35623-60-0; **43**, 35623-61-1; **44**, 35623-62-2; **45**, 4963-91-1; **46**, 703-03-7; **47**, 35623-32-6; **48**, 35623-33-7; **49**, 4963-95-5; **50**, 676-96-0; **51**, 597-50-2; **52**, 35623-35-9.

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Carbon-13 Nuclear Magnetic Resonance of Organophosphorus Compounds. V. The Effect of Changes in Phosphorus Oxidation State in Four-Membered Phosphorus Heterocycles

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^{13}C chemical shifts and ^{13}C–^{31}P nuclear spin coupling constants have been determined for cis and trans isomers of 1-X,1-Y 2,2,3,4,4 pentamethylphosphetanes for X = phenyl, methyl, and chloro and Y = lone pair, methyl, and oxide. The data are interpreted in terms of compound isomerism, exocyclic phosphorus substituents, and formal phosphorus oxidation state. Three types of phosphine → phosphonium salt → phosphetane oxide shift behavior are noted for carbons directly bound to the phosphorus. This divergent behavior is rationalized in terms of competing charge-density and π bond-order contributions to the P(III) → P (IV) shifts. Large (presumable negative) ^{13}C–^{31}P one-bond couplings are present in some of the P(III) compounds and are discussed in terms of modern theories of spin coupling. Several strong stereospecific shifts and couplings are noted, some of which involve atoms which *do not change their relative orientation* within the cis–trans isomer pairs.

The four-membered phosphorus heterocycles, or phosphetanes, are a class of compounds that command sizable current interest in their bonding, steric interactions, and chemical reactions. We have explored the sensitivity and utility of ^{13}C chemical shifts and ^{13}C–^{31}P nuclear spin coupling constants in parts II,[2] III,[3] and IV,[4] particularly as a function of methyl substituents bound to the ring atoms. Most of the data thus far have been obtained on phosphetanium salts and phosphetane oxides possessing four-coordinate phosphorus. The data clearly pointed out a greater sensitivity to ring methyl substitution and exocyclic phosphorus substitution than phosphorus "oxidation state." To explore the importance of changes in phosphorus bonding we have now examined some P(III) analogs, and can draw some conclusions concerning the role of phosphorus oxidation state and the corresponding sensitivity of the ^{13}C nmr parameters.

Experimental Section

^{13}C spectra were obtained on a Varian HA-100 spectrometer operating at 25.14 MHz in a field/frequency locked mode. The instrument was controlled by a Varian 620-i 8K computer which also served for time averaging. A Varian V-3512-1 provided a noise-modulated proton decoupling rf field which eliminated C–H splittings in the ^{13}C spectra. The V-4335-1 probe accommodated spinning 8-mm tubes and was double-tuned for 25 and 100 MHz. The field/frequency lock signal was derived from the resonance of 60% enriched $^{13}CH_3I$ contained in a sealed 2-mm-o.d. capillary tube supported by teflon collars which could be inserted in the sample tube. Chemical shifts and coupling constants were taken from computer readouts of from usually 10 to 100 spectral accumulations for signal enhancement and accurate peak placement. The line positions were determined to ±0.1 Hz by direct frequency counting of peaks in scans usually 25–50 Hz in width. Scanning rates were normally 1–3 Hz/sec.

Some of the data were taken using a modification of the standard Varian equipment. In these situations the ^{13}C center band was derived from a 251-MHz signal generated by a Hewlett-Packard 500-MHz synthesizer. This 251-MHz signal, digitally divided by ten and amplified, replaced the crystal-generated rf frequency in the V-4311 rf unit. The analytical frequency sweep was also replaced by a computer-driven Wavetek voltage-controlled oscillator. Using this option, the Varian 620-i computer generates a digital voltage ramp which, under software control, is keyed to the memory locations. The Wavetek oscillator was stable to ±0.1 Hz over a period of hours.

The oxides were run as saturated solutions (1–2 *M*) in $CHCl_3$. The salts (X = CH_3, C_6H_5) were run as saturated solutions in water; the chloro salts were run in a CH_2Cl_2:CH_3Cl mixture. The ambient probe temperature was not measured under proton decoupling but was usually significantly higher than room temperature. The chemical shifts of the P(III) compounds are referenced to ~10% internal tetramethylsilane-^{13}C (natural abundance) contained in the neat samples.

All the salt and oxide data have been converted to the TMS-^{13}C scale by subtracting 20.97 ppm[3] from the shift from the $^{13}CH_3I$ present in the lock capillary. Positive shifts are defined as low-field or deshielded chemical shifts.

Assignments of the P(III) resonances were made on the basis of intensity and peak behavior under low-power off-resonance proton noise decoupling. This technique distinguishes quaternary carbons from those having proton substituents. The assignments of the salts and oxides for X = C_6H_5 and X = CH_3 have been documented in part III.[3] Assignments for *cis*- and *trans*-1-chloro-1,2,2,3,4,4 hexamethylphosphetanium tetrachloroaluminate were made using the C-3 and C-7 methyl shift and coupling stereospecificities noted for P(IV) salts in part III. The C-7 methyl and PCH_3 carbons were distinguished by the broader PCH_3 resonance. The latter's proton shift is significantly higher than typical proton methyl shifts and thus was not decoupled as efficiently by the noise decoupler. The small available amounts of these materials precluded more definitive off-resonance coherent decoupling experiments.

The preparation of the cis and trans isomers of 1-phenyl-2,2,3,4,4-pentamethylphosphetane was reported earlier.[5] It should be noted that the isomer assignments in that paper have been reversed as a result of later work.[6]

Cis and Trans Isomers of 1,2,2,3,4,4-Hexamethylphosphetane.—The preparation of a predominance of *trans*-1,2,2,3,4,4-hexamethylphosphetane in benzene solution has been described.[6] A 7:3 (cis:trans) mixture was prepared by treatment of a 7:3 (trans:cis) mixture of 1-chloro-2,2,3,4,4-pentamethylphosphetane (see below) in ether solution at 30° with methyllithium; the reaction went with inversion of configuration about phosphorus.[7] The pure product was obtained in 35% yield upon aqueous work-up of the reaction mixture and subsequent distillation, bp 36–40° (4.5 mm). The ^1H nmr (neat) of the trans isomer (1- and 3-methyl groups) showed peaks (TMS standard) at τ 7.46 (1 H, q, J_{HCCH} = 7.5 Hz), 8.90 (6 H, d, J_{PCCH} = 17.5 Hz), 8.91 (3 H, d, J_{PCH} = 3 Hz), 9.13 (6 H, d, J_{PCCH} = 7 Hz), and 9.36 (3 H, d, J_{HCCH} = 7.5 Hz). The cis isomer showed absorption at τ 7.88 (1 H, dq, J_{HCCH} = 7.5, J_{PCCH} = 2.5 Hz), ~8.95 (6 H, d, $J_{PCCH} \cong$ 17 Hz), ~9.07 (3 H, d, $J_{PCH} \cong$ 3 Hz), 9.05 (6 H, d, $J_{PCCH} \cong$ 6 Hz), and 9.29 (3 H, dd, J_{HCCH} = 7.5, J_{PCCCH} = 1.0 Hz).

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Preparation of a Cis and Trans Mixture of the 1-Chloro-1,2,2,-3,4,4-hexamethylphosphetanium Tetrachloroaluminate Salts.—The isomeric mixture of salts was prepared by treatment of 2,4,4-trimethyl-2-pentene with methylphosphonous dichloride–aluminum chloride in methylene chloride by a previously described procedure;[5] the intermediate tetrachloroaluminate salts were isolated prior to the quench with water. The solvent was evaporated and the product was recrystallized from dry acetonitrile (minimum) and dry diethyl ether. All work-up procedures were carried out in a glove box under nitrogen and strictly anhydrous conditions. The isomeric salts had mp 225–250° dec.

Anal. Calcd for $C_9H_{19}AlCl_5P$: C, 29.82; H, 5.28; Cl, 48.91; P, 8.55. Found: C, 29.67; H, 5.57; Cl, 48.72; P, 8.33.

1-Chloro-2,2,3,4,4-pentamethylphosphetane 1-Sulfide.—To 57 g (0.29 mol) of freshly recrystallized acid chloride[8] in a 500-ml flask equipped with an air condenser and drying tube was added 25 g (0.11 mol) of phosphorus pentasulfide. The mixture was rapidly heated to 150–155° and maintained at that temperature for 6 hr. The air condenser was replaced by a Dry Ice condenser with a vacuum take-off. The solid product sublimed on the cold finger when aspirator vacuum was applied; the mixture was maintained at 150–170°. The product was periodically removed and the process was continued until no further sublimate was collected. The combined material was recrystallized from about 50 ml of petroleum ether (bp 30–60°); the solution was cooled in a refrigerator and then filtered to give 32 g of an isomer mixture of thioacid chlorides, mp 113–120°. An additional 6.5 g was obtained by concentration of the mother liquors. The nmr spectrum (benzene) of the major isomer showed peaks at τ 8.85 (6 H, d, J_{PCCH} = 24.8 Hz), 8.89 (6 H, d, $J_{PCCH} \cong$ 23 Hz), 9.43 (3 H, dd, J_{HCCH} = 7, J_{PCCH} = 1.2 Hz) and that of the minor isomer at τ 8.78 (6 H, d, J_{PCCH} = 24.9 Hz), 8.91 (6 H, d, $J_{PCCH} \cong$ 23 Hz), 9.36 (3 H, dd, J_{HCCH} = 7, $J_{PCCH} \cong$ 1 Hz). The ring hydrogen for the isomers overlapped at τ 7.8–8.35 (1 H, m). The isomer ratio was *ca.* 2:1.

Anal. Calcd for $C_8H_{16}ClPS$: C, 45.60; H, 7.65. Found: C, 45.94; H, 7.25.

1-Chloro-2,2,3,4,4-pentamethylphosphetane.—A mixture of 28 g (0.13 mol) of the phosphetane sulfide and 53 g (0.2 mol) of triphenylphosphine was heated at 230° in a flask equipped with a distillation head and nitrogen capillary bleed (extended below the surface of the liquid). A rapid stream of nitrogen was passed directly into the hot mixture. The nitrogen flow gradually carried over the product into a cold receiver; the distillation head was heated with a heat gun to accelerate product collection. The distillate was redistilled through a 12-in. Vigreux column to give a colorless liquid, bp 36–38° (0.1 mm) [lit.[7] bp 87° (20 mm)], in 90% yield. The nmr (neat) showed an isomer ratio of 2:1 (trans:cis). The trans isomer gave peaks at τ 7.20 (1 H, dq, J_{HCCH} = 7.5, J_{PCCH} = 1.5 Hz), 8.78 (6 H, d, J_{PCCH} = 21 Hz), 8.86 (6 H, d, J_{PCCH} = 7.5 Hz), 9.23 (3 H, d, J_{HCCH} = 7.5 Hz). The cis isomer showed τ 7.81 (1 H, dq, $J_{HCCH} \cong$ 7, $J_{PCCH} \cong$ 2.5 Hz), 8.80 (6 H, d, $J_{PCCH} \cong$ 21 Hz), 8.83 (6 H, d, J_{PCCH} = 6 Hz), 9.12 (3 H, dd, $J_{HCCH} \cong$ 7, $J_{PCCH} \cong$ 1 Hz).

Anal. Calcd for $C_8H_{16}ClP$: C, 53.80; H, 9.03. Found: C, 53.91; H, 9.07.

Results

There are three actual variables: cis–trans isomerism, exocyclic phosphorus substituent X, and phosphorus oxidation state. There are definite stereospecificities evident in the data (Tables I and II) but they are highly dependent on phosphorus oxidation state. In the P(III) phosphines the C-2/C-4 shifts are uniformly higher for the cis isomer by 2–4 ppm. The other two types of phosphorus-bound carbon show mixed behavior in this regard. The dependence on isomerism is greatly attenuated in going to the salts or oxides for all directly bonded carbons. The C-3 shift is sensitive to isomerism, especially for the oxides, while the α methyls on C-2 and C-4 show stereospecific shifts in the P(III) compounds. A pronounced stereospecific effect is evident in the ortho (C-13) carbon shift in the P(III) isomers for X = phenyl. Effects such as these in one-bond couplings to exocyclic phosphorus substituents and three-bond couplings to C-7 in the salts and oxides were discussed in parts II[2] and III.[3] Although there are definite isomer-dependent one-bond couplings in the P(III) compounds, no pattern is yet evident. However, the α-methyl two-bond couplings, essentially insensitive to isomerism in the salts and oxides, clearly reflect their cis–trans nature with respect to the exocyclic phosphorus substituent in the P(III) compounds.[4] It is assumed that the signs of the one- and two-bond couplings, and probably the three-bond couplings, reverse in the transition P(III) → P(IV) or "P(V)", as pointed out by McFarlane.[9] The stereospecificities are not simply related to the number of bonds between the coupled nuclei, since the coupling for C-3 does not show isomer dependence. The C-7 couplings are sensitive to isomer in the P(III) compounds, especially where carbon is present as the exocyclic atom bound to phosphorus.

The data, in general, roughly support additivity of substituent effects, although there are several serious reversals. While the P(III) C-2/C-4 shifts for X = Cl and X = C_6H_5 are very close, they diverge by 10 ppm for the oxides. Chemical shift substituent effects seem more additive for salt → oxides. The chloro substituent seems to give the greatest deviations from additivity, while the shifts for the phenyl and methyl substituents generally follow one another. Even within these cases there are, however, instances of deviation of several parts per million.

The C-2/C-4 coupling oxidation state trends do not follow one another very closely, especially for the cis isomer. However, there is good uniformity in the trends for the α methyls. Serious reversals are present in the C-7 coupling trends.

The most interesting changes are those for P(III) → P(IV). The P(III) → P(IV) values range from 17 ppm for C-2/C-4, through −2 ppm for PCH_3, to −19 ppm for C-12. The α methyls trans to the lone pair show minimal variation in shift with phosphorus oxidation state, probably reflecting attenuated inductive effects, while the α methyls cis to the lone pair show an increased shift. Nowhere does a change in phosphorus oxidation state result in such a meteoric change than in the directly bonded couplings of C-2/C-4, PCH_3, and C-12. In contrast to the variety of trends in their shifts, no disparity occurs here for the coupling trends, but there is a spread in sensitivity for the average of P(III) → P(IV) with 51 Hz for C-2/C-4, 68 Hz for PCH_3, and 93 Hz for C-12.

Discussion

Chemical Shifts.—^{13}C chemical shifts have been treated theoretically by a number of approaches,[10–17]

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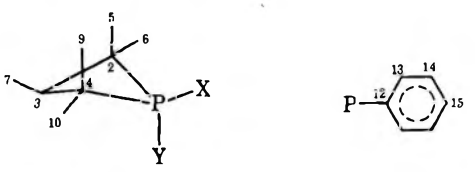
TABLE I

^{13}C CHEMICAL SHIFTS[a]

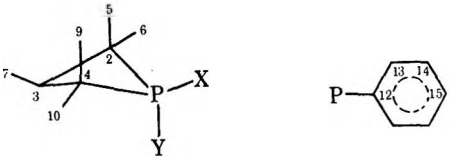


Registry no.	Y	X	C-2/C-4	C-12	PCH$_3$	C-3	C-5/C-9	C-6/C-10	C-7	C-13[d]	C-14[d]	C-15
16083-95-7	C_6H_5		30.22	137.71		54.02	26.24	26.52	9.96	135.11	127.57	128.16
35621-97-7	CH_3		26.37		6.74	51.43	25.06	25.00	9.31			
25145-24-8	Cl		31.65			51.55	22.04	25.48	9.36			
22434-51-1		C_6H_5	34.52	140.09		49.70	20.92	32.71	8.12	129.50	127.64	126.15
35622-00-5		CH_3	28.61		5.23	51.13	19.16	32.46	8.65			
25145-23-7		Cl	35.10			48.04	19.53	30.00	8.94			
35616-93-4	C_6H_5	CH_3[b]	41.41	119.15	5.93	53.49	20.57	25.43	9.69	135.01	131.28	135.79
35616-94-5	CH_3	CH_3[b]	38.07		*c*	51.42	18.96	24.43	8.75			
35616-95-6	Cl	CH_3	48.25		10.11	52.89	19.54	25.49	13.45			
35616-96-7	CH_3	C_6H_5[b]	42.11	120.68	6.90	50.43	20.17	24.94	8.08	133.81	131.55	135.65
35616-97-8	CH_3	Cl	48.38		9.72	50.55	19.82	24.54	11.74			
16083-91-3	C_6H_5	O[b]	46.68	129.94		44.88	18.90	24.00	7.33	133.32	128.85	132.33
33530-51-7	CH_3	O[b]	45.41		9.79	42.61	17.28	24.71	7.31			
26674-18-0	Cl	O[b]	57.35			42.79	18.27	26.09	7.37			
20047-46-5	O	C_6H_5[b]	46.45	131.88		48.03	20.41	24.81	8.69	132.65	129.12	132.37
28672-43-7	O	CH_3[b]	44.05		11.47	46.89	19.83	24.66	9.71			
25145-33-9	O	Cl[b]	57.05			46.20	20.74	24.50	9.38			

[a] In parts per million relative to TMS-^{13}C. Shifts are accurate to ±0.01 ppm when comparing carbons in the same molecule. Solvent, concentration, and bulk susceptability changes from sample to sample will reduce accuracy of comparison to probably ±0.2 ppm. A positive shift represents a higher frequency (downfield) shift or deshielding of the carbon atoms. [b] Data from ref 3. Data for the phosphetanes [P(III) compounds] are internally referenced while the salts and oxides are referenced originally to the $^{13}CH_3I$ in the lock capillary and have been corrected to the TMS-^{13}C scale by subtracting 20.97 ppm.[3] [c] Y methyl shift 4.15 ppm, X methyl shift 4.94 ppm. [d] Assignments for P(III) C-13 and C-14 made on the basis of the large differences in ^{13}C–^{31}P couplings (Table II). See F. J. Weigert and J. D. Roberts, *J. Amer. Chem. Soc.*, 91, 4940 (1969).

TABLE II

^{13}C–^{31}P NUCLEAR SPIN COUPLING CONSTANTS[a]



Y	X	C-2/C-4	C-12	PCH$_3$	C-3	C-5/C-9	C-6/C-10	C-7	C-13	C-14	C-15
C_6H_5		−5.9	−41.3		2.7	31.8	2.5	0.0	20.2	6.6	1.1
CH_3		−7.7		−33.7	3.3	30.5	2.1	0.0			
Cl		−7.8			2.1	37.1	0.0	2.4			
	C_6H_5	−2.6	−42.8		5.9	4.9	27.8	13.5	13.1	2.9	1.8
	CH_3	−6.5		−37.9	2.9	4.3	26.9	8.9			
	Cl	−11.1			7.8	2.5	33.5	1.8			
C_6H_5	CH_3[b]	45.2	54.9	31.1	10.2	2.1	3.7	17.6	8.5	11.7	0.0
CH_3	CH_3[b]	45.2		*c*	11.2	2.5	3.7	18.1			
Cl	CH_3	35.5		20.1	6.3	0.0	6.6	12.0			
CH_3	C_6H_5[b]	45.3	48.9	35.9	10.5	3.1	3.4	22.2	8.5	11.3	0.0
CH_3	Cl	48.1		19.7	9.8	5.8	3.0	17.9			
C_6H_5	O[b]	58.7	59.5		6.2	4.6	3.5	23.1	9.0	9.7	2.9
CH_3	O[b]	59.4		40.9	6.3	4.6	3.6	23.0			
Cl	O[b]	56.8			1.6	3.8	6.8	30.1			
O	C_6H_5[b]	58.4	54.5		11.2	1.3	4.6	16.9	8.8	10.1	2.7
O	CH_3[b]	59.4		36.9	10.0	2.2	4.4	12.6			
O	Cl[b]	55.4			1.8	5.4	5.3	20.5			

[a] To ±0.1 Hz. Signs are assigned based on McFarlane's determination of signs in representative compounds.[9] [b] Data from ref 3. [c] Y methyl 34.7 Hz, X methyl 29.1 Hz.

TABLE III

^{13}C SHIFT AS A FUNCTION OF NEIGHBOR ATOM OXIDATION STATE[a]

	P(III) → P(IV) Values, ppm					
	C_α	C_β	C_γ	C_δ	δ (PCH_3), ppm	Ref
$(Me)_3P \rightarrow (Me)_4P^+$	−5.1				20.7 → 15.6	*b*
$(Et)_3P \rightarrow (Et)_4P^+$	−7.0	−3.7				*b*
$(n\text{-Bu})_3P \rightarrow (n\text{-Bu})_4P^+$	−6.3	−5.2	−3.9	−0.9		*c*
$(n\text{-Bu})_3P \rightarrow (n\text{-Bu})_3PCH_3^+$	−4.6	−5.2	−4.1	−0.7	→ 5.0	*c*
$(Ph)_3P \rightarrow (Ph)_3PCH_3^+$	−18.8	−1.3	1.0	5.6	→ 9.4	*c, d*
$(Me)_2PhP \rightarrow (Me)_2PhPH^+$	−8.4 (methyl)				21.1 → 12.7	*b*
$(Me)_3N \rightarrow (Me)_4N^+$	9.2				47.2 → 56.4	*e*
Py → Py H^+	−7.8					*f*
	P(IV) → "P(V)" Values, ppm					
$(Me)_4P^+ \rightarrow (Me)_3PO$	3.3				15.6 → 18.6	*b, g*
$(Et)_4P^+ \rightarrow (Et)_3PO$	4.2	6.0				*b, g*

[a] Me = methyl, Et = ethyl, *n*-Bu = *n*-butyl, Ph = phenyl, Py = pyridine. All shifts have been placed on the TMS-^{13}C scale by using the shift of 128.4 ppm for benzene and 198.5 ppm for the carbonyl carbon of acetic acid. [b] Reference 9. [c] Reference 22. [d] H. J. Jakobsen and O. Manscher, *Acta Chem. Scand.*, 25, 680 (1971). [e] H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, 33, 1888 (1960). [f] Reference 25. [g] Reference 3.

starting from Ramsey's formulation[18] and employing approximations thereto. Recently, Mason[19] has questioned the usual assumption that the diamagnetic contribution, σ_d, to the ^{13}C chemical shift varies negligibly when carbon substituents are changed. Based on a predictive relationship for σ_d formulated by Flygare and Goodisman,[20] Mason corrected the observed shifts for variations in σ_d and analyzed the resulting σ_p's in terms of variations in the average excitation energy. Ditchfield, *et al.*,[21] using *ab initio* techniques, have calculated σ_d and σ_p contributions to ^{13}C shifts. However, the primary burden for changes in shielding was placed on changes in carbon orbital size through inductive charge withdrawal.

The phosphetane shifts can be analyzed in terms of the above ideas. No change in substitution occurs for any of the carbons in going from phosphine to salt or oxide. Therefore, any change in σ_d for phosphorus-bonded carbon should be negligible, since substituent Z/r values are essentially unchanged.[20] The observed changes in phosphorus-bonded carbon shifts should reflect only changes in σ_p. The same holds in the other carbons, of course, since they are more than one bond away.

All of the phosphorus-bonded carbons behave similarly in the salts and oxides. However, when P(III) → P(IV) is considered, opposite sensitivities are apparent. Relevant data on other compounds are presented in Table III. The acyclic data serve as "normal" benchmarks for oxidation state dependence. The only cyclic compounds on which pertinent data have been accumulated are phosphacyclopentane[22] and 1-phenylphosphacyclopentane 1-oxide,[3] a phosphine–oxide pair if replacement of a hydrogen by phenyl is ignored. The C-2/C-4 change of −1.2 ppm in this pair is very far removed from the large positive values in the phosphetanes. Clearly, the C-2/C-4 shifts are sensitive to electronic effects in a different way from the exocyclic phosphorus-bound carbons, even though this electronic effect is propagated through phosphorus. Since this electronic influence is thus anisotropic, it cannot be described by a simple change of effective electronegativity of phosphorus resulting from change in the Y group, and no arguments based on simple inductive charge density polarization can accommodate *opposing* effects at atoms *geminal* to the inductive center. If *no* double-bond character is present in C-2/C-4 bonds to phosphorus, then the large positive P(III) → P(IV) values for C-2/C-4 could result from inductive charge withdrawal by Y *via* the phosphorus, and all the phosphorus-bonded carbons should experience at least a polarization of the same direction, if not the same magnitude. Then, the large negative P(III) → P(IV) value for C-12 could result from offsetting this *positive* charge density contribution by a still larger *negative* contribution *via* loss of double-bond character[17] present in the P(III) compound. Since normal $alk_2PCH_3 \rightarrow alk_3PCH_3^+$ P(III) → P(IV) values for PCH_3 are in the region of −5 to −9 ppm, the smaller P(III) → P(IV) value for PCH_3 in the phosphetanes could simply imply that the effect of the cyclic nature of the other phosphorus substituents is to place more charge density on the exocyclic PCH_3 than in acyclic counterparts. This has some experimental backing in that the exocyclic PCH_3 have chemical shifts which are smaller than those in $P(CH_3)_3$ by ~14–15 ppm. Based on steric contributions to ^{13}C shifts alone,[23] the carbons in $P(CH_3)_3$ should have a smaller shift since their steric interactions should be significantly larger. Thus, in going to the P(IV) compounds the charge density variation is greater for the exocyclic PCH_3 than for $P(CH_3)_3$, and a corresponding positive P(III) → P(IV) contribution is made to the total shift. Loss of partial double-bond character in P(III) → P(IV) would then have to make a contribution of similar magnitude but opposite in sign[17] to achieve a small net P(III) → P(IV) value. This large contribution from partial double-bond character in the P(III) compounds with exocyclic phosphorus-bound phenyl may indicate a more planar arrangement around the phosphorus than in the oxides or salts. Unfortunately, there have been no X-ray studies of P(III) phosphetanes.

The N(III) → N(IV) value for $(CH_3)_3N$ is positive

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(23) D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, **89**, 6612 (1967); D. M. Grant and B. V. Cheney, *ibid.*, **89**, 5315 (1967).

while the analogous value for $P(CH_3)_3$ is negative. Again a reversal is noted for the α carbon in pyridinium ion. The former is to be expected on charge density grounds but the latter was explained[24] by invoking variations in ΔE. In these cases the shift of one type of carbon was rationalized by a change in one parameter, but it is difficult to explain the three types of sensitivity observed here for directly bonded carbons by variation of one parameter.

The other phosphetane ring carbon, C-3, has a shift which is most sensitive for oxide → salt and about 2–3 times as sensitive in the trans isomer as in the cis isomer. The α-methyl shifts could be explained on the basis of steric interaction with the exocyclic phosphorus substituent cis to the α methyl, which is not present in the P(III) compound. This steric crowding is present in all the compounds except for the α methyls C-5/C-9 in trans isomers and C-6/C-10 in cis isomers. On this basis the steric contribution to the shifts of the α methyls in the other cases would be ~ -6 ppm.[25] C-7 is apparently not sensitive to phosphorus oxidation state, except for the P(IV) chloro compound. No explanation is apparent for the deviation.

^{13}C–^{31}P Coupling Constants.—There has been much activity in the last decade expended toward the understanding and prediction of nuclear spin couplings. Fairly little work, in comparison, has been directed toward nuclei other than protons, and most of this has been centered on couplings of protons to other nuclei. A detailed coverage of previous theories and calculations was given in part I.[26] In particular, considerable attention was paid to the relatively little work that has been done investigating ^{13}C–^{31}P couplings. The only available theoretical treatments of ^{13}C–^{31}P couplings have been by Cowley and White,[27] who calculated ^{13}C–^{31}P couplings in CH_3PH_2, CF_3PH_2, and $CH_3PH_3^+$ by a parametrized LCAO–SCF–MO theory in the Pople–Santry[28] approximation; Jameson and Gutowsky,[29,30] who developed a qualitative model of spin coupling based on the Fermi contact and "core electron polarization" contributions to spin coupling; and Gray (part I),[27] who used the finite perturbation–INDO–SCF–MO theory of Pople, McIver, and Ostlund[31] for ^{13}C–^{31}P couplings in a series of phosphonates $(C_2H_5O)_2P(O)CH_2X$. Here the relationship between "s character" and ^{13}C–^{31}P couplings was examined and it was found that the coupling followed the calculated bond order but varied about twice as fast. The site of variable substitution was on the phosphonate carbon as opposed to the phosphorus itself as in the phosphetanes. The relationship between one-bond couplings and the C_{2s}–P_{3s} bond order in this different kind of bonding situation is as yet unexplored. However, analogous treatments of spin coupling involving carbon[31,32] offer good promise that changes in coupling involving carbon, especially for carbons not undergoing substitution, reflect to some degree the changes in valence s orbital bond order between the directly bonded atoms, provided that the Fermi contact mechanism is dominant.

The C-2/C-4 couplings to P(III) are small and probably negative. However, the exocyclic P(III) substituents, whether methyl or phenyl, have a coupling of relatively large magnitude. Large negative one-bond ^{13}C–^{31}P couplings have been found recently for $(t\text{-Bu})_2PF$ (−34.6 Hz)[33] and CH_3PCl_2 (−45 Hz).[34] It is reasonable to assume that the exocyclic carbon couplings are negative, as all ^{13}C–^{31}P(III) directly bonded couplings have been found to date. If contributions from "core-polarization" are always small[28,29] then a surprisingly sizable Fermi contact contribution of negative sign must be present.

Although the C-2/C-4 and PCH_3 one-bond couplings are apparently very different in magnitude, the oxidation state behavior makes them look very similar, apart from a constant offset of ~20 Hz. The large difference between phosphine → salt and salt → oxide behavior indicates a substantial change in bonding character for the former, but much less for the latter. This may support the frequent assertion that phosphine oxides are really more like P^+–O^- than P=O.

Additivity ideas certainly suffer in considering the C-2/C-4 couplings. The couplings vary depending on X substituent and isomer. Of particular note is the large stereospecificity in C-2/C-4 coupling for X = Cl in the P(IV) compounds. If the correlation of ^{13}C–^{31}P coupling and P_{3s}–C_{2s} bond order has at least some validity for four-coordinate phosphorus, this difference then shows a significant decrease in P_{3s} orbital character in the C-2/C-4 phosphorus bonds in the cis isomer with respect to the trans isomer.

Of special significance are the large negative couplings for exocyclic P(III) PCH_3 and C-12. No halogen atoms[33,34] are used here to effect the change from what one would consider to be the "normal" small negative values. Even if further experimental work shows the C-12 and P-CH_3 couplings to be of positive sign, the large magnitudes will still be exceptional for P(III)-bound carbon and provide a very stringent test for theoretical prediction.

The two-bond couplings exhibit a large stereospectivity in α-methyl couplings which is analogous to that previously found for PCH two-bond couplings.[35] The only three-bond phosphetane ring carbon coupling is that for C-7. It is sensitive to both X substituent and isomer and difficult to rationalize. It is important

(24) A. J. Jones, D. M. Grant, J. G. Russell, and G. Fraenkel, *J. Phys. Chem.*, **73**, 1624 (1969).

(25) There does seem to be other evidence for this in comparing 1-phenyl-2,2,3,4,4-pentamethylphosphetane 1-oxide to 1-phenyl-2,2,4,4-tetramethylphosphetane 1-oxide. Here the C-5/C-9 shift (averaged over both isomers) in the latter is about 5.3 ppm smaller than the C-5/C-9 shift in the former (unpublished results). The pseudoequatorial C-7 methyl that is removed is analogous to the pseudoequatorial phosphorus-bound methyl removed in going from P(IV) to P(III).

(26) Part I: G. A. Gray, *J. Amer. Chem. Soc.*, **93**, 2132 (1971).

(27) A. H. Cowley and W. D. White, *ibid.*, **91**, 1917 (1969).

(28) J. A. Pople and D. P. Santry, *Mol. Phys.*, **8**, 1 (1964).

(29) C. J. Jameson and H. S. Gutowsky, *J. Chem. Phys.*, **51**, 2790 (1969).

(30) C. J. Jameson and H. S. Gutowsky, *J. Amer. Chem. Soc.*, **91**, 6232 (1969).

(31) J. A. Pople, J. W. McIver, Jr., and N. S. Ostlund, *Chem. Phys. Lett.*, **1**, 456 (1967); (b) J. A. Pople, J. W. McIver, Jr., and N. S. Ostlund, *J. Chem. Phys.*, **49**, 2960, 2965 (1968); N. S. Ostlund, M. D. Newton, J. W. McIver, Jr., and J. A. Pople, *J. Magn. Resonance*, **1**, 185 (1969).

(32) G. E. Maciel, J. W. McIver, Jr., N. S. Ostlund, and J. A. Pople, *J. Amer. Chem. Soc.*, **92**, 1, 11, 4151, 4497, 4506 (1970); P. D. Ellis and G. E. Maciel, *ibid.*, **92**, 5829 (1970).

(33) C. Schumann, H. Dreeskamp, and O. Stelzer, *Chem. Commun.*, 619 (1970).

(34) J. P. Albrand and D. Gagnaire, *Chem. Commun.*, 874 (1970).

(35) (a) J. P. Albrand, D. Gagnaire, and J. B. Robert, *Chem. Commun.*, 1469 (1968); (b) L. D. Hall and R. B. Malcomb, *Chem. Ind. (London)*, 92 (1968); (c) G. Mavel, *J. Chim. Phys.*, **65**, 1692 (1968); (d) J. P. Albrand D. Gagnaire, J. Martin, and J. B. Robert, *Bull. Soc. Chim. Fr.*, 40 (1969); (e) L. D. Quin and T. P. Barket, *J. Amer. Chem. Soc.*, **92**, 4303 (1970); (f) W. G. Bentrude and J. H. Hargis, *ibid.*, **92**, 7136 (1970); (g) J. P. Albrand D. Gagnaire, M. Picard, and J. B. Robert, *Tetrahedron Lett.*, 4593 (1970).

to remember that differences in C-2/C-4, C-3, and C-7 coupling between isomers are present *even though the relative spatial orientation of the coupled atoms remains the same.* It is not a case of dehedral angle dependence, as it is for the α methyls. No satisfactory general model for this has emerged. The utility of the stereospecificities need not be hampered by lack of understanding of their precise mechanisms. Isomer identification is made quite easily, especially for the P(III) compounds, using the α-methyl stereospecificities.

Registry No.—1-Chloro-2,2,3,4,4-pentamethylphosphetane 1-sulfide, 35623-65-5 (isomer A), 35623-66-6 (isomer B).

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Investigations of Doubly Connected Phosphorus Cations. Diaminophosphenium Ions from 2-R-2-Phospha-1,3-diazacyclohexanes[1]

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Mass spectral analysisof a series of *N,N'*-dimethyl-2-R-2-phospha-1,3-diazacyclohexanes (R = Cl, OCH_3, CH_3, C_2H_5, C_6H_5) reveals a primary fragmentation pathway affording loss of the phosphorus R group and generation of a divalent phosphenium species as the major (base) fragment. Diequatorial orientation of the *N*-alkyl groups is important to stabilization of the cations, as deduced from the failure of certain bicyclic derivatives to provide phosphenium ions when the *N*-alkyl groups are locked in axial positions. Treatment of 2-chloro-2-phospha-1,3-diazacyclohexanes with PCl_5 gave an ionic species which is best interpreted (pmr, ^{31}P nmr, conductance measurements) in terms of a doubly connected phosphorus cation salt.

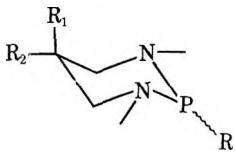
Higher and lower valent cations of many nonmetallic elements (*i.e.*, carbon, halogen, sulfur, nitrogen) have been well recognized and occupy a fundamental place in mechanistic organic chemistry with recent attention being given to pentavalent carbocations (carbonium ions)[2] and divalent nitrenium ions.[3] Somewhat surprisingly, however, very little is known of the behavior, or even existence, of lower valent phosphorus cations (phosphenium ions[4]), although tetracoordinate phosphonium species have played a significant role in phosphorus chemistry for many years.

In the course of conformational analysis studies on 2-R-2-phospha-1,3-diazacyclohexanes,[5] electron impact spectra were recorded as an aid to characterization of these compounds. The observation of a primary fragmentation pathway leading to extremely stable divalent phosphorus cations prompted further exploration in this area, with interest in the factors governing the stability of such cations and possible implications of such species in the mechanisms of trivalent organophosphorus reactions.

Results and Discussion

Diaminophosphenium Ions in the Mass Spectrometer.—The mass spectrum of phosphorus trichloride has been reported to display PCl_2^+ as the most abundant positive ion with a low appearance potential of approximately 12 eV.[6] Other trivalent phosphorus compounds, *e.g.*, $(CH_3)_3P$,[6] Ph_2PCl,[7] and $(Me_2N)_3P$,[7] also give rise to varying populations of divalent positive species by loss of one ligand. However, it is uncommon for the relative abundance of divalent ions derived in this fashion to be very large if further fragmentations are readily achievable;[8] that is, the significance of a high abundance of an individual ion becomes much greater as its opportunity for further decomposition is increased.[9] Along this line, triethylphosphine readily expels ethylene to form $PH(C_2H_5)_2^+$ in abundant amounts, rather than giving up an ethyl group to form the divalent ion, $P(C_2H_5)_2^+$.[10]

On the contrary, electron-impact spectra at 70 eV of various 2-R-2-phospha-1,3-diazacyclohexanes (**1**) bearing phenyl, ethyl, chloro, methyl, and methoxy substituents on phosphorus have disclosed a primary



1a, $R_1 = R_2 = H$; $R = C_6H_5$
b, $R_1 = R_2 = CH_3$; $R = C_6H_5$
c, $R_1 = H$; $R_2 = CH_3$; $R = C_6H_5$
d, $R_1 = R_2 = H$; $R = C_2H_5$
e, $R_1 = R_2 = CH_3$; $R = C_2H_5$
f, $R_1 = H$; $R_2 = CH_3$; $R = C_2H_5$
g, $R_1 = R_2 = H$; $R = Cl$
h, $R_1 = R_2 = CH_3$; $R = Cl$
i, $R_1 = R_2 = H$; $R = OCH_3$
j, $R_1 = R_2 = R = CH_3$

(1) Extracted from the Ph.D. Thesis of B. E. M., Drexel University, June 1972.

(2) See G. A. Olah, *J. Amer. Chem. Soc.*, **94**, 808 (1972), and references cited therein.

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

(4) This nomenclature follows the system promoted by Olah (see ref 2) in which higher electron-deficient states of an element are designated "onium" and the lower "enium" ions.

(5) R. O. Hutchins, B. E. Maryanoff, J. Albrand, A. Cogne, D. Gagnaire, and J. B. Robert, *J. Amer. Chem. Soc.*, in press.

(6) See M. Halman, *Top. Phosphorus Chem.*, **4**, 49 (1967). Herein is contained some general information on the behavior of trivalent phosphorus compounds in the mass spectrometer; see pp 70–77.

(7) R. O. Hutchins and B. E. Maryanoff, unpublished results.

(8) See H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, pp 645–653.

(9) F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, New York, N. Y., 1967.

(10) Y. Wada and R. W. Kiser, *J. Phys. Chem.*, **67**, 2290 (1964).

fragmentation pathway involving loss of the R group and leading to long-lived divalent phosphorus cations (see eq 1). Even phenyl was readily lost before other, usually facile cleavages could occur (*e.g.*, carbon–carbon bond cleavage) to an appreciable extent. Conceivably, the R group may have departed as a negative ion from the un-ionized ground-state parent or as a radical species from the molecular ion. However, the high ionization potential employed coupled with the fact that abundant even-electron ions at high mass are formed by loss of a neutral radical from the molecular ion (or by loss of a neutral molecule from another even-electron ion)[11] point to the latter mechanism (eq 1).[12] It should be noted that in all the compounds studied the divalent ion was the most intense (base) peak in the mass spectrum (see Table I).

TABLE I

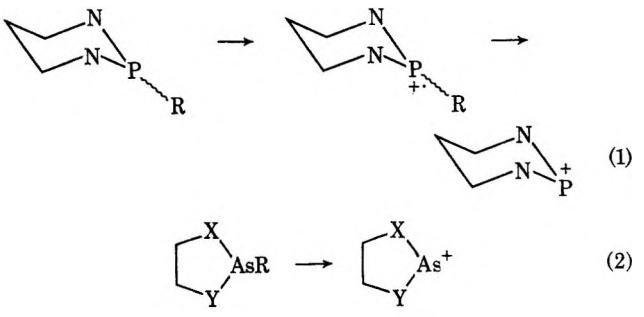
INDICATION OF THE STABILITY OF THE PHOSPHENIUM IONS DERIVED FROM THE 2-R-PHOSPHA-1,3-DIAZACYCLOHEXANES

Compd				Rel intensity, %	
				Molecular	Phosphenium
R	R_1	R_2	No.	ion	ion
C_6H_5	H	H	1a	34, 46[a]	100
C_6H_5	CH_3	CH_3	1b	23, 90[a]	100
C_6H_5	CH_3	H	1c	79	100
Et	H	H	1d	17	100
Et	CH_3	CH_3	1e	12	100
Et	CH_3	H	1f	1	100
Cl	H	H	1g	8	100
Cl	CH_3	CH_3	1h	9	100
OMe	H	H	1i	76	100
Me	CH_3	CH_3	1j	12	100

[a] Two different runs.

Surprisingly, representative dioxa and dithia analogs of **1** did not give similar results. For instance, 2-phenyl-2-phospha-1,3-dioxacyclohexane (**2**) did give an analogous divalent ion which, however, was not the base peak and 3-methoxy-3-phospha-2,4-dioxaspiro-[5.3]nonane (**3**) gave no peak attributable to a divalent ion. For the dithia system (*i.e.*, **4**), no mass peaks were observed which could have been ascribed to such ions.[13] Evidently, the divalent ions in these cases are not exceptionally stabilized and other pathways compete favorably. This behavior is in contrast to the situation with comparable arsenic heterocycles, which readily lose the arsenic R substituent in the mass spectrometer to give intense cyclic divalent arsenium ions, even though the arsenic atom was flanked by oxygen and sulfur in most of the compounds studied[14] (see eq 2).

Although the results may be rationalized in terms of the weaker nature of the P–O and P–S bonds, it also appears that the nitrogen atoms may exert a stabilizing influence on the electron-deficient phosphorus atom. This latter supposition is based on the fact the delocalization is known to increase when nitrogen is implaced in a system in comparison to, *e.g.*, oxygen[15a] and presumably it is this enhanced delocalization which stabilizes the divalent cation.

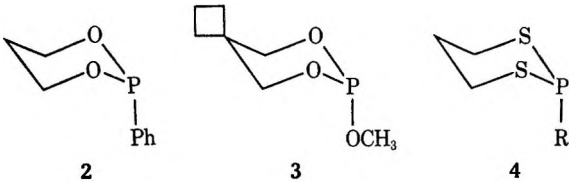


(1)

(2)

X, Y = O, S, or NMe
R = Ph, Et, NR_2

In order to elucidate the factors involved in stabilization, the bicyclic aminophosphines **5**–**7** were examined. Previous studies[5] have suggested that the nitrogen lone pairs in the phosphadiazacyclohexanes are axial and, under such conditions, should stabilize the vacant orbital of an incipient phosphenium ion with ease. The diaxial situation, however, is not necessary, since an equatorially disposed lone pair on nitrogen would be free to accept an axial position on demand without much difficulty. In **5**–**7**, the orientation of the nitrogen lone-pair electrons is manipulated by their location at bridgehead positions, which impedes coplanar interaction between the lone pairs and the cationic center.[19] The mass spectra of **5**–**7** may be compared with that of **1c**, a representative model compound (see Table II).



2 **3** **4**

Constraining one nitrogen lone pair at a bridgehead position, as in **5**, does not grossly alter the mass spectrum with respect to the model compound **1c**. There

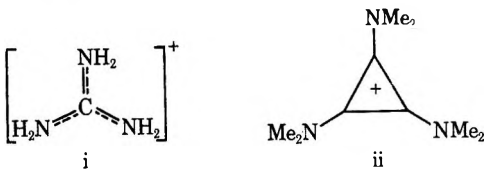
(11) Reference 9, p 68.

(12) It is reasonable to suspect, however, that the *P*-chloro compounds **1g** and **1h** may also undergo fragmentation to produce initially a chloride ion–phosphenium ion pair, which then separates within the mass spectrometer; see M. Halmann and Y. Klein, *J. Chem. Soc.*, 4324 (1964). Negative ion mass spectrometry also has revealed heterolytic decomposition of the halophosphorus compounds in other instances; see T. Kennedy and D. S. Payne, *ibid.*, 1228 (1959); B. L. Donnally and H. E. Carr, *Phys. Rev.*, **93**, 111 (1954).

(13) An exception to this was the *P*-chloro derivative of **4** (R = Cl), which did give a minor amount (10%) of the corresponding divalent ion.

(14) R. H. Anderson and R. H. Cragg, *Chem. Commun.*, 1414 (1971).

(15) (a) This is reflected in Hammett σ^+ constants, which are −1.3 and −1.7 for NH_2 and NMe_2 substituents but are only −0.92 and −0.78 for OH and OMe substituents, respectively.[16] Furthermore, an amino moiety exhibits a much greater electron-donating π-conjugative effect (σ_R) than an electron-withdrawing σ-inductive effect (σ_I) in comparison to an oxygen (or any other neutral) moiety.[16] (b) The large resonance stabilization which may be afforded by amino substituents is notably exemplified by the qualification of the guanidinium ion (i) as "the world's most stable carbonium ion"[17] and the remarkable stability of aminocyclopropenium ions (ii).[18]



i ii

(16) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, pp 241–243.

(17) P. Gund, *J. Chem. Educ.*, **49**, 100 (1972).

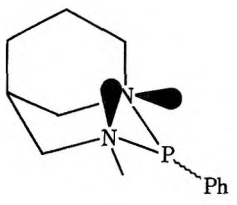
(18) Z. Yoshida and Y. Tawara, *J. Amer. Chem. Soc.*, **93**, 2573 (1971).

(19) This is a consequence of the near orthogonal orientation of the nitrogen lone pairs with respect to the empty (presumably p) orbital on phosphorus and probably the hampering of planarity in the region of N–P–N overlap; *cf.* Bredt's rule in E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, pp 298–302, 378.

TABLE II
COMPARISON OF THE MASS SPECTRA OF 6-8 WITH THAT OF MODEL PHOSPHADIAZACYCLOHEXANES

		Characteristic peaks, %						
Compd	Parent	P − Ph	109	108	107	78	77	60	39
1c	78	100	37	18	25	0	0	60	10
5	89	100	43	19	21	15	15	64	19
6	60	32	32	20	14	100	85	0	17
7	100	0	37	16	17	16	27	0	16
8	25	100	20	4	8	2	7	5	9

is a change in the *m/e* 77 and 78 peaks, perhaps as a result of the one bridgehead nitrogen, but the significance of this is elusive. When both electron pairs are held fixed at the bridgeheads (**6** and **7**), an entirely new



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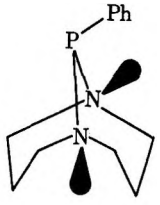

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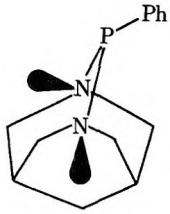

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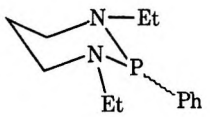


8

fragmentation pattern is observed. This is exemplified by marked reductions of the P − phenyl peak, the absence of a *m/e* 60 fragment, and the appearance of considerable *m/e* 77 and 78 peaks. It should be noted that *all* the phosphadiazacyclohexane derivatives studied (see Table I) had a P − R base peak and all except **8** had a *m/e* 60 fragment of 40–75% relative abundance. Consideration of the data for **8** (Table II) demonstrates that the absence of the *m/e* 60 peak may be a consequence of having groups other than methyl substituted on the nitrogens (as in **7** and **8**). Nevertheless, the other criteria are valid with respect to **6** and **7** and indicate "abnormal" mass spectral behavior for these compounds. Since **5**, with one bridgehead nitrogen, still followed the general trend observed for the phosphadiazacyclohexanes, it seems that two bridgehead nitrogens are required to heavily disfavor a phosphenium ion. Evidently the stability of the diaminophosphenium ions is dependent on the nitrogen stereochemistry.

In a previous investigation[5] the phosphorus-31 nmr chemical shifts of the cyclic and bicyclic aminophosphines were demonstrated to depend upon the nitrogen stereochemistry. Briefly, compounds **6** and **7** with two bridgehead nitrogen atoms were significantly deshielded (−104 and −109 ppm, respectively) in comparison to compound **5** with a single bridgehead nitrogen (−94 ppm). Furthermore, all these were deshielded with respect to model monocyclic aminophosphines, *i.e.*, **1a**, **1b**, **1c**, and **8**, which ranged from −92 to −81 ppm. This strong deshielding of phosphorus was rationalized in terms of the probable decrease in (p − d) π interaction between the nitrogen lone pairs and the phosphorus and lends some support to a directional influence

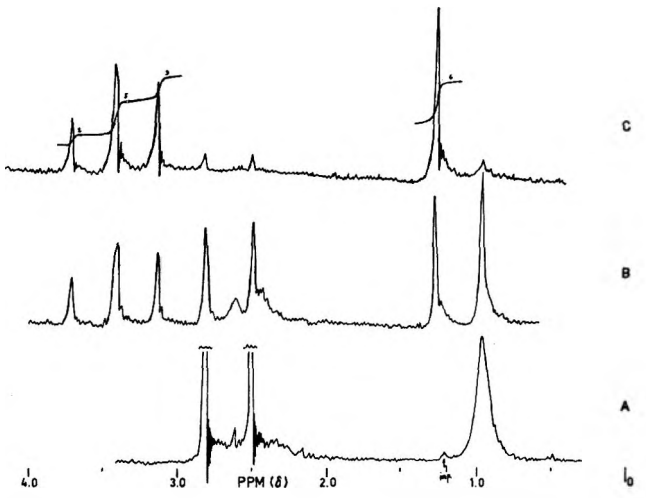
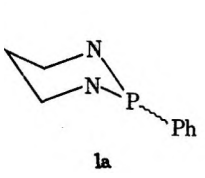
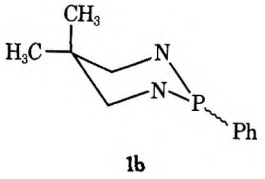


Figure 1.—Reaction of 2-chloro-5,5,*N*,*N*′-tetramethyl-2-phospha-1,3-diazacyclohexane (**1h**) with PCl_5 in nitrobenzene. (A) Pmr spectrum of **1h** in nitrobenzene in the absence of PCl_5; spectrum indicates substantial Cl exchange which averages the signals. (B) Addition of *ca.* 10 mg of PCl_5. (C) Addition of *ca.* 20 mg of PCl_5.



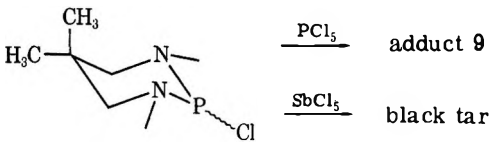
1a



1b

of the nitrogen lone pairs in the divalent cations, which presumably results in a stable situation when the lone pairs are parallel and coplanar with the unoccupied p orbital on phosphorus.

Reaction of 1h with Phosphorus Pentachloride.—In light of the preceding observations, 2-chloro-5,5,*N*,*N*′-tetramethyl-2-phospha-1,3-diazacyclohexane (**1h**) was treated with halide acceptors (Lewis acids) with the aim of chemically producing a stable doubly connected phosphorus cation by removal of chloride anion (see eq 3). Treatment of **1h** in nitrobenzene with phosphorus pentachloride (in an nmr tube) resulted in formation of some sort of adduct (viewed by pmr), whereas treat-



ment with antimony pentachloride afforded a black, metallic mixture (tar) that was not investigated further. The pmr examination of the adduct formation is given in Figure 1.

Treatment of the chloro compound **1h** (spectrum A) with incremental portions of PCl_5 (spectra B and C) caused the original absorptions to gradually disappear, coincident with the appearance of new resonances at lower field. The new resonances were ostensibly derived from a new molecular species and are evidently, from left to right, the methylene (δ 3.55), *N*-methyl (δ 3.35), and *gem*-methyl (δ 1.29) protons of the "adduct;" integration of spectrum C gave the ratio 2:5:3:6.

The pmr spectrum of the pure chloro compound **1h** in dilute solution is presented in Figure 2 and reveals

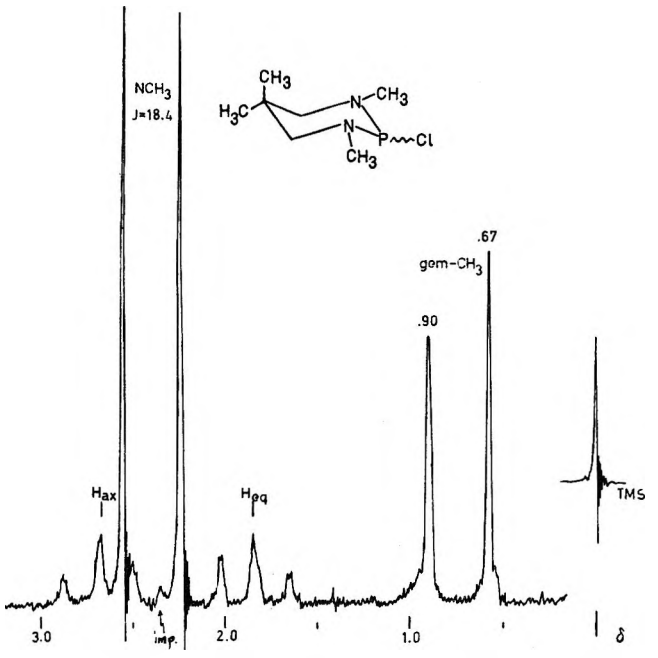
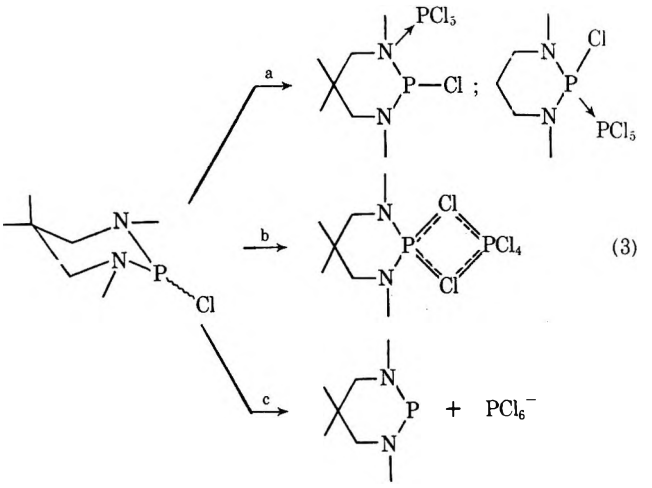


Figure 2.—Pmr spectrum of 2-chloro-5,5,*N*,*N*′-tetramethyl-2-phospha-1,3-diazacyclohexane dilute solution in benzene solvent. The low-field methyl signal δ(0.90) is assigned to the axial methyl group.

the geometry of the ring (unexchanged) to be virtually a single chair conformation with three-bond coupling of phosphorus to the methylene protons of approximately 10 Hz and to the methyl groups of 18.6 Hz. An increase in concentration brings about halogen exchange[20] with attendant degeneration of substituent stereochemistry. This is evident to some degree in spectrum A (Figure 1), and even more so in spectrum B. In the latter, unreacted **1h** is apparently undergoing more rapid exchange in response to acid or chloride-ion catalysis.[5] It is important to note that the adduct formed (spectrum C) also exhibits no substituent stereoisomerism but rather appears as some type of averaged spectrum, as in the case of **1h**, which is rapidly exchange inverting.

In consideration of the nature of the "adduct" three likely possibilities emerge: (a) a complex in which a nonbonded pair of electrons on phosphorus or nitrogen is donated to the PCl_5; (b) a complex in which chlorine supplies the electron pair and which is probably chlorine-bridged; and (c) a diaminophosphenium ion, a consequence of complete abstraction of chloride to form it and PCl_6^- (see eq 3). The first possibility is the least likely, as such a complex would have to be exceptionally labile to account for the conformational mobility evident in the nmr. The second and third species would lack substituent stereoisomerism in agreement with the observations. Furthermore, the strong deshielding of the protons is suggestive of cation formation, since the electron density about nitrogen would be expected to decrease in a mesomeric diaminophosphenium ion. This latter interpretation is further supported by the enhanced three-bond phosphorus–methylene coupling of 17.5 Hz (10 Hz in **1h**), demonstrating an increased P–N bond order. In addition,

(20) The diamino *P*-Cl derivatives are capable of bimolecular chlorine exchange, which inverts the configuration at phosphorus. Coupled with consequent ring inversion, this results in the averaging of the nmr parameters; see ref 5.

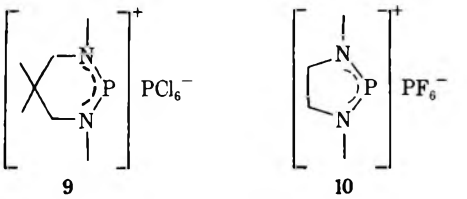


(3)

the adduct showed a highly deshielded phosphorus-31 nmr absorption at −222 ppm (*vs.* −150 ppm for **1h**), thus connoting a very electron-deficient phosphorus atom.

The adduct **9** was generated on a larger scale and was isolated as a hygroscopic, crystalline substance. Protected in a sealed capillary, the substance was viewed under a microscope and appeared as minute, irregular prisms. The adduct **9** was both air and water sensitive; however, **9** could be preserved indefinitely *in vacuo* or under an atmosphere of dry nitrogen. The adduct **9** was apparently inert to benzene, chlorobenzene, nitrobenzene, and nitromethane, but it reacted quickly with dimethyl sulfoxide, liberating dimethyl sulfide (deoxygenation) and, with acetonitrile, forming a white, unidentified precipitate (complex?). Elemental analysis confirmed a 1:1 adduct and conductance measurements in nitromethane (see Experimental Section) were in agreement with an ionic material. The pmr spectrum of the pure salt **9** shows the doublet due to the phosphorus-coupled methylene protons, which was difficult to see in the previous spectrum of the *in situ* generated adduct. Again, the coupling is an unusually large 17.5 Hz and the integration gives the expected intensity ratio of 2:5:3:6. Taken together, the data seem best explained by a relatively stable phosphenium ion salt.

Our interpretation in terms of the formation of a stable phosphenium ion is in accordance with the recent work of Fleming and coworkers,[21] in which the five-membered ring diaminophosphenium ion (**10**) was



9 **10**

produced and described. These authors recorded a ^{31}P chemical shift of −264 ppm for this species. Interestingly, Fleming, *et al.*,[21] found that when BF_3 was used as a fluoride acceptor an equilibrium between a 1:1 complex (at nitrogen) and the cation–anion system $[CH_3NCH_2CH_2(CH_3)NP]^+$ $(B_2F_7)^-$ occurred, the concentration of the salt increasing with an increasing

(21) S. Fleming, M. K. Upton, and K. Jekot, private communication; *Inorg. Chem.*, in press. We thank Dr. Fleming for communicating their results prior to publication. The compound investigated was 2-fluoro-*N*,*N*′-dimethyl-2-phospha-1,3-diazacyclopentane (**11**).

excess of BF_3. Figure 1 illustrates that the final adduct in our case is formed directly; there is no evidence for any intervening species. This contrast reflects a decreased ability for BF_3 to act as a halide acceptor in relation to PCl_5 and probably PF_5, although the intervention of a complex in this latter case was not mentioned.[21]

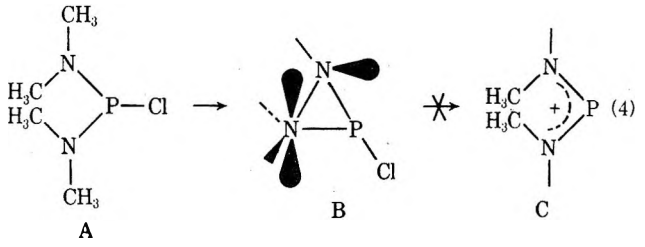
To furnish a comparison between **9** and **10** the nmr spectral data for the unreacted ligands (**1h** and **11**, respectively) and the derived cations, **9** and **10**, are given in Table III.

TABLE III
NMR SPECTRAL DATA FOR **1h** AND **9** AND THE CORRESPONDING UNREACTED LIGANDS[a]

Compd	δ_{NCH_3}	δ_{NCH_2}	$^3J_{PNCH_3}$	$^3J_{PNCH_2}$	δ (^{31}P)
1h (exch)[b,c,d]	2.66	2.82	~19	~10	−150 ± 1
11[e,f]	2.72	3.15	13	d	−138
9[b,g]	3.28	3.59	16.5	17.5	−222
10[f,h]	3.10	3.83	11	5	−264[i]

[a] Chemical shifts are in parts per million downfield from TMS or 85% H_3PO_4; coupling constants are in hertz. [b] In nitrobenzene. [c] Geminal methyl groups at δ 1.02. Complex multiplet reported (ref 21); however, the spectral parameters reported by Albrand, *et al.*, would afford an averaged coupling of *ca.* 5–6 Hz: J. P. Albrand, A. Cogne, D. Gagnaire, and J. B. Robert, *Tetrahedron*, **78**, 819 (1971); J. P. Albrand, A. Cogne, D. Gagnaire, J. Martin, J. B. Robert, and J. Verrier, *Org. Magn. Resonance*, **3**, 75 (1971). [d] Reference 7. [e] No solvent. [f] Reference 21. [g] Geminal methyl groups at δ 1.28. [h] In acetonitrile-d_3. [i] In 1,2-dichloroethane.

Curiously, treatment of bis(dimethylamino)chlorophosphine did not produce similar proton or ^{31}P nmr results as for **1h**. At best, the substrate merely partially complexed with the PCl_5 in a similar manner as may be observed for aminophosphines which cannot lose a ligand '(*e.g.*, complexation occurred between PCl_5 and **1b**). There was no evidence for cation formation using pmr (*N*-methyl doublet shifted from 2.68 to 2.83, ^3J was virtually unchanged) or ^{31}P nmr [δ (^{31}P) merely shifted from −163.6 to −167.5 ppm]. It might be speculated that the attainment of coplanarity is impossible in the diaminophosphenium ion of this molecule because of severe steric interactions. This is illustrated in eq 4, where the planar situation A would



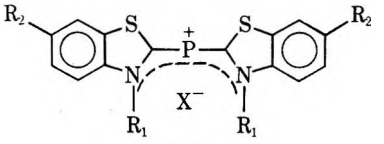
(4)

be very sterically unfavored, thus favoring situation B. Consequently, the necessary planarity in the mesomeric ion C would also be disfavored by steric interactions. Of course, this type of steric interplay would be eschewed in the cyclic systems, which do give phosphenium ions.

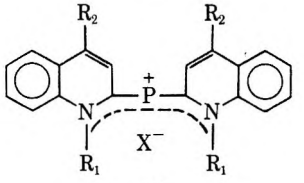
It should also be mentioned that diphenylchlorophosphine did not appear to form a divalent cation, Ph_2P^+, with PCl_5, although the ion is abundant in the mass spectrometer. This is presumably because phenyl cannot sufficiently stabilize the positive charge under normal conditions.

Another type of dicoordinate phosphorus cation has been reported by Dimroth and Hoffman.[22] These "phosphacyanines," **12** and **13**, were stable salts (much more stable than **9** and **10**) and possessed a large amount of resonance stabilization, attested to by their uv–visible spectra [ν_{max} 472–605 nm (ϵ 3.35–5.15 × 10^4)] and ^{31}P chemical shifts (*ca.* −24.9 ppm for type **12** and *ca.* −48.8 ppm for type **13**).[23] The molecular structure of **12** (R_1 = C_2H_5; R_2 = H) was determined by X-ray crystallography.[24] The compound was found to exist in the cis form (as depicted) with each group mutually twisted 6° out of the molecular plane; the C–P–C angle was 104.6° and the pertinent bond lengths were in support of a mesomeric structure.

Thus, it appears that doubly connected phosphorus cations can be stable molecular species under ambient conditions but only when a delocalized bonding system is available. This work suggests that a favorable disposition of the lone pairs on nitrogen and the ability to approach planarity is necessary for the formation of stable diaminophosphenium ions. The implication of such species in reactions of tervalent phosphorus derivatives is currently under investigation.



12



13

$X = BF_4^-$, ClO_4^-

Experimental Section

All melting points and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 457 spectrophotometer. Pmr spectra were obtained on a Varian A-60 spectrometer using tetramethylsilane (TMS) as an internal reference. Phosphorus-31 nmr spectra were recorded at 40.5 MHz on a Varian HA-100 spectrometer using 85% phosphoric acid as an external reference. Mass spectra were obtained using a Perkin-Elmer Hitachi RMU-6 mass spectrometer operating at 70 eV. Microanalyses was performed by Alfred Bernhardt Mikroanalytisches Laboratorium, West Germany. All reactions involving trivalent phosphorus were carried out under an atmosphere of dry nitrogen.

Materials.—All the cyclic diaminophosphines employed in this study were synthesized and characterized as previously described.[5] Tris(dimethylamino)phosphine was purchased from Aldrich Chemical Co., Milwaukee, Wis., and was purified by distillation. Diphenylchlorophosphine was kindly supplied by Stauffer Chemical Co., New York, N. Y., as a free sample; it was distilled prior to use. Phosphorus pentachloride was reagent grade and was used from a freshly opened bottle without further purification. Antimony pentachloride and nitrobenzene were purified by distillation. Nitromethane, which was employed as a solvent for conductance measurements, was reagent grade; it was deoxygenated by bubbling dry nitrogen through it and then

(22) (a) K. Dimroth and P. Hoffman, *Angew. Chem., Int. Ed. Engl.*, **3**, 384 (1964); (b) *Chem. Ber.*, **99**, 1325 (1966).

(23) In fact, Dimroth and Hoffman were astounded at the "unexpectedly large" (*i.e.* highly shielded) ^{31}P chemical shifts for such an expectedly electron-deficient phosphorus atom; ref 22a.

(24) R. Allmann, *Chem. Ber.*, **99**, 1332 (1966).

stored over molecular sieves (3A) under an atmosphere of dry nitrogen.

Bis(dimethylamino)chlorophosphine.—According to the report of Van Wazer and Maier,[25] phosphorus trichloride (0.682 g, 5 mol) was cooled to −78° in Dry Ice–acetone and, with stirring, treated with tris(dimethylamino)phosphine (1.63 g, 10 mol), bp 70–71° (30 mm), which was added all at once. The mixture was allowed to warm to ambient temperature, stirred for 15 min, and then distilled at reduced pressure. After a forerun was collected [up to 82° (25 mm)], the product came over, bp 83–84° (25 mm) [lit. bp 64° (10 mm),[26a] 93–97° (47–49 mm)];[26b] the yield was 1.05 g (45%).

Nmr Study of Reaction of 1h with Phosphorus Pentachloride.—A pmr sample of **1h** in nitrobenzene was prepared (0.3 ml of *ca.* 10% solution) with the intention of examining the reaction of **1h** with phosphorus pentachloride. Nitrobenzene was selected because of its high polarity and anticipated inertness. The pmr spectrum was recorded (Figure 1). Subsequently, small portions (*ca.* 10 mg) of PCl_5 were added incrementally and a spectrum was recorded after each treatment (see Figure 1). A colorless solid was observed to precipitate from the solution, contrasting with some pale yellow PCl_5 which remained undissolved and deposited in the bottom of the nmr tube. For the ^{31}P nmr study a similar mode of operation was taken. In this case the peak assigned to **1h** at −150 ppm gradually diminished upon addition of small portions of PCl_5, while a peak at −222 ppm gradually increased in intensity.

Reaction of 1h with Phosphorus Pentachloride.—In line with the positive results obtained in the nmr study of this reaction, a scaled-up reaction was performed in order to isolate the adduct which had been formed. About 5 drops (*ca.* 50 mg) of the *P*-chloro compound **1h** were placed in a 5-ml flask which had been meticulously cleaned and flushed with dry nitrogen. The flask had one neck which was equipped with a stopcock. During the course of the reaction nitrogen was continuously admitted through the stopcock to prevent air from entering the reaction flask during manipulations. A saturated solution of PCl_5 in nitrobenzene (3 ml) (an excess of theory) was added in a stream of nitrogen *via* a syringe. An immediate and slightly exothermic reaction took place and a colorless, apparently crystalline solid precipitated. The flask was swirled gently. After 30 min, the supernatant solution was extracted by means of a long-stemmed pipet and discarded. The precipitate was then rinsed with two portions of chlorobenzene followed by two portions of *n*-hexane or benzene. The rinses were conducted by a pipet which was inserted through the open stopcock, under a steam of nitrogen. Drying was initially effected by the passage of a stream of nitrogen into the vessel, after which the white solid was further dried and preserved under high vacuum (*ca.* 0.008 mm). Because of its hygroscopic nature and decomposition under normal conditions, the material was always handled under a stream of nitrogen, or better, in a glove bag. The solid in a sealed capillary melted at 213–215° with decomposition and evolution of a gas: ir (KBr) 3000–2800 (m), 1470 (m), 1375 (w–m), 1252 (m–s), 1195 (m), 1180 (m), 1095 (s), 1037 (s), 1003 (m–s), 780 (m–s, shoulder 790), 725 (w), 600 (vs), 552 (m–s), 508 (m–s), 440–430 (vs), 340 cm^{-1} (vw). *Anal.* Calcd for $C_7H_{16}Cl_6N_2P_2$: C, 20.86; 4.00. Found: C, 21.09; H, 4.17.

2,5,5,*N*,*N*′-Pentamethyl-2-phenyl-2-phospha-1,3-diazacyclohexane Iodide.—The phosphine **1b** (4 drops) was dissolved in *ca.* 5 ml of dry ether. An excess of methyl iodide was added and the solution was stoppered and allowed to stand. After just 5 min, a white precipitate was deposited. An hour elapsed and the mixture was filtered. The solid was rinsed with some dry ether and dried. Pale yellow needles (slight iodine discoloration) were obtained from 2-propanol, mp 188–189°. *Anal.* Calcd for $C_{14}H_{24}IN_2P$: C, 44.48; H, 6.40; I, 33.52. Found: C, 44.42; H, 6.27; I, 33.74.

(25) J. R. Van Wazer and L. Maier, *J. Amer. Chem. Soc.*, **86**, 811 (1964).

(26) (a) G. Ewart, D. Payne, A. Porte, and A. Lane, *J. Chem. Soc.*, 3984 (1962); (b) H. Noeth and H. Vetter, *Chem. Ber.*, **96**, 1109 (1963).

Conductance Measurements.—Conductivities were measured on approximately 0.0008–0.005 *M* solutions at 25° with an A. H. Thomas Model RCM 15 Bl conductance bridge at 1000 Hz; the bridge was connected to a Yellow Springs Instrument Co. Model 3403 conductivity cell (K = 1.0). The solvent employed in all instances was deoxygenated, anhydrous nitromethane. In Table IV the molar conductances for the adduct **9** and for some compounds offered for comparison are presented. The weighing and other handling of **9** was done in a glove bag containing a nitrogen atmosphere and its conductance was measured under nitrogen. The data indicate beyond a doubt that **9** is an ionic material; however, the conductance value for **9** is somewhat lower than would be expected by comparison with the ammonium salt or the phosphonium salt. A partial explanation may reside in the fact that the measurement of **9**, which was plagued by its sensitivity to both air and moisture, may have reflected some impurities created during handling. On the other hand, that **9** in solution may be a mixture of an ionic species (1:1 electrolyte) and a nonionic species (*e.g.*, a chlorine-bridged complex) in rapid equilibrium cannot be excluded.

TABLE IV

MOLAR CONDUCTANCES FOR 9 AND SOME COMPOUNDS OFFERED FOR COMPARISON[a]

Compd	Concn, *M*[b]	λ, mho/cm²-mol[c]
9	0.000819	44.4
$(n\text{-}C_4H_9)_4N^+ClO_4^-$	0.000849	95.6
2,5,5,*N*,*N*′-Pentamethyl-2-phenyl-2-phospha-1,3-diazacyclohexane iodide	0.00102	82.6
PCl ($PCl_4^+PCl_6^-$)	0.00225	10.2
Pyridine–borane	0.0046	0

[a] The cell was calibrated to a 0.01 *N* KCl solution. The "Handbook of Chemistry and Physics," 50th ed, Chemical Rubber Co., Cleveland, Ohio, p D-121, gives the value of 141.27 for the equivalent conductance of a 0.01 *N* KCl solution at 25°. [b] Error is *ca.* ±1%. [c] Error is *ca.* ±2%.

Nmr Study of the Reaction of Bis(dimethylamino)chlorophosphine with Phosphorus Pentachloride.—Addition of PCl_5 to a nitrobenzene solution of $(Me_2N)_2PCl$ (0.3 ml of *ca.* 15% solution) gave a slow reaction and no heat was evolved. The pmr spectrum showed the slow appearance of a new doublet centered at δ 2.83 and the decrease in intensity of the original doublet at δ 2.68. Decomposition, which resulted in a number of unassignable peaks, quickly ensued, at which point about 20% of the "complex" was present. ^{31}P nmr gave a similar result as pmr. A new peak accounting for 20–25% material balance arose at a slightly downfield position (−167.5 ppm compared to −163.6 ppm for starting material) upon treatment with PCl_5, but would not increase in intensity in response to subsequent doses. Decomposition products were not observed.

Pmr Study of the Reaction of Diphenylchlorophosphine with Phosphorus Pentachloride.—This study was performed in the above-described manner. Very little change in the pmr spectrum was observed on treatment of a nitrobenzene-d_5 solution of Ph_2PCl with PCl_5. Some complexation may have occurred but was not well defined (the evidence was very slight shifts of some resonance lines).

Registry No.—**1c**, 35661-63-3; **1h**, 35661-64-4; **5**, 35661-65-5; **6**, 35661-66-6; **7**, 35820-68-9; **8**, 35661-67-7; **9**, 35665-40-8; 2,5,5,*N*,*N*′-pentamethyl-2-phenyl-2-phospha-1,3-diazacyclohexane iodide, 35737-17-8; phosphorus pentachloride, 10026-13-8.

Studies on the Chemistry and Structure of the 1,4-Dithioniabicyclo[2.2.2]octane Cation

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The synthesis and characterization of several salts of the 1,4-dithioniabicyclo[2.2.2]octane cation ($C_6H_{12}S_2^{+2}$) are described. The tetrachlorozincate salt, $C_6H_{12}S_2ZnCl_4$, crystallizes in space group *Pnma* of the orthorhombic system with four molecules in a cell. The $C_6H_{12}S_2^{+2}$ cage forms a tightly packed oblate spheroid of approximate D_{3h} symmetry in which the S–S distance (3.130 ± 0.004 Å) is significantly less than the van der Waals S–S separation. With nucleophiles the 1,4-dithioniabicyclo[2.2.2]octane cation gives compounds of general formula Nuc-$CH_2CH_2SCH_2CH_2SCH_2CH_2$Nuc; the vinyl-1,4-dithianesulfonium ion is an important intermediate.

The 1,4-dithioniabicyclo[2.2.2]octane cation ($C_6H_{12}S_2^{+2}$, which will be referred to in this paper as the disulfonium cation) was first synthesized by Stahmann, Fruton, and Bergman[1] during their exhaustive work on mustard gas during World War II. The cage structure of this ion is common to the related molecules triethylenediamine, quinuclidine, and the parent hydrocarbon bicyclo[2.2.2]octane, all of which have been extensively studied either because their crystal structures undergo thermal transitions to plastic crystals[2] or because of controversy concerning the symmetry of the hydrocarbon cage.[3] The disulfonium cation is also one member of a class of compounds, sulfonium derivatives of mustard gas, that has provided valuable cytostatic agents for cancer chemotherapy.[4] Our particular interest in the disulfonium ion stems from its strained structure and its potential use as a bifunctional substrate in nucleophilic substitution reactions. To characterize this substrate we have undertaken studies designed to establish the physical and chemical properties of its salts.

Experimental Section

Preparation and Reaction of Disulfonium Compounds.—All melting points were determined in open end capillaries and are uncorrected. Analyses were performed by the Schwarzkopf Microanalytical Laboratory and by PCR Inc. No attempt was made to maximize yields. Pmr spectra were recorded on a Varian A-60 at 37°; all integrations were within ±5% of theoretical for the proposed structures.

Disulfonium Tetrachlorozincate.—This compound was prepared as originally described[1] and other disulfonium salts were derived from it or prepared *via* a similar procedure. Steam distillation of the filtrate from this preparation yielded *p*-dithiane: mp (methanol) 110°; pmr ($CDCl_3$) τ 7.09 (s, CH_2). *Anal.* Calcd for $C_4H_8S_2$: C, 39.96; H, 6.71; S, 53.34. Found: C, 39.99; H, 6.77; S, 52.72. The crude disulfonium tetrachlorozincate was crystallized from dilute hydrochloric acid to yield clear, thick tubular to short prismatic, polyhedral crystals: mp 276–278° dec; pmr (D_2O) τ 5.91 (s, CH_2). *Anal.* Calcd for $C_6H_{12}S_2ZnCl_4$: C, 20.27; H, 3.40; S, 18.04; Zn, 18.39; Cl, 39.89. Found: C, 20.40; H, 3.35; S, 17.94; Zn, 18.11; Cl, 40.06.

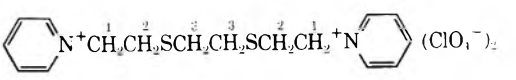
Disulfonium Perchlorate.—Disulfonium tetrachorozincate was dissolved in warm water, excess 72% perchloric acid added, and the solution cooled to yield crystals of disulfonium perchlorate: mp (H_2O) 276–277° dec; pmr (D_2O) τ 5.91 (s, CH_2). *Anal.* Calcd for $C_6H_{12}S_2(ClO_4)_2$: C, 20.76; H, 3.48; S, 18.47. Found: C, 20.87; H, 3.30; S, 18.44.

Disulfonium Chloride.—Disulfonium chloride was prepared from disulfonium tetrachlorozincate by exchanging tetrachlorozincate anions for chloride ions on a Dowex AG1-X8 anion-exchange resin. The desired product was recrystallized twice from water–isobutyl alcohol, and the resulting hydrated crystals were washed with 50% methanol–water and air dried. On being heated in a melting point capillary they partially dissolved from 40 to 110° in the water of crystallization and finally melted from 196 to 200°: pmr (D_2O) τ 5.91 (s, CH_2). *Anal.* Calcd for $C_6H_{12}S_2Cl_2 \cdot H_2O$: C, 30.38; H, 5.95; S, 27.03; Cl, 29.89; H_2O, 7.60. Found: C, 29.91; H, 5.94; S, 26.83; Cl, 29.86; H_2O, 8.16. On being dried *in vacuo* over P_2O_5 the hydrate was converted to the anhydrous form: mp 195–198°; pmr (D_2O) τ 5.91 (s, CH_2). *Anal.* Calcd for $C_6H_{12}S_2Cl_2$: C, 32.89; H, 5.52; S, 29.26; Cl, 32.35. Found: C, 32.93; H, 5.80; S, 29.41; Cl, 32.42.

Disulfonium Tetraphenylborate.—When an aqueous solution of sodium tetraphenylborate was added slowly to an aqueous solution of disulfonium tetrachlorozincate, disulfonium tetraphenylborate was quantitatively precipitated. This precipitate was crystallized from acetonitrile–95% ethanol, washed with 95% ethanol, and dried *in vacuo* over P_2O_5: pmr (DMF) τ 5.93 (s, CH_2). *Anal.* Calcd for $C_6H_{12}S_2[B(C_6H_5)_4]_2$: C, 82.44; H, 6.66; S, 8.15. Found: C, 81.22; H, 6.85; S, 7.92.

Tetra(disulfonium)cobalt(II) Decachloride Hydrate.—Cobaltous chloride hexahydrate, thiodiglycol, and concentrated HCl were refluxed according to the procedure given for the preparation of disulfonium tetrachlorozincate. The initial yield of blue crystals was dissolved in water and the resulting pink solution was washed with benzene. The addition of absolute ethanol and HCl yielded light orange crystals which were then crystallized from water–isopropyl alcohol. On being dried *in vacuo* over P_2O_5, or on being washed with absolute ethanol, this compound turned blue implying the conversion of octahedral cobalt(II) to tetrahedral cobalt(II) *via* dehydration. The pink derivative analyzes as $(C_6H_{12}S_2)_4CoCl_{10} \cdot 15H_2O$ and the blue derivative as $(C_6H_{12}S_2)_4CoCl_{10} \cdot 2H_2O$. DTA–TGA curves indicate that the pink compound is losing water even at room temperature. Addition of sodium tetraphenylborate to a water solution of either compound yielded disulfonium tetraphenylborate. *Anal.* Calcd for $(C_6H_{12}S_2)_4CoCl_{10} \cdot 15H_2O$: C, 22.58; H, 6.16; S, 20.09; Co, 4.62; Cl, 27.76. Found: C, 23.17; H, 6.29; S, 20.62; Co, 4.01; Cl, 27.58. Calcd for $(C_6H_{12}S_2)_4CoCl_{10} \cdot 2H_2O$: C, 27.65; H, 5.03; S, 24.60; Co, 5.65; Cl, 34.00. Found: C, 28.06; H, 5.28; S, 24.81; Co, 5.56; Cl, 34.03.

Dipyridinium 1,1′-[Ethylenebis(thioethylene)] diperchlorate.—



Disulfonium perchlorate (0.01 mol) and pyridine (0.1 mol) were added to 15 ml of dimethylformamide and the mixture refluxed for 2 hr. *p*-Dioxane was added to the warm solution which was then cooled to yield 3.6 g (71%) of white crystals. This product was crystallized from ethanol–water and then from warm water to yield 2.0 g of white plates: mp 175–177° dec; pmr (DMSO-d_6) τ 5.18 (t, H_1), 6.80 (t, H_2, J_{12} = 6.5 Hz), 7.18 (s, H_3), 0.78–1.95 (m, H_{py}). *Anal.* Calcd for $(C_5H_5NCH_2CH_2SCH_2)_2(ClO_4)_2$: C, 38.03; H, 4.39; N, 5.54; S, 12.69. Found (two separate

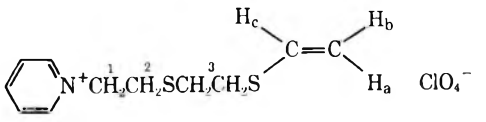
(1) M. A. Stahmann, J. S. Fruton, and M. Bergman, *J. Org. Chem.*, **11**, 704 (1946).

(2) (a) S. Change and E. F. Westrum, Jr., *J. Phys. Chem.*, **64**, 1551 (1960); (b) J. C. Trowbridge and E. F. Westrum, Jr., *ibid.*, **67**, 2381 (1963); (c) G. W. Smith, *J. Chem. Phys.*, **43**, 4325 (1965).

(3) (a) J. D. Dunitz and O. Ermer, Paper XIII-1, *Collect. Abstr., Int. Union Crystallogr., Eighth Gen. Assem. Int. Congr.*, 126 (1969); (b) O. Ermer and J. D. Dunitz, *Helv. Chim. Acta*, **52**, 1861 (1969); (c) A. F. Cameron, G. Ferguson, and D. G. Morris, *J. Chem. Soc.*, 1249 (1968).

(4) A. Luttringhaus and H. Machatzke, *Justus Liebigs Ann. Chem.*, **671**, 165 (1964), and references therein.

determinations of independently prepared samples): C, 38.45, 38.30; H, 4.71, 4.43; N, 5.50, 5.40; S, 12.74, 12.84. Work-up of the original filtrate yielded a small amount of *N*-[3,6-bis(thia)-7-octenyl]pyridinium perchlorate: pmr (DMSO-d_6) τ 5.16 (t, H_1), 6.76 (t, H_2, J_{12} = 6.5 Hz), 7.09 (m, H_3); the vinyl protons



yielded four doublets which can be accounted for by the reasonable[5a] parameters H_a = 4.85, H_b = 4.74, and H_c = τ 3.46 and J_{ab} = 0, J_{bc} = 10, and J_{ac} = 17 Hz.

Dipyridinium 1,1′-Ethylenediperchlorate.—Dipyridinium 1,1′-ethylenedibromide was prepared from 1,2-dibromoethane and pyridine according to published procedures.[5b] This was dissolved in water and excess 72% perchloric acid added to precipitate the perchlorate salt which was then recrystallized twice from water to yield white crystals: mp 307.5–308° dec: pmr (DMSO-d_6) τ 4.72 (s, CH_2), 0.87–1.93 (m, H_{py}). *Anal.* Calcd for $(C_5H_5NCH_2)_2(ClO_4)_2$: C, 37.42; H, 3.66; N, 7.27. Found: C, 37.49; H, 3.47; N, 7.37.

X-Ray Structure Determination. Unit Cell and Space Group.—Preliminary precession photographs (*hk*0, 0*kl*, *hk*1, 1*kl*) were taken at room temperature on a crystal of disulfonium tetrachlorozincate of approximate dimensions 0.25 × 0.20 × 0.30 mm using Cu K_α radiation. The observed systematic absences ($k + l$ odd for 0*kl*, h odd for *hk*0) are characteristic of the orthorhombic space groups *Pnma* and $Pn2_1a$. Final refinement was carried out in the centric space group *Pnma*, the reasons for this choice being discussed later. The cell dimensions, determined[6] from powder diffraction measurements (Table I),[7] were found to be a = 13.18 ± 0.015, b = 8.38 ± 0.01, and c = 11.55 ± 0.015 Å in good agreement with those determined from the precession photographs. An observed density of 1.83 ± 0.01 g/cm³, obtained by flotation in $CHBr_3$–CCl_4 solutions, agrees with that of 1.837 g/cm³ calculated for four formula units in the cell. These observations require that in *Pnma* both the $ZnCl_4^{-2}$ and $C_6H_{12}S_2^{+2}$ ions lie on the planes of symmetry.

Collection and Reduction of Intensity Data.—Three-dimensional X-ray intensity data were collected at room temperature on a disulfonium tetrachlorozincate crystal of approximate dimensions 0.25 × 0.35 × 0.35 mm using a Philips automated linear diffractometer, PAILRED; monochromatized Mo K_α radiation was obtained *via* a silicon crystal reflecting from the 111 plane. The crystal was mounted with the b axis colinear with the ω axis and data were collected by the ω-scan method (rate = 1.5°/min) for layers *hk*0 through *hk*16, the range of scan varying from ±1.5 to ±3.0° from the calculated peak. For layers *hk*0 through *hk*3 background was counted for 20 sec on each end of the scan, while for layers *hk*4 through *hk*16 this time was doubled. A total of 4448 reflections was examined within 2θ (Mo K_α) ≤ 60°, which, after rejection of observations with unacceptably high background counts and averaging of symmetry related peaks, yielded 908 nonzero reflections the intensities of which were corrected for Lorentz and polarization effects in the usual manner. Refinement was initiated using only these nonzero reflections and then completed with a total of 1915 nonzero and zero observations. A 360° ω scan of the 040 reflection gave a variation in intensity of less than ±10% and therefore no corrections for absorption effects were made (the linear absorption coefficient for disulfonium tetrachlorozincate using Mo $K\alpha$ radiation is 23.3 cm^{-1}). The intensities of two standard reflections monitored during the data collection showed only random fluctuations, although the crystal itself exhibited slight yellowing by the end of data collection.

Solution of Structure.—The structure was solved by a standard application of Patterson–Fourier and least-squares techniques.[8] In the least-squares calculations the sum of $w(|F_o| - |F_c|)^2$ was minimized, where $|F_o|$ and $|F_c|$ are the observed and calculated structure amplitudes, respectively. In the final refinement weights were defined as $1/\sqrt{w}$ = 6.0 − 0.2 $|F_o|$ for $|F_o| < 25$, $1/\sqrt{w}$ = 1.0 + 0.02($|F_o|$ − 130) for $|F_o| < 130$, and $1/\sqrt{w}$ = 1.0 otherwise. Atomic scattering factors for Zn^{+2}, Cl^-, S, C, and H, and values for the anomalous scattering terms for Zn, Cl, and S were taken from Ibers[2] tabulation.[9a]

Refinement of the structure was carried out using two different models, the first of which required anisotropic carbon atoms C(1) and C(2) to lie on the mirror plane. However, this model led to large thermal motions perpendicular to the mirror plane for these atoms, as well as to chemically unreasonable C–C bond lengths (*vide infra*). Therefore a second model, assuming a disordered $C_6H_{12}S_2^{+2}$ unit (two ions with respective left- and right-handed twists about the S–S vector superposed at every cationic site, each C atom being given half weight), was introduced. Refinement of this model with isotropic carbon atoms yielded values of R_1 and R_2 of 0.110 and 0.0409, respectively, where

$$R_1 = \frac{\Sigma(|F_o| - |F_c|)}{\Sigma|F_o|} \text{ and } R_2 = \left[\frac{\Sigma w(|F_o| - |F_c|)^2}{\Sigma w|F_o|}\right]^{1/2}$$

Hamilton's R-factor test[10] showed that this second model with disordered, isotropic C atoms better describes the data than the first model with ordered, anisotropic C atoms at the 99.5% significance level.

Final difference Fourier syntheses for both models were quite similar, showing peaks around the Zn atom of 1.4–1.6 e/Å³ and a continuum of peaks ranging downward from 1.0 e/Å³ (corresponding to ~20% of the height of a C atom in this structure) throughout the rest of the lattice. Lists of the observed and calculated structure factors for both models are given in Tables II[7] and III.[7] Both models gave average refined C–H bond distances of 1.0 Å.

Results and Discussion

Preparation and Properties of Disulfonium Salts.—The disulfonium cation is easily prepared from thiodiglycol, the original preparation of Stahmann, Fruton, and Bergman[1] being advantageous in that the halogenating mixture contains tetrachlorozincate which selectively precipitates the disulfonium cation. The HCl–$CoCl_2$ preparation probably is successful for the same reason, although it is not obvious why a salt of the unusual stoichiometry $(C_6H_{12}S_2)_4CoCl_4 \cdot nH_2O$ should be formed. Combined DTA–TGA curves of this salt and of disulfonium chloride show that the cobalt salt is not a simple mixture of the disulfonium chloride and tetrachlorocobaltate, although in later stages of decomposition there is formed a compound of stoichiometry $C_6H_{12}S_2CoCl_4$ which powder diffraction measurements show to be isomorphous with disulfonium tetrachloro-

(5) (a) R. M. Silverstein and G. C. Bassler, "Spectrophotometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967, pp 138, 144–145; (b) J. L. Hartwell and M. A. Pogorelskin, *J. Amer. Chem. Soc.*, **72**, 2040 (1950).

(6) We are grateful for the loan of equipment and expertise by Professor Paul Moore (Department of Geophysical Sciences, University of Chicago) towards this determination.

(7) The following tables and figures will appear in the microfilm edition of this volume of the journal: Table I, "Powder Diffraction Data for Disulfonium Tetrachlorozincate;" Combined Tables II and III, "Observed and Calculated Structure Factors for both Ordered and Disordered Models;" Table IV, "Positional and Thermal Parameters for Ordered Model;" Table V, "Selected Interatomic Distances and Angles for Ordered Model;" Table VII, "Positional and Thermal Parameters for Disordered Model;" Table IX, "Root-Mean-Square Displacements in Disordered Model;" Figure 1, "A Perspective Drawing of Disulfonium Tetrachlorozincate in the Ordered Model"; Figure 3, "A Perspective Drawing of one Disordered SCH_2CH_2S Linkage." Also included are statistical arguments in favor of the centric space group *Pnma*. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D. C. 20036, by referring to code number JOC-72-3481. Remit check or money order for $9.00 for photocopy or $2.00 for microfiche.

(8) In addition to the Sly–Shoemaker–Vanden Hende ERFR2 Patterson and Fourier synthesis program, the main programs used in this work were Dewar's SORFLS least-squares program and SORFEE function and error program (substantially modified versions of ORFLS and ORFEE by Busing, Martin and Levy) and C. K. Johnson's ORTEP thermal ellipsoid plotting program. All calculations were performed on the University of Chicago IBM 7094 computer.

(9) J. A. Ibers, "International Tables for X-ray Crystallography," Vol. 3, The Kynoch Press, Birmingham, England, 1965: (a) Tables 3.3.1A and 3.3.2C. (b) Table 4.1.10.

(10) W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).

zincate.[11] Sulfuric acid (50%)also converts thiodiglycol into the disulfonium cation, as evidenced by the appearance of its characteristic pmr peak in the reaction mixture. No solid product could be isolated from this mixture, but steam distillation affords good yields of *p*-dithiane. All efforts to synthesize the disulfonium cage by combining *p*-dithiane and 1,2-dibromoethane failed, despite the use of a variety of solvents and metal ion catalysts. These observations indicate that *p*-dithiane is the thermodynamically stable end of the thiodiglycol–disulfonium–dithiane chain.

In general, the solubilities of disulfonium and trimethylsulfonium salts are similar. Thus, disulfonium chloride is very soluble in water, but insoluble in common organic solvents, while the tetraphenylborate salt is completely insoluble in water but soluble in polar organic solvents. The tetrachlorozincate and perchlorate salts are only slightly soluble in water: the solublility of the $ZnCl_4^{-2}$ salt is 33.3 mg/g of 0.01 *F* HCl solution and 26.4 mg/g of 0.1 *F* HCl solution at 25.0° (at 10.0° these values are 28.3 and 23.0); the solubility of the ClO_4^- salt is 12.8 mg/g of solution at 25.0° and 6.0 mg/g of solution at 10.0°. The tetrachlorozincate salt is generally insoluble in organic solvents, but the perchlorate salt will dissolve in polar solvents such as DMF.

Aqueous solutions of the $C_6H_{12}S_2^{+2}$ ion show no discernible light absorption in the ultraviolet, visible, or near-infrared regions of the spectrum. However, the solid disulfonium salts give characteristically simple infrared absorption spectra, exemplified by the following data for $C_6H_{12}S_2ZnCl_4$ in a KBr pellet at room temperature: 2930 (s), 2925 (s), 1400 (s), 1310 (m), 1205 (sh), 1200 (m), 1160 (vw), 1105 (w), 1000 (w), 810 (sh), 800 (s), 720 (m) cm^{-1}. By comparison with the infrared absorption spectra of triethylenediamine[12] and bicyclo[2.2.2]octane[13] it is reasonable to assign the bands at 2980 and 2925 cm^{-1} to CH_2 stretching, the band at 1400 cm^{-1} to CH_2 bending, and the band at 800 cm^{-1} to CH_2 rocking. With considerably less certainty the band at 1310 cm^{-1} may be assigned to CH_2 twisting, and the band at 720 cm^{-1} to C–S–C bending.

Description of Crystal Structure of $C_6H_{12}S_2ZnCl_4$.— The crystal structure of $C_6H_{12}S_2ZnCl_4$ consists of discrete $C_6H_{12}S_2^{+2}$ cations and $ZnCl_4^{-2}$ anions, each of which have site symmetry *m*. The $ZnCl_4^{-2}$ ion is a distorted tetrahedron, the Zn–Cl distances ranging from 2.259 ± 0.003 to 2.282 ± 0.003 Å and the Cl–Zn–Cl angles ranging from 107.16 ± 0.06 to 112.11 ± 0.07°. As pointed out by Meek and Ibers,[14] this situation is not unusual even in structures where hydrogen bonding to Cl cannot be invoked. The $C_6H_{12}S_2^{+2}$ ion is a tightly packed oblate spheroid with a S–S distance of 3.130 ± 0.004 Å. This is significantly less than the shortest van der Waals S–S separation observed to date, while it is almost exactly the same S–S distance as is observed within the layers of molybdenite[15] [sulfur atoms on opposite faces of a layer are connected by three molybdenum(IV) bridges analogous to the three ethylene bridges of the disulfonium cage] and as the transannular S–S distance in 1-acetonyl-1-thionium-5-thiacyclooctane perchlorate.[16] (See Table VI.[9b,17-26]) It is likewise noteworthy that the disulfonium S–S distance also falls within the range of inter- and intraligand S–S

Table VI
S–S Distances (Å)

A. S–S Bonds	
1.89[9b]	S_2 (gas phase)
1.99[17a]	$S_2O_3^{-2}$
2.00–2.15[18]	Polysulfides and disulfides
2.39[17b]	$S_2O_4^{-2}$
B. Not Bonded, Weak Interaction	
2.15–2.55[19]	Thiathiophthenes
2.58[20]	Intramolecular S–S distance in S_4N_4
C. Not Bonded, Unknown Interaction	
2.80[21]	Average intraligand S–S distance in several 1,1-dithiclato metal chelates
2.89[22]	Interligand S–S distance in bis(dithiobiureto)nickel(II)
2.99, 3.06[21]	Average inter- and intraligand S–S distances for six square planar 1,2-dithiolato metal chelates
3.06, 3.07[21]	Average intra- and interligand S–S distances for three trigonal prismatic 1,2-dithiolato chelates
3.12[16]	Transannular S–S distance in 1-acetonyl-1-thionia-5-thiacyclooctane perchlorate
3.13[a]	S–S distance in disulfonium cation
3.15[15]	Across layer S–S distance in molybdenite
3.17[15]	Along layer S–S distance in molybdenite
D. Van der Waals Distances	
3.37[23]	Shortest intermolecular distance in S_8
3.45–3.48[24]	Intramolecular S–S distance in *p*-dithiane and *p*-dithiane derivatives
3.49[25]	S^+–S^+ distance in tri-*n*-butylsulfonium fluoride hydrate
3.50[15]	Interlayer distance in molybdenite
3.50[23]	Shortest intermolecular distance in S_6
3.64[20]	Shortest intermolecular S–S distance in S_4N_4
3.70[26]	Pauling's value

[a] This work.

(11) We are grateful for the loan of equipment, time, and expertise by Dr. Henry Hoekstra (Argonne National Laboratory) toward all the DTA-TGA measurements.

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(13) J. J. Macfarlane and I. G. Ross, *J. Chem. Soc.*, 4169 (1960).

(14) D. W. Meek and J. A. Ibers, *Inorg. Chem.*, **9**, 465 (1970), and references therein.

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(24) (a) R. E. Marsh, *Acta Crystallogr.*, **8**, 91 (1955); (b) G. Y. Chao and J. D. McCullough, *ibid.*, **13**, 727 (1960); (c) H. T. Kalff and C. Romers, *ibid.*, **18**, 164 (1965).

(25) P. T. Beurskens and G. A. Jeffrey, *J. Chem. Phys.*, **40**, 2800 (1964).

(26) L. Pauling, "Nature of the Chemical Bond," 2nd ed, Cornell University Press, Ithaca, N. Y., 1944, p 189.

distances observed[21,27a] in many square planar and trigonal prismatic 1,2-dithiolato metal chelates. This short, relatively constant S–S distance has been used to infer residual S–S bonding in 1,2-dithiolato complexes,[21,27] and this bonding has in turn been invoked to explain the unusual coordination geometries of these complexes. However, since the geometry of the disulfonium cation restricts the nonbonding sulfur electrons to orbitals which are directed away from the S–S axis, it is clear that there can be no direct S–S interaction in this ion (although "through-bond coupling," as described by Hoffmann[28] for triethylenediamine, is possible) and the short S–S distance must merely be caused by the strained carbon framework. This result implies that factors other than S–S electronic interaction could cause the short S–S distances observed in 1,2-dithiolato metal chelates. The wide range of S–S distances listed in Table VI indicates that it is relatively easy to force sulfur atoms to significantly less than van der Waals distances, and it may be purely geometrical and packing considerations that determine the resulting S–S separation.

As mentioned previously, this structure was solved using two different models. The first model, involving ordered anisotropic C atoms, was discarded because it statistically did not fit the data as well as the second model and because it led to two sets of parameters that were chemically unreasonable. First, the average C–C bond distance (1.450 ± 0.007 Å) was much too short for sp^3-hybridized carbon atoms; 1.526 Å is the accepted "normal" value for this type of bond,[29] and values of 1.54,[12] 1.53,[3b] and 1.54[3c] Å have been measured for the comparable C–C distance in other 1,4-bicyclo-[2.2.2]octane derivatives showing that the bicyclic cage system does not in itself lead to unusual C–C bond lengths. Second, abnormally large thermal parameters for C(1) and C(2) perpendicular to the mirror plane [and the corresponding combined parameters for C(3) and C(4)] were observed. These two anomalous parameters of the first model can most reasonably be accounted for by a model in which the disulfonium cage is distorted *via* right- and left-handed twists about the S–S vector. This can occur by the symmetric cage undergoing a torsional mode of vibration in the crystal lattice, or by a true disordered crystal structure involving equal amounts of randomly packed right-handed and left-handed twisted ions (in terms of the resultant diffraction data, this is equivalent to a crystal containing both twisted forms, each at half weight, superposed at each cationic site). These two mechanism for achieving disorder are crystallographically equivalent, the only difference between them being the magnitude of the energy barrier separating the right- and left-handed conformations, a small barrier corresponding to rapid torsional vibration and dynamic disorder and a large barrier corresponding to a static disorder with equal numbers of the two twisted forms distributed throughout the lattice. Refinement of the first ordered model in the presence of this disorder accounts for the observed elongated C atoms, since each ordered carbon ellipsoid would tend to stretch out to encompass the two disordered atoms, and for the observed short C–C distances, since these numbers would really represent the distance between midpoints of vectors joining two related disordered C atoms and not true C–C bond lengths.

The second model takes into account the distortion about the S–S axis by approximating electron density at a C atom position as two overlapping spheres rather than as an elongated ellipsoid. Tables VII,[7] VIII, and IX[7] give, respectively, the positional and thermal parameters, the principal interatomic distances and angles, and the pertinent root-mean-square thermal displacement values for this second model with disordered C atoms. Figure 2 shows two different views of the left-handed form of the disordered cage, the distortion from D_{3h} symmetry being quite obvious (average angle of twist is ±7.8°). In this model the average observed C–C bond distance, S–C bond distance, C–S–C angle, and S–C–C angle [1.52 (2) Å, 1.80 (2) Å, 100.6° (7) and 114.6° (11), respectively) are in very good agreement with the normal values for these parameters observed in simple sulfonium ions and *p*-dithiane derivatives (1.53 Å for a C–C bond,[3b,c,16,24] 1.82 Å for a sulfonium S–C bond,[16,30] 100° for a C–S–C angle, [16,24] and 112–

TABLE VIII
SELECTED INTERATOMIC DISTANCES AND ANGLES ($C_6H_{12}S_2ZnCl_4$, DISORDERED MODEL)

Bond distances, Å	Bond angles, deg
Zn–Cl(1), 2.283 (3)	Cl(1)–Zn–Cl(2), 109.40 (9)
Zn–Cl(2), 2.260 (3)	Cl(1)–Zn–Cl(3), 107.16 (6)
Zn–Cl(3), 2.267 (2)	Cl(2)–Zn–Cl(3), 112.15 (7)
Average, 2.270	Cl(3)–Zn–Cl′(3), 108.62 (6)
	Average, 109.33
S(1)–S(2), 3.130 (4)	
	C(1D)–S(1)–C(3DA), 98.2 (7)
S(1)–C(1D), 1.808 (10)	C′(1D)–S(1)–C(3DB),[a] 102.1 (7)
S(2)–C(2D), 1.794 (9)	C(2D)–S(2)–C(4DA), 101.5 (7)
S(1)–C(3DA), 1.807 (16)	C′(2D)–S(2)–C(4DB), 100.5 (7)
S(1)–C(3DB), 1.753 (16)	Average, 100.6
S(2)–C(4DA), 1.794 (17)	
S(2)–C(4DB), 1.834 (15)	C(2D)–C′(1D)–S(1),[a] 113.5 (7)
Average, 1.798	C(4DA)–C(3DB)–S(1), 115.2 (12)
	C(4DB)–C(3DA)–S(1), 116.1 (12)
C(1D)–C′(2D),[a] 1.523 (12)	C(1D)–C′(2D)–S(2), 114.4 (7)
C(3DA)–C(4DB), 1.450 (21)	C(3DA)–C(4DB)–S(2), 115.5 (10)
C(3DB)–C(4DA), 1.582 (24)	C(3DB)–C(4DA)–S(2), 112.4 (13)
Average, 1.518	Average, 114.6

Nonbonded distances, Å	Dihedral angles,[b] deg
C(1D)–C′(1D), 0.521 (22)	C(1D)–C(2D)–S(1), C′(1D)–C′(2D)–S(1)[a] } 21.9 (18)
C(2D)–C′(2D), 0.393 (27)	C(1D)–C(2D)–S(2), C′(1D)–C′(2D)–S(2) } 12.6 (10)
C(3DA)–C(3DB), 0.389 (23)	C(3DA)–C(4DA)–S(1), C(3DB)–C(4DB)–S(1) } 13.8 (14)
C(4DA)–C(4DB), 0.401 (24)	C(3DA)–C(4DA)–S(2), C(3DB)–C(4DB)–S(2) } 14.2 (15)
Average, 0.426	Average, 15.6
	C′(1D)–C′(2D)–S(1), C(3DB)–C(4DB)–S(1) } 122.7 (15)
	C′(1D)–C′(2D)–S(2), C(3DB)–C(4DB)–S(2) } 120.7 (14)
	C(1D)–C(2D)–S(1), C(3DA)–C(4DA)–S(1) } 115.4 (14)
	C(1D)–C(2D)–S(2), C(3DA)–C(4DA)–S(2) } 123.5 (14)
	Average, 120.6

[a] Primed atoms are generated from unprimed ones by operation of mirror plane at $y = 1/4$. Each cage consists of three primed and three unprimed carbon atoms. [b] Between planes each defined by three atoms.

(27) (a) E. I. Steifel, Z. Dori, and H. B. Gray, *J. Amer. Chem. Soc.*, **89**, 3353 (1967); (b) R. J. Gillespie, Paper No. 16 in "Werner Centennial," *Advan. Chem. Ser.*, **62**, 221 (1967); (c) H. B. Gray, R. Eisenberg, and E. I. Steifel, *ibid.*, Paper No. 42, **62**, 641 (1967).

(28) R. Hoffmann, *Accounts Chem. Res.*, **4**, 1 (1971).

(29) D. R. Lide, Jr., *Tetrahedron*, **17**, 125 (1962).

(30) A. Lopez-Castro and M. R. Truter, *Acta Crystallogr.*, **17**, 465 (1964).

116° for a S–C–C angle[16,24]). These comparisons show first that the strain induced in the bicyclic cage (by forcing the S–S distance to be less than the van der Waals separation) is not large enough to distort seriously its geometry from that which would be predicted from simple models, and second that the disordered model leads to more chemically reasonable bond parameters than does the ordered model.

It must be noted at this point that, in the first model, the elongation of C(1) and C(2) perpendicular to the mirror plane could possibly be due to an incorrect assignment of the space group to *Pnma* instead of to $Pn2_1a$. There has been much discussion recently[31] concerning the difficulty in deciding between such related space groups and unfortunately there does not seem to be a direct least-squares solution to the problem.[32] However, we believe *Pnma* to be the correct space group since the other five atoms on the mirror plane do *not* exhibit large thermal parameters perpendicular to the mirror as they would if $Pn2_1a$ were the correct space group, refinement being carried out in *Pnma*. This implies that the anomaly is peculiar to the carbon atoms, and indeed the thermal parameters for C(3) and C(4) (in the first model) are abnormally large in those directions corresponding to vibration about the S–S axis. In addition, the usual statistical tests[7] indicate that the data are better described by a centric space group.

While X-ray data cannot differentiate between the dynamic and static mechanisms of disorder, three indirect arguments can be made which favor, but do not establish, the dynamic mechanism. (1) In studying the pmr of solid triethylenediamine, Smith[2c] observed a line narrowing at −85° which is ascribed to restricted reorientation about the N–N axis. While it is difficult to assess quantitatively the effect of increasing the size and charge of the heteeroatoms in this cage system, qualitatively both effects would tend to favor the symmetrical D_{3h} transition state (in which the heteroatoms are furthest apart) at the expense of the enantiomers of D_3 symmetry and therefore lower the activation energy of torsional rotation in the disulfonium system relative to that observed for triethylenediamine. Thus it is very reasonable to describe the disulfonium cage as undergoing rapid torsional vibration at room temperature, which is 100° higher than the temperature at which triethylenediamine begins to show this vibration. (2) Combined DTA–TGA curves from 30 to 600° for the solids $C_6H_{12}S_2ZnCl_4$, $C_6H_{12}S_2Cl_2$ (anhydrous and monohydrate), $C_6H_{12}S_2(ClO_4)_2$, and $(C_6H_{12}S_2)$-$CoCl_{10}\cdot nH_2O$ show no consistent phase transformation that can be ascribed to the onset of torsional vibration.[11] Although this is negative evidence, it is consistent with the proposition that rapid torsional vibration is already occurring at room temperature. (3) The root-mean-square component of thermal displacement[7] for a disordered C atom along the vector defined by itself and its related disordered atom varies from 37 to 53% of the distance between these two atoms. To explain this result within the static mechanism would require invoking a large energy barrier (obtained *via* a crystal lattice locking effect) between two geometrically very similar ions. This seems to be less reasonable than a simple torsional vibration which carries one form into the other.

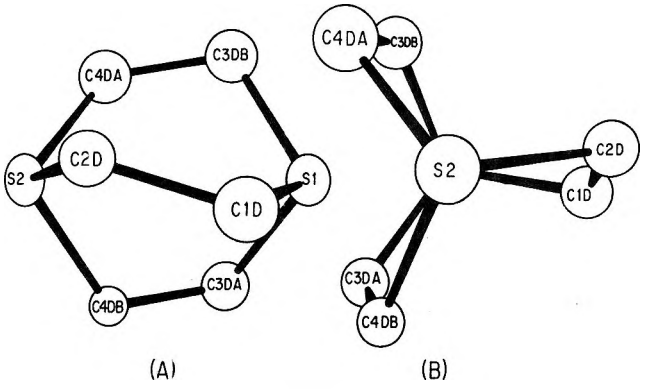
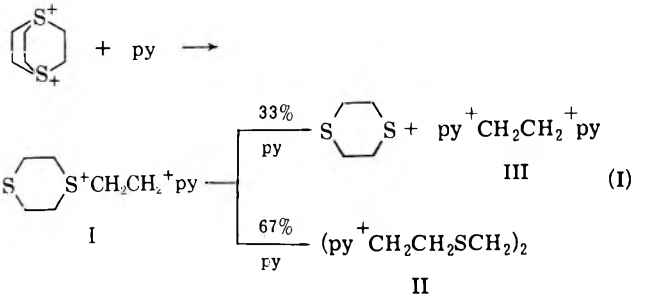


Figure 2.

Pmr Solution Spectra.—The pmr spectra of the $C_6H_{12}S_2^{+2}$ ion at room temperature in a variety of solvents consists of a single sharp peak (width at half height about 1 Hz, depending on concentration, etc.) at τ 5.91. The position of this peak indicates that the net dipositive charge of the disulfonium cation deshields the CH_2 protons relative to those in the ethyldimethylsulfonium ion (τ 6.52, center of quartet in D_2O), but that deshielding is not so effective as in the methylenebis(dimethylsulfonium) ion (τ 4.80 in trifluoroacetic acid).[33] The narrowness of the $C_6H_{12}S_2^{+2}$ signal indicates that both protons of the CH_2 group experience the same average environment and thus in solution the disulfonium ion has effective D_{3h} symmetry. If this situation arises because of rapid torsional vibration about the S–S axis, cooling a sample solution should lead to line broadening and eventually to splitting of the signal as the disulfonium ion approaches D_3 symmetry. This experiment does lead to significant line broadening, but the results are equivocal since the sample could not be cooled far enough to cause splitting.

Nucleophilic Attack.—Nucleophiles such as hydroxide ion, pyridine, and tributylphosphinebis(dimethylglyoximato)cobalt(I)[34] rapidly rupture the disulfonium cage. When pyridine is the attacking nucleophile, a simple mechanism involving two successive nucleophilic attacks on sulfonium centers (mechanism I) is



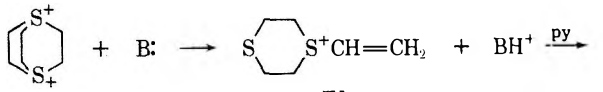
shown not to be effective since III is not observed as a reaction product. In addition, III does not accumulate as an intermediate since its characteristic CH_2 pmr signal cannot be detected in the reaction mixture even though independent experiments show that this ion is stable under the reaction conditions. Several additional observations indicate that these reactions proceed

(31) (a) B. van Dijk and G. J. Visser, *Acta Crystallogr., Sect. B*, **27**, 846 (1971); (b) H. Einspahr and J. Donohue, *ibid.*, **27**, 846 (1971); (c) J. D. Lef, *ibid.*, **27**, 847 (1971); (d) J. Donohue, *ibid.*, **27**, 1071 (1971).

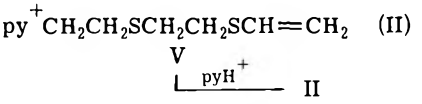
(32) We are indebted to the referees for bringing this point to our attention.

(33) C. P. Lillya and P. Miller, *J. Amer. Chem. Soc.*, **88**, 1559 (1966).

(34) G. N. Schrauzer and E. Deutsch, *ibid.*, **91**, 3341 (1969).

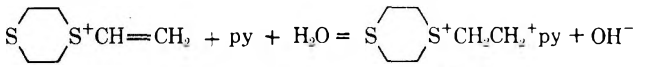


IV



(II)

through intermediate IV (mechanism II). (1) The reaction of 1 equiv of sodium hydroxide with aqueous disulfonium perchlorate yields IV. (2) Both I and IV have been isolated[1] and shown to be interconvertible *via* the rapid equilibrium III. (3) When the pyridine–



IV I (III)

disulfonium reaction is run in dimethylformamide, the pmr spectra of the reaction solutions exhibit signals characteristic of vinyl protons and V is obtained as a by-product. Independent experiments show that II will not undergo elimination to give V under the reaction conditions and therefore V arises from nucleophilic attack by pyridine on IV (which is not expected to yield *p*-dithiane and *N*-vinylpyridinium ion in light of the inertness of vinyl halides to nucleophilic attack[35]). (4) Doering[36] has shown that the reaction of hydroxide ion with 2-bromoethyldimethylsulfonium ion rapidly yields the vinyldimethylsulfonium ion by elimination of HBr. (He has also observed that hydroxide rapidly attacks 1-thioniabicyclo[2.2.1]heptane.[37])

(35) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold, New York, N. Y., 1961, p 341.

(36) W. von E. Doering and K. Schreiber, *J. Amer. Chem. Soc.*, **77**, 514 (1955).

(37) W. von E. Doering and A. K. Hoffmann, *ibid.*, 521 (1955).

The magnitudes of the rates of OH^- attack on the two disulfonium centers, relative to H–D exchange, are indicated by the observation that, when molar deuterioxide is allowed to react with disulfonium chloride, mass spectral analysis of the resultant *p*-dithiane shows that it has undergone exactly 50% H–D exchange. This can be understood if deuterioxide rapidly attacks the disulfonium ion before H–D exchange can take place, giving either intermediate IV or the –OD analog of intermediate I. This intermediate is then subject to deuterioxide-catalyzed H–D exchange *via* the accepted mechanism for sulfonium ions.[38] Thus only those hydrogens on carbons bound to the sulfonium sulfur will exchange before the second, slower hydroxide attack occurs, leading to the observed 50% deuterium content of the *p*-dithiane product.

Registry No.—Disulfonium tetrachlorozincate, 35616-90-1; *p*-dithiane, 505-29-3; disulfonium perchlorate, 35624-14-7; disulfonium chloride, 5344-51-4; disulfonium tetraphenylborate, 35616-91-2; tetra(disulfonium)cobalt(II) decachloride hydrate, 35616-92-3; dipyridinium 1,1′-[ethylenebis(thioethylene)]diperchlorate, 35624-16-9; *N*-[3,6-bis(thia)-7-octenyl]pyridinium perchlorate, 35624-17-0; dipyridinium 1,1′-ethylenediperchlorate, 6601-41-8.

Acknowledgments.—Funds for this work were provided by ARPA and by a Du Pont Young Faculty Grant. The author is grateful to Dr. Ernst Habicht, Jr., for originally bringing the disulfonium ion to his attention, as well as to Dr. JoAnn Molin-Case, Professor E. Fleischer, Professor R. Elder, and Mr. G. Christoph for invaluable assistance with the X-ray analysis.

(38) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1962, pp 153–155.

The Synthesis of 2,4-Diketo-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.4.0]decane and 2,4-Diketo-3-phenyl-Δ^5-7-oxa-1,5-diazabicyclo[4.4.0]decane[1]

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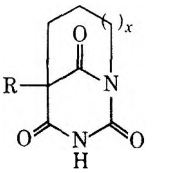
In an attempt to secure 5-phenyl bicyclo barbiturates, *N*-(haloalkyl)-5-phenylbarbituric acids were prepared and converted to their corresponding thallous salts. Nitrourea and alkanolamines were allowed to react to produce *N*-(hydroxyalkyl)ureas, which were converted to the corresponding *N*-(hydroxyalkyl)-5-phenylbarbituric acids and *via* these alcohols to the halides. When cyclization of the thallous salts of the *N*-(halopropyl)-5-phenylbarbituric acids was attempted in benzene–water, no intramolecular C-alkylation occurred and the only product isolated was 2,4-diketo-3-phenyl-Δ^5-7-oxa-1,5-diazabicyclo[4.4.0]decane. Utilizing anhydrous benzene as the solvent for the cyclization reaction, the product obtained was 2,4-diketo-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.4.0]decane.

As part of a study on the steric aspects of selective central nervous system depression, attempts have been made to find general synthetic routes to bridged barbiturates, **1**, to be investigated as antiepileptic agents.

One such barbituric acid, 5-phenyl-7-methoxy-2,4,9-triketo-1,3-diazabicyclo[3.3.1]nonane (**2**), was prepared by base-catalyzed intramolecular attack of an



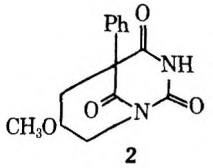
1

R = alkyl, aryl

x = 0, 1, 2

imide nitrogen on the primary bromo function of 5-phenyl-5-(2-methoxy-3-bromopropyl)barbituric acid

(1) Taken in part from the dissertation presented by J. W. Ayres, August 1970, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy degree.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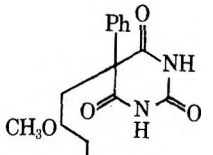
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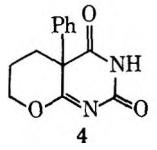
(3).[2] This did not prove to be a general method for the desired compounds, since intramolecular cyclization of 5-substituted 3-halopropyl- and 2-halopropylbarbituric acids failed to give the N-alkylated system but rather the O-alkylated pyrano- and furopyrimidines, **4** and **5**, respectively.[3]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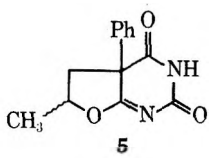
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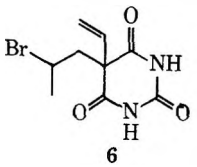
The intramolecular N-alkylation of **6** was reported to give the bicyclo barbiturate 5-vinyl-2,4,8-triketo-1,3-diazabicyclo[3.2.1]barbituric acid (**7**) through N-alkylation.[4] The data reported (ir absorption at 1650 cm^{-1}, acid lability) indicates that the structure reported as **7** is actually **8**.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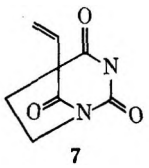
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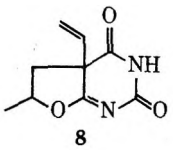
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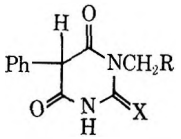
Taylor and McKillop[5] have reported exclusive C-alkylation upon heating the thallous salts of 1,3-dicarbonyl compounds with alkyl iodides. In order to prepare the desired compounds utilizing their method, it was necessary to synthesize barbituric acids with functional groups located on an N-alkyl side chain. These compounds could give the barbiturate **1** by intramolecular attack of the carbon atom at C-5 on the proper side chain substituent.

N-Allyl-5-phenylbarbituric acid (**9**) and *N*-allyl-5-phenylthiobarbituric acid (**10**) were obtained by allowing allylurea or allylthiourea to react with diethyl phenylmalonate in the presence of sodium ethoxide.



9, X = O; R = CH=CH$_2$
10, X = S; R = CH=CH$_2$
11, X = O; R = CH_2CH_2Br
12, X = O; R = CH_2OH
13, X = O; R = CH_2CH_2OH
14, X = O; R = $CH_2CH_2CH_2OH$
15, X = O; R = $CH_2CH_2CH_2Br$
16, X = O; R = CH_2CH_2I
17, X = O; R = CH_2CH_2OTs

An attempt was made to obtain the *N*-bromopropyl compound **11** by reaction of **9** with hydrogen bromide under free-radical conditions; however, no identifiable products could be isolated.

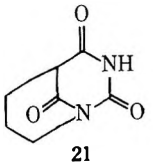
The treatment of nitrourea with ethanolamine was reported[6] to give *N*-(2-hydroxyethyl)urea (**18**). In a similar manner, *N*-(3-hydroxypropyl)urea (**19**) and

18, $n = 0$
19, $n = 1$
20, $n = 2$

N-(4-hydroxybutyl)urea (**20**) now have been prepared. The condensation of **18**, **19**, and **20** with diethyl phenylmalonate produced **12**, **13**, and **14**, respectively. The treatment of **13** or **14** with hydrogen bromide in acetic acid produced the corresponding bromides **11** and **15**.

The thallous salts of **11** and **16** were prepared by the addition of thallium ethoxide in dimethoxyethane (DME) to a solution of the barbiturate in the same solvent. Kornblum[7] and coworkers reported the importance of solvent in determining the ratio of C-alkylation to O-alkylation in the alkylation of ambident anions. Higher ratios of the C-alkylated products were obtained when the reactions were performed in water or fluorinated alcohols. With this fact in mind, the thallous salts of the barbiturates **11** and **16** were refluxed in a 50:50 benzene–water solvent system.

The product isolated had an empirical formula consistent with the bicyclic structures **21**, **22**, and **23**. The nmr spectrum [δ 3.4 (s), one proton)] indicated structure **23**, which is the only possibility with a benzylic proton. The presence of an ir peak at 1630 cm^{-1} (C=N) is consistent with **23** and eliminates **21**. A minor impurity proved to be **22**.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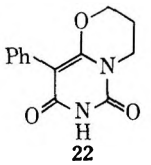
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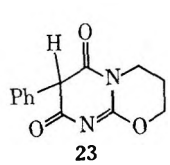
23

When the thallous salt of **11** was refluxed in anhydrous benzene the only product isolated was **22**. This compound had no benzylic absorption in the nmr but showed a one-proton singlet at δ 11.2 for the imide hydrogen, which is consistent with the assigned structure which has been reported previously.[8]

Experimental Section[9]

N-Allyl-5-phenylbarbituric Acid (**9**).—A mixture of allylurea (40 g, 0.40 mol) and diethyl phenylmalonate (94 g, 0.40 mol) was added to a solution of Na (18 g, 0.78 g-atom) in dry EtOH (600 ml) and refluxed for 2 days. The EtOH was removed *in vacuo* and the residue was dissolved in 500 ml of H_2O. The solution was made acidic with 10% HCl and the precipitate was collected and washed with 300 ml of hot C_6H_6. Recrystallization ($C_6H_5CH_3$) yielded **9** (57 g, 60%), mp 122–123°.

(2) E. E. Smissman, R. A. Robinson, J. B. Carr, and A. J. Matuszak, *J. Org. Chem.*, **35**, 3821 (1970).
(3) E. E. Smissman, R. A. Robinson, and A. J. B. Matuszak, *ibid.*, **35**, 3823 (1970).
(4) M. Konieczny, *Arch. Immunol. Ther. Exp.*, **15**, 920 (1967).
(5) E. C. Taylor and A. McKillop, *Accounts Chem. Res.*, **3**, 338 (1970).
(6) R. W. Charlton and A. R. Day, *J. Org. Chem.*, **1**, 552 (1937).
(7) N. Kornblum, P. J. Berrigan, and W. J. LeNoble, *J. Amer. Chem. Soc.*, **85**, 1141 (1963).
(8) E. E. Smissman and J. W. Ayres, *J. Org. Chem.*, **36**, 2407 (1971).
(9) Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Ir data were recorded on a Backman IR-10 spectrophotometer and nmr data on Varian Associates A-60, A-60A, and HA-100 spectrometers (TMS). Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M 185 C, H, N analyzer, University of Kansas.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.46. Found: C, 63.72; H, 4.74; N, 11.69.

N-**Allyl-5-phenylthiobarbituric Acid (10).**—A mixture of allylthiourea (52.6 g, 0.453 mol) and diethyl phenylmalonate (107.0 g, 0.453 mol) was added to a stirred solution of Na (20.8 g, 0.905 g-atom) in 500 ml of dry EtOH and refluxed overnight. The EtOH was removed *in vacuo* and the residue was dissolved in 500 ml of H_2O. The solution was made acidic (10% HCl) and the precipitate was collected to yield **10** (112 g, 95%), mp 198–201° (Me_2CO).

Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.64; N, 10.76. Found: C, 60.21; H, 4.61; N, 10.89.

N-(**2-Hydroxyethyl**)**urea (18).**—The procedure used was essentially that of Charlton and Day.[6] Nitrourea (25 g, 0.238 mol) was added slowly to a stirred solution of aminoethanol (12.2 g, 0.200 mol) in 15 ml of H_2O cooled in an ice bath. The mixture was allowed to stir overnight and the H_2O was removed *in vacuo*. The residual oil solidified on standing in the freezer and was crystallized from a large volume of dioxane to yield **18** (14.6 g, 70.4%), mp 95° (lit. mp 94–95°).

Anal. Calcd for $C_3H_8N_2O_2$: C, 34.61; H, 7.74; N, 27.14. Found: C, 34.68; H, 8.04; N, 27.14.

N-(**3-Hydroxypropyl**)**urea (19).**—Nitrourea (50.0 g, 0.475 mol) was added in small portions to a stirred solution of aminopropanol (30.0 g, 0.400 mol) in 40 ml of H_2O cooled in an ice bath. The mixture was stirred for 24 hr and the H_2O was removed *in vacuo*. The residual oil formed a waxy solid after standing for 4 days to give a quantitative yield of **19**, mp 50–52°.

Anal. Calcd for $C_4H_{10}N_2O_2$: C, 40.66; H, 8.53; N, 23.71. Found: C, 40.97; H, 8.79; N, 23.90.

N-(**4-Hydroxybutyl**)**urea (20).**—Nitrourea (14.28 g, 0.136 mol) was added over a period of 45 min to a stirred solution of 4-amino-1-butanol (11.0 g, 0.124 mol) in 40 ml of H_2O while being cooled in an ice bath. The reaction mixture was allowed to warm to 25° and stirred for 10 hr. The H_2O was removed *in vacuo* to yield a yellow oil. The oil was washed three times with C_6H_6; the last time the C_6H_6 was removed by distillation in order to azeotrope traces of H_2O. The yellow oil (14.2 g, 87%) did not crystallize. The spectral data were consistent with the assigned structure.

N-(**2-Hydroxyethyl**)-**5-phenylbarbituric Acid (12).**—A mixture of diethyl phenylmalonate (26.9 g, 0.114 mol) and *N*-(2-hydroxyethyl)urea (**13**) (11.4 g, 0.114 mol) was added to a stirred solution of Na (5.30 g, 0.230 g-atom) in 120 ml of dry EtOH and refluxed overnight. The EtOH was removed *in vacuo* and the residue was dissolved in H_2O. The solution was made acidic (10% HCl) and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to leave an oil which was triturated with Et_2O to yield **12** (18.7 g, 66%), mp 120° [EtOAc–petroleum ether (bp 60–70°)].

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.29; H, 4.90; N, 11.22.

N-(**3-Hydroxypropyl**)-**5-phenylbarbituric Acid (13).**—A mixture of diethyl phenylmalonate (60.0 g, 0.254 mol) and *N*-(3-hydroxypropyl)urea (**19**) (30.0 g, 0.254 mol) was added to a stirred solution of Na (11.5 g, 0.500 g-atom) in 300 ml of dry EtOH and refluxed overnight. The EtOH was removed *in vacuo* and the residue was dissolved in H_2O. The solution was made acidic (10% HCl) and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to yield **13** (32.5 g, 49%), mp 170° (EtOAc).

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.32; H, 5.54; N, 10.45

N-(**4-Hydroxybutyl**)-**5-phenylbarbituric Acid (14).**—Essentially the same procedure was utilized as reported above. A white solid was obtained from 29.26 g (0.124 mol) of diethyl phenylmalonate and 16.4 g (0.124 mol) of 4-hydroxy-*n*-butylurea in the presence of 5.7 g (0.248 g-atom) of Na dissolved in 300 ml of EtOH. The solid was recrystallized (EtOAc) to yield 12.5 g (36%) of the desired product **14**, mp 186–188°. The spectral data were consistent with the assigned structure.

Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.85; H, 5.83; N, 10.13. Found: C, 61.03; H, 6.04; N, 10.01.

N-(**3-Bromopropyl**)-**5-phenylbarbituric Acid (11).**—A stirred solution of *N*-(3-hydroxypropyl)-5-phenylbarbituric acid (**10**) (10.0 g, 0.038 mol) in 100 ml of 32% HBr–HOAc was refluxed overnight in a stoppered Wheaton glass pressure bottle. The HOAc was removed *in vacuo* and the residue was added to 400 ml of crushed ice. The solution was made acidic and decanted from the gummy precipitate, which was dissolved in Me_2CO, dried ($MgSO_4$), and concentrated to leave a solid which was washed with Et_2O to yield 11 (9.2 g, 74.2%), mp 120° (EtOAc–petroleum ether).

Anal. Calcd for $C_{13}H_{13}N_2O_3Br$: C, 48.01; H, 4.02; N, 8.61. Found: C, 47.71; H, 4.08; N, 8.59.

N-(**4-Bromobutyl**)-**5-phenylbarbituric Acid (15).**—The procedure was essentially that used for the preparation of 11. The crude product was recrystallized from Me_2CO–petroleum ether (bp 60–68°) to yield white crystals (70%), mp 125–127°.

Anal. Calcd for $C_{14}H_{15}N_2O_3Br$: C, 49.57; H, 4.46; N, 8.26. Found: C, 49.56; H, 4.26; N, 8.55.

2,4-Diketo-3-phenyl-Δ^5-7-oxa-1,5-diazabicyclo[4.4.0]decane (23).—*N*-(3-bromopropyl)-5-phenylbarbituric acid (**11**) (2.0 g, 0.006 mol) was dissolved in 250 ml of anhydrous dimethoxyethane (DME) at 25°. To this solution was added, at one time, a solution of thallium ethoxide ($TlOC_2H_5$) (1.54 g, 0.006 mol) in 50 ml of anhydrous DME. A white, crystalline product formed immediately. This material was filtered, washed with water, and refluxed in 500 ml of C_6H_6–H_2O (1:1) for 12 hr. The two-phase system was cooled and the aqueous layer was acidified with 10% HCl and extracted with EtOAc (3 × 150 ml). The extracts were combined, dried ($MgSO_4$), and filtered and the solvent was removed to yield 0.81 g (55%) of **23** as a white solid which was recrystallized from EtOAc: mp 294–297° dec; ir (KBr) 3400, 3190, 1700, 1630, 1590, 1490, 1280 cm^{-1}; nmr (DMSO-d_6) δ 2.0–2.5 (2 H, multiplet, $-CH_2CH_2CH_2-$), 3.4 (1 H, singlet, benzylic H), 3.8–4.0 (2 H, triplet, $-NCH_2-$), 4.3–4.5 (2 H, triplet, $-OCH_2-$), 7.4 (5 H, singlet, aromatic).

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.46. Found: C, 64.22; H, 5.09; N, 11.30.

The same procedure utilizing the thallous salt of *N*-(3-iodopropyl)-5-phenylbarbituric acid (**16**) afforded a 28% yield of **23**.

2,4-Diketo-5-phenyl-Δ^5-7-oxa-1,3-diazabicyclo[4.4.0]decane (22).—The thallous salt of 11 was prepared as in the preparation of **23** and 1.55 g (0.0029 mol) of the white solid was refluxed in anhydrous C_6H_6 for 8 hr. Water was added to dissolve the yellow precipitate (TlBr) The aqueous layer was acidified with 10% HCl and extracted with EtOAc (3 × 150 ml). The extracts were combined, dried ($MgSO_4$), and filtered and the solvent was removed to yield 350 mg (49%) of **22** as a white solid which was recrystallized from EtOAc: mp 292–295°; ir (KBr) 3400, 3160, 2990, 1710–1590, 1480, 1430, 1270, 1200, 1170, 1130, 1095 cm^{-1}; nmr (DMSO-d_6) δ 2.0–2.5 (2 H, multiplet, $-CH_2CH_2CH_2-$), 3.7–3.9 (2 H, triplet, $-NCH_2-$), 4.2–4.4, (2 H, triplet, $-OCH_2-$), 7.8 (5 H, singlet, aromatic), 11.2 (1 H, singlet, O=CNHC=O).

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.46. Found: C, 63.98; H, 4.74; N, 11.56.

Registry No.—**9**, 35359-11-6; **10**, 35359-12-7; **11**, 35359-13-8; **12**, 35359-14-9; **13**, 35359-15-0; **14**, 35359-16-1; **15**, 35427-24-8; **18**, 2078-71-9; **19**, 16517-53-6; **20**, 34486-68-5; **22**, 30409-28-0; **23**, 35359-21-8.

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The Peripheral Synthesis of Medium-Ring Nitrogen Heterocycles *via* β-Elimination Reactions[1]

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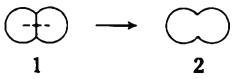
A series of 5-substituted *N*-methylazacyclononanes have been prepared from several $\Delta^{4(9)}$-dehydroindolizidines by (i) nucleophilic addition to the ternary iminium group, (ii) quaternization with methyl iodide, and (iii) selective cleavage of the central carbon–nitrogen bond by β elimination. α-Picolyllithium, benzylmagnesium chloride, allylmagnesium bromide, and the ethyl bromoacetate–zinc reagent were used as nucleophiles, and ring opening was accomplished with sodium amide, sodium ethoxide, *n*-butyllithium, or by a thermal aminodecarboxylation. The structures of the products were proven by nmr and ir and in one case by oxidative cleavage of the carbon–carbon double bond to a nine-membered ring amino ketone **17** which displayed the anticipated transannular reactions and interactions and could be reduced to *N*-methylazacyclononane.

Interest in medium-sized carbocyclic and heterocyclic rings originates from common sources; both undergo transannular reactions[3-6] and both occur in important natural products.[7-9] Unfortunately the ready availability of the former series[10,11] is not paralleled for the latter.

The preparation of medium-ring nitrogen heterocycles by ring expansion,[12] cyclization,[13,14] or peripheral synthesis,[15] while valuable for specific compounds, is limited in scope either by the availability of the starting materials or the reaction conditions. The goal of the research described in this and subsequent papers[16,17] was to develop an efficient, general synthesis of such compounds, particularly those with functional groups transannular to nitrogen.

Peripheral synthesis, in which the medium ring is first constructed on the periphery of a bicyclic system of normal-sized rings and the central bond is then cleaved (**1** → **2**), was selected as the most suitable



1 **2**

method of preparation since it would circumvent undesirable transannular effects and also would permit the unambiguous prior placement of substituents. This concept is based on early structural studies of the berberine alkaloids[18] and was first utilized to synthesize the protopine alkaloids allocryptopine,[19] protopine,[20] and cryptopine.[21] Recognition of the more general utility of this method is due to Leonard[15] and Wharton[22] in the azacyclic and carbocyclic series, respectively, and has led to many recent applications directed at the synthesis of sesquiterpenes,[23] indole alkaloids,[8,24] and medium-ring heterocycles in general.[25] Bicyclic precursors (**1**) with bridged[25a] or fused [25b-f] ring systems containing various functional groups and heteroatoms in various positions have been utilized. Our own method[25b] is based on the biogenetic relationship of the berberine and the protopine alkaloids[26] in that it begins with fused 1-azabicycloalkanes (**3**) and requires selective cleavage of the central carbon–nitrogen bond. Although the details of this cleavage in nature remain obscure,[26,27] the hypothetical sequence,[28] oxidation (**3** → **4**), hydration (**4** → **5**), methylation (**5** → **6**), and elimination (**6** → **7**), serves as a useful model for these synthetic studies.

Fused 1-azabicycloalkanes (**3**) are readily available[29] and their oxidation to iminium salts (**4**) with mercuric acetate is well known.[29-31] The fact that nucleophiles will add to ternary iminium groups[32] and that structures such as **6** and **7** are easily interconvertible[3] provides the remaining analogies for this scheme. The

(1) Taken from the Ph.D. Dissertations of (a) L. R. Kray, University of California, Riverside, 1965, and (b) R. F. Francis, Texas Christian University, 1967.

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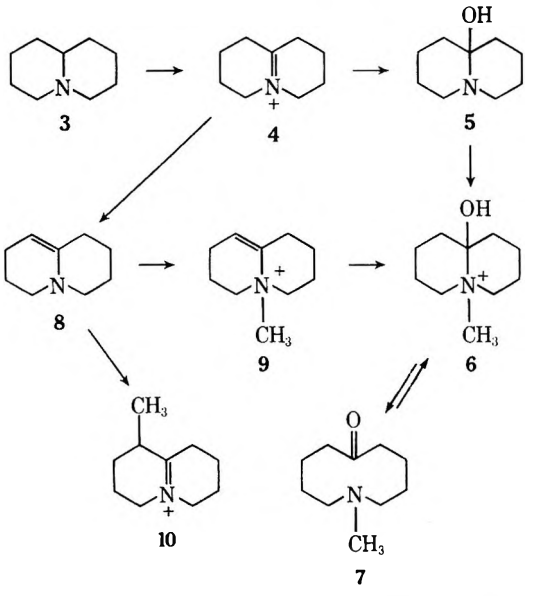
TABLE I
STRUCTURES AND YIELDS IN RING-OPENING SEQUENCE

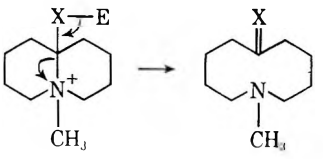
Series	R_1	R_2	X	M	B	% yields 13 → 14	→ 14 MeI	→ 15
a	H	H	α-Pyridyl	Li	$NaNH_2$	64	93	25
b	H	H	Phenyl	MgCl	$NaNH_2$	93	94	100
c	CH_3	H	Phenyl	MgCl	$NaNH_2$	90	89	90
d	H	H	Vinyl	MgBr	$NaNH_2$	97	93	96
e	H	H	COOEt	ZnBr	NaOEt	87	87	84[a]
f	H	CH_3	COOEt	ZnBr	NaOEt	88	89	89[b]
g	H	Et	COOEt	ZnBr	NaOEt	83	85	80

[a] One of the isomers 20 (see Results and Discussion). [b] Mixture of 15f and 21 (see Results and Discussion).

key to extending the scope of this method is the use of nucleophiles other than the hydroxide ion which, *in vitro*, doesn't add to **4** at all but gives the enamine **8**.[30,31] The preparation of **6** from **8** *via* the quaternary enammonium salt **9** is not generally possible since enamines such as **8** sometimes undergo methylation on carbon[33] (**8** → **10**) as well as on nitrogen (**8** → **9**).[30]

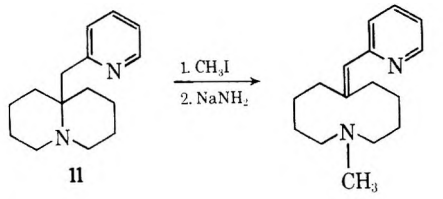


In the present study the nucleophile (XE) was selected so as to facilitate cleavage of the central carbon–nitrogen bond by the β elimination of a group E without its bonding electrons. Subsequent papers[16,17] deal with other ring-opening reactions and hence other nucleophiles are necessary.

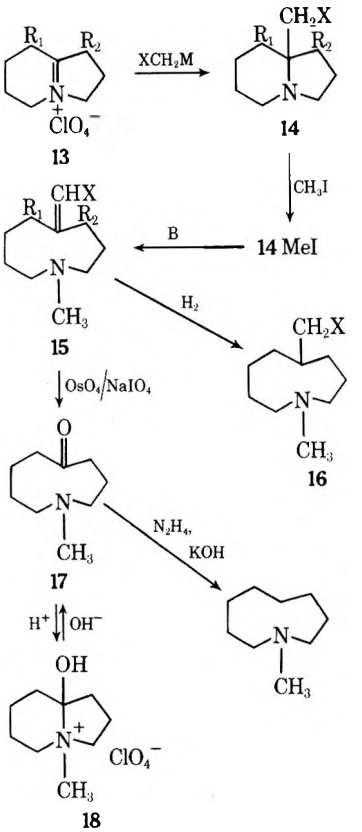


Results and Discussion

Initially, ring opening was attempted on the known[32] methiodide of **11** available from dehydroquinolizidine and α-picolyllithium. Although the sodium amide induced elimination of the model methiodide of **12** proceeded smoothly as shown, the product from **11** was obtained in low yield as an unstable, uncharacterizable mixture. The methiodide of the related indolizidine **14a** (Table I) was prepared from dehydroindolizidine



13a analogously to **11** and also gave a low yield of an unstable product **15a**, but in this case pure crystalline



derivatives were obtained. The nmr spectrum of **15a** displayed only one olefinic proton peak, indicating that the central and not one of the peripheral carbon–nitrogen bonds had been cleaved. This conclusion was substantiated by the clean catalytic reduction of **15a** to a dihydro compound **16a**, whose nmr spectrum contains neither vinyl hydrogen nor *C*-methyl peaks.

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The double bond in **15a** was assigned to the conjugated position as shown on the basis of infrared (1630 cm^{-1}) and nmr (no vicinal coupling of vinyl–hydrogen singlet) evidence. The fact that the uv spectrum of **15a** was more like that of 2-ethyl, rather than 2-vinylpyridine, while perhaps due to steric effects, suggested that additional evidence might be desirable. Attempted oxidative cleavage of the double bond of **15a** gave no characterizable products, however.

While extension of this ring-opening sequence with α-picolyllithium to the substituted indolizidine **13c** failed at the very first step (68% recovery of **13c**), both **13b** and **13c** reacted readily with benzylmagnesium chloride as the nucleophile. Furthermore, in contrast to the **a** series, stable products were produced throughout the **b** and **c** series in high yield (Table I) and purity. The assigned structures **15b,c** follow from analytical and spectral evidence similar to that cited for the **a** series (Tables II and III). Catalytic reduction of **15b** gave a dihydro compound **16b**, while oxidation of either **15b** or **c** with OsO_4/HIO_4 led to benzoic acid as the only isolable product. With $OsO_4/NaIO_4$ as the oxidizing agent, **15b** gave benzaldehyde (90% yield) and an amino ketone **17** (98% yield) whose spectral properties, in particular[3] the disappearance of the infrared carbonyl absorption at 1686 cm^{-1} on formation of the salt **18**, support the indicated structure. Final proof of the presence of a nine-membered ring in these compounds comes from the Wolff–Kishner reduction of **17** to *N*-methylazacyclononane.

The sequence **13b** → **17** has been repeated[34] as well as extended[35] to the quinolizidine series by Sisti and Lohner with the same excellent yields as obtained in our laboratory (Table I). Substitution of an allyl for a benzyl group (**d** series) also has no adverse effects on the course of reaction. The resulting diene **15d** is a stable colorless liquid displaying diene absorptions in the infrared and peaks for four vinyl hydrogens in the nmr.

In an extension of the analogy[32] between carbonyl and ternary iminium groups, a Reformatsky reaction was carried out on the indolizidinium salts **13e–g** as well as on $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate. The resulting amino esters (**14e–g**, **19**) were obtained in good yields (Table I) as stable colorless liquids. Ring opening of the indolizidine methiodides occurs readily with sodium ethoxide to give **15e–g**. Spectral properties indicate that **15g** has the structure shown (nonconjugated vinyl hydrogen peak in the nmr and a conjugated carbonyl group in the infrared), that **15e** is actually one of the nonconjugated isomers **20** (triplet vinyl hydrogen peak in nmr and nonconjugated carbonyl in infrared), and that **15f** is a mixture of *ca.* 30% **15f** and 70% **21** (two kinds of vinyl hydrogens in the nmr and two carbonyls in the infrared).

The formation of the more stable[36] endocyclic olefins **20** and **21** suggests that, in contrast to sodium amide, sodium ethoxide induced ring opening leads to isomerization of the initially formed conjugated olefins **15**. Some support for this view comes from the formation

TABLE II

PHYSICAL PROPERTIES OF AZACYCLONONANES AND THEIR DERIVATIVES

Compd	Mp, or bp, °C (mm)	Calcd, % C	Calcd, % H	Found, % C	Found, % H
15a	135–136 (0.05)	78.21	9.62	77.97	10.32
15a picrate	203–204	47.09	4.09	47.21	4.33
15a MeI	143–145	50.27	6.59	50.34	6.81
15b	94–95 (0.1)	83.78	10.10	83.76	10.14
15b MeI	169–170.5	54.98	7.07	55.05	7.25
15b TNBS[a]	143–144	50.57	5.02	50.58	5.31
15c MeI	200–203 dec	56.10	7.32	56.07	7.50
15d	40–41 (0.6)				
15d MeI[b]	138–139	48.60	7.53	48.78	7.64
20	75–77 (1.0)				
20 MeI	97.5–100	45.78	7.16	45.93	7.44
20 TNBS[a]	132–133 dec	44.01	5.05	43.77	4.91
15g	80–82 (1.0)				
15g TNBS[a]	140–142	46.08	5.50	46.09	5.41
22 MeI	184–185	54.99	9.22	55.29	9.07
24	38–39 (0.12)				
24 picrate[c]	305 dec	50.25	5.79	50.27	5.82
16a MeI	113–115	52.73	7.06	52.97	6.76
16b TNBS[a]	204–206 dec	53.88	4.99	53.81	4.81
18	272–273 dec[d]	42.28	7.09	42.40	7.10

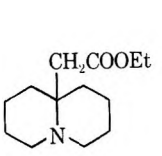
[a] 2,4,6-Trinitrobenzenesulfonate.[29] [b] % N: calcd, 4.36; found, 4.43. [c] % N: calcd, 14.65; found, 14.51. [d] Lit.[34] 270°; % N: calcd, 5.48; found, 5.59.

TABLE III

SELECTED SPECTRAL PROPERTIES OF AZACYCLONONANES

Compd	Nmr, δ	Ir, cm^{-1}
15a[a]	6.35 (s, 1)	1630 (w)
15b	6.32 (s, 1)	1650 (w)
15c	6.35 (s, 1), 1.05 (d, 3, J = 9 Hz)	1650 (w)
15d	5.84 (m, 4)	1631 (s), 1585 (w)
15d MeI	6.00 (m, 4)	
20	5.32 (t, 1, J = 9.6 Hz)	1735
20 MeI	5.55 (t, 1, J = 9.5 Hz)	1740
15f + **21**	5.60 (s, 0.3), 5.3 (m, 0.7)	1710, 1735
15g	5.60 (s, 1)	1715
22	5.14 (d, 1, $J \approx 1$ Hz)	1645 (w)
24	5.23 (d, 2, J = 4.4 Hz)	1640, 880
17[b]		1686[c]
18		3420, 3170, 3040[d]

[a] Uv max (95% EtOH) 261 mμ (ε 3660); 2-ethylpyridine, 261 mμ (ε 5780); 2-vinylpyridine, 235, 277 mμ (ε 5640). [b] Mass spectrum *m/e* (rel intensity) 155 (47), 140 (10), 126 (11), 112 (17), 99 (68), 98 (100), 84 (88), 71 (53), 70 (72), 57 (82). We would like to thank Professor Carl Djerassi for obtaining this spectrum for us. [c] Lit. 1675 cm^{-1}; *N*-methylazacyclooctan-5-one (**25**), 1683 cm^{-1};[14] *N*-methylazacyclodecan-6-one (**26**), 1694 cm^{-1}.[14] [d] Lit. HBr salt, 3180 cm^{-1}; **25** $HClO_4$, 3380 cm^{-1};[14] **26** $HClO_4$, 3400 cm^{-1}.[14]



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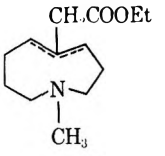

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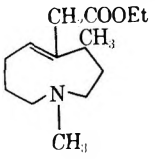

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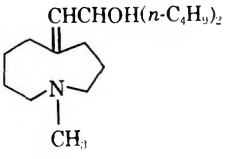

22

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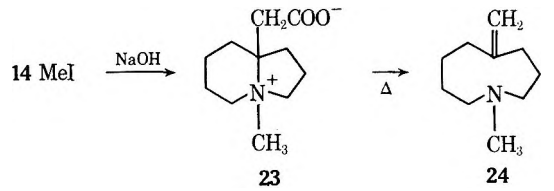
(35) A. Sisti and D. Lohner, *J. Org. Chem.*, **32**, 2026 (1967).
(36) A. Cope, D. Ambros, E. Ciganek, C. Howell, and Z. Jacura, *J. Amer. Chem. Soc.*, **82**, 1750 (1960).

of the exocyclic olefin **22** from the ring opening of **14e** MeI with *n*-butyllithium. Presumably before the initially formed **15e** can isomerize to **20**, it reacts further at the carbonyl group, thereby deactivating the molecule to base-catalyzed isomerization. The variation of isomer composition with the nature of R_2 in **15e–g** reflects a steric effect either on the stability of the various olefins or on the ease of their formation.

A final example of ring opening by β elimination was carried out in the absence of base, thus permitting the preparation of a medium-ring nitrogen heterocycle containing the less stable[36] exocyclic methylene group. Treatment of **14e** MeI with 1 equiv of sodium hydroxide led to the betaine **23** which, when heated to



23 **24**

200° in a dry state, gave **24**. A similar aminodecarboxylation has been reported for the morphine alkaloid metaphanine.[37]

Experimental Section

Melting points and boiling points are corrected. Analyses were performed by Mr. C. F. Geiger, Ontario, Calif., and by M-H-W Laboratories, Garden City, Mich. Nmr spectra were determined on a Varian A-60 instrument using $DCCl_3$ (for solids) and CCl_4 (for liquids) as solvents and TMS as an internal standard. Infrared spectra were measured on Perkin-Elmer 421, 237 or Beckman IR-10 instruments as films (liquids) or KBr disks (solids). A Cary Model 15 spectrophotometer was used to obtain the uv spectra.

Iminium Salts (13).—These compounds were prepared as described previously[29,31,38] by $Hg(OAc)_2$ oxidation of the corresponding 1-azabicycloalkanes which, in turn, were synthesized by the two-step reductive cyclization[29] of the appropriate pyridyl alcohols modified as follows for the large-scale preparation of indolizidine. The catalytic reduction of the pyridine ring[29] was replaced by a chemical reduction.[39] Although the yields by this procedure were lower (75 *vs.* 92%), an overall saving of time and/or expense was possible since: (i) the Pt catalyst in the original method[29] had to be either regenerated or discarded after several runs; (ii) a simpler work-up procedure not requiring hydrolysis of the intermediate acetate ester[29] was possible; and (iii) scale-up was not as limited by the size of the equipment.

Reactions of Iminium Compounds with Nucleophiles. A. With α-Picolyllithium.—Following the procedure of Leonard and Hay[32] $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate[38] was converted to 10-(α-picolyl)quinolizidine (**11**) in 55% yield, $\Delta^{4(9)}$-dehydroindolizidinium perchlorate (**13a**)[38] was converted to 9-(α-picolyl)-indolizidine (**14a**) in 64% yield, and $\Delta^{4(9)}$-dehydro-8-methylindolizidinium perchlorate (**13c**)[29] failed to react (68% recovery of **13c**). The properties of the products **11** and **14a** and their methiodides are found in Table IV.

B. With Benzylmagnesium Chloride.—To a solution of 108 mmol of $PhCH_2MgCl$ in 300 ml of ether was slowly added 36 mmol of the dried (55°, P_2O_5, *in vacuo*) iminium salts **13b**[38] or **13c**.[29] After the vigorous reaction had subsided, the mixture was heated to reflux for 4 hr, cooled, and treated with 100 ml of 6 *M* HCl. The separated aqueous layer was washed with two 150-ml portions of ether, basified with 48 g of NaOH in 150 ml of H_2O, and subjected to continuous liquid–liquid extraction with ether for 48 hr. The ether extract was dried (K_2CO_3) and concentrated on a rotary evaporator to give 9-benzylindolizidine (**14b**) or 9-benzyl-8-methylindolizidine (**14c**) as viscous colorless oils in 93 and 90% yields, respectively. Vpc analysis[40] of **14b** showed only one peak; so the derivatives in Table IV were prepared from undistilled material.

TABLE IV
PROPERTIES OF BRIDGEHEAD SUBSTITUTED 1-AZABICYCLOALKANES AND THEIR DERIVATIVES

Compd	Mp or bp, °C (mm)	Calcd, % C	Calcd, % H	Found, % C	Found, % H
11	140–142 (1.0)[a]				
11 picrate	152–153[b]				
11 MeI	212–213[c]				
14a	125–126 (1.5)				
14a picrate	138.5–140 dec	53.93	5.20	54.08	5.07
14a MeI	204–205	50.28	6.47	50.23	6.61
14b	97–98 (0.25)				
14b picrate	167–168.5 dec	56.75	5.44	57.05	5.52
14b TNBS[d]	180–182	49.60	4.75	49.90	4.95
14b MeI	300–302	53.78	6.77	54.00	7.06
14c picrate	138–139	57.85	5.72	57.66	5.50
14c TNBS[d]	164–166 dec	50.38	4.83	50.40	4.85
14c MeI	230–232 dec	54.99	7.06	55.22	7.28
14d	61–62 (1.3)				
14d MeI[e]	216.5–218	46.91	7.22	46.92	7.42
14e	95–97 (1.0)	68.20	10.01	68.01	9.94
14e MeI	145–147	44.20	6.85	44.18	7.01
14f	100–102 (1.0)				
14f MeI	170–171	45.78	7.13	45.48	7.12
14g	101–104 (1.0)				
14g MeI	174–175	47.13	7.38	47.25	7.55
19	99–102 (1.0)				
19 MeI	180–182 dec	45.78	7.13	45.48	7.41

[a] Lit.[23] 137 (0.3). [b] Lit.[32] 152.5–153.5. [c] Lit.[32] 212–213. [d] TNBS = 2,4,6-trinitrobenzenesulfonate.[29] [e] % N: calcd, 4.56; found, 4.56.

C. With Allylmagnesium Bromide.—Application of the above procedure to 40 mmol of allylmagnesium bromide and 20 mmol of **13d**[38] led to 9-allylindolizidine (**14d**) (97%) as a light yellow oil which slowly darkened on exposure to air and gave only one peak in the vpc.[40] The properties of **14d** and its methiodide are listed in Table IV.

D. With Ethyl Bromoacetate and Zinc.—In a 500-ml three-necked Morton flask fitted with a mechanical stirrer, reflux condenser, and gas inlet tube was placed 18.5 g of powdered zinc (previously washed with 1 *M* HCl and acetone and dried at 100°), 100 ml of dry ether, 6.68 g (40 mmol) of ethyl bromoacetate, 40 mmol of the appropriate iminium perchlorate (**13e**,[38] **13f**,[29] **13g**,[31] or $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate[38]), and a crystal of iodine. The mixture was heated to reflux with rapid stirring and five 18.5-g portions of zinc and an iodine crystal were added at 45-min (12 hr for **13f** and **13g**) intervals. During the second (fourth for **13f** and **13g**) addition, another 6.68 g of ethyl bromoacetate was added. Heating was continued for another 12 hr, 20 ml of H_2O was slowly added, and the zinc was removed by decantation and washed with four 50-ml portions of 1 *M* HCl. The washings and decantate were intimately mixed, and the aqueous portion was separated, washed with two 100-ml portions of ether, basified with K_2CO_3, and extracted with three 100-ml portions of ether. These latter extracts were combined and dried(K_2CO_3), and the solvent was removed on a rotary evaporator to leave the amino esters **14e**, **14f**, **14g**, and **19** in 87, 89, 85, and 90% yields, respectively, as pale green oils which were distilled at reduced pressure before conversion to the methiodides (Table IV).

Ring Opening of Indolizidine Methiodides (14 MeI) to Azacyclononanes (15). A. With Sodium Amide.—In a 500-ml three-necked Morton flask equipped with a mechanical stirrer, gas inlet tube, and a Dry Ice–acetone filled cold-finger condenser was prepared[41] 76 mmol of $NaNH_2$ in 200 ml of liquid NH_3. One of the dried solid methiodides of **14a–d** was added (40 mmol) and the mixture was stirred for 2 hr, at which time 200 ml of

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(38) N. J. Leonard, W. Middleton, P. Thomas, and D. Choudhury, *J. Org. Chem.*, **21**, 344 (1956).
(39) C. S. Marvel and W. Lazier, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1944, p 93.
(40) Aerograph A-700; 20 ft × 3/8 in. column of 30% SE-30 on Chromosorb W.
(41) F. Bergstrom, *Org. Syn.*, **20**, 86 (1940).

ether was cautiously added. The NH_3 was allowed to evaporate overnight in a stream of N_2 and 50 ml of H_2O was then added. The ether layer was combined with two additional 75-ml portions of ether used to extract the H_2O, dried (K_2CO_3), and concentrated on a rotary evaporator to give **15a** as a dark viscous oil and **15b-d** as colorless liquids. Three successive molecular distillations of **15a** gave a colorless liquid (30% yield) which darkened rapidly on exposure to air, did not give satisfactory analytical values, but could be converted to crystalline derivatives. In a similar reaction with the methiodide of the quinolizidine **11**, more tars, less product, and no crystalline derivatives were formed. The physical and spectral properties of **15a-d** are found in Tables II and III, respectively.

B. With Sodium Ethoxide.—A solution of 33 mmol of NaOEt and 30 mmol of one of the methiodides of **14e-g** was heated under reflux under N_2 for 4 hr. The solution was cooled, acidified with 1:1 concentrated HCl in EtOH, and evaporated to dryness on a rotary evaporator. A solution of the residue in 50 ml of H_2O was basified with 4 *M* NaOH and extracted with three 50-ml portions of ether. The extracts were dried (K_2CO_3) and the ether was removed on a rotary evaporator to leave the amino esters **20**, **15f** + **21**, and **15g** as pale green oils which gave colorless liquids on vacuum distillation and whose properties are listed in Tables II and III.

C. With *n*-Butyllithium.—A mixture of 1.0 g (2.8 mmol) of **14e** MeI, 11.2 mmol of *n*-BuLi in 7 ml of hexane, and 50 ml of anhydrous ether was heated under reflux for 6 hr. The excess *n*-BuLi was destroyed with water and the organic layer was separated and dried (K_2CO_3), and the solvent was removed on a rotary evaporator to leave 0.64 g (80%) of **22** as a viscous, pale green oil which was purified by molecular distillation. The spectral properties of **22** are listed in Table III and the physical properties of its methiodide are listed in Table II.

D. By Aminodecarboxylation.—A solution of 10.7 g (30 mmol) of **14e** MeI and 1.4 g (35 mmol) of NaOH in 50 ml of H_2O was heated under reflux for 3 hr. Removal of the water with a rotary evaporator and drying of the residue over P_2O_5 in a vacuum for 12 hr gave the betaine **23** as a glassy solid whose ir displayed characteristic COO^- absorption at 1490 and 1590 cm^{-1}. The dry **23** was placed in a 50-ml distillation flask connected to a vacuum pump *via* a sidearm test tube serving as a collector. The flask was evacuated and immersed in an oil bath. Between 180–200°, 2.9 g (63%) of **24** distilled over as a colorless liquid whose vpc[40] contained only one peak. The spectral properties of **24** are listed in Table III and its physical properties and those of its picrate are listed in Table II.

Preparation of 12 MeI and Its Reaction with $NaNH_2$.—The known[42] amine **12** was converted to its methiodide, a hygroscopic white powder, mp 120–121°.

Anal. Calcd for $C_{13}H_{21}N_2I$: C, 46.99; H, 6.37. Found: C, 46.79; H, 6.60.

Reaction of **12** MeI with $NaNH_2$ and work-up as described above led to a polymeric mass which was triturated with three 100-ml portions of H_2O. Extraction of this aqueous solution with ether, drying (K_2CO_3), and distillation gave 2.5 g (61%) of *N*-methylpiperidine: bp 106° (lit.[43] 105.5°); picrate mp 220–222° (lit.[43] 223–224°).

Catalytic Reduction of Azacyclononanes 15a-b.—A MeOH solution of **15a** or **15b** was hydrogenated at 1 atm and 25° in the presence of PtO_2 until H_2 uptake ceased (30–60 min, 90% theoretical). Removal of the catalyst by filtration and the solvent by evaporation left **16a** and **16b** in quantitative yield as viscous colorless oils which were converted to a monomethiodide and a TNBS derivative, respectively, whose physical properties are listed in Table II. The nmr and infrared spectra of **16a** and **16b** were devoid of vinyl hydrogen or C=C absorptions.

Oxidation of *N*-Methyl-5-benzylideneazacyclononane (15b).—A mixture of 1.5 g (6.5 mmol) of **15b**, 50 mg of OsO_4, 25 ml of dioxane, and 15 ml of H_2O was stirred for 15 min at 25°. To the now dark brown mixture was added 2.8 g of $NaIO_4$ in small portions over a period of 30 min. After being stirred at 25° for an additional 3 hr, the mixture was treated with enough 3 *M* HCl to dissolve the solids present and extracted with three 100-ml portions of ether. The extracts were dried (Na_2SO_4), the ether was removed by distillation, and the residue was distilled to give 0.62 g (90%) of benzaldehyde (comparison of infrared spectrum and retention time with those of an authentic sample).

The acid solution was basified with 40% NaOH and continuously extracted with ether for 48 hr. The ether was dried (K_2CO_3) and removed with a rotary evaporator to leave 1 g (98%) of **17** as an oil. A sample collected by preparative vpc[40] for spectral analysis (Table III) was a low melting white solid.

The perchlorate salt **18** of **17** was prepared in 1:1 ether–absolute EtOH with 1:1 absolute EtOH–70% $HClO_4$ and recrystallized from EtOH–ether. The properties of **18** are listed in Tables II and III.

Reduction of *N*-Methylazacyclonona-5-one (17).—A solution of 1.0 g of **17**, 2.0 g of 95% $N_2H_4 \cdot H_2O$, and 5 ml of diethylene glycol was heated under reflux for 5 hr, distilled until the boiling point reached 200°, at which time 2 g of KOH were added, and then heated for an additional 5 hr. The reaction was steam distilled, the distillate was saturated with K_2CO_3 and extracted with three 75-ml portions of ether, and the extracts were dried (K_2CO_3) and evaporated on a rotary evaporator to afford 0.3 g (30%) of *N*-methylazacyclononane identified by comparison of its nmr and infrared spectra and the melting point and mixture melting point of its picrate with those of an authentic sample.[44]

Registry No.—12 MeI, 35225-83-3; **14a**, 35225-84-4; **14a** picrate, 35225-85-5; **14a** MeI, 35225-86-6; **14b**, 4753-49-5; **14b** picrate, 4870-83-1; **14b** TNBS, 4795-24-8; **14b** MeI, 5588-55-6; **14c** picrate, 35225-90-2; **14c** TNBS, 35225-91-3; **14c** MeI, 35225-92-4; **14d**, 35225-93-5; **14d** MeI, 35225-94-6; **14e**, 35225-95-7; **14e** MeI, 35225-96-8; **14f**, 35225-97-9; **14f** MeI, 35225-98-0; **14g**, 4753-53-1; **14g** MeI, 4795-26-0; **15a**, 35226-01-8; **15a** picrate, 35226-02-9; **15a** MeI, 35226-03-0; **15b**, 4753-50-8; **15b** MeI, 4795-25-9; **15b** TNBS, 4753-51-9; **15c**, 35226-07-4; **15c** MeI, 35261-97-3; **15d**, 35226-08-5; **15d** MeI, 35261-98-4; **15f**, 35226-09-6; **15g**, 4753-54-2; **15g** TNBS, 4870-85-3; **16a** MeI, 35212-74-9; **16b** TNBS, 35212-75-0; **17**, 4753-52-0; **18**, 35212-77-2; **19**, 35212-78-3; **19** MeI, 35212-79-4; **20**, 11-141-121; **20** MeI, 11-141-143; **20** TNBS, 11-141-132; **21**, 35212-80-7; **22**, 35212-81-8; **22** MeI, 35212-82-9; **24**, 35212-83-0; **24** picrate, 35212-84-1.

Acknowledgments.—This research was generously supported by The Robert A. Welch Foundation, the T. C. U. Research Foundation, and by NIH and NSF fellowships to L. R. K.

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The Peripheral Synthesis of Medium-Ring Nitrogen Heterocycles by Displacement Reactions[1]

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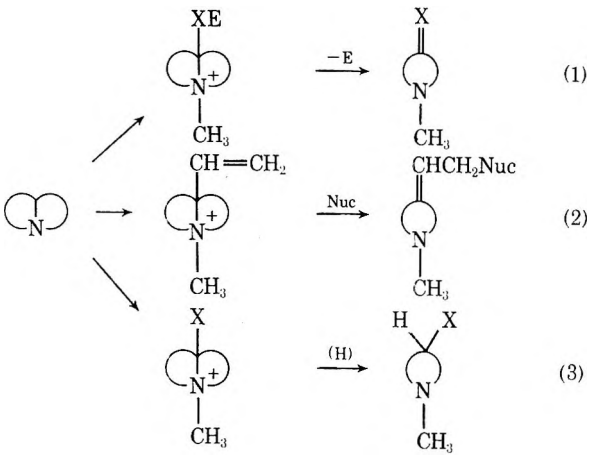
A series of 5-substituted *N*-methyl-1-azacyclononanes has been prepared by the selective cleavage of the central carbon–nitrogen bond of 9-substituted indolizidines with Grignard reagents, $LiAlH_4$, and alkali metals in liquid ammonia. 9-Vinylindolizidine (**3**) reacts *via* its methiodide with ethyl or phenyl Grignard reagents in an abnormal displacement reaction to give the butylidene and phenylethylidene derivatives **4a** and **4b** in high yield. The ethylidene and vinyl compounds **6** and **7** are produced from $LiAlH_4$ and **3** MeI in varying proportions depending on the solvent. Reduction of either **6** or **7** gives the 5-ethyl derivative **8**. Both **6** and **4a** can be oxidized to *N*-methyl-1-azacyclonona-5-one (**5**). 9-Ethynylindolizidine (**9**) is efficiently converted with $LiAlH_4$ to the 5-allenyl compound **10**, which can also be reduced to **8**. The metal–ammonia cleavage of the methiodides of **3** and **9**, as well as those of 9-phenyl- (**12**) and 9-acetylindolizidine (**18**), also leads to 5-substituted *N*-methylazacyclononanes in good to excellent yields. The phenyl compound ring opens normally to **14**, **3** undergoes a double bond shift during the process to give **6**, which is also the major product from **9**, and **18** gives in addition to **20** some of the corresponding alcohol **21**. The synthesis of the starting materials, structure proof of the products, and some mechanistic implications of the cleavage reactions are discussed.

The peripheral synthesis of medium-ring azacycles as developed in our laboratory[2,3] involves the selective cleavage of the central carbon–nitrogen bond of a fused 1-azabicycloalkane. This was achieved in the preceding paper[3] by introduction of a bridgehead substituent containing a group E which could be induced to leave, without its bonding electrons, in a β-elimination reaction (eq 1). The present paper describes a



second ring-opening method in which an unsaturated group is placed at the bridgehead and ring opening occurs by either abnormal (eq 2) or normal (eq 3) displacement reactions with Grignard reagents, $LiAlH_4$, or alkali metals in liquid ammonia (Emde cleavage).[4]

As a prototype for the ring opening shown in eq 2, the reactions of 9-vinylindolizidine (**3**) were investigated. In common with the reactions of other ternary iminium salts with Grignard reagents,[5,6] vinylmagnesium chloride failed to add directly to $\Delta^{4(9)}$-dehydroindolizidinium perchlorate (**1**) to give **3**. This compound was obtained in 94% yield, however, by first converting **1** to the tertiary α-aminonitrile **2**, a type of compound which undergoes a facile displacement of the cyano group by the alkyl moiety of Grignard reagents.[5-9] The structure of **3** follows from elemental analysis and the presence of characteristic vinyl group absorptions in its infrared and nmr spectra.

Treatment of **3** methiodide with ethylmagnesium bromide gave **4a** in 92% yield as a colorless oil which contained only one olefinic hydrogen peak in its nmr and gave the appropriate analytical values. Further proof for the assigned structure was obtained by the oxidative cleavage of the carbon–carbon double bond of **4a** to give the known[3] amino ketone **5** and *n*-butyraldehyde, isolated as their perchlorate and 2,4-DNP derivatives, respectively.

In an analogous reaction, phenylmagnesium bromide was added to the vinyl group of **3** methiodide to give the ring-opened product **4b** in 96% yield. The double bond was assigned to the nonconjugated position on the basis of the nmr spectrum of **4b**, which shows one olefinic proton coupled to two benzylic protons.

The cleavage of quaternary ammonium salts with Grignard reagents is a well-known reaction[10,11] which usually proceeds by normal displacement of a group attached to nitrogen. The occurrence of abnormal displacement had been considered previously for the metal salt catalyzed reaction of Grignard reagents with allyltrimethylammonium bromide,[11] but no unambiguous examples were available. The possibility that the uncatalyzed abnormal displacements described above are restricted to those heterocyclic ring systems examined in this paper has been discounted by other studies in our laboratory.[12]

On the assumption that the attacking species is a nucleophile (eq 2) rather than a radical,[11] a second ring-opening reagent, $LiAlH_4$, was investigated. The preparation of nine- and ten-membered azacycles by the reaction of quaternary ammonium salts with $LiAlH_4$

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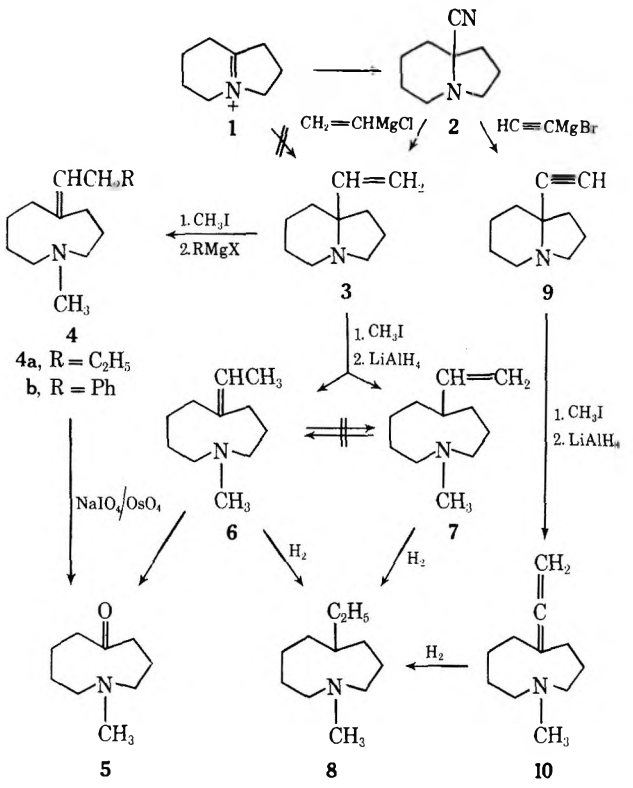


is known,[13,14] but requires the presence of an appropriately placed active hydrogen atom in the molecule, since the mechanism probably involves an elimination–addition process.[14] Even when this prerequisite is filled, however, the reaction is not general.[14b,15]

Reaction of **3**-methiodide with $LiAlH_4$ leads to two products, **6** and **7**, the former predominating in THF and the latter predominating in ether. The assigned structures are based on analytical and spectral data; the nmr spectrum of **6** shows one olefinic hydrogen peak coupled to an allylic methyl group, while both the nmr and infrared spectra of **7** display characteristic vinyl group absorptions. Further proof was obtained by the oxidation of **6** to the amino ketone **5** and by catalytic reduction of **6** and **7** to the same saturated amine **8**.

The formation of two products (**6** and **7**) in the reaction of **3** methiodide with $LiAlH_4$ may be due to competition between normal (eq 3) and abnormal (eq 2) displacement, respectively. Alternatively, this may represent complete or partial equilibration of **6** and **7** under the reaction conditions. This latter possibility was shown to be incorrect by resubjecting pure **6** or a 30:70 mixture of **6** and **7** to the reaction conditions and recovering them unchanged. The marked solvent effect on the product distribution (Table I) is probably due to a complex interplay of solubility and concentration effects which was not unraveled in this study.

As a second substrate for the ring-opening sequence in eq 2, 9-ethynylindolizidine (**9**) was prepared in 96% yield from the reaction of ethynylmagnesium bromide and the aminonitrile **2**. Similar replacements of the

(13) (a) L. J. Dolby and S. Sakai, *J. Amer. Chem. Soc.*, **86**, 1890 (1964); (b) J. Kutney, N. Abdurahman, C. Gletsos, P. LeQuesne, E. Piers, and I. Vlattas, *ibid.*, **92**, 1727 (1970).

(14) (a) L. J. Dolby and D. Booth, *J. Org. Chem.*, **30**, 1550 (1965); (b) P. Aeberli and W. Houlihan, *ibid.*, **34**, 1720 (1969).

(15) (a) D. Herbst, R. Rees, G. Hughes, and H. Smith, *J. Med. Chem.*, **9**, 864 (1966); (b) L. J. Dolby and G. Gribble, *J. Org. Chem.*, **32**, 1391 (1967); (c) A. Kubo, *Yakugaku Zasshi*, **90**, 224 (1970).

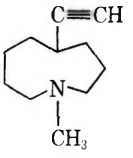
TABLE I
REACTIONS OF **3** MeI WITH $LiAlH_4$

Reactants				Products		
	mmol			Mole ratios		wt, %
Solvent (ml)	**3** MeI	$LiAlH_4$	Time, hr	**6**	**7**	**3** MeI
THF (75)	20	10	12	100	0	46
THF (100)	10	5	72	97	3	24
THF (150)	10	50	48	85	15	0
THF (25)	20	60	72	67	33	0
THF (25)	10	50	48	70	30	0
Et_2O (75)	20	50	12	16	84	82
Et_2O (50)	15	50	72	17	83	73

cyano group of aminonitriles by an ethynyl group are known.[16] The structure of **9** follows from its analysis and infrared spectrum.

Treatment of **9** methiodide with $LiAlH_4$ in either THF or ether gave a single product in 96% yield which was assigned the allene structure **10** on the basis of its analysis and the presence of characteristic allene absorptions in its infrared and nmr spectra.[17] Substantiating evidence for structure **10** was obtained from its catalytic reduction to the same saturated amine **8** obtained from the alkenes **6** and **7**.

Since only one product (**10**) is obtained from the ring opening of **9** methiodide, it is not possible to say if it is formed directly by an abnormal displacement or indirectly by rearrangement of the normal displacement product **11**. It is not unreasonable to assume that the



11

same factors which stabilize endocyclic *vs.* exocyclic olefins in medium-ring compounds[18] would also favor the allene **10** over the acetylene **11** in an equilibration. On the other hand, the not unrelated $LiAlH_4$ dehalogenation of some propargyl halides also gives only allenes to the exclusion of acetylenes and has been formulated as an abnormal displacement reaction.[19]

A third reaction utilized for ring opening in this study is the reductive cleavage of quaternary ammonium salts by means of alkali metals. This 85-year-old reaction[20] was developed by Emde[4] into a useful alkaloid degradation which can lead to medium-ring compounds according to eq 3. Recent applications of this reaction to various β-carboline[14a,15,21] and isoquinoline[15a,22] derivatives have culminated[13b,23] in the synthesis of several medium-ring containing alkaloids. The only examples of medium rings prepared by this method which do not contain other fused rings (and hence are better suited for the study of transannular

(16) D. Lednicer and J. Babcock, *J. Org. Chem.*, **27**, 2541 (1962).

(17) E. Snyder and J. D. Roberts, *J. Amer. Chem. Soc.*, **84**, 1582 (1962).

(18) A. Cope, D. Ambros, E. Ciganek, C. Howell, and Z. Jacura, *ibid.*, **82**, 1750 (1960).

(19) T. L. Jacobs and R. Wilcox, *ibid.*, **86**, 2240 (1964).

(20) C. M. Thompson and J. T. Curdall, *J. Chem. Soc.*, **53**, 781 (1888).

(21) E. Wenkert, S. Garratt, and K. G. Dave, *Can. J. Chem.*, **42**, 489 (1964).

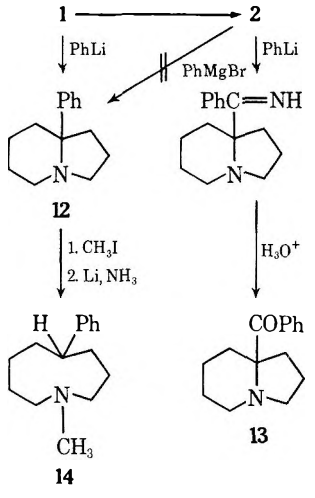
(22) M. Winn and H. E. Zaugg, *J. Org. Chem.*, **33**, 3779 (1968).

(23) J. P. Kutney, W. J. Cretney, P. LeQuesne, B. McKague, and E. Piers, *J. Amer. Chem. Soc.*, **92**, 1712 (1970); J. Harley-Mason, Atta-Ur-Rahman, and J. A. Beisler, *Chem. Commun.*, 743 (1966).

interactions)[24] are those of Arata, *et al.*,[25] and nicely complement those described in this paper.

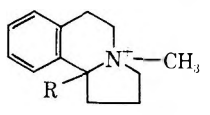
Selective cleavage of the central carbon–nitrogen bond by the Emde reaction, as in eq 3, requires that the group X be able to preferentially stabilize an intermediate carbanion or radical[26] at the bridgehead carbon atom. At the time this study was initiated[1] only aromatic rings (phenyl[4,15a,22] or indolyl[4,14a,15,21]) had been used for this purpose, although subsequently[25] carboxamido and cyano groups also were utilized. For this reason ring opening was initially investigated with 9-phenylindolizidine (**12**).

Since phenyl Grignard reagents do not react with ternary iminium salts,[5,6] the preparation of **12** *via* the

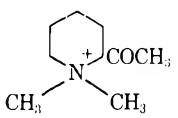


α-aminonitrile **2** was attempted. Although this procedure succeeded for the preparation (*vide supra*) of the vinyl and ethynyl analogs (**3** and **9**) it failed for **12**. Phenyllithium did react with **2** but by addition to, rather than displacement of, the nitrile function to give the benzoylamine **13** after hydrolysis. Similar additions by lithium reagents to tertiary α-aminonitriles are known.[8,9] Treatment of the iminium salt **1** directly with phenyllithium finally gave the desired precursor **12** in 47% yield.

Emde cleavage of **12** MeI with lithium in liquid ammonia[15a] proceeded in 80% yield to give the azacyclononane (**14**) which was identified from its spectral and analytical properties. Products from the cleavage of the peripheral carbon–nitrogen bonds were not detected. This contrasts with the behavior of other indolizidines,[22] which suggested that two activating benzene rings as in **15** were required for com-



15, R = Ph
16, R = CH_3

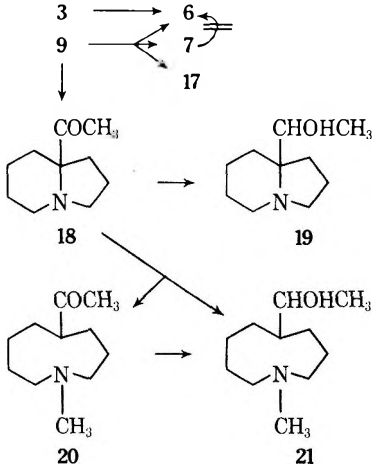


22

pletely selective fission of the central carbon–nitrogen bond. The fact that **12** MeI but not **16**[22] cleaves exclusively to an azacyclononane indicates that a single phenyl group can elicit this selectivity if it is at a bridgehead but not if it is a fused position.

Reductive cleavage of allyl groups under Emde conditions from both oxygen[27] and nitrogen[28] is known. In the present study the reaction of 9-vinylindolizidine methiodide (**3** MeI) with either sodium or lithium in liquid ammonia[15a] gave a single product in nearly quantitative yield which proved to be identical to *N*-methyl-5-ethylideneazacyclononane (**6**). The possibility that **7** might be the initial cleavage product which then rearranged to the probably more stable[18] **6** was eliminated by subjecting a sample of **7** to the reaction conditions and recovering it unchanged. Rearrangements accompanying the reductive cleavage of allyl groups from oxygen are often observed and have been rationalized as arising from kinetically controlled protonation of an intermediate, resonance-stabilized anion.[29] A similar mechanism could be operative for the reaction **3** MeI → **6**, but additional factors may be involved[30] as well. From a synthetic point of view it is clear that the Emde cleavage is preferred over the $LiAlH_4$ ring opening (*vide supra*) of **3** MeI for the preparation of **6**.

The reverse is true for the ring opening of the methiodide of the ethynylamine **9** which gives only the allene **10** in high yield with $LiAlH_4$ (*vide supra*) but which gives a variety of products under Emde conditions. With 2 or 3 equiv of lithium, three products are obtained in a ratio of ~8:1:1 (vpc). The major product was identified as the ethylidene compound **6** and one of the minor components was identified as the vinyl isomer **7**. The remaining compound, **17**, has absorptions in the infrared at 3110, 1702, and 1600 cm^{-1} which are not present in the infrared spectrum of the crude reaction product, and it is therefore probably an artifact. This view is supported by the fact that these infrared peaks appear at the expense of ones at 3300 and 2100 cm^{-1} after the crude reaction product is passed through the vpc.



A possible origin of the major product **6** was suggested by the reaction of **9** MeI with only 1 equiv of lithium in liquid ammonia. The major product was once again **6** but substantial quantities of the allene **10**

(24) A. C. Cope, M. M. Martin, and M. A. MeKervey, *Quart. Rev. Chem. Soc.*, **20**, 119 (1966).

(25) (a) Y. Arata, S. Yoshifuji, and Y. Yasuda, *Chem. Pharm. Bull.*, **17**, 1363 (1969); (b) Y. Arata, T. Kobayashi, M. Nakamura, and T. Yasuda, *Yakugaku Zasshi*, **90**, 1424 (1970).

(26) H. Smith, "Organic Reactions in Liquid Ammonia," Interscience, New York, N. Y., 1963, pp 151–153.

(27) Ref 26, pp 158–166.

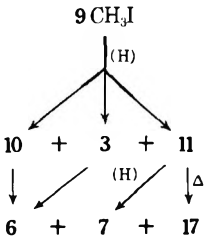
(28) S. Bhattacharji, A. J. Birch, A. Brack, A. Hoffmann, H. Kobel, D. C. C. Smith, H. Smith, and J. Winter, *J. Chem. Soc.*, 421 (1962).

(29) Ref 26, pp 158–159.

(30) E. Grovenstein, Jr., and R. W. Stevenson, *J. Amer. Chem. Soc.*, **81**, 4850 (1959).

were present according to the nmr and ir spectra of the reaction mixture. Allene **10** may be the source of **6**, since upon reaction with 2 equiv of lithium in liquid ammonia it gave only **6** in 91% yield. Other partial reductions of allenes with metal–ammonia systems have been observed,[31] but, since the partial reduction of acetylenes to olefins with lithium in liquid ammonia is also a well known process,[32] the possibility that **6** arises from **9** MeI *via* **3** MeI cannot be excluded.

Emde cleavage of **9** MeI must proceed by still another path, however, since neither **10** nor **3** MeI give any of the vinyl amine **7** on treatment with lithium in liquid ammonia, nor does **10** decompose in the vpc to give **17**. A reasonable source of **7** and **17** would be the acetylene **11** formed by cleavage of **9** MeI without rearrangement. This compound could account for the infrared absorptions in the crude reaction mixture at 3300 and 2100 cm^{-1} and would be likely[32] to be reduced to **7** under the reaction conditions. The possibility that **9** was formed by demethylation during the Emde cleavage and then decomposed to **17** in the vpc was eliminated by its complete stability to this process. The following scheme therefore summarizes the probable course of the Emde cleavage of **9** MeI.



As a final example of ring opening by reductive cleavage (eq 3), the reaction of a compound with a carbonyl activating group was investigated. The desired substrate, 9-acetylindolizidine (**18**), was prepared in 82% yield by the mercuric salt catalyzed hydration of the ethynylamine **9**. More than an equivalent of $HgSO_4$ was actually required, apparently because the basic nitrogen atom complexes with the mercuric ions.[33] The structure of **18** was deduced from its spectral and analytical properties as well as from those of the corresponding alcohol **19** prepared by $LiAlH_4$ reduction in 90% yield.

The Emde cleavage of **18** MeI with either lithium or sodium in liquid ammonia gave two products. Spectral and analytical values indicated that the major product was the ring-opened ketone **20**, and that the minor product was an alcohol different from **19**, probably **21**. Reduction of **20** with $LiAlH_4$ gave this same alcohol in 94% yield, thus substantiating its structure as **21**. That the alcohol **21** probably originates from overreduction of **20** during the Emde fission was shown by the formation of only **21** when the original product mixture was resubjected to the reaction conditions.

A recent study of the Emde cleavage of α-amino ketones[34] also reveals that the intervening carbon–nitrogen bond is selectively ruptured and the ketone is reduced to an alcohol. Interestingly the carbonyl group must be exocyclic to the nitrogen-containing ring as in **22** or **18**, otherwise simple demethylation occurs. This rather surprising observation is reminiscent of the situation with the phenyl-substituted compounds **12**, **15**, and **16** (*vide supra*) and suggests that the Emde cleavage of activated quaternary ammonium salts may have specific stereochemical requirements.

Experimental Section

Melting points and boiling points are corrected. Analyses were performed by M-H-W Laboratories, Garden City, Mich. Nmr spectra were determined on a Varian A-60 instrument as 30–40% solutions in CCl_4 for liquids and 10–20% solutions in $DCCl_3$ for solids with TMS as an internal standard. Ir spectra were recorded on Beckman IR-10 or Perkin-Elmer 237 spectrophotometers as thin films or KBr disks. Vpc analyses were obtained on an Aerograph A-700 chromatograph with a 20 ft × 3/8 in. column of 30% SE-30 on Chromosorb W unless otherwise noted.

9-Vinylindolizidine (3).—A mixture of 3 g (20 mmol) of 9-cyanoindolizidine (**2**)[6] in 50 ml of THF and 44 ml of 0.0091 *N* vinylmagnesium chloride[35] in THF was heated to reflux for 3 hr with the usual precautions against air and water. The excess Grignard reagent was decomposed with wet ether and the mixture was continuously extracted with ether for 48 hr. The ether extracts were dried (K_2CO_3) and concentrated on a rotary evaporator to give 2.9 g (94%) of **3** as a light-yellow oil which produced only one peak on vpc analysis and could be collected as a colorless oil: bp 66–67° (3.9 mm); ir 3070, 1655, 995, 908 cm^{-1}; nmr τ 3.47 (m, 3, vinyl H). A crystalline methiodide was prepared: mp 265–265.5°; nmr τ 3.9 (m, 3, vinyl H), 6.22 (m, 4, CH_2N), 6.8 (s, 3, NCH_3).

Anal. Calcd for $C_{11}H_{20}NI$ (**3** MeI): C, 45.07; H, 6.87; N, 4.78. Found: C, 44.89; H, 7.05; N, 4.49.

***N*-Methyl-5-butylidene-1-azacyclononane (4a).**—A mixture of 0.1 mol of ethylmagnesium bromide in 150 ml of THF and 5.86 g (0.02 mol) of **3** MeI was heated to reflux for 12 hr with the usual precautions against air and moisture. Excess Grignard reagent was destroyed with 20 g of ice and the resulting mixture was continuously extracted with ether for 24 hr. The ether extracts were dried (K_2CO_3) and the solvent was removed by distillation and at reduced pressure with a rotary evaporator to leave 3.31 g (92%) of **4a** as a colorless oil. A vpc collected sample (no other peaks except traces of solvent) had bp 62–63° (0.55 mm); ir 3017 and 1665 cm^{-1}; nmr τ 4.76 (t, 1, J = 6.2 Hz, vinyl H), 7.77 (s, 3, NCH_3).

A crystalline methiodide was prepared: mp 159–160°; nmr τ 4.52 (t, 1, J = 6.2 Hz, vinyl H), 6.57 (s, 6, NCH_3).

Anal. Calcd for $C_{14}H_{28}NI$ (**4a** MeI): C, 49.85; H, 8.37; N, 4.15. Found C, 50.01; H, 8.35; N, 4.14.

Oxidation of 4a.—A mixture of 2 g of **4a**, 50 mg of OsO_4, 35 ml of dioxane, and 12 ml of H_2O was stirred at 25° for 15 min. To the resulting dark brown mixture was added 4.4 g of $NaIO_4$ in small portions over a period of 40 min. After an additional 3 hr, the solid present was dissolved with 6 *M* HCl and the solution was extracted with four 50-ml portions of ether. The combined ether extracts were dried (Na_2SO_4), shown to give only one peak in the vpc beside solvent, and distilled through a 4-cm Vigreux column. The fraction of bp 70–100°, was treated with 2,4-dinitrophenylhydrazine to give 250 mg (10%) of butyraldehyde DNP, mp 122.5–123.5° (lit.[36] 122–122.5°).

The acid solution was basified (40% NaOH) and extracted with four 50-ml protions of ether. The extracts were dried (K_2CO_3), concentrated by distillation, and shown to contain only one product besides solvent by vpc analysis. The residue was dissolved in 1:1 ether–absolute EtOH and 1:1 absolute EtOH–70% $HClO_4$ added until no more solid formed. The 620 mg (24%) of *N*-methyl-9-hydroxyindolizidinium perchlorate (5 $HClO_4$) thus formed was identical in melting point, mixture melting point, and ir spectra with an authentic sample.[3]

(31) D. Devaprabhakara and P. D. Gardner, *J. Amer. Chem. Soc.*, **85**, 648 (1963).

(32) Ref 26, pp 213–216.

(33) J. W. Smith, in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968, pp 198–200.

(34) E. A. Mistryukov and G. Katvalyan, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 2800 (1969); *Chem. Abstr.*, **72**, 78821z (1970).

(35) H. Ramsden, J. Leebrick, S. Rosenberg, E. Miller, J. Walburn, A. Blaint, and R. Cserr, *J. Org. Chem.*, **22**, 1602 (1957).

(36) M. S. Newman and W. Edwards, *J. Amer. Chem. Soc.*, **76**, 1840 (1954).

N-Methyl-5-(2′-phenylethylidene)-1-azacyclononane (4b).—A mixture of 0.1 mol of PhMgBr in 100 ml of THF and 5.86 g (0.02 mol) of **3** MeI was heated to reflux for 48 hr with the exclusion of air and moisture. The mixture was poured on 20 g of ice, acidified with 3 *M* HCl, and extracted with 100 ml of ether. The ether extract was washed with four 50-ml portions of 3 *M* HCl, and the combined acid solutions were basified with 50% NaOH and continuously extracted with ether for 48 hr. The resulting ether extract was dried (K_2CO_3) and concentrated by distillation and rotary evaporation to leave 3.49 g (96%) of **4b** as a vpc pure colorless oil. A vpc collected sample had bp 104–105° (0.13 mm); ir 3090, 3060, 3040, 1601, 1488, 725, 685 cm^{-1}; nmr τ 2.61 (s, 5, ArH), 4.35 (t, 1, J = 7.5 Hz, vinyl H), 6.52 (d, 2, J = 7.5 Hz, $ArCH_2$), 7.7 (s, 3, NCH_3). A crystalline methiodide, mp 165–166°, was obtained.

Anal. Calcd for $C_{18}H_{28}NI$ (**4b** MeI): C, 56.11; H, 7.32; N, 3.63. Found: C, 56.32; H, 7.64; N, 3.77.

Reaction of 3 MeI with $LiAlH_4$.—A mixture of **3** MeI and $LiAlH_4$ in either THF or ether was heated to reflux. The quantities used are found in Table I. At the end of the specified reaction times the excess $LiAlH_4$ was destroyed with wet ether, 100 ml of additional ether was added, and the solids were removed by filtration and washed with three 10-ml portions of ether.

The precipitate was triturated with three 30-ml portions of boiling EtOH. Addition of ether to the EtOH precipitated unreacted starting material (**3** MeI) identified by melting point and ir data.

The filtrate was dried (K_2CO_3), and the solvent was removed by distillation and a rotary evaporator to leave a colorless oil (85–95% yield) which was analyzed by vpc (see Table I for product analyses). Pure samples of the two products were obtained by preparative vpc.

N-Methyl-5-ethylidene-1-azacyclononane (**6**) had bp 39–41° (0.26 mm); ir 3020, 1658 cm^{-1}; nmr τ 4.68 (q, 1, J = 6.5 Hz, vinyl H), 7.76 (s, 3, NCH_3), 8.4 (d, 3, J = 6.5 Hz, CCH_3). A crystalline methiodide was formed, mp 177–177.5°.

Anal. Calcd for $C_{12}H_{24}NI$ (**6** MeI): C, 46.64; H, 7.77; N, 4.53. Found: C, 46.48; H, 7.94; N, 4.59.

N-Methyl-5-vinyl-1-azacyclononane (**7**) had bp 42–43° (0.6 mm); ir 3070, 1635, 986, 900 cm^{-1}; nmr τ 4.36 (m, 3, vinyl H), 7.63 (s, 3, NCH_3). A methiodide had mp 173.5–174°.

Anal. Calcd for $C_{12}H_{24}NI$ (**7** MeI): C, 46.64; H, 7.77; N, 4.53. Found: C, 46.89; H, 7.73; N, 4.62.

N-Methyl-5-ethyl-1-azacyclononane (**8**).—A mixture of 1.4 g (9 mmol) of **6**, 50 ml of glacial HOAc, and 0.5 g of PtO_2 was hydrogenated in a Parr apparatus until there was no further pressure drop (24 hr). The solution was decanted from the catalyst, which was washed with three 10-ml portions of glacial HOAc. The acid solution was basified (40% NaOH), saturated with K_2CO_3, and extracted with three 50-ml portions of ether. The extracts were dried (K_2CO_3) and concentrated by distillation and rotary evaporation to afford 1.5 g (89%) of **8** as a colorless oil which gave only one peak on vpc analysis and did not display olefinic protons in either its nmr or ir spectra. A methiodide was prepared: mp 195.5–196°; nmr τ 6.58 (s, 6, NCH_3).

Anal. Calcd for $C_{12}H_{26}NI$ (**8** MeI): C, 46.31; H, 8.42; N, 4.49. Found: C, 46.19; H, 8.58; N, 4.49.

Reduction of a mixture of 67% **6** and 33% **7**, as described above, also produced only **8** (90% yield), identified by its vpc retention time, infrared, and nmr spectra.

Oxidation of 6.—Using the procedure described above for the oxidation of **4a**, a sample of **6** was treated with OsO_4–$NaIO_4$ to give 5 $HClO_4$ in 32% yield, identified by comparison of its melting point, mixture melting point, and infrared and nmr spectra with those of an authentic sample.[3]

Attempted Interconversion of 6 and 7.—A 30:70 mixture of **6**:**7** was treated with $LiAlH_4$ in THF under the conditions which produce a 67:33 mixture of **6**:**7** (Table I). Upon work-up, a 93% recovery of **6** and **7** (identified from the ir spectra of vpc collected samples) was obtained with the mole ratios unchanged.

9-Ethynylindolizidine (**9**).—To a solution of 40 mmol of ethynylmagnesium bromide[37] in 70 ml of THF was added 3 g (20 mmol) of **2** in 5 ml of THF, and the mixture was heated to reflux for 6 hr with stirring and the usual precautions against air and moisture. The mixture was treated with 20 g of ice and extracted with three 100-ml portions of ether, and the ether extracts were dried (K_2CO_3) and concentrated by distillation and rotary evaporation to leave 2.87 g (96%) of **9** as a vpc pure liquid. A vpc collected sample had bp 42–44° (2.7 mm); ir 3300 and 2080 cm^{-1}; nmr τ 7.6 (s, 1, ethynyl H). The methiodide of **9** had mp 250–251.5° dec.

Anal. Calcd for $C_{11}H_{18}NI$ (**9** MeI): C, 45.39; H, 6.18; N, 4.81. Found: C, 45.72; H, 6.43; N, 4.98.

N-Methyl-5-allenyl-1-azacyclononane (**10**).—A mixture of 5.82 g (20 mmol) of **9** MeI, 30 mmol of $LiAlH_4$, and 150 ml of THF was heated under reflux for 48 hr. Sufficient wet ether was added to decompose the excess $LiAlH_4$, the solids were removed by filtration, and the filtrate was dried (K_2CO_3) and concentrated by distillation and rotary evaporation to leave 1.59 g (95%) of **10** as a vpc pure colorless oil. A sample of **10** collected by preparative vpc had bp 55–56° (0.1 mm); ir 3033 and 1950 cm^{-1}; nmr τ 5.33 (q, 2, J = 2.8 Hz, allenyl H),[17] 7.75 (s, 3, NCH_3). The methiodide had mp 229–230°.

Anal. Calcd for $C_{12}H_{22}NI$ (**10** MeI): C, 46.91; H, 7.22; N, 4.56. Found: C, 46.82; H, 7.25; N, 4.57.

An identical reduction using ether instead of THF led to **10** in 96% yield.

Reduction of 10.—Using the same procedure described above for the reduction of **6** to **8**, a sample of **10** was converted to **8** (vpc, ir, nmr) in 89% yield.

9-Phenylindolizidine (**12**).—A mixture of 0.2 mol of PhLi (prepared from 2.8 g of Li wire and 31.4 g of PhBr)[38] in 250 ml of ether, 2.24 g (10 mmol) of the iminium perchlorate **1**,[39] and 100 ml of dry benzene was heated to reflux for 72 hr. The cooled reaction mixture was decomposed with water and acidified with 3 *M* HCl, and the organic portion was extracted with four 50-ml portions of 3 *M* HCl. The combined acid extracts were basified with 40% NaOH and extracted with four 50-ml portions of ether, and the ether extracts were dried (K_2CO_3) and evaporated to leave 1.8 g of yellow oil which darkened on standing. Vpc analysis indicated that the oil consisted of a 13:87 mixture of Δ^8-dehydroindolizidine (identified by comparison of its ir spectrum with that of an authentic sample)[39,40] and **21** (47% yield) which was collected by preparative vpc from a 4 ft × 0.25 in. column as a viscous yellow oil: bp 83–84° (0.25 mm); ir 3060, 3020, 1600, 760, 700 cm^{-1}; nmr τ 2.66 (m, 5, ArH), 7.52 (m, 4, CH_2N), 8.53 (m, 10). A crystalline methiodide, mp 184–185°, was formed.

Anal. Calcd for $C_{15}H_{22}NI$ (**12** MeI): C, 52.49; H, 6.46; N, 4.08. Found: C, 52.43; H, 6.84; N, 4.10.

9-Benzoylindolizidine (**13**).—The reaction and work-up described above, but utilizing 0.4 mol of PhLi and 3 g of 9-cyanoindolizidine (**2**)[5] instead of **1**, gave 4.2 g (92%) of **13** as a vpc pure, viscous, yellow oil. A sample collected by preparative vpc had: bp 112–113° (0.3 mm); ir 3060, 1675, 775, 705 cm^{-1}; nmr τ 1.64 (m, 2, *o*-ArH), 2.66 (m, 3, ArH). A methiodide, mp 164–165°, was obtained.

Anal. Calcd for $C_{16}H_{22}NOI$ (**13** MeI): C, 51.76; H, 5.97; N, 3.77. Found: C, 51.79; H, 6.12; N, 3.76.

When the above reaction was repeated without the use of acid in the work-up (decomposition of PhLi with water, ether extraction, drying, evaporation), a viscous yellow oil was obtained which had infrared peaks at 3174 (NH) and 1611 cm^{-1} (C=N) and which, on dissolution in 3 *M* HCl, yielded only **13**.

9-Acetylindolizidine (**18**).—To a stirred mixture of 1.27 ml of concentrated H_2SO_4, 40 g of 60% HOAc, and 5.44 g (18 mmol) of $HgSO_4$ at 80° was added a solution of 2.17 g (15 mmol) of 9-ethynylindolizidine (**9**) in 10 ml of 60% HOAc. After the mixture had been stirred at 80° for 4 hr, it was cooled with ice, basified with 40% NaOH, and extracted with three 50-ml portions of ether. The combined ether extracts were dried (K_2CO_3) and concentrated by distillation to give 2 g (82%) of vpc pure **18** as a light yellow oil: bp 69–70° (1.4 mm); ir 1707 cm^{-1}; nmr τ 7.06 (m, 4, CH_2N), 7.92 (s, 3, CH_3CO). A methiodide was prepared: mp 238–239°; nmr τ 5.9 (m, 4, CH_2N), 6.60 (s, 3, NMe), 7.56 (s, 3, CH_3CO).

Anal. Calcd for $C_{11}H_{20}NOI$ (**18** MeI): C, 42.74; H, 6.52; N, 4.53. Found: C, 42.65; H, 6.72; N, 4.56.

9-(1′-Hydroxyethyl)indolizidine (**19**).—To a solution of 1.6 g (10 mmol) of **18** in 30 ml of ether was slowly added a solution of 20 mmol of $LiAlH_4$ in 40 ml of ether and the mixture was heated to reflux overnight with the usual precautions against air and

(37) E. R. H. Jones, L. Skattebøl, and M. C. Whiting, *J. Chem. Soc.*, 4765 (1956).

(38) L. A. Walter, *Org. Syn.*, **23**, 83 (1943).

(39) N. J. Leonard, W. J. Middleton, P. D. Thomas, and D. Choudhury, *J. Org. Chem.*, **21**, 344 (1956).

(40) M. G. Reinecke and L. R. Kray, *ibid.*, **31**, 4215 (1966).

moisture. The cooled reaction mixture was treated with wet ether and filtered, and the filtrate was dried (K_2CO_3) and evaporated to give 1.52 g (90%) of **19** as a colorless oil: bp 68–70° (0.62 mm); ir 3390 cm^{-1}; nmr τ 6.14 (m, 2, CHOH), 7.16 (m, 4, CH_2N), 9.18 (d, 3, J = 7 Hz, CH_3). The crystalline methiodide melted at 263–264° dec.

Anal. Calcd for $C_{11}H_{22}NOI$ (**19** MeI): C, 42.45; H, 7.12; N, 4.49. Found: C, 42.51; H, 7.31; N, 4.43.

General Procedure for Metal–Ammonia Emde Cleavage.—To a 1000-ml three-necked Morton flask equipped with a gas inlet tube, a mechanical stirrer, a cold-finger condenser containing Dry Ice–acetone, and a $CaCl_2$ tube at the exit to the atmosphere was added 300 ml of liquid NH_3, the compound to be reduced, and an equivalent amount of either ethanol (A) or 1-methoxy-2-propanol (B).[15a] The mixture was rapidly stirred as the Li or Na was added in small pieces to give a blue color which sometimes was discharged immediately and sometimes remained until NH_4Cl was added after 10–15 min. Work-up consisted of adding 100 ml of ether, allowing the NH_3 to evaporate, and drying (K_2CO_3) and evaporating the ether. Any ether-insoluble residue in the reaction flask was taken up in hot ethanol to recover unreacted starting material. Reactant and product compositions are listed in Table II. Identification of **6** and **7** was made by comparison with authentic samples and **14**, **20**, and **21** from the analytical and spectral data given below.

5-Phenyl-*N*-methylazacyclononane (**14**) had bp 118–119° (1.8 mm); ir 3060, 3020, 1600, 745, 695 cm^{-1}; nmr τ 2.9 (s, 5, ArH), 7.67 (s, 3, NMe). The crystalline methiodide melted at 187.5–188°.

Anal. Calcd for $C_{16}H_{26}NI$ (**14** MeI): C, 53.49; H, 7.29; N, 3.89. Found: C, 53.55; H, 7.33; N, 3.90.

5-Acetyl-*N*-methylazacyclononane (**20**) had bp 68–69° (0.6 mm); ir 1705 cm^{-1}; nmr τ 7.6 (m, 4, CH_2N), 7.72 (s, 3, NMe), 7.98 (s, 3, CH_3CO). A methiodide was prepared, mp 172.5–173.5°.

Anal. Calcd for $C_{12}H_{24}NOI$ (**20** MeI): C, 44.31; H, 7.44; N, 4.30. Found: C, 44.45; H, 7.61; N, 4.38.

5-(1′-Hydroxyethyl)-*N*-methylazacyclononane (**21**) had bp 79–80° (1.7 mm); ir 3360 cm^{-1}; nmr τ 6.45 (s, 1, OH), 7.67 (m, 4, CH_2N), 7.74 (s, 3, NMe), 8.92 (d, 3, J = 7 Hz, CH_3C). The methiodide had mp 199–200°.

Anal. Calcd for $C_{12}H_{26}NOI$ (**21** MeI): C, 44.05; H, 8.01; N, 4.28. Found: C, 44.17; H, 8.14; N, 4.31.

Reduction of 20.—With the same procedure used to reduce **18** to **19**, 370 mg of **20** was converted to 350 mg (94%) of vpc pure **21** identified by comparison of its ir spectrum with that of a sample prepared as above.

Table II
Reactant and Product Compositions for Emde Cleavage

Reactant (mmol)	Alcohol	Metal (mmol)	Products (%)
12 MeI (10)	A	Li (20)	**14** (59); **12** MeI (37)
3 MeI (15)	B	Li (30)	**6** (92)
3 MeI (15)	A	Li (30)	**6** (95)
3 MeI (15)	B	Na (30)	**6** (96)
7 (10)	A	Li (20)	**7** (100)
9 MeI (20)	B	Li (40)	**7, 6, 17** (6:84:10)[a]
9 MeI (20)	B	Li (60)	**7, 6, 17** (12:80:8)[a]
9 MeI (15)	B	Li (15)	**6, 10**[b]
10 (10)	A	Li (20)	**6**, (91)
18 MeI (10)	A	Li (20)	**20** (68), **21** (28)[c]
18 MeI (10)	A	Na (20)	**20** (78), **21** (17)[c]
20 + **21** (4:1) (10)	A	Li (20)	**21** (94)

[a] In order of increasing retention time; **17** appears to be an artifact formed from probably **11** during vpc treatment at 150°, 200 cm^3/min (see discussion). [b] Spectral analysis of the crude product showed, in addition to absorptions for **6** and **11**, characteristic peaks for **10** at 1950 cm^{-1} in the ir and τ 5.33 (q, J = 2.8 Hz) in the nmr. [c] Separated on a 15 ft × 0.25 in. 15% Carbowax 20M on Chromosorb W column.

Registry No.—**3**, 35201-24-2; **3** MeI, 10478-78-1; **4a**, 35201-26-4; **4a** MeI, 35201-27-5; **4b**, 35201-02-6; **4b** MeI, 35201-03-7; **6**, 35249-63-9; **6** MeI, 35201-04-8; **7**, 35201-05-9; **7** MeI, 35201-06-0; **8** MeI, 35201-07-1; **9**, 35201-08-2; **9** MeI, 35201-09-3; **10**, 35201-10-6; **10** MeI, 35201-11-7; **12**, 35201-12-8; **12** MeI, 35201-13-9; **13**, 35201-14-0; **13** MeI, 35249-64-0; **14**, 35201-15-1; **14** MeI, 35201-16-2; **18**, 35201-17-3; **18** MeI, 35249-65-1; **19**, 35201-18-4; **19** MeI, 35201-19-5; **20**, 35201-20-8; **20** MeI, 35201-21-9; **21**, 35201-22-0; **21** MeI, 35201-23-1.

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2*H*-Cyclopenta[*d*]pyridazines. Acylation with Trifluoroacetic Anhydride[1,2]

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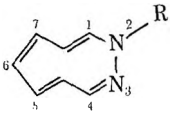
2-Methyl-2*H*-cyclopenta[*d*]pyridazine (**2**) reacts with 1 equiv of trifluoroacetic anhydride in the absence of a catalyst to give the 5- and 7-trifluoroacetyl derivatives (**4**, **5**) in a ratio of *ca.* 1:3. Compounds **4** and **5** react more slowly with the anhydride to form the 5,7-bis(trifluoroacetyl) derivative (**8**). 2-Phenyl-2*H*-cyclopenta[*d*]-pyridazine (**3**) also gives the 5,7-disubstituted compound **10**, but the parent molecule **1** gives only the 7-monosubstituted product **9**. Hydrolysis and esterification of **4** and **5** provide the first route to the corresponding acids (**12**, **14**) and esters (**13**, **15**). Methylation of the anion of **9** occurs only at the 2 position to yield **5**. The nmr and electronic spectra of **4** and **5** are described and discussed.

Subsequent to the demonstration[5] that 2*H*-cyclopenta[*d*]pyridazine (**1**) and its 2-methyl (**2**) and 2-phenyl (**3**) derivatives exhibited spectra and protonation characteristics analogous to those of azulene and simple π-excessive heteroanalogs of azulene, attention



1, R = H
2, R = CH_3
3, R = C_6H_5

(1) Support from the National Science Foundation (GP-5776, GP-9293) is gratefully acknowledged.

(2) From the Ph.D. Theses of David M. Forkey (1967) and Larry D. Grina (1970), University of Washington.

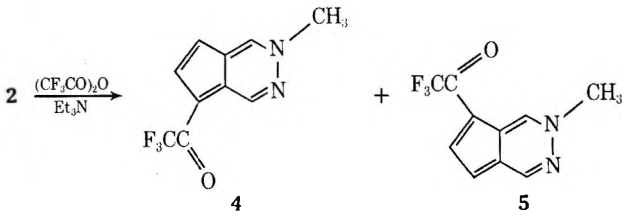
(3) 3M Fellow, 1964–1965; National Science Foundation Summer Fellow, 1965.

(4) National Science Foundation Trainee, 1965–1966; National Defense Education Act Fellow, 1966–1968; National Institutes of Health Fellow, 1968–1970.

(5) A. G. Anderson, Jr., and D. M. Forkey, *J. Amer. Chem. Soc.*, **91**, 924 (1969).

was directed to electrophilic substitution. Trifluoroacetic anhydride was selected as an electrophile, as this reacts rapidly with azulene at room temperature in the absence of a catalyst to give the 1-trifluoroacetyl derivative in high yield.[6] Since the 2*H*-cyclopenta[*d*]pyridazine structure is nonsymmetric, a mixture of the 5- and 7-substitution products was anticipated.

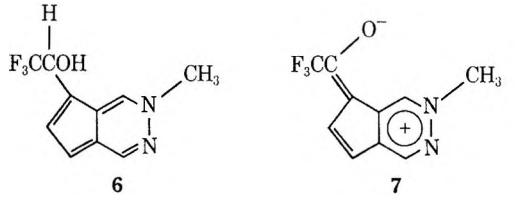
Treatment of 2 with slightly more than 1 equiv of trifluoroacetic anhydride in the presence of 1.5 equiv of triethylamine[7] gave two products, **4** and **5**, in 23



4 **5**

and 59% yields, respectively. This product ratio corresponds closely to that of the corresponding conjugate acids formed in trifluoroacetic acid.[5] The spectral characteristics of **4** and **5** did not serve to clearly distinguish between them and, accordingly, this was done by X-ray crystallographic analysis of **4** and the 5-bromo derivative of **5**.[8] The peaks in the nmr spectrum of the more soluble isomer, **5**, were assigned as follows: the doublet (J = 1.3 Hz) at δ 9.02 to H-1 (coupling with H-4); the broad singlet at δ 9.58 to H-4 (coupling with H-1 and H-5 not resolved); the doublet (J = 4.2 Hz) at δ 6.77 with subsplitting (J = 1 Hz) to H-5 (coupling with H-6 and H-4, respectively); the singlet (3 H) at δ 4.45 to the *N*-methyl; the multiplet at δ 7.82 to H-6. The limited solubility of **4** required the use of CAT to obtain a spectrum and the couplings between the 1 and 4 and 1 and 7 hydrogens were not resolved. Therefore singlets were observed for H-1 (δ 9.39) and H-4 (δ 9.19), a doublet (J = 4.5 Hz) for H-7 (δ 6.74), a singlet (3 H, δ 4.42) for the *N*-methyl, and, again, a multiplet for H-6 (δ 7.55).

The multiplets for H-6 in these spectra were shown to be due to the H-5(7) and H-6 being part of an ABX_3 system in which H-6 was coupled with the three fluorine atoms of the acetyl group (the fluorine nmr spectrum showed a doublet with J = 2.2 cps). Molecular models showed the most favorable conformation allowing conjugative interaction of the carbonyl with the aromatic ring to be with the trifluoromethyl group directed toward H-6, bringing the hydrogen and fluorines in close proximity and suggesting the possibility of through-space coupling. Reduction of **5** with sodium borohydride afforded the corresponding alcohol **6**. A



6 **7**

molecular model of **6** showed that the change from a trigonal to a tetrahedral carbon had moved the fluorine atoms away from the 6 hydrogen such that through-space coupling would no longer be possible. In the spectrum of **6** the signals for H-5 and H-6 appeared as a pair of doublets (J = 3.5 Hz) at δ 6.73 and 7.48, respectively.[9] Coupling of H-4 and H-5 (J = 1 Hz) further split the doublet for the former. The peak (couplings of J = 1 Hz with both H-1 and H-5 not resolved) for H-4 was at δ 9.15 and the doublet (J = 1 Hz) for H-1 at δ 8.84. The quartet (J = 8 Hz) for the α hydrogen was at δ 5.57 and the singlet (3 H) for the *N*-methyl at δ 4.19. These data were at first thought to indicate through-space coupling in **4** and **5** for the 6-H–fluorine interaction. The structure of **5** as shown by X-ray analysis,[8] however, indicated that **7** makes an important contribution to the ground state in the solid state, thus effectively extending the π conjugation to the carbon bearing the trifluoromethyl group. Through-bond coupling is therefore also possible.

The visible spectra of **4** and **5** were remarkable in that the long-wavelength absorptions were at 365 and 403 nm, respectively, as compared to 395 nm for **2**. Thus the 7-trifluoroacetyl group caused a bathochromic shift and the 5-trifluoroacetyl group a hypsochromic shift, whereas all acyl groups in the analogous positions on azulene and previously known π-excessive heteroanalogs of azulene had caused hypsochromic shifts. A similar difference in the behavior of **4** and **5** was noted in the effect of solvent polarity on the long-wavelength transition (Table I). As the polarity

TABLE I

EFFECT OF SOLVENT POLARITY ON THE LONG-WAVELENGTH TRANSITION OF 4 AND 5

Compd	Ether (4.34)[a]	Methanol (32.6)	Acetonitrile (37.9)	Formamide (109)
4	365.0	372.0	369.0	378.0
5	403.0[b]	403.0	401.5	404.5

[a] Dielectric constants from N. A. Lange and G. M. Forker, "Handbook of Chemistry," Revised 10th ed, McGraw-Hill, New York, N. Y., 1967, pp 1234–1237. [b] λ_{max}, nm.

was increased, the absorption of **5** changed only slightly, whereas that of **4** exhibited a pronounced bathochromic shift. The carbonyl bands in the infrared spectra indicated about the same degree of interaction of the carbonyl with the aromatic ring for the two isomers, and the nmr absorptions for the *N*-methyl groups (δ 4.42 and 4.45) were very similar.[10] These results were interpreted to indicate that the electronic ground states of the molecules were similar and, therefore, the differences were in the first excited states[11] with an appre-

(6) A. G. Anderson, Jr., and R. G. Anderson, *J. Org. Chem.*, **27**, 3578 (1962).

(7) The amine was added to prevent unreacted **2** from participating as the base to form the conjugate acid, which would not undergo acylation.

(8) H. L. Ammon, P. H. Watts, Jr., A. G. Anderson, Jr., D. M. Forkey, L. D. Grina, and Q. Johnson, *Tetrahedron*, **26**, 5707 (1970).

(9) The spectrum of 1-trifluoroacetyl-4,6,8-trimethylazulene also shows a multiplet for H-2 at δ 2.09, whereas the signal for the corresponding hydrogen in 2-trifluoromethyl-2-hydroxy-5,7-dimethyl-1,2-dihydrocyclopent[*cd*]azulene is a doublet at δ 2.57 ppm: R. G. Anderson, Ph.D. Thesis, University of Washington, 1961; A. G. Anderson, Jr., R. G. Anderson, and G. T. Hollander, *J. Org. Chem.*, **30**, 131 (1965).

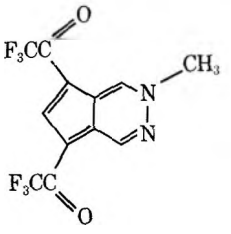
(10) Data on other substitution products have shown the position of the *N*-methyl nmr peak to be sensitive to the electron-withdrawing power of substituents at the 5 and 7 positions: A. G. Anderson, Jr., D. M. Forkey, and L. D. Grina, unpublished results.

(11) It was assumed that the electronic transitions for the two molecules are the same. Alternatively, it is possible that the nonidentity of these transitions is the primary factor involved.

ciable change in the distribution of electronic charge for **4** but little for **5**.[5,12]

The luminescence spectra for **4** and **5** were obtained by Gouterman, Smith, and Seybold.[13a] These spectra showed a factor of 10 difference in the quantum yields of fluorescence for **4** as compared to **5**, while the phosphorescence yields differed by less than a factor of 2 in the opposite direction. Compound **4** lost more than 80% and **5** lost 50% of the absorbed energy by radiationless processes.[13b] Since the lifetimes and quantum yields of phosphorescence were comparable for **4** and **5**, the low quantum yield of fluorescence observed for **4** was not due to increased phosphorescence or a radiationless process from the triplet state, but to a radiationless transition from the singlet to the ground state. This also pointed to a difference in the excited states of **4** and **5**.

Reaction of **2** with an excess of trifluoroacetic anhydride at room temperature gave an 85% yield of the 5,7-bistrifluoroacetyl derivative **8**. The nmr spectrum

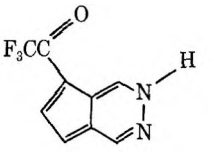


8

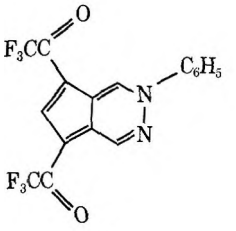
of **8** showed a pair of doublets (J = 1.3 Hz) at δ 9.74 and 10.00 (H-1 coupled with H-4), a multiplet at δ 8.29 (H-6 coupled with the fluorine atoms), and a singlet (3 H) for the N-methyl at δ 4.72.

Since azulene undergoes only monotrifluoroacetylation, even in the presence of Lewis acids,[6] the ease of formation and high yield of **8** was surprising and prompted further experiments. The reaction of **2** with 1 equiv of trifluoroacetic anhydride in the presence of a large excess of triethylamine was carried out to see if **8** might have been formed but not isolated in the earlier run. Only a trace of **8** was found, along with 19% of **4** and 62% of **5**. No unchanged **2** was recovered. Because **2** is relatively unstable, some of it undoubtedly decomposed during the reaction and thus a small excess of anhydride was present. The same reaction except that *ca.* 0.5 equiv of **5** was present in addition to **2** gave 77% of **5** (including unchanged starting material), 18% of **4**, and 9.2% (based on anhydride) of **8**, with no **2** recovered. These results, and those obtained when several separate reactions of **2** with the anhydride were monitored by tlc analysis, indicated that **2** was rapidly converted to **4** and **5** and these products were more slowly converted to **8**. There was no indication of the formation of **8** while **2** was still detectable. Thus the 5- and 7-trifluoroacetyl groups cause some deactivation to further substitution, though much less than in the case of azulene.

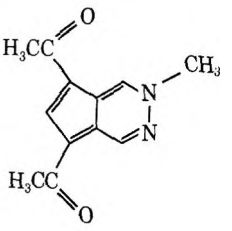
Treatment of **1** with excess trifluoroacetic anhydride and triethylamine for 7 days (the reactions with **2** were complete in 2 days or less), in contrast, gave 49% of the 7-substituted compound **9**, and this reaction with



9



10

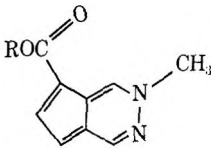


11

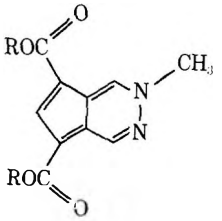
3 (5 days) gave 74% of the 5,7-disubstituted derivative **10** as the only products obtained in significant amounts. The reactivity of the cyclopenta[*d*]pyridazine ring to electrophiles is therefore apparently sensitive to the nature of the substituent on the 1 position with a reactivity order of Me > Ph > H. The methyl group (inductive effect) and the phenyl group (resonance effect) are able to stabilize the transition state relatively more than hydrogen. Compound **9** is indicated to be more stable than the 5-substituted tautomer, and also less reactive to further substitution than **5** and the corresponding derivative of **3**. Further comparative studies on **1**–**3** are planned.

In a single experiment **2** was treated with a large excess of acetic anhydride in the presence of stannic chloride. A 39% yield of the 5,7-diacetyl compound **11** was obtained and the low yield was attributed to side reactions of **2**, **11**, and/or the intermediate monosubstitution products with the stannic chloride.

The hydrolysis of 1-trifluoroacetylazulene in base provides perhaps the best route to 1-azuloic acid and its derivatives.[6] This reaction with **5** provided a product which was judged to be a hydrate of the corresponding carboxylic acid **12**. It was obtained in *ca.* 100% yield and underwent decomposition with decarboxylation[14] on melting or recrystallization. Treatment with diazomethane formed the stable ester **13**. In the same fashion, **14** and **15** were obtained in high yield from **8**. Diacid **14** was also unstable to heat.



12, R = H
13, R = CH_3



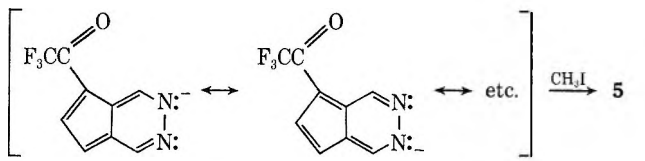
14, R = H
15, R = CH_3

The anion of **9** would exist as a resonance hybrid **16** having the potential of undergoing alkylation at

(12) A. G. Anderson, Jr., and B. M. Stecker, *J. Amer. Chem. Soc.*, **81**, 4941 (1959); A. G. Anderson, Jr., W. F. Harrison, and R. G. Anderson, *ibid.*, **85**, 3448 (1963); A. G. Anderson, Jr., and W. F. Harrison, *ibid.*, **86**, 708 (1964).

(13) (a) P. Seybold, Ph.D. Thesis, Harvard University, 1967. (b) Less than 5% of nonradiative energy loss was observed for **8**.

(14) This behavior corresponds to that of 1(3)-azuloic acids.[6]



16

either nitrogen. When **9** was treated with barium oxide and then methyl iodide, however, only one product, **5**, was obtained. A tlc analysis of the reaction mixture did not reveal any trace of the isomeric **4**, and the reaction under the conditions employed was completely selective.

Experimental Section

Melting points were taken on a Fisher or Kofler hot stage and are uncorrected. Ultraviolet and visible spectra were recorded on a Cary Model 14 spectrophotometer. Nmr spectra were recorded on a Varian Model A-60, T-60, or DA-60-11 spectrometer with reference to internal tetramethylsilane. Mass spectra were recorded on an Associated Electrical Industries MS-9 spectrometer. The mass of the parent peak (P) was determined with reference to known peaks of perfluorotributylamine. Hydrocarbon solvents were purified by shaking with sulfuric acid, distillation, and passage through a column of silica gel and basic alumina. Dichloromethane and chloroform were purified by distillation from phosphorus pentoxide and passage through a column of basic alumina. Ether was dried over sodium and distilled. Dimethyl sulfoxide was distilled from the presence of calcium hydride and stored over molecular sieves. Petroleum ether (bp 20–40°) was used and other solvents were reagent grade. Triethylamine was dried over potassium hydroxide pellets. All acylation reactions were monitored by tlc using silica gel G or Merck silica gel GF-254. Unless otherwise specified, organic solutions of products were dried over anhydrous magnesium sulfate.

5- and 7-Trifluoroacetyl-2-methyl-2*H*-cyclopenta[*d*]pyridazine (4 and 5). Method A.—A mixture of 150 mg (1.14 mmol) of **2**, 0.16 ml (1.14 mmol) of trifluoroacetic anhydride, 0.24 ml of triethylamine, and 10 ml of dichloromethane was stirred at room temperature. Unreacted **2** was present (tlc) after 14 hr; so a few drops of the anhydride were added over a period of several hours until analysis for **2** was negative. The mixture was placed in a freezer (−25°) for 16 hr, during which time a solid separated. The precipitate was filtered, washed with H_2O, and air dried to give 58.6 mg (23%) of **4** as a pale, cream-colored solid, mp 233–235°. Three recrystallizations from acetone afforded colorless needles: mp 236–237°; uv max (dry ether) 234 nm (ϵ 20,200), 244 (18,400), 261 (15,900), 266 (16,100), 293 (18,400), 299 (21,000), and 365 (11,300); nmr (acetone, CAT) δ 9.39 (s, 1), 9.19 (s, 1), 7.55 (m, 1), 6.74 (d, 1, J = 4.5 Hz), and 4.42 ppm (s, 3); ir ($HCCl_3$) 1640 cm^{-1} (C=O); molecular ion at m/e 228.052 (calcd 228.050).

Anal. Calcd for $C_{10}H_7ON_2F_3$: C, 52.63; H, 3.09. Found: C, 52.45; H, 3.11.

Chromatography of the residue from the original filtrate on 200–325 mesh silica gel (dichloromethane eluent) gave 170 mg of **5** as a yellow solid, mp 124.5–130°, which after recrystallization from heptane amounted to 153 mg (59%) of yellow needles, mp 127–129.5°. An additional recrystallization and vacuum drying gave an analytical sample: mp 130.8–131°; uv max (dry ether) 247 nm (ϵ 23,900), 260 (sh, 15,200), 285 (5720), 295 (5680), 330 (7050), and 403 (9030); nmr (acetone) δ 9.58 (broad s, 1), 9.02 (d, 1, J = 1.3 Hz), 7.82 (m, 1), 6.77 (d of d, 1, J = 4.2 and 1 Hz), and 4.45 ppm (s, 3); ir ($HCCl_3$) 1631 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_7ON_2F_3$: C, 52.63; H, 3.09. Found: C, 52.99; H, 3.26.

Method B. With 1 Equiv of Trifluoroacetic Anhydride.—The procedure of method A was used with 114.8 mg (0.973 mmol) of **2**, 0.136 ml (0.973 mmol) of trifluoroacetic anhydride, 0.25 ml (1.8 mmol) of triethylamine, and 10 ml of dichloromethane. The mixture was kept at −25° for 24 hr and yielded 39.5 mg (19%) of **4**, mp 234–235°, and 129.4 mg (62.5%) of **5**, mp 121–123°. Recrystallization of the latter from acetone or heptane, sublimation at *ca.* 10^{-3} mm, and drying over P_2O_5 (vacuum) gave material having mp 123–125°. A trace of **8** was identified by tlc (comparison with an authentic sample).

Method C. Trifluoroacetylation of 2 in the Presence of 5.—The procedure of Method B was followed using 103.4 mg (0.885 mmol) of **2**, 71.9 mg (0.336 mmol) of **5**, 0.124 ml (0.885 mmol) of trifluoroacetic anhydride, 0.25 ml (1.8 mmol) of triethylamine, and 10 ml of dichloromethane. The reaction yielded 24.6 mg (18%) of **4**, mp 234–235°, 13.1 mg (9.2%) of **8** as the less polar band from the chromatography, mp 171–172° and, after precipitation from dichloromethane with petroleum ether, 180–181°, and 200.7 mg (77%) of **5**, mp 121–123° (identical with authentic **5** by comparative tlc).

7-(2,2,2-Trifluoro-1-hydroxyethyl)-2-methyl-2*H*-cyclopenta[*d*]pyridazine (6).[15]—To a magnetically stirred solution of 0.185 g (0.813 mmol) of **5** in 15 ml of methanol was added over *ca.* 10 min a solution of 0.034 g (0.9 mmol) of $NaBH_4$ in 2 ml of methanol. The yellow color of the mixture deepened during the addition. Tlc analysis (silica gel G, dichloromethane, uv light) 25 min after addition showed unchanged **5**, and an additional 3 mg of $NaBH_4$ was added. After 10 min the analysis showed only traces of **5** and the bright yellow solution was chromatographed on a preparative tlc plate (silica gel G, dichloromethane). The material from the separated main yellow band was eluted (dichloromethane) and gave 0.121 g (64.7%) of **6** as a yellow solid, mp 123–133°, molecular ion at m/e 230.0663 (calcd 230.0666). A second tlc procedure afforded yellow crystals from dichloromethane: mp 133–135°; nmr (acetone) δ 9.15 (m, 1), 8.84 (d, 1, J = 1 Hz), 7.48 (d, 1, J = 3.5 Hz), 6.73 (q, 1, J = 3.5 and 1 Hz), 5.57 (q, 1, J = 8 Hz), and 4.19 (s, 3).

Anal. Calcd for $C_{10}H_9ON_2F_3$: C, 52.18; H, 3.94. Found: C, 52.24; H, 3.83.

5,7-Bis(trifluoroacetyl)-2-methyl-2*H*-cyclopenta[*d*]pyridazine (8).—To a cold (ice bath) solution of 110.7 mg (0.841 mmol) of **2** and 0.3 ml of triethylamine in 10 ml of dichloromethane was added 0.35 ml of trifluoroacetic anhydride over a period of 5 min. After another 5 min, the ice bath was removed and the mixture was stirred for 8 hr. An additional 0.1 ml of trifluoroacetic anhydride was added and stirring was continued for 16 hr (tlc analysis showed no **5** to be present and the solution had become red). The solvent was removed (vacuum) and the residue was chromatographed on a 200–325 mesh silica gel column (dichloromethane). Separation of the fluorescent (uv light) portion of the eluate, removal of the solvent (vacuum), and recrystallization of the residue from hexane–dichloromethane gave 231 mg (85%) of **8** as colorless needles: mp 180–180.8°; uv max (dry ether) 252 nm (ϵ 14,900), 284 (34,800), 302 (17,600), 339 (11,100) and 370 (8300); nmr (acetone) δ 10.0 (d, 1, J = 1.3 Hz), 9.74 (d, 1, J = 1.3 Hz), 8.29 (m, 1), and 4.72 ppm (s, 3); ir ($HCCl_3$) 1653 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_6O_2N_2F_6$: C, 44.46; H, 1.86; N, 8.64. Found: C, 44.45; H, 1.69; N, 8.63.

7-Trifluoroacetyl-2*H*-cyclopenta[*d*]pyridazine (9).—To a cold (ice bath) solution of 613.4 mg (5.7 mmol) of **1** and 3 ml of triethylamine in 25 ml of dichloromethane and 25 ml of chloroform was added slowly 3 ml of trifluoroacetic anhydride. The mixture was allowed to come to room temperature and stand for 24 hr. Triethylamine (4 ml) and trifluoroacetic anhydride (2 ml) were added. After 7 days the solvent was removed (vacuum) and the residue was chromatographed on a 2 × 10 in. silica gel column. Elution with dichloromethane and then chloroform developed several closely spaced fluorescent (uv light) bands which were collected by final elution with acetone. Chromatography of the residue from the acetone eluate on a 2 × 14 in. silica gel column and elution with chloroform developed four bands, which were removed with 1:10 acetone–chloroform. The major (most polar) band yielded 339.4 mg (49%) of **9** as a yellow solid, mp 175–178°. Recrystallization from dichloromethane gave the analytical sample: mp 178–178.5°; uv max (dry ether) 243 nm (ϵ 30,500), 287 (sh, 11,100), 294 (11,700), 327 (10,000), and 398 (10,600); nmr (acetone) δ 9.67 (s, 1), 9.11 (s, 1), 7.88 (m, 1), and 6.85 (d, 1).

Anal. Calcd for $C_9H_5N_2OF_3$: C, 50.47; H, 2.34; N, 13.08. Found: C, 50.59; H, 2.28; N, 12.92.

5,7-Bis(trifluoroacetyl)-2-phenyl-2*H*-cyclopenta[*d*]pyridazine (10).—To a cold (ice bath) solution of 109 mg (0.562 mmol) of **3** and 0.3 ml of triethylamine in 15 ml of dichloromethane was added slowly with stirring 0.3 ml of trifluoroacetic anhydride, and

(15) We wish to thank Allan R. Banks and Lucinda Hickernell for performing this experiment.

the mixture was then allowed to come to room temperature. Another 0.5 ml of triethylamine and 0.3 ml of trifluoroacetic anhydride were added after 1 day, and another 0.5 and 0.3 ml of the anhydride after 3 and 4 days, respectively. After 5 days the mixture was chromatographed on a 0.75 × 8 in. silica gel column. The fluorescent (uv light) eluate (dichloromethane) yielded a yellow solid which, after recrystallization from aqueous acetone, gave 159.6 mg (74%) of **10** as yellow needles: mp 181–182°; uv max (dry ether) 258 nm (ε 15,700), 293 (38,100), 345 (10,500), and 392 (11,000).

Anal. Calcd for $C_{17}H_8N_2O_2F_6$: C, 52.85; H, 2.09; N, 7.26. Found: C, 53.04; H, 2.20; N, 7.45.

5,7-Diacetyl-2-methyl-2*H*-cyclopenta[*d*]pyridazine (11).—To a solution of 0.36 ml (3.1 mmol) of anhydrous stannic chloride in 5 ml of acetic anhydride was added a solution of 47.3 mg (0.358 mmol) of **2** in 2 ml of dichloromethane, whereupon the mixture rapidly turned red-brown. After 90 min the mixture was poured into a mixture of 70 ml of 2 *N* NaOH, 50 ml of dichloromethane, and 50 g of ice. The whole was shaken, the layers were separated, and the aqueous layer was extracted with six 35-ml portions of dichloromethane. The solvent was removed (vacuum) from the combined, dried organic solutions and the residue was chromatographed on a 6 × 8 in. silica gel plate using ether and then 3:1 ether–95% ethanol as eluents. The second (more polar) of two fluorescent (uv light) bands yielded a tan solid, which after trituration with a small amount of 95% ethanol and filtration gave 29.9 mg (38.7%) of **11** as a yellow solid: mp 221–224° before and 222–225° after vacuum (*ca.* 10^{-3} mm) sublimation; uv max (dry ether) 225 nm (sh, ε 17,000), 274 (34,000), 291 (11,000), 342 (5600), and 384 (3600); nmr (DMSO) δ 9.62 (s, 1), 9.46 (s, 1), 8.21 (s, 1), and 4.32 (s, 3).

Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.67; H, 5.56; N, 12.95. Found: C, 66.65; H, 5.70; N, 12.83.

Methyl 2-Methyl-2*H*-cyclopenta[*d*]pyridazine-7-carboxylate (13).—A mixture of 98.9 mg (0.434 mmol) of **5**, 4 ml of 10% NaOH, and 2 ml of 95% ethanol was refluxed for 1.75 hr. After it cooled to room temperature, the yellow solution was poured into 20 ml of H_2O and the whole was extracted with three 10-ml portions of ether. Acidification of the cold (ice) aqueous phase with concentrated hydrochloric acid formed a yellow precipitate, which was collected (filtration), washed with H_2O, and dried (vacuum) to yield 83.6 mg of the carboxylic acid **12** as a yellow solid, mp 223–224.5° dec. Attempts to recrystallize **12** from acetone or 95% ethanol gave material having a lower melting point and containing **2** (isolated by extraction of a basic solution with ether and identified by uv and visible spectra).

To a mixture of 123 mg of **12**, 10 ml of dichloromethane, and 10 ml of methanol was added slowly a solution of diazomethane (from 316 mg of *N*-methyl-*N*-nitrosourea)[16] in 5 ml of dry ether. After the acid had been allowed to react, the solution was poured into 10 ml of dilute acetic acid and the separated aqueous layer was extracted with two 10-ml portions of dichloromethane. The residue from the combined, washed (10 ml of 5% sodium bicarbonate and 10 ml of saturated NaCl), dried (sodium sulfate) organic layers was chromatographed on a preparative silica gel G plate. Elution of the least polar band with dichloromethane gave **13** as a yellow solid, mp 109–112°, which after sublimation at 60° (10^{-3} mm) amounted to 72.1 mg (74%) of material: mp 111.2–112.5°; uv max (dry ether) 237 nm (ε 28,600), 253 (22,000), 257 (20,400), 276 (12,300), 282 (12,700), 321 (10,000), and 392 (3470); nmr (acetone) δ 8.96 (broad s, 1), 8.52 (d, 1, *J* = 1.2 Hz), 7.52 (d, 1, *J* = 3.7 Hz), 6.43 (d of d, 1, *J* = 3.7 and 0.7 Hz), and 4.17 (s, 3); ir ($HCCl_3$) 1692 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30. Found: C, 62.81; H, 5.48.

2-Methyl-2*H*-cyclopenta[*d*]pyridazine-5,7-dicarboxylic Acid (14).—A solution of 280.4 mg (0.865 mmol) of **8** in 20 ml of 95% ethanol and 15 ml of 10% NaOH was heated on a steam bath until no **8** (tlc analysis) remained (3.5 hr). The cooled, stirred solution was acidified slowly with concentrated hydrochloric acid and the precipitate was collected (filtration) and dried (vacuum over P_2O_5) to give **14** as a gray solid which became purple at 200–220° and then black but did not melt below 275°: uv max (0.1 *N* NaOH) 255 nm (ε 33,000), 270 (sh, 24,000), 281 (sh, 7000), 322 (6800), and 372 (sh, 2500); uv max (ether) 282 nm (1.39), 329 (0.76), 374 (0.37), and on dilution 253 (0.55), 269 (0.25), and 282 (0.17).

Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.54; H, 3.67; N, 12.18. Found: C, 54.37; H, 3.68; N, 12.51.

Dimethyl 2-Methyl-2*H*-cyclopenta[*d*]pyridazine-5,7-dicarboxylate (15).—An excess of diazomethane in ether was added slowly to a stirred suspension of 79.3 mg (0.361 mmol) of **14** in 20 ml of methanol. After 30 min, the excess diazomethane was decomposed (dilute hydrochloric acid) and the solution was then poured into a mixture of 75 ml of H_2O and 30 ml of chloroform. The whole was shaken well and the separated aqueous layer was extracted with two 25-ml portions of chloroform. The residue from the combined, dried organic layers was chromatographed on a 0.75 × 3 in. silica gel column using chloroform and then acetone as eluents. The fluorescent (uv light) band gave 87.3 mg (97.8%) of **15** as a pale tan solid, mp 179–180°. Recrystallization by adding petroleum ether to a concentrated dichloromethane solution formed cream-colored microcrystals: mp 180–180.5°; uv max (dry ether) 253 nm (ε 43,900), 268 (22,300), 280 (12,000), 329 (6120), and 371 (3260); nmr ($DCCl_3$) δ 9.58 (d, 1, *J* = 1 Hz), 9.30 (d, 1, *J* = 1 Hz), 8.28 (s, 1), 4.36 (s, 3, NMe), 3.93 (s, 3, CO_2Me), and 3.91 (s, 3, CO_2Me).

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.10; H, 4.84; N, 11.30. Found: C, 58.00; H, 4.90; N, 11.13.

Conversion of 7-Trifluoroacetyl-2*H*-cyclopenta[*d*]pyridazine (9) to 7-Trifluoroacetyl-2-methyl-2*H*-cyclopenta[*d*]pyridazine (5).—A mixture of 44.2 mg (0.206 mmol) of **9**, 3 g of BaO, 5 ml of methyl iodide, and 5 ml of dimethyl sulfoxide was shaken occasionally for 24 hr while protected from moisture. Dichloromethane (100 ml) and H_2O (75 ml) were added and the whole was shaken well and filtered (suction). The solid was washed with 25 ml of H_2O and then 25 ml of dichloromethane, and the filtrate was then made slightly acidic with dilute hydrochloric acid and shaken well. The tan residue from the separated, washed (two 100-ml portions of H_2O), and dried organic layer was chromatographed on a 6 × 8 in. silica gel plate using dichloromethane and then 3:2 dichloromethane–petroleum ether as eluents. The second (more polar) fluorescent (uv light) band gave a yellow solid, mp 145–155°, which after recrystallization from aqueous acetone afforded 7.4 mg (18%) of **5** as tiny yellow needles, mp 127–129°, uv and visible spectra identical with those of an authentic sample.

Registry No.—**4**, 32377-07-4; **5**, 35426-58-5; **6**, 35426-59-6; **8**, 35426-60-9; **9**, 35426-61-0; **10**, 35426-62-1; **11**, 35426-63-2; **12**, 35426-64-3; **13**, 35426-65-4; **14**, 35454-84-3; **15**, 35426-66-5; trifluoroacetic anhydride, 407-25-0.

(16) F. Arndt, "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 165.

1,4-Dimethyl-1,4-dihydro-1,2,4,5-tetrazine and Its *N*-Alkyl Salt. Synthesis, Structure, and Chemistry[1a]

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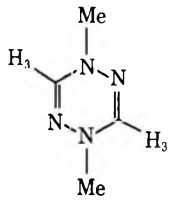
1,4-Dimethyl-1,4-dihydro-1,2,4,5-tetrazine (1) has been prepared by a convenient two-step route and shown to rearrange to a triazoline (11) in base. Attempts to differentiate between the several possible planar and boat conformations for the 8-π-available electron system (1) by nmr failed, but data pertinent to this problem were obtained from studies of the mechanism of the process, 1 → 11, and of the alkylation of 1, which occurs at nitrogen already bearing a methyl substituent (→ 12). Standard 6-π-electron model compounds (*e.g.*, polyazoles), when confronted with a similar choice, always react at an unsubstituted nitrogen. The pmr absorption for methyl attached to the positively charged nitrogen in the *N*-alkyl salts (12) is found at *higher* field than the peak attributed to methyl bonded to the formally neutral nitrogen atom, an observation which yields valuable information concerning the detailed structure of 12.

Although several substances for which a 1,4-dihydro-1,2,4,5-tetrazine structure has been proposed can be found in the literature, initial reports have usually been followed after varying time periods by retractions and structural reassignment.[2] At the time the work described here was begun, the only authenticated 1,4-dihydrotetrazines contained aryl substituents in the 1 and 4 positions.[3-5]

The goals of the present investigation were the synthesis of 1,4-dimethyl-1,4-dihydro-1,2,4,5-tetrazine (1) and its *N*-alkyl salt (2) and the comparison of the



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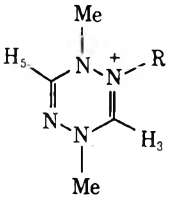
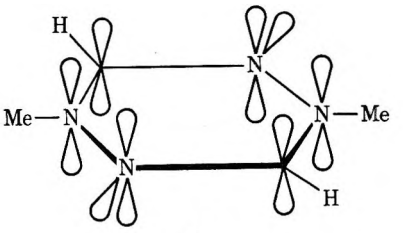


2

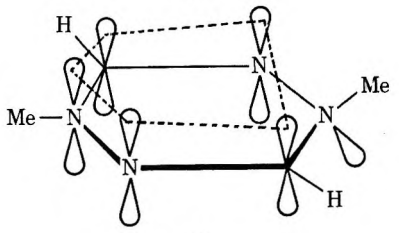
kinetic acidities (C–H_3 in 1 and C–H_3 and C–H_5 in 2) of these compounds with the values for possible tetrazole and tetrazolium cation model substrates.

The hope of differentiating between conceivable planar (**1a–d**) and boat (**1e–g**) conformations for 1, an 8-π-available electron system, provided an attractive added incentive.[6]

The related 1,4-dithiadiene has been shown by X-ray crystallography to possess a boat structure,[7] but nearly planar geometries are preferred for 1,4-diphenyl-, 1,4-di-*p*-chlorophenyl-, and 1,4-di-*p*-tolyl-1,4-dihydro-1,2,4,5-tetrazine because of their small dipole moments (0.8, 0.65, and 0.75 D, respectively[7]). Since conjugation



1a



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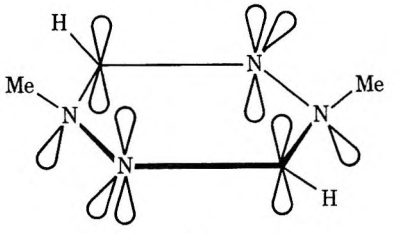

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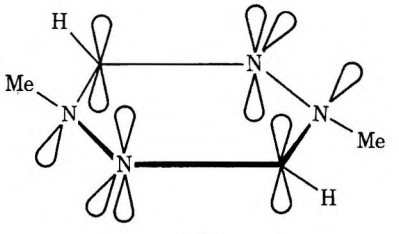

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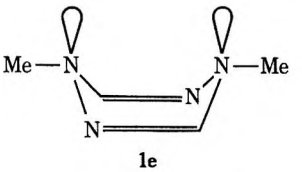

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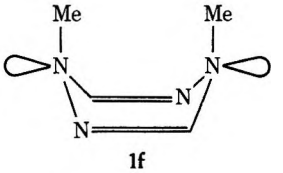

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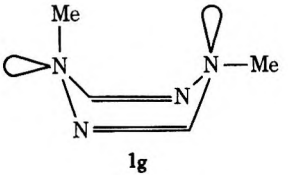


1g

(1) (a) This research has been supported in part by a grant from the U. S. Public Health Service (GM-13980). We are also indebted to Mr. F. J. Bobick and Mr. K. D. Lotts for experimental assistance. (b) NSF Predoctoral Trainee, 1966–1969; NIH Predoctoral Fellow, 1969–1970. Abstracted from Ph.D. dissertation of this author. Additional structure proof, discussion, and experimental and spectral data may be found in this reference.

(2) V. P. Wystrach in "Heterocyclic Compounds," Vol. 8, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1967, p 105; P. F. Wiley in "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience, New York, N. Y., 1956.

(3) W. Baker, W. D. Ollis, and V. D. Poole, *J. Chem. Soc.*, 3389 (1950).

(4) P. G. Edgerley and L. E. Sutton, *ibid.*, 3394 (1950).

(5) Prepared by rearrangement of *N*-arylsydnones with P_2S_5 in hot toluene or treatment of *N*-aryl-*N'*-thioformylhydrazines (from $ArNHNH_2$ + $HCS_2^-Na^+$) with NaOMe.[3]

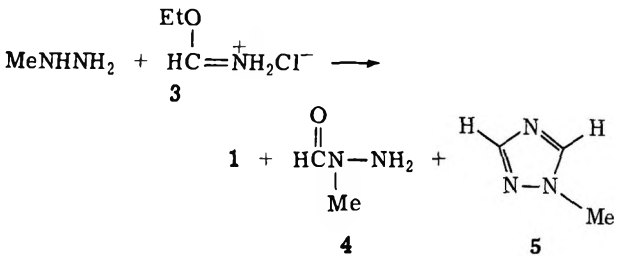
(6) The unusual potential of **1** as a ligand, which provided yet another reason to undertake its synthesis, will be examined in a future publication.

(7) W. E. Parham, H. Wynberg, W. R. Hasek, P. A. Howell, R. M. Curtis, and W. N. Lipscomb, *J. Amer. Chem. Soc.*, 76, 4957 (1954).

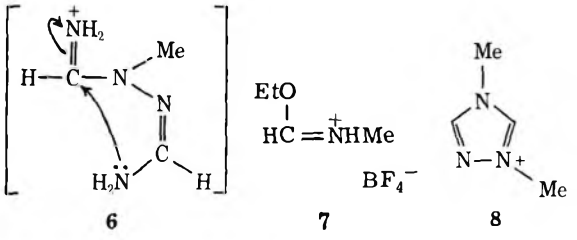
of the nitrogen lone pairs with the aryl π systems is an important added complication in these latter substrates, the use of this data to predict a similar structure for **1** would not be justified. 1,4-Dialkyl-1,4-dihydropyrazines, which could also be utilized to provide answers to the geometric and electronic structure questions exemplified by **1a–g**, are not known.

Results and Discussion

The dimethyldihydrotetrazine (**1**) was prepared in one step in 38% isolated yield by treatment of ethyl formimidate hydrochloride[8] (**3**) with methylhydrazine in ether.



In addition to NH_4Cl, which was removed by filtration, two by-products, *N*-formyl-*N*-methylhydrazine[9] (**4**, 9%) and 1-methyl-1,2-4-triazole[10] (**5**, 27%), were also obtained. The latter compound codistilled with **1** but could be separated by selective precipitation as the oxalate salt from a solution of **1** and **5** in ether. Because **5** is probably generated by dehydrative cyclization of a diacylhydrazide intermediate such as **6**, the use of **7** in

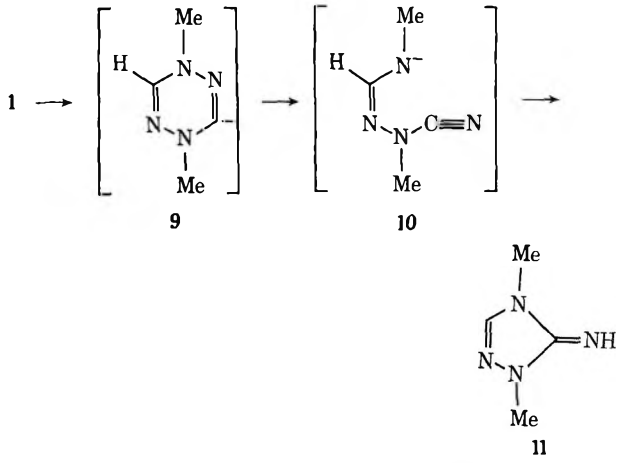


the synthesis in place of **3** was investigated. Unfortunately, the yield of **1** from **7** and methylhydrazine was only 4%. One contaminant identified was the triazolium cation[10] (**8**).

The dihydrotetrazine **1** is a volatile, pale yellow solid, mp 45–46°, whose nmr spectrum in $CDCl_3$ contains only two singlets: δ 6.36 (area 1) and 3.01 (area 3). Other analytical and spectroscopic data are in accord with the claimed structure (see Experimental Section), and Tolles, McBride, and Thun[11] have recently isolated and identified a compound with the same properties from the mixture obtained by oxidation of (1) 1,4-dimethylhexahydro-*s*-tetrazine with HgO (14% yield before vpc purification), (2) 1,1-dimethylhydrazine with HIO_3 (trace yield), and (3) **4** with I_2 (0.1% yield). An attempt to measure the pK_B of **1** in water was unsuccessful because acid-catalyzed hydrolysis to yield a complex mixture of products occurred rapidly below pH 2.

The nmr spectrum of **1** in $CDCl_3$ did not change as the probe temperature was lowered. Even at −99°, the lowest experimentally accessible temperature, the spectrum consisted of the same unbroadened pair of singlets. Therefore, either conformational equilibration remains rapid on an nmr time scale at −99° or possible geometries for **1** are limited to the symmetrical structures, **1a,c–f**. Since the former explanation is not improbable, a choice between these alternatives based only on the negative nmr result is not justified. Further structure clues, however, can be garnered from the chemistry of **1**.

5-Imino-1,4-dimethyl-Δ^2-1,2,4-triazoline (**11**), the product expected from ring cleavage of an intermediate carbanion **9**, was obtained on treatment of **1** with



aqueous sodium hydroxide. Baker, Ollis, and Poole[3] have reported similar base-induced isomerizations of 1,4-diaryl-1,4-dihydro-1,2,4,5-tetrazines, but formulations analogous to **11** were never considered for the products, though all published data are in accord with such structures.[12] The known triazoline **11** has previously been made by methylation of 1-methyl-5-amino-1,2,4-triazole[13] and also isolated as the HI salt from reaction of 1-amino-1,2-dimethylguanidine hydriodide with formic acid.[14]

Attempts to measure the kinetic acidity of **1** directly were unsuccessful. In Na_2CO_3–D_2O no exchange of the annular protons was observed and in NaOD–D_2O ring scission was a rapid reaction. The generation of **9** as a discrete intermediate, however, was demonstrated by reisolation of partly C_3 deuterated **1** (40–50% D) from a solution of **1** in D_2O containing 0.2 equiv of NaOD.[15] The discovery that the ring scission, **9** → **10**, is a two-step process is of special interest here. Such observations are often interpreted as an indication that the two bonds broken in the cleavage are not in the

(8) R. Ohme and E. Schmitz, *Angew. Chem., Int. Ed. Engl.*, **6**, 566 (1967).

(9) C. T. Pedersen, *Acta Chem. Scand.*, **18**, 2199 (1964).

(10) R. A. Olofson and R. V. Kendall, *J. Org. Chem.*, **35**, 2246 (1970).

(11) W. M. Tolles, W. R. McBride, and W. E. Thun, *J. Amer. Chem. Soc.*, **91**, 2443 (1969). These authors made **1** in order to compare the esr spectrum of the derived cation radical with the spectra of the related verdazyl and tetrazolinyl radicals. The conformational and electronic structure questions introduced here were not considered.

(12) A 1-aryl-3-arylamino-1,2,4-triazole structure was proposed. No reaction pathway was presented.

(13) G. Cipens and V. Grensteins, *Latv. PSR Zinat. Akad. Vestis, Khim. Ser.*, 263 (1962); *Chem. Abstr.*, **59**, 12790*h* (1962). Since the melting point listed in the original article was 56–58° while that found for the product from **1** was 66–68°, the latter compound was also converted to the known HI salt, mp 225–225.5° (lit.[14] mp 226°).

(14) C.-F. Kröger, G. Schoknecht, and H. Beyer, *Chem. Ber.*, **97**, 396 (1964).

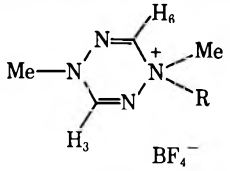
(15) Using estimates based on these experimental observations, the kinetic acidity is between that of 1- and 2-methyltetrazole: R. A. Olofson, H. Kohn, R. V. Kendall, and W. P. Piekielek, Abstracts, 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, ORGN 76. The significance of this result will be discussed elsewhere.

planar trans relationship required for a concerted E2 elimination[16]—a requirement only fulfilled in **1** by one of the boat conformations, **e–g**. However, enough exceptions to this generalization are known[16] so that it cannot be used to definitely exclude structures **a–d** for **1**.

When **1** was alkylated with $Me_3O^+BF_4^-$, the product was not the cation **2**, but instead 1,1,4-trimethyl-1,4-dihydro-1,2,4,5-tetrazinium BF_4^- (**12a**) in 83% yield (Table I). A similar salt (**12b**) was isolated from reaction of **1** with $Et_3O^+BF_4^-$.

TABLE I

NMR (CD_3CN) FOR **12a** AND **12b**



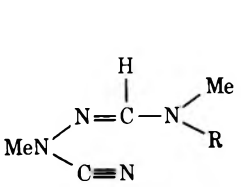
BF_4^-

12a, R = Me
b, R = Et

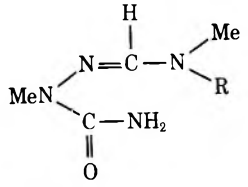
	12a	12b
Proton Spectra, δ (J, Hz)		
H_3 and H_6	7.78,[a] 7.06[b]	7.83, 7.04
NMe	3.50	3.48
$^+$NMe	3.35	3.28
$^+NCH_2$		3.71 (q, 7.5)
CCH_3		1.31 (t, 7.5)
^{13}C Spectra (and $J_{^{13}C-H}$), ppm from TMS (J, Hz)		
H_3 and H_6	150.4 (207)	150.3 (206)
	126.5 (235)	125.4 (235)
NMe	42.5 (~141)	42.3 (142)
$^+$NMe	54.0 (148)	52.3 (147)
$^+NCH_2$		63.2 (148)
CCH_3		8.80 (~138)

[a] $J_{^{13}C-H}$ = 207 Hz; also J = 0.1 Hz with NMe and 0.3 Hz with $^+$NMe (from decoupling); also splitting by N. [b] $J_{^{13}C-H}$ = 238 Hz; also splitting by N.

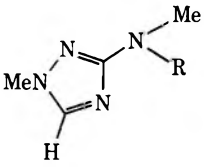
The nmr data reproduced here unambiguously eliminate structure **2** for these salts.[17] Because of the equivalence of one NMe and NR in **12a** (peak remains a singlet at −50°) and the nonequivalence of the two NMe's in **12b**, the new *N*-alkyl must be situated on one of the N atoms already bearing a methyl substituent. A small coupling (*ca.* 1.5 Hz) between H_3 and H_6 is partially masked by further coupling to nitrogen. Other analytical and spectral data consistent with structures **12** are recorded in the Experimental Section. In addition, **12a** and **12b** both underwent ready ring cleavage to the expected nitriles (**13a,b**) on short treatment with base. On longer reaction with aqueous NaOH, the ureas **14** were obtained along with the triazoles **15**. The triazole structure assignment is only tentative; some isomeric triazole structures have not been excluded. Spectral and analytical data for **13–15** are summarized in Table II. The nitriles were shown to be precursors to both the ureas and the triazoles, and the ureas were shown to be neither intermediates on the pathway from nitrile to triazole nor possible sources of triazole. Because product ratios varied dramatically



13a, R = Me
b, R = Et



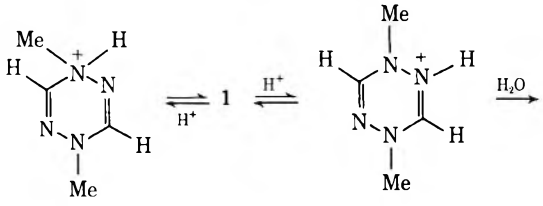
14a, R = Me
b, R = Et



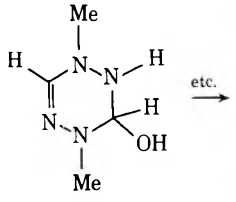
15a, R = Me
b, R = Et

with reaction conditions, this proof required the use of crossover experiments in which, for example, methyl salt **12a** was treated with NaOH in the presence of ethyl nitrile **13b** or ethyl urea **14b** (see Experimental Section).

The salt **12a** is stable in water below pH 8 (even in 0.1 *N* HCl). At higher pD in D_2O, exchange of both H_3 and H_5 seems to be competitive with ring opening to **13a**, but this conclusion is only tentative since partly deuterated **12a** could not be reisolated from the reaction solution. The stability of **12** in dilute acid might seem surprising in view of the ready hydrolysis of its precursor **1** in this medium. This apparent contradiction is easily resolved if hydrolysis of **1** does not involve protonation at N_1, but rather protonation at N_2 to give **16**, which then adds water and proceeds to prod-



stable 16



ucts. Attempts to thermally isomerize **12a** to **2** (R = Me) were unsuccessful.

The discovery that the pmr absorption of methyl attached to the positively charged nitrogen in **12a** occurs at higher field (δ 3.35) than the peak assigned to the methyl bonded to the formally neutral nitrogen atom (δ 3.50) was most unexpected and was especially fascinating, since introduction of a positive charge normally has a strong deshielding effect at adjacent positions (Me_4N^+ δ 3.2 *vs.* Me_3N δ 2.2, both in D_2O) but a much smaller effect at more distant sites.[18] This observation becomes even more significant because of the gross symmetry considerations which make the second *N*-methyl an ideal model for most of the other structure factors included in the variation of chemical

(16) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, Chapter 9.

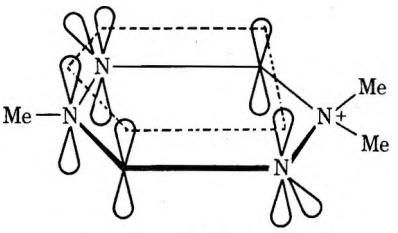
(17) The proton spectrum has been measured in several solvents (see Experimental Section). Note also the nmr and mass spectral evidence for the RNMe unit in degradation products **13–15** (Table I, including footnotes).

(18) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Part 2, Pergamon Press, New York, N. Y., 1969.

TABLE II
SPECTRAL AND ANALYTICAL DATA FOR 13, 14, AND 15

	13a	13b	14a	14b	15a	15b
Nmr, δ, in	CCl_4	CCl_4	$CDCl_3$	$CDCl_3$	CCl_4	$CDCl_3$
H—C=N[a]	7.69	7.76	7.34	7.38	7.36	7.40
MeN—	2.98	2.99	3.18	3.16	3.67	3.70
R—N—Me	2.85	2.83	2.88	2.83	2.82	2.86
R[b]	↑	3.24, 1.12	↑	3.25, 1.13	↑	3.18, 1.14
NH_2[c]			5.53	5.86		
Ir, μ,[d] in	CCl_4	CCl_4	$CHCl_3$	$CHCl_3$	CCl_4	$CHCl_3$
C≡N	4.58 (m)	4.56 (m)				
—C=N	6.09 (s)	6.14 (s)	6.08 (s), 6.47 (s)	6.09 (s), 6.44 (s)		
—C=O						
$—NH_2$			2.83 (w), 2.94 (w)	2.83 (w), 2.94 (w)		
Mass spectrum, m/e,[d] P	126	140	144	158	126	140
Analysis	$C_5H_{10}N_4$	$C_6H_{12}N_4$	$C_5H_{12}N_4O$	$C_6H_{14}N_4O$	$C_5H_{10}N_4$	$C_6H_{12}N_4$
Calcd C	47.60	51.41	41.65	45.55	47.60	51.41
Found C	47.89	51.51	41.97	45.42	47.40	51.38
Calcd H	7.99	8.63	8.39	8.92	7.99	8.63
Found H	8.21	8.36	8.62	8.99	8.02	8.81
Calcd N	44.41	39.97	38.86	35.41	44.41	39.97
Found N	43.99	40.21	39.10	35.36	44.27	39.87

[a] Not NH; not washed out with D_2O. [b] Quartet and triplet; J = 7.5 Hz for **13b** and 7Hz for **14b** and **15b**. [c] Broad singlet; exchanged with D_2O. [d] More extensive ir and mass spectral data in ref 1b. Of particular significance is the finding that the mass spectral ion $C_3H_8N^+$ (from MeNEt unit) is the base (100%) peak in **13b**, **14b**, and **15b**; see Experimental Section.



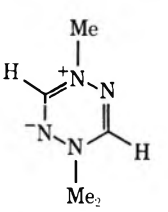
12a′

shift. An attractive rationalization of this dichotomy involves the postulation of the detailed structure **12a′** for the *N*-methyl salt of **1**.

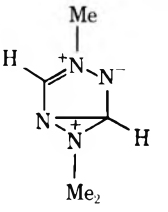
The six π electrons are assumed to constitute an aromatic Hückel sextet, at least to the extent that an appreciable ring current can be induced in a magnetic field. For such a system, as in other benzene derivatives, the methyl protons in the ring plane should be greatly deshielded while the methyl protons above and below the plane in **12a′** should be affected to a much lesser extent.[18,19] In ^{13}C magnetic resonance spectra, electron density factors are of primary importance while anisotropic (ring current) effects generally play a much smaller role in the determination of chemical shift than in proton spectra.[20] The ^{13}C resonance for $^+NMe_2$ in **12a′** should therefore be found at lower field than the absorption for NMe, the reverse of the proton order. As can be verified from an examination of the data given, this expectation is in accord with the experimental result.

If the interpretation of the nmr data elucidated here is correct, **12** qualifies as a "homoaromatic" compound.[21] In comparison with other species whose assignment to this class is based on experimental data, however, **12** is unusual in that no formal charge is associated with the π system. In earlier examples the instability inherent in such a charged system (or in an excited state) was required to bring into operation the amount of "homoaromatic stabilization" necessary for an experimentally observable effect. For example, structural and nmr evidence relating to the question of cyclic electron delocalization (monohomobenzene character) in tropylidene is ambiguous.[22] Enhanced homoaromaticity in **12** *vs.* tropylidene and related substances[22] would be readily explained in terms of the spatial distance and geometrical factors which permit maximum overlap without increased angle strain. The positive charge as well as the number and placement of the nitrogen atoms could also be important, since their combined effect is to increase the resonance contribution from the canonical structure **12a″** and as a further consequence also from **12a‴**.

Structure **12a′** as depicted is π isoelectronic with the pentadienyl anion and thus subject to the same orbital



12a″



12a‴

(19) A qualitatively similar argument can be derived just from considerations of the diamagnetic anisotropy of isolated C=N bonds. However, such effects are generally much too small in magnitude at the distances required in **12** to account for the present observations.[18]

(20) A. J. Jones, T. D. Alger, D. M. Grant, and W. M. Lichtman, *J. Amer. Chem. Soc.*, **92**, 2386 (1970), and references cited therein.

(21) S. Winstein in "Aromaticity," Special Publication No. 21, The Chemical Society, London, 1967, pp 5–45.

(22) See footnotes 52a–c and 53a–b in ref 21. Even the exaltation of its molecular diamagnetic susceptibility is not large: H. J. Dauben, J. D. Wilson, and J. L. Laity, *J. Amer. Chem. Soc.*, **91**, 1991 (1969). For a review of data on other hydrocarbons (*e.g.*, triquinacene, *cis,cis,cis*-cyclonona-1,4,7-triene), see ref 21, pp 42–43.

symmetry determined 1,5 π-bonding interactions[23] which make the planar "U" conformation of this anion experimentally more stable than the alternative "W" and "sickle" forms.[24] It is also useful to note that, in molecular orbital calculations, the insulating methylene group of the cyclohexadienyl anion mixes in to stabilize the highest occupied molecular orbital just as it does in methylallyl anion (a rationalization for the known greater stability of the cis form).[23,25] The replacement of the CH_2 in cyclohexadienyl anion by $^+NMe_2$ is expected to enhance this stabilization. Since its physical consequences are unknown, the operation of the final hypothetical "hyperconjugation" effect above could alone explain the nmr data.

The arguments above increase the attractiveness of those geometries and electronic configurations of **1** in which "homoaromatic character" can be visualized as a significant factor (*e.g.*, **1b**, **1g**). The simple fact of the isolation of **12** (instead of **2**) itself testifies to the unique nature of **1**, since, among the thousands of cases published, there is no known instance of a potentially Hückel-aromatic heterocycle in which alkylation by an electrophilic reagent occurs at an electron pair which can be contributed by ring nitrogen to the π system when a second, necessarily orthogonal sp^2 electron pair on nitrogen is also available for alkylation. For example, 1,2-dimethylpyrazolium cation, not the 1,1-dimethyl isomer, is the product from methylation of 1-methylpyrazole.[26]

Experimental Section[27]

1,4-Dimethyl-1,4-dihydro-1,2,4,5-tetrazine (1).—(Since HCN is a possible minor side reaction product, this experiment, including early isolation steps, should be performed in a hood!) Ethyl formimidate hydrochloride (from $HCONH_2$, EtOH, and PhCOCl[8]) (163 g, 1.5 mol) was added (45 min) in small aliquots *via* a powder funnel to a stirred mixture of $MeNHNH_2$ (69 g, 1.5 mol) and a few milliliters of anhydrous ether. The exothermic reaction was kept under control (moderate ether reflux) by adjusting the rate of formimidate addition and by cooling the mixture with an ice bath. During the reaction small amounts of ether (total 80–100 ml) were added to facilitate manipulation of the bright yellow pasty mixture. The precipitated NH_4Cl was filtered off and washed with 100 ml of ether. The total filtrate was concentrated and then vacuum distilled at 1 Torr using (a) an oil bath to prevent overheating and the possibility of detonation, (b) a large distilling flask to minimize problems caused by bumping of the very viscous liquid, (c) an inefficient condenser to avoid solidification of higher melting fractions, and (d) a Dry Ice–acetone bath to cool the collection flasks and thus effect complete condensation of each fraction. The distillation fraction, bp 45–55°, 51.9 g, contained a mixture of the desired product and 1-methyl-1,2,4-triazole. Lower boiling fractions contained only ethanol, ether, and methylhydrazine. A side product, *N*-formyl-*N*-methylhydrazine, which distilled at 65° (10.2 g, 9%), was purified by vpc and compared with an authentic sample.[9]

The ratio of **1** to **5** in the distillate fraction could be determined by nmr analysis [1.5:1.0 tetrazine (41%) to triazole (27%)] and the two compounds separated by selective precipitation of the latter as the oxalate salt from an ether solution. Oxalic acid (18.9 g, 0.21 mol; 1 mol per assayed mol **5**) in 200 ml of ether was added dropwise to a stirred solution of the distillate fraction in 100 ml of ether. During the addition a white granular solid precipitated. (If additional oxalic acid was added, the oxalate salt of **1** began to precipitate as a fluffy white solid, and this change in the character of the precipitate could also be used as an end point and as a crude assay of **5**.) After addition was complete the mixture was stirred for 30 min and filtered, and **1** was isolated from the filtrate by vacuum distillation: yield 32.0 g (38%); bp 55–60° (1.0 Torr); mp 45–46° (lit.[11] mp 44–46°); vpc retention time 31 min (10 ft × 0.25 in. 20% Carbowax 20M on 60/80 Chromosorb W, 152°, 38 cc/min); ir (CCl_4) 3.46 (s), 3.57 (m), 6.27 (s), 7.90 (s), 9.72 (s), 11.35 μ (s); uv (cyclohexane) 240 nm (ϵ 6200), (absolute ethanol) 236 (5900), (water) 230 (7500); mass spectrum *m/e* 112.0745 (P, calcd 112.0748), 97 (P − Me), 83 (P − MeN); nmr ($CDCl_3$) δ 6.36 (s, $J_{^{13}C-H}$ = 200 Hz, 1), 3.01 (s, $J_{^{13}C-H}$ = 137 Hz, 3), same at 60, 100, and 220 megacycles; at −99° in CD_2Cl_2 (*vs.* CH_2Cl_2, A-60A) two singlets were still found, δ 6.46 and 2.92); ^{13}C spectra (in CD_3CN *vs.* TMS) 40.7 (J = 137 Hz), 142.4 ppm [J = 200 (d), 5 (q) Hz].

Anal. Calcd for $C_4H_8N_4$: C, 42.84; H, 7.19; N, 49.96. Found: C, 42.48; H, 7.02; N, 50.08.

5 was regenerated from the oxalate salt (42.4 g) by treatment with aqueous KOH. The filtrate obtained after removal of the insoluble potassium oxalate was extracted with CH_2Cl_2 and **5** was isolated from this extract by distillation and compared with an authentic sample.[10]

1,4-Dimethyl-1,4-dihydro-1,2,4,5-tetrazine (*N*-Methylformimidate Method).—Ethyl *N*-methylformimidate HBF_4 salt was obtained as a colorless oil (99%) by reaction of HCONHMe with $Et_3O^+BF_4^-$. While the crude product was a mixture of geometrical isomers, it was otherwise uncontaminated by impurities: nmr (CD_3NO_2) δ 8.6–10.3 (broad, 1), 8.2–8.5 (broad asymmetrical d, 1), 4.5–5.0 (m, 2), 2.9–3.3 (asymmetrical d, 3), 1.2–1.8 (m, 3). This salt (13.0 g, 0.074 mol) was added (30 min) to a stirred, cooled (0°) solution of $MeNHNH_2$ (3.46 g, 0.075 mol) in 15 ml of ether (under N_2). The mixture was then stirred overnight at room temperature and evaporated at reduced pressure, and the multicomponent mixture was analyzed by nmr. Two species identified were **1**, which was isolated (0.16 g, 4%) by vacuum distillation, and 1,4-dimethyl-1,2,4-triazolium BF_4^- [nmr (CD_3CN) δ 9.29 (s, 1), 8.59 (s, 1), 4.07 (s, 3), 3.93 (s, 3)], which could be partially purified by selective extraction of more soluble salts into ethanol followed by fractional precipitation from nitromethane–ether. Comparison of this sample (nmr, 85% pure) with material[10] obtained by alkylation of **5** confirmed the structural assignment.

5-Imino-1,4-dimethyl-Δ^2-1,2,4-triazoline (11).—**1** (1.2 g, 0.011 mol) was dissolved in 25 ml of aqueous 4% NaOH (0.025 mol) and stirred at room temperature for 18 hr. The solution was then saturated with NaCl and extracted with 3 × 40 ml of CH_2Cl_2. The dried (Na_2SO_4) extract was evaporated, affording a white solid which was purified by vacuum sublimation: yield 0.54 g (45%); mp 66–68° (lit.[13] mp 56–58°); nmr ($CDCl_3$) δ 7.23 (s, 1), 3.94 (s, 1), 3.39 (s, 3), 3.25 (s, 3); mass spectrum *m/e* 112 (P), 111 (P − H).

Anal. Calcd for $C_4H_8N_4$: C, 42.84; H, 7.19; N, 49.96. Found: C, 42.68; H, 7.44; N, 49.84.

The known HI salt of the triazoline was made by reaction with aqueous hydriodic acid, mp 225–225.5° (lit.[14] mp 226°).

Annular Proton Exchange of 1 in NaOD–D_2O.—**1** (0.82 g, 0.0073 mol) dissolved in 10 ml of 0.135 *N* NaOD–D_2O (>99.8% D), was kept at 30 ± 1° for 4 hr. The solution was then extracted with 3 × 10 ml of $CHCl_3$ and the extracts were dried (Na_2SO_4) and evaporated at reduced pressure, yielding a semisolid residue whose nmr spectrum showed it to be a mixture (6.5:1 molar ratio) of partly deuterated **1** and N-deuterated and partly C_3-deuterated **11**. **1** (0.21 g) could be isolated pure by fractional vacuum sublimation. The extent of deuteration at the annular positions was 47% by nmr analysis and 38% from

(23) R. Hoffmann and R. A. Olofson, *J. Amer. Chem. Soc.*, **88**, 943 (1966).

(24) R. B. Bates, R. H. Carnighan, and C. E. Staples, *ibid.*, **85**, 3031 (1963). Steric effects most easily explain the dichotomy between this result and that of H. Kloosterziel and G. J. Heiszwolf, *Recl. Trav. Chim. Pays-Bas*, **89**, 413 (1970). Note incompleteness of delocalization: H. Kloosterziel and J. A. A. van Drunen, *ibid.*, **89**, 368 (1970).

(25) This is also true for cyclopropene and cycloheptatriene but not for cyclobutenyl anion, cyclohexadienyl cation, and cyclopentadiene, all of which have nodes which pass through the methylene group in the relevant orbital.[23]

(26) Similarly, 1,7a-diazaindene is alkylated at the 1 position and 1-methylpyridone-4 is alkylated on oxygen, not nitrogen.

(27) Melting points were determined in Kimax, soft glass capillary tubes using a Thomas-Hoover melting point apparatus equipped with a calibrated thermometer. Pmr spectra were run on a Varian A-60A (equipped with V-6040 variable temperature controller), HA-100, or 220 spectrometer using an internal TMS standard; ^{13}C spectra and $J_{^{13}C-H}$ values were measured on a JOEL PS100 with a JEM-PFT-100 Fourier Transform spectrometer equipped with a Nicolet Model 1080E extended memory unit. Solvents and reactants were of the best commercial grade available and were used without further purification. Mass spectral data were obtained at 70 eV on an MS-902 double-focusing spectrometer.

less accurate mass spectral data (39% H_2, 47% HD, and 14% D_2 compound).

Acid Hydrolysis of 1.—An attempt to determine the pK_B of **1** (uv) was unsuccessful because hydrolytic decomposition occurred below pH 2. When the hydrolysis was performed on a 20% by weight solution of 1 in 10% DCl-D_2O in an nmr tube, the initial yellow color almost immediately darkened to orange but after 20 min the solution was colorless. The nmr spectrum continually changed during this period and for several days thereafter and became more and more complicated. None of the products were identified.

1,1,4-Trimethyl-1,4-dihydro-1,2,4,5-tetrazinium Fluoroborate (12a).—$Me_3O^+BF_4^-$ (5.92 g, 0.04 mol) in 90 ml of CH_3NO_2 was added dropwise to a stirred solution of 4.48 g (0.04 mol) of 1 in 30 ml of CH_3NO_2. The red solution was stirred at room temperature for 5 hr and the product was isolated by precipitation with ether. Purification of the white solid was accomplished by reprecipitation with ether from a 1:1 CH_3NO_2–CH_2Cl_2 solution: yield 7.10 g (83%); mp 119.5–122°; ir (Nujol) BF_4^- at 9.3–9.7 μ (s); uv (CH_3CN) 275 nm (ϵ 1200), 208 (3700), (H_2O) 268 (1700), 205 (4400), (0.1 *N* HCl-H_2O) 269 (1700), 205 (4200); nmr (CD_3CN) δ 7.78 (broad s, 1), 7.06 (broad s, 1), 3.50 (s, 3), 3.35 (s, 6) (the peak at 3.35 remained a singlet at −50°). Spectra were also measured in DMSO-d_6, CF_3CO_2D, CF_3CO_2D–D_2O (1:1), and 0.1 *N* DCl-D_2O buffers below pD 8 (at higher pD hydrolysis occurred). Except for minor position variations and sharpening of the ring protons to doublets [in DMSO-d_6 δ 8.23 (broad, 1.3 Hz), 7.44 (distinct d, 1.5 Hz)], the spectra were unchanged. The $^+NMe_2$ peak never was found at lower field than the NMe resonance and both absorptions were always found as singlets.

Anal. Calcd for $C_5H_{11}N_4BF_4$: C, 28.07; H, 5.18; N, 26.18. Found: C, 27.94; H, 5.40; N, 26.13.

1-Ethyl-1,4-dimethyl-1,4-dihydro-1,2,4,5-tetrazinium Fluoroborate (12b).—Ethylation of 1 was achieved using the procedure described in the previous experiment with $Et_3O^+BF_4^-$ (7.60 g, 0.04 mol) as the alkylating agent and CH_2Cl_2 as the reaction solvent: yield of white solid 6.49 g (71%); mp 125–127°; ir (Nujol) BF_4^- at 9.2–9.7 μ (s); nmr (CD_3CN) δ 7.83 (broad s, width at half-height 4 Hz, 1), 7.04 (broad d, 1.5 Hz, 1), 3.71 (q, 7.5 Hz, 2), 3.48 (s, 3), 3.28 (s, 3), 1.31 (t, 7.5 Hz, 3).

Anal. Calcd for $C_6H_{13}N_4BF_4$: C, 31.61; H, 5.75; N, 24.57. Found: C, 31.86; H, 6.05; N, 24.87.

***N*-Cyano-*N*-methyl-*N'*,*N'*-dimethylformamidrazone (13a).**—A 2 *N* aqueous NaOH solution (8 ml, 0.016 mol) was added dropwise with stirring to a solution of **12a** (2.00 g, 0.00935 mol) in water (32 ml). The solution was immediately extracted with 3 × 40 ml of CH_2Cl_2, and the combined extracts were dried (Na_2SO_4) and concentrated to a yellow oil, which afforded **13a** on distillation as a colorless liquid, yield 0.79 g (67%), bp 71–72° (0.6 Torr).

***N*-Cyano-*N*-methyl-*N'*-ethyl-*N'*-methylformamidrazone (13b).**—The preceding reaction was repeated using 2.00 g (0.0088 mol) of **12b** in place of **12a**: yield 0.88 g (72%); bp 69–70° (0.6 Torr). Important peaks in the mass spectrum of **13b** besides the parent (intensity 99%) included $C_4H_7N_2^+$ [found 83.0600, calcd 83.0609 (71%)], $C_3H_5N_2^+$ [found 69.0452, calcd 69.0453 (50%)], $C_3H_8N^+$ (found 58.0660, calcd 58.0657).

***N*-Carbamyl-*N*-methyl-*N'*,*N'*-dimethylformamidrazone (14a).**—**13a** (1.00 g, 0.0079 mol) was dissolved in 10 ml (0.002 mol) of 0.2 *N* NaOH and the solution was allowed to stand at room temperature for 18 hr. The reaction mixture was then extracted with 3 × 40 ml of CH_2Cl_2, and the combined extracts were dried (Na_2SO_4) and pumped to near dryness. The nmr spectrum of this semisolid residue indicated it to be a 2.3:1 mixture of **14a** and **15a**. **14a** was isolated by several precipitations with hexane from a 1:4 CH_2Cl_2–CCl_4 solution, yield 0.41 g (36%), mp 116–118°.

***N*-Carbamyl-*N*-methyl-*N'*-ethyl-*N'*-methylformamidrazone (14b).**—The above reaction was repeated using 1.00 g (0.0071 mol) of **13b** instead of **13a**. The ratio of **14b** to **15b** determined by nmr analysis of the initial residue was 13:1. Isolation and purification of **14b** was accomplished by three recrystallizations from CCl_4–hexane, yield 0.46 g (41%), mp 72–74°. Important **14b** mass spectral peaks besides the parent mass ion (33%) included $C_5H_{13}N_3^+$ [found 115.1110, calcd 115.1109 (30%)], $C_4H_9N_2^+$ [found 85.0760, calcd 85.0766 (31%)], $C_4H_{10}N^+$ [found 72.0808, calcd 72.0813 (24%)], $C_3H_8N^+$ [found 58.0650, calcd 58.0657 (100%)].

14b could be recovered after 16 hr at room temperature in 65% yield (0.11 g) by the extraction procedure above from a solution made of 0.17 g (0.0011 mol) of substrate and 5 ml (0.0025 mol) of 0.5 *N* aqueous NaOH. There was no evidence for the presence of any **15b** in the extract.

1-Methyl-3-dimethylamino-1,2,4-triazole (15a).—A solution of **12a** (2.96 g, 0.0138 mol) in 38 ml (0.016 mol) of 0.42 *N* aqueous NaOH was kept at room temperature for 12 hr and then extracted with 3 × 40 ml of CH_2Cl_2. The extracts were dried (Na_2SO_4), concentrated, and distilled, yield 0.96 g (55%), bp 43.5° (0.5 Torr).

15a was also converted to its HI salt by reaction with aqueous HI. The salt, which turned brown after a few days, was isolated by repeated trituration of the initial product with ether: mp 133.5–136°; nmr ($CDCl_3$) δ 11.51 (s, 1), 8.13 (s, 1), 4.08 (s, 3), 3.47 (s, 6).

The pot residue remaining after distillation of **15a** contained 0.07 g of crude **14a** (nmr).

1-Methyl-3-ethylmethylamino-1,2,4-triazole (15b).—This compound, bp 45° (0.6 Torr), was prepared in 55% yield (0.92 g) from 2.70 g (0.012 mol) of **12b** in 38 ml (0.015 mol) of aqueous 0.4 *N* NaOH using the method described in the preceding experiment. An important mass spectral fragment besides P (7%), P − Me (19%), and P − Et (10%) was $C_3H_8N^+$ [found 58.0655, calcd 58.0657 (100%)].

The unstable **15b** HI salt was also made: mp 96–100°; nmr ($CDCl_3$) δ 11.48 (broad s, 1), 8.06 (s, 1), 4.05 (s, 3), 3.75 (q, 7 Hz, 2), 3.43 (s, 3), 1.39 (t, 7 Hz, 3).

Concentration of the initial distillation residue afforded 0.09 g of crude **14b**.

15b was recovered by extraction in 68% yield (0.27 g) from a solution (0.40 g, 0.0029 mol) in 4.0 ml (0.0008 mol) of 0.2 *N* aqueous NaOH after 14 hr at room temperature. No **14b** was present along with the crude **15b** in the product (nmr).

Reaction of a Mixture of 12a and 14b with Aqueous NaOH.—Only **15a** (0.2 g) and no **15b** (<1%) was found (nmr) in the crude triazole distillate obtained from reaction of a solution of 1.24 g (0.0058 mol) of **12a** and 0.92 g (0.0058 mol) of **14b** in 18.9 ml (0.0075 mol) of 0.4 *N* aqueous NaOH at room temperature for 15 hr followed by the normal extraction work-up.

Reaction of a Mixture of 12a and 13b with Aqueous NaOH.—The preceding experiment was repeated with **13b** (0.81 g, 0.0058 mol) in place of the derived urea. The crude triazole distillate (0.41 g) was shown (nmr) to be a mixture of **15a** and **15b** (1.4:1).

Registry No.—**1**, 35341-96-9; **11**, 23350-29-0; **12b**, 35541-98-1; **12b**, 35341-99-2; **13a**, 35342-00-8; **13a**, 35342-01-9; **14a**, 35342-02-0; **14b**, 35342-03-1; **15a**, 35342-04-2; **15b**, 35342-05-3.

Biosynthesis of Phenazines

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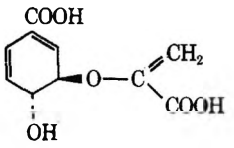
[G-^{14}C]- and [1,6-^{14}C]-DL-shikimic acid were fed to *Pseudomonas aureofaciens*, producer of phenazine-1-carboxylic acid, and to *Pseudomonas aeruginosa*, producer of pyocyanine. Incorporation was 16 and 9%, respectively, into phenazine-1-carboxylic acid and 12 and 7%, respectively, into pyocyanine. The products were degraded to phenazine + CO_2, 1-hydroxyphenazine, pyrazinetetracarboxylic acid, pyrazine, and carbon dioxide. The labeling data are in agreement with a pairing scheme of two shikimic acid molecules, whereby carbons 5 and 6 of shikimic acid become part of the center ring of the phenazine system.

During the past two decades about 30 phenazine (**1**) derivatives have been isolated from natural sources.[1,2] Microorganisms constitute the exclusive source of these compounds and there is considerable overlap in the production pattern: several microorganisms produce the same compound while also the same microorganism produces several phenazines. In addition, a dihydrophenazine derivative was found in several species of a green alga.[3] The isolated phenazines possess antibiotic properties, a feature which can be related to their interaction with deoxyribonucleic acid, presumably by intercalation of the planar aromatic ring system.[4]

Inspection of the presently known phenazine structures reveals a symmetrical pattern: C or O substituents are often found at the 1, 4, 6, and 9 positions with identical substituents often attached at the diagonally opposed positions 1, 6 (or 4, 9). This is also true for the algal dihydrophenazine derivative. The ring system as well as its unique substitution pattern has challenged several investigators to study the biosynthetic origin of the phenazine nucleus. The symmetrical element suggested strongly a generation of the phenazine ring system by dimerization of oppositely oriented aromatic precursors. The role of anthranilic acid as an attractive possibility for a coupling partner has been investigated.[5-9] Feeding phenazine producing microorganisms with ^{14}C-labeled anthranilic acid led to inconclusively low incorporation levels of label,[5,8] a result which may be interpreted in two opposite ways: either anthranilic acid is poorly transported through the cell wall or the low incorporation rates result from a nonspecific utilization of anthranilic acid or its breakdown products. Feeding of inactive anthranilic acid led invariably to inhibition of phenazine production.[6,7,9] This may indicate that the phenazines are formed from an anthranilic acid precursor whose formation is blocked through feedback inhibition by excess anthranilic acid.

We have presently reinvestigated the biosynthesis of phenazine-1-carboxylic acid (**2**), produced by *Pseudomonas aureofaciens*, and of pyocyanine (**3**), produced by *Pseudomonas aeruginosa*. If anthranilic acid causes indeed feedback inhibition it appeared worthwhile to test precursors of anthranilic acid for incorporation into the phenazine nucleus. We chose chorismic acid (**4**), intermediate between shikimic acid and anthranilic acid. This compound is an important branch point from which besides anthranilic acid a variety of other compounds is formed. [U-^{14}C]-Chorismic acid was prepared from [U-^{14}C]glucose using Gibson's mutant of *Aerobacter aerogenes*.[10] The compound was fed to *Ps. aureofaciens*. The low incorporation of label (0.23%) into phenazine-1-carboxylic acid left again unanswered the alternative whether chorismic acid or its degradation products are incorporated nonspecifically or whether there was a poor transport through the cell membrane. Indications that shikimic acid (see a) is incorporated had already been reported for iodinin, phenazine-1-carboxylic acid, chlororaphin (a complex of phenazine-1-carboxamide and its dihydro product), 2-hydroxyphenazine, and pyocyanine.[9,11-13] In our hands the incorporation of label from [G-^{14}C]-DL-shikimic acid into phenazine-1-carboxylic acid (**2**) amounted to 16%, substantially higher than previously reported for direct feeding experiments. The relative high activity made possible suitable dilution with inactive phenazine-1-carboxylic acid, obtained from 1-methylphenazine.[14,15]



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Similarly [1,6-^{14}C]-DL-shikimic acid was incorporated to the extent of 9%. The incorporation of [G-^{14}C]- and [1,6-^{14}C]-DL-shikimic acid into pyocyanine (**3**), produced by *Ps. aeruginosa*, was 12 and 7%, respectively. The two pigments were degraded to phenazine (**1**) + CO_2, 1-hydroxyphenazine (**5**), pyrazinetetracarboxylic acid (**6**), pyrazine (**7**), and CO_2.[9b,16] The labeling data, presented in Table I, are in agreement with incorporation of two shikimic acid residues. They are also in agreement with the finding that **2** is a precursor of

(1) N. N. Gerber, *J. Heterocycl. Chem.*, **6**, 297 (1968), and ref 2 therein.
(2) C. D. Tipton and K. L. Rinehart, Jr., *J. Amer. Chem. Soc.*, **92**, 1425 (1970).
(3) G. Aguilar-Santos, *J. Chem. Soc. C*, 842 (1970).
(4) U. Hollstein and R. J. VanGemert, Jr., *Biochemistry*, **10**, 497 (1971); U. Hollstein and P. L. Butler, *ibid.*, **11**, 1345 (1972).
(5) R. E. Carter and J. H. Richards, *J. Amer. Chem. Soc.*, **83**, 495 (1961).
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(7) M. E. Levitch and E. R. Stadtman, *Arch. Biochem. Biophys.*, **106**, 194 (1964).
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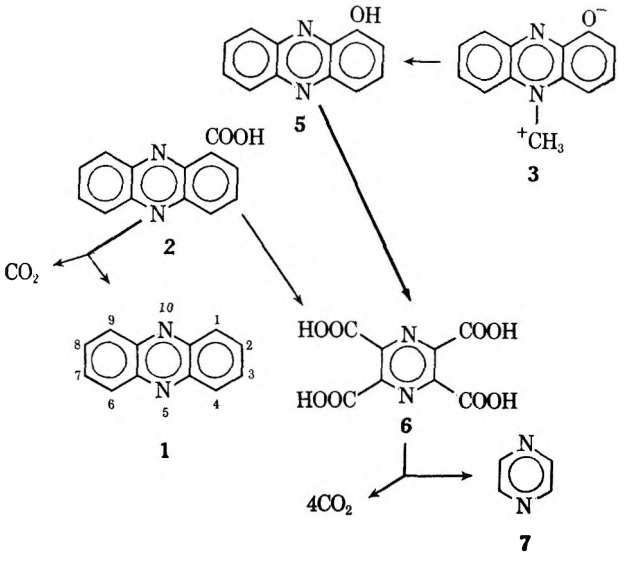
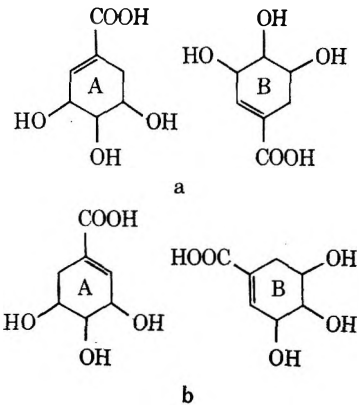
(9) (a) M. Podojil and N. N. Gerber, *Biochemistry*, **6**, 2701 (1967); (b) *ibid.*, **9**, 4616 (1970).
(10) F. Gibson, *Biochem. J.*, **90**, 256 (1964).
(11) P. C. Chang and A. C. Blackwood, *Can. J. Biochem.*, **46**, 925 (1968).
(12) M. E. Levitch and P. Rietz, *Biochemistry*, **5**, 689 (1966).
(13) W. M. Ingledew and J. J. R. Campbell, *Can. J. Microbiol.*, **15**, 535 (1968).
(14) U. Hollstein, *J. Heterocycl. Chem.*, **5**, 299 (1968).
(15) G. R. Clemo and H. McIlwain, *J. Chem. Soc.*, 1991 (1935).
(16) D. L. Vivian, *Nature (London)*, **178**, 753 (1956).



3.[17,18] Our data are not in agreement with the pairing arrangements based on labeling data in studies on the biosynthesis of iodinin[9b,19] (a and b). A salient point

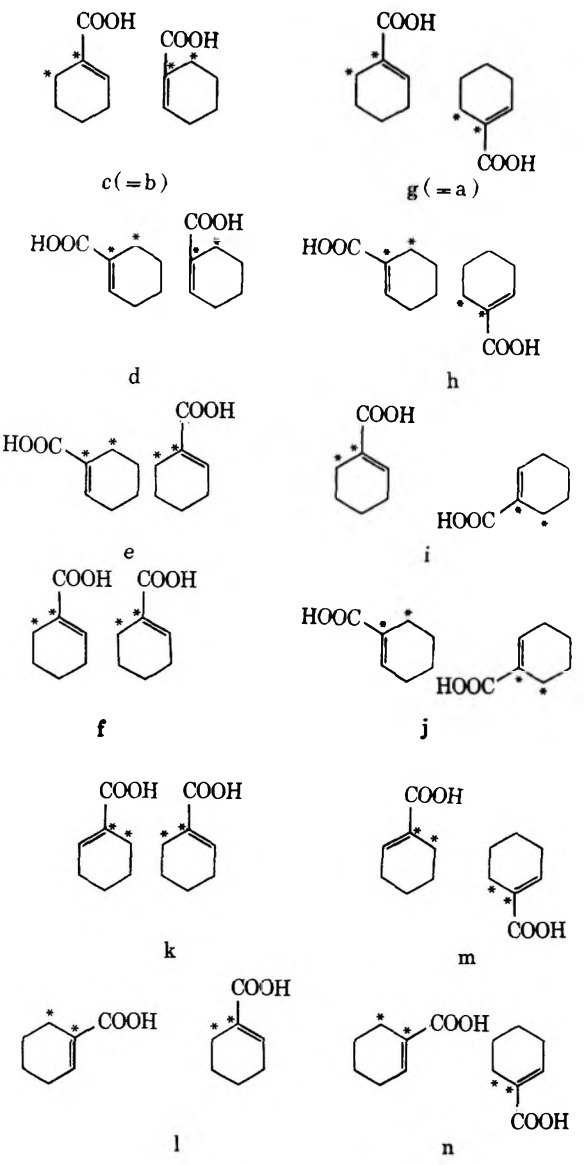


in the iodinin studies is that one of the hydroxyls is present before formation of the phenazine system.

A detailed analysis[20] of the problem shows that there are eight possible pairing schemes of two shikimic acid molecules which accommodate the labeling data in iodinin[9b] (c–j; hydroxyls have been omitted for clarity).

There are four pairing schemes of two shikimic acid molecules which accommodate the labeling data for 2 and 3 in the present work (k–n).

For kinetic reasons the two nitrogen bridges are formed in different reaction steps. After formation of the first nitrogen bridge, either ring can rotate 180° around the N–C bond prior to locking through the second nitrogen bridge. Thus, there is a correlation between the schemes of the set c–j with those of the set k–n. Furthermore, the labeling data indicate strongly that the phenazine system is formed from two identical units so that no dilution in specific activity occurs between the one and the other. It is significant that only e, which correlates with m, satisfies this condition.



On this basis, the biosynthetic pathway shown on page 3512 is proposed.

Nitrogen enters shikimic acid at the 5 position. The first nitrogen bridge is formed by attack of the nitrogen in one unit on the 6 position of the other unit. Rotation of one ring around the N–C bond and cyclization between N and C_4 leads, after aromatization, to 6-hydroxyphenazine-1-carboxylic acid and subsequently to iodinin.[19] Cyclization between N and C_6 leads to phenazine-1,6-dicarboxylic acid and subsequently to 2 and 3.[17,18] The latter ring closure would also be required to explain the formation of several other 1,6-dicarbon substituted natural phenazines, such as griseolutin A and B,[21] phenazine-1,6-dicarboxylic acid,[1] lomofungin,[2] and caulerpin.[3]

It has been shown that ^{2}H-labeled phenazine-1,6-dicarboxylic acid is not incorporated into pyocyanin,[18] as would be required by our proposed pathway. Also, phenazine-1,8-dicarboxylic acid, whose formation is suggested by our pathway, has not so far been isolated. These negative results must, however, be interpreted with caution.

Although the original idea of a coupling of two aromatic precursors, such as anthranilic acid, must now

(17) M. E. Flood, R. B. Herbert, and F. G. Holliman, *Chem. Commun.*, 1514 (1970).

(18) M. E. Flood, R. B. Herbert, and F. G. Holliman, *J. Chem. Soc., Perkin Trans. 1*, **1**, 622 (1972).

(19) R. B. Herbert, F. G. Holliman, and D. N. Ibberson, *Chem. Commun.*, 355 (1972).

(20) We gratefully acknowledge valuable suggestions made by Professor F. G. Holliman, which led to this analysis.

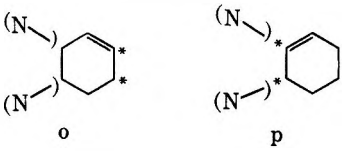
(21) K. Yakishita, *J. Antibiot. (Tokyo)*, **13A**, 83 (1960).

TABLE I

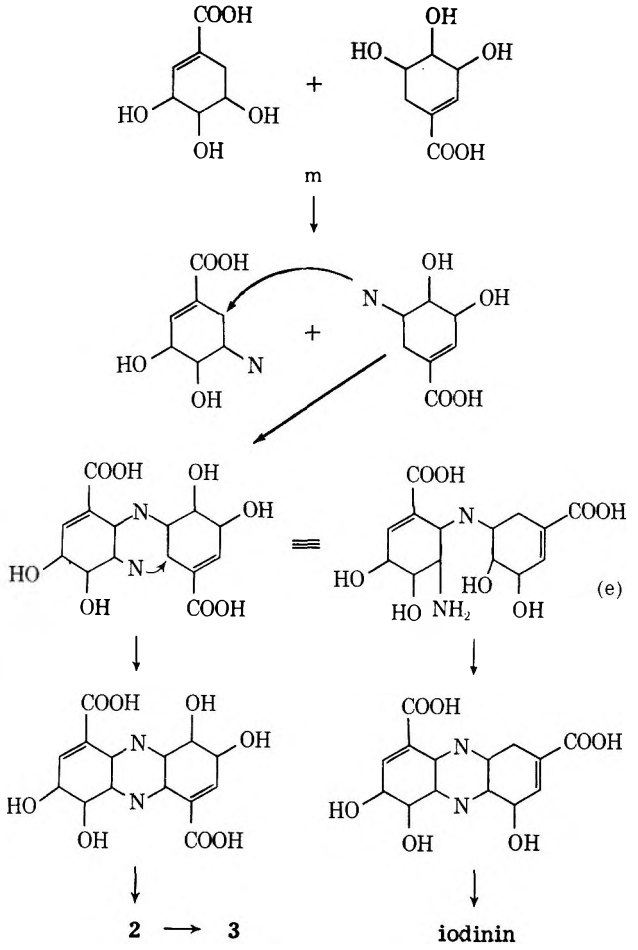
LABELING RESULTS

	Feeding with [G-^{14}C]Shikimic acid			Feeding with [1,6-^{14}C]Shikimic acid							
						% calcd					
Compd	dpm/mmol	% found	% calcd[a]	dpm/mmol	% found	k–n	a, b	b	c	d	e
Phenazine-1-carboxylic acid	230,000	100	100	64,000	100	100	100	100	100	100	100
CO_2 (from C_1-COOH)	25,100	10.9	7.7	1,690	2.6	0	0	0	0	0	0
Phenazine	205,000	88.4	92.3	59,000	92.2	100	100	100	100	100	100
Pyrazine-tetracarboxylic acid	151,000	65.7	61.5	62,000	96.9	100	75	100	50	0	100
CO_2	73,500	32.0	30.8	29,000	45.3	50	50	50	50	0	0
Pyrazine	80,050	34.8	30.8	33,000	51.6	50	25	50	0	0	100
Pyocyanine	23,100	100	100	16,800	100	100	100	100	100	100	100
1-Phenazinol	21,900	94.9	100	16,100	95.8	100	100	100	100	100	100
Pyrazine-tetracarboxylic acid	13,300	57.6	66.7	14,900	88.7	100	75	100	50	0	100
CO_2	6,250	27.0	33.3	7,170	42.7	50	50	50	50	0	0
Pyrazine	7,340	31.7	33.3	8,440	50.2	50	25	50	0	0	100

[a] For pairing of one or two shikimic acid molecules. [b] For incorporation of one shikimic acid molecule positioned as ring A in a. [c] For incorporation of one shikimic acid molecule positioned as ring B in a. [d] For incorporation of one shikimic acid molecule positioned as o.



[e] For incorporation of one shikimic acid molecule positioned as p.



be abandoned, the possibility of an aromatic oxidative coupling between N and C is still an open question. The mechanism of phenazine formation is contrasted by the pathway leading to microbial phenoxazines, which are generated by aromatic oxidative coupling of two *o*-hydroxyaniline derivatives.[22]

Experimental Section

Melting points were obtained on a Kofler hot stage apparatus. Counting was done with a Beckman liquid scintillation spectrometer. Ultraviolet determinations were made with a Cary recording spectrophotometer, Model 14. Infrared spectra were determined with a Perkin-Elmer Model 621 grating spectrophotometer. Vapor phase chromatography was done with a Varian Aerograph Model 700.

Microorganisms.—With the single substitution of Tryptone (Difco) for Peptone (Difco), the storage slants, inoculum medium, and production medium were taken from the literature for *Pseudomonas aureofaciens*[23] and for *Pseudomonas aeruginosa*.[24] *Ps. aureofaciens*, ATCC 13985, and *Ps. aeruginosa*, ATCC 10145, were started from lyophilized cultures on storage slants. The integrity and viability of the cultures was preserved by monthly transfers to new slants. In both cases, loop inoculations from these slants were used to start several 250-ml inoculum flasks, each containing 100 ml of inoculum medium, which were grown on an Eberbach shaker rotating through an orbit of 2 in., 60 times per minute. Growth was allowed to continue until an arbitrarily specified optical density could be visually determined. With *Ps. aeruginosa*, the optical density was allowed to become twice that of *Ps. aureofaciens*. Two milliliters of *Ps. aeruginosa* inoculum medium were used to inoculate 1 l. of the production medium in a 2800-ml Fernbach flask.

Growth Curves.—With sterile technique, 10-ml aliquots were regularly withdrawn from the *Ps. aureofaciens* production medium for determination of cell density. The relative number of cells present in the aliquot was determined using a spectrophotometer by measuring the absorbance at 500 nm. Production of **1** was measured after extraction of a 5-ml aliquot of the bacterial suspension with chloroform as a change in absorbance at the $\lambda_{max}^{CHCl_3}$ of 370 nm. The maximum rate of phenazine-1-carboxylic acid production per cell was then determined by plotting the phenazine-1-carboxylic acid production rate per cell *vs.* time. This

(22) E. Katz and H. Weissbach, *J. Biol. Chem.*, **237**, 882 (1962).

(23) W. C. Haynes, F. H. Stodola, J. M. Locke, T. G. Pridham, H. F. Conway, V. E. Sohns, and R. W. Jackson, *J. Bacteriol.*, **72**, 415 (1956).

(24) L. H. Frank and R. D. DeMoss, *ibid.*, **77**, 776 (1959).

occurred at 16 hr at 28.5°. The beginning of pyocyanine production in the flasks of *Ps. aeruginosa* was visually determined to coincide with a sudden increase in optical density at 14 hr of growth at 33°. The intensity of blue color in the flasks reached a plateau at approximately 40 hr.

Labeled Feeding.—[G-^{14}C]-DL-Shikimic acid (2 μCi) (New England Nuclear, 1.86 mCi/mmol) or 1 μCi of [1,6-^{14}C]-DL-shikimic acid[25] were added under sterile conditions to each production flask of *Ps. aureofaciens*, which was grown for 12 hr at 28.5°. Growth was continued for 12 hr.

G-^{14}C-Labeled shikimic acid (2 μCi) or 1 μCi of [1,6-^{14}C]-shikimic acid were fed to each flask of *Ps. aeruginosa* after 14 hr of growth at 33°. Growth was continued for another 26 hr.

Pigment Extraction and Purification.—With *Ps. aureofaciens* each liter of bacterial medium was extracted three times with 500 ml of chloroform after the pH was adjusted to 5 with hydrochloric acid. Crude **2** (100 mg) was obtained after evaporation of chloroform and chromatographed on a 20 × 400 mm Florisil column. Elution was started with chloroform and gradually changed to 100% methanol. **2** comes down as a yellow-green band in the 50–100% methanol fractions. The fractions were determined spectrophotometrically, combined, and evaporated to dryness. This material, which did not melt below 360°, was presumably the Mg salt of phenazine-1-carboxylic acid. It was dissolved in 6 *N* HCl and, after adjustment of the pH to 3–5 with alkali, phenazine-1-carboxylic acid, mp 242° (reported[26] mp 243°), could be extracted with chloroform. The yield per liter of bacterial medium was between 25 and 50 mg. This material was radioactive. It was diluted 5–20 times with inactive phenazine-1-carboxylic acid and further purified by recrystallization from isopropyl alcohol to constant specific activity.

From *Ps. aeruginosa* pyocyanine was obtained by three extractions with chloroform at pH 7. The extract was evaporated below 30° in order to prevent decomposition. Crude pyocyanine (80 mg) was purified on a 20 × 300 mm silica column (G. F. Smith, 50–200 mesh). Elution with 200 ml of chloroform brought down one yellow band. Through gradual increase to 25% methanol another yellow band and blue pyocyanine were eluted successively. The yield per liter of bacterial medium was 11 mg. This material was radioactive. It was diluted five times with inactive pyocyanine and recrystallized from water to constant specific activity. The melting point was 131° (reported[27] mp 133°).

Scintillation Solutions.—Pyocyanine, phenazine-1-carboxylic acid, and their degradation products 1-phenazinol, phenazine, pyrazinetetracarboxylic acid, and pyrazine were counted in 10 ml of a solution containing 3 g of PPO (Amersham-Searle, Scintillation Grade), 0.25 g of POPOP (Nuclear-Chicago, Scintillation Grade), 500 ml of methanol (A. R.), and 500 ml of toluene (A. R.). Carbon dioxide was counted in a mixture of 3 ml [0.75 ml of methanol (A. R.), 0.75 ml of phenethylamine (Packard), and 1.5 ml of toluene (A. R.)] and 7 ml (6 g of PPO, 0.5 g of POPOP, 1000 ml of toluene).[28] Counting efficiency in each of these scintillation solutions was determined with standards. They were 78 and 80%, respectively.

Determination of Specific Activity.—Specific activities in dpm/mmol were determined in all cases by extrapolating to zero concentration the logarithm of the specific activity as a function of concentration. The effect of quenching, which was pronounced for phenazine-1-carboxylic acid, phenazine, and 1-phenazinol, could thus be eliminated. Phenazine-1-carboxylic acid from [U-^{14}C]- and [1,6-^{14}C]shikimic acid showed an incorporation of label of 16 and 9%, respectively. For pyocyanin the corresponding values were 12 and 7%, respectively.

[U-^{14}C]Chorismic acid (**4**).—The labeled compound was prepared with *Aerobacter aerogenes* mutant 62-1.[29] Gibson's[13] procedure for inactive **4** was generally followed. To 6 l. of broth, 108 g of glucose, containing 48 μCi of [U-^{14}C]glucose, was fed. ^{14}C-Labeled **4** (3.35 g) with a spectral purity of 98% [$\lambda_{max}^{H_2O}$ 275 nm (ϵ 2630) for the hemihydrate, mol wt 235], mp 114–116° (reported[30] mp 112° dec for the hemihydrate), was obtained. The specific activity, 3.05 × 10^4 dpm/mmol of carbon, showed that all its activity was derived from [U-^{14}C]glucose.

Phenazine (**1**) + **CO$_2$.**—Phenazine-1-carboxylic acid (10 mg) in admixture with an equal amount of copper(II) chromite[31] was heated to 290° in a porcelain boat placed in a 10-mm-diameter tube. A stream of CO_2-free nitrogen was passed through the tube and through five successive traps each containing 7 ml of a 0.2 *N* barium chloride and a 0.2 *N* sodium hydroxide solution. **1** sublimed into the cold region of the tube and was removed with methanol (2.5 ml). The concentration was determined spectrophotometrically, using λ_{max}^{MeOH} 248 nm (ϵ 124,000), 362 (13,200),[32] an aliquot was dried, mp 171° (reported[27] mp 171°), and the methanol solution was, after proper dilution with scintillator solution, used for counting. Barium carbonate was filtered, dried at 110°, and weighed, giving 95% of the theoretical amount. An aliquot of $BaCO_3$ was suspended in 5 ml of CO_2-free water in a three-neck 50-ml flask closed by a septum. The second neck carried a tube and valve and the third neck was connected to a 50-ml flask containing 8 ml of a 1:1:2 mixture of phenethylamine (Packard), methanol (A. R.), and toluene (A. R.).[28] The entire system was purged with nitrogen and closed off. Carbon dioxide was generated by addition through the septum of a fivefold excess of hydrochloric acid; 24 hr was allowed for absorption of carbon dioxide by the magnetically stirred phenethylamine solution. The efficiency of the entire system had previously been determined by using a known activity of barium carbonate and found to be 99.1%. The phenylethylamine solution was, after proper dilution with scintillator solution, used for counting.

Pyrazinetetracarboxylic Acid (**6**) **from Phenazine-1-carboxylic Acid.**—Phenazine-1-carboxylic acid (100 mg) was dissolved in 2 ml of 1% aqueous potassium hydroxide. Hot 17% potassium permanganate (5 ml) was added with stirring over a period of 5 min. After additional heating at 90° for 2 hr, excess permanganate was destroyed by dropwise addition of ethanol. Manganese dioxide was removed by filtration and washed with hot water to give a total filtrate of 4 ml, which was passed through an ion exchange column (IR-120-CP, H^+ form, 35-ml bed volume) and eluted with distilled water. Elution of **6** was followed in the ultraviolet at its λ_{max} of 295 nm. Fractions containing the oxidation product were stored at 5° or were immediately evaporated to dryness, yielding 80% of the crude product. After hot filtration and several recrystallizations from 20% hydrochloric acid to constant specific activity, the melting point was 205–208° (reported[33] mp 205° dec), $\lambda_{max}^{H_2O}$ 291 nm (ϵ 8100) [reported[34] 291 nm (ϵ 8310).

Pyrazine (**7**).—The method described in the literature[9b] could not be repeated. Extremely volatile **7** is difficult to condense and its high water solubility precludes recrystallization of small quantities from this solvent. A modification of the isolation procedure is described here. To a 10-ml pear-shaped flask, 100 mg of **6** and 5 ml of diethyl phthalate [Fisher Scientific, pure, redistilled at 148° (2 mm)] were added. Upon heating at 190° for 1 hr, **7** distilled into the neck of the flask, from which it was carried through a connected tube by a gentle stream of dry nitrogen into a 10-mm-diameter U-shaped tube. The latter contained 5 ml of methanol and was cooled in Dry Ice. The pyrazine solution was rinsed out with additional methanol and diluted to a known volume. The yield was 17% as determined spectrophotometrically using the reported[35] values λ_{max}^{EtOH} 261 nm (ϵ 6030), 310 (850). Due to the volatility of **7**, the purity of small samples could not be efficiently determined by the melting point. However, in addition to spectrophotometric determination the identity of the trapped compound was established by its infrared spectrum ($CHCl_3$) and its gas chromatographic behavior (20% SF 96, 100°) in comparison with an authentic sample (Aldrich analyzed).

Carbon Dioxide from Phenazinetetracarboxylic Acid (**6**).—**6** (10 mg) was decarboxylated with copper chromite as described for **2**. The specific activity was multiplied by four prior to comparison with the other degradation products because four molecules of carbon dioxide are obtained from each molecule of **6**.

1-Hydroxyphenazine (**5**).—**3** (100 mg) was dissolved in 120 ml of water, 8.4 ml of 8 *N* sodium hydroxide was added to the solution, and the mixture was allowed to stand for 16 hr at room

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temperature. The maroon solution was filtered, and the filtrate was extracted with an equal volume of ether. The organic layer was discarded. After the aqueous layer was acidified with glacial acetic acid, it was extracted twice with equal volumes of ether. The ether layers were combined to yield crude **5**. Purification was achieved by sublimation at 115° (0.1 mm). The yield varied from 50 to 70% and the compound melted at 155–158° (reported[16] mp 159–160°).

Pyrazinetetracarboxylic Acid (6) from 1-Hydroxyphenazine (5).—**5** (100 mg) was oxidized to **6** as described for **2**, in 70% yield.

Registry No.—**2**, 2538-68-3; **3**, 85-66-5; DL-shikimic acid, 138-59-0.

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δ-Chloro Alcohols and Tetrahydrofurans from Primary and Secondary Alkyl Hypochlorites[1]

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The photodecomposition of primary and secondary alkyl hypochlorites in the presence of *cis*- or *trans*-dichloroethylene and similar chloro olefins which act as chlorine atom traps leads to greatly improved yields of δ-chloro alcohols (or tetrahydrofurans after treatment with base). Yields of 50–90% are obtained from a number of hypochlorites, and the method appears to offer substantial advantages over lead tetraacetate oxidations and other more complex techniques for carrying out intramolecular alkoxy radical reactions.

Tertiary alkyl hypochlorites containing a side chain of at least four carbons are readily converted to δ-chloro alcohols on irradiation or treatment with a free-radical source[2,3] *via* a sequence involving intramolecular hydrogen abstraction. The reaction has been

$$\underset{\text{A}}{\underset{|}{\overset{\cdot}{\text{O}}}}\text{CH}_2\text{CH}_2\text{CH}_2\text{CR}_1\text{R}_2 \longrightarrow \underset{\text{B}}{\text{RCHCH}_2\text{CH}_2\underset{|}{\text{CR}_1\text{R}_2}}\quad \underset{|}{\text{OH}} \qquad (1)$$

$$\text{B} + \text{RCH}_2\text{CH}_2\text{CH}_2\underset{|}{\text{CR}_1\text{R}_2} \longrightarrow \text{RCHCH}_2\text{CH}_2\underset{|}{\text{CR}_1\text{R}_2} + \text{A} \qquad (2)$$

$$\qquad\qquad\quad \underset{|}{\text{OCl}} \qquad\quad \underset{|}{\text{Cl}} \qquad\quad \underset{|}{\text{OH}}$$

much less successful with primary and secondary hypochlorites, presumably because of competing steps initiated by α-hydrogen attack.

$$\text{X}\cdot + \text{RCH}_2\text{OCl} \longrightarrow \text{HX} + \dot{\text{R}}\text{CHOCl} \qquad (3)$$

$$(\text{X} = \text{Cl}, \text{RCH}_2\text{O}\cdot)$$

$$\dot{\text{R}}\text{CHOCl} \longrightarrow \text{RCHO} + \text{Cl}\cdot \qquad (4)$$

$$\text{HCl} + \text{RCH}_2\text{OCl} \longrightarrow \text{RCH}_2\text{OH} + \text{Cl}_2 \qquad (5)$$

$$\text{Cl}_2 + 2\text{RCH}_2\text{OH} \longrightarrow 2\text{RCHO} + 2\text{HCl} \qquad (6)$$

$$\text{Cl}_2 + \text{RH} \longrightarrow \text{RCl} + \text{HCl} \qquad (7)$$

In short, molecular chlorine is introduced into the system, and is continually regenerated *via* eq 5–7, making the reaction no longer intramolecular and specific. In fact, the aldehydes produced are chlorinated further to acid chloride, which ends up largely as ester.

$$\text{RCHO} + \text{Cl}_2 \longrightarrow \text{RCOCl} + \text{HCl} \qquad (8)$$

$$\text{RCOCl} + \text{RCH}_2\text{OH} \longrightarrow \text{RCOOCH}_2\text{R} + \text{HCl} \qquad (9)$$

Modest yields of δ-chloro alcohols have only been obtained under special conditions (the presence of $NaHCO_3$ and reflux under reduced pressure) designed to remove HCl and thus prevent eq 5.[2,4]

Adventitious chlorine sometimes complicates the reactions of tertiary hypochlorites by similarly introducing chlorine atom chains, but here the effect can be largely eliminated[5] by adding olefins with strong electron-withdrawing groups which are inert toward alkoxy radicals but act as chlorine atom traps.

$$\text{Cl}\cdot + \text{CHCl}{=}\text{CCl}_2 \longrightarrow \text{CHCl}_2\dot{\text{C}}\text{Cl}_2 \qquad (10)$$

$$\text{CHCl}_2\dot{\text{C}}\text{Cl}_2 + \text{ROCl} \longrightarrow \text{CHCl}_2\text{CCl}_3 + \text{RO}\cdot \qquad (11)$$

This paper describes application of the same technique to the intramolecular chlorination of long-chain primary and secondary hypochlorites, and demonstrates that the reaction can be made to give high yields of δ-chloro alcohols (or, subsequently, tetrahydrofurans), making it a remarkably simple and specific synthetic procedure.

Results

Initial experiments were carried out with *n*-butyl hypochlorite, irradiated under N_2 or in sealed, degassed tubes, and are summarized in Table I. In the absence of a chlorine atom trap yields are low and erratic and a wide spectrum of products is produced. In the presence of trichloroethylene, yields of 4-chloro-1-butanol rise to 50–60%, and the remaining products are quite cleanly 1-butanol, butyl butyrate, and pentachloroethane, giving overall material balances of 90–100%. Since the stoichiometry of the ester-forming reaction should be eq 12, a small amount of random chlorination

$$4\text{RCH}_2\text{OCl} + 2\text{C}_2\text{HCl}_3 \longrightarrow \text{RCOOCH}_2\text{R} + 2\text{ROH} + 2\text{C}_2\text{HCl}_3 \qquad (12)$$

must be taking place as well. In the presence of olefin, base appears to have no further beneficial effect, and yields decrease only slightly when the temperature is raised from 0 to 50°.

In Table II the reaction is extended to 1-pentyl hypochlorite and several radical traps investigated. Yields are higher than in Table I, presumably because of the greater reactivity of secondary hydrogens in the intramolecular process, and *cis*- or *trans*-dichloroethylene appear to be the most efficient chlorine atom

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Table I

Photodecomposition of *n*-Butyl Hypochlorite in the Presence of Trichloroethylene

[ROCl]	$[C_2HCl_3]$/[ROCl]	Conditions[a]	Products[b] 4-Chloro-1-butanol	1-Butanol	Ester	Butanal	C_2HCl_5	Balance, % RO	Cl
1.7	0[c]	$NaHCO_3$, N_2	18.1	32	19.2	8		77.3	18.1
0.62	0	$NaHCO_3$, N_2	7.3	25.2	11.4	1.6		45.5	7.3
0.62	6.0	$NaHCO_3$, N_2	46.4	37.1	11.1		41.2	94.6	87.6
0.79	5.0	$NaHCO_3$, N_2	46.8	36.6	11.8		43.6	95.2	90.4
0.79	5.0	$NaHCO_3$, N_2	45.9	36.3	11.8		42.6	94.0	88.5
0.74	5.0	$NaHCO_3$	59.6	32.4	8.6		38.2	100.6	97.8
0.74	5.0		60.7	33.2	9.0		40.6	102.9	101.3
0.39	5.0	$NaHCO_3$	58.9	31.7	6.1		36.0	96.7	94.5
0.37	5.0		59.6	32.5	6.3		36.9	98.4	96.5
0.88	4.8	50°	50.7	33.7	7.6		40.2	92.0	90.9
0.88	4.8	50°	50.9	33.1	7.5		39.3	91.5	90.2
0.74	5.0	−3°, dark	19.6	20.3	14.9		54.5	54.8	74.2

[a] In 1,1,2-trichlorotrifluoroethane at 0° in sealed, degassed tubes unless indicated. N_2 indicates experiments in flasks under N_2. [b] By glc analysis, based on hypochlorite. [c] Reference 2.

Table II

Effect of Olefins on the Photodecomposition of *n*-Pentyl Hypochlorite[a]

[ROCl]	Olefin	Olefin/ROCl	Yield, % 4-Chloro-1-pentanol	1-Pentanol
	None[c]		35.6[b]	27
1.3	*cis*-CHCl=CHCl	1.0	68.0 ± 4.6	22.5 ± 1.1
0.934		5.0	83.5 ± 2.8	12.8 ± 1.4
0.923		5.0	75.0 ± 1.5[b]	
1.17	*trans*-CHCl=CHCl	2.0	60.9 ± 0.5[b]	
1.06		3.5	69.0 ± 1.3[b]	
0.923		5.0	74.6 ± 1.2[b]	
0.549		15.0	78.5 ± 0.8[b]	
0.934	CH_2=CCl_2	5.0	70.1 ± 3.3	14.1 ± 0.1
1.30	C_2HCl_3	1.0	58.6 ± 2.3	23.9 ± 0.9
0.934		5.0	70.8 ± 0.3	20.5 ± 0.3
0.934	C_2Cl_4	5.0	73.2 ± 3.9	23.2 ± 1.1
0.934	Cyclohexane	5.0	49.6 ± 0.2	

[a] Duplicate runs at 0° in CCl_4. [b] Determined as 2-methyltetrahydrofuran after treatment of product with KOH in ethanol. [c] Reference 2.

traps. Most of the remaining hypochlorite is recovered as 4-pentanol, although other products were only examined in the trichloroethylene experiments which yielded 5–10% C_2HCl_5 and under 1% ester.

Table III summarizes additional experiments in which δ-chloro alcohols were either isolated or converted to the corresponding tetrahydrofurans. Results with two secondary hypochlorites are comparable to those in Tables I and II, reactions involving attack on secondary hydrogen giving the highest yields. Also included are three preparatory-scale experiments, which show quite satisfactory isolated yields although no attempt was made to optimize isolation procedures. The poorer yield of 4-chloro-1-pentanol compared with 2-methyltetrahydrofuran, however, was shown to arise from the former's decomposition to the furan during vacuum distillation.

Discussion

Our results show clearly that chlorine radical traps such as dichloroethylene lead to substantial improvements in the conversion of primary and secondary hypochlorites to the corresponding δ-chloro alcohols or tetrahydrofurans. Hypochlorite decompositions are only one of a number of techniques for carrying out intramolecular reactions of alkoxy radicals; others include nitrite photolysis, alcohol oxidation by lead tetraacetate, and the use of iodine in the presence of base or lead tetraacetate.[6] Perhaps the simplest of these is the use of lead tetraacetate, developed by Mihailovic,[7,8] which leads directly to the corresponding tetrahydrofuran. A comparison with our results is given in Table IV. Admittedly, yields are not strictly comparable since some of ours are based on glc analysis and quantitative conversion of alcohol to hypochlorite is assumed. On the other hand, the major by-product in the hypochlorite reaction is starting alcohol, which can readily be recycled, making the reaction in principle almost quantitative. In view of this, the simplicity of the procedures and the low cost of reagents, we suggest that our technique may prove the method of choice for conversion of many alcohols to either δ-chloro alcohols or furans.

Experimental Section

Materials unless noted were commercial reagents, distilled and purity checked by glc before use. Authentic 4-chloro-1-butanol was prepared by treating tetrahydrofuran with gaseous HCl in the presence of BF_3 etherate. Authentic 4-chloro-1-pentanol was obtained from 1-pentyl hypochlorite as described below.

Hypochlorites were prepared by the procedure of Walling and McGuinness[5] by reaction of the appropriate alcohol in chlorocarbon solvent with 2 equiv of acetic acid and commercial sodium hypochlorite (Clorox) at 0°. They were used without isolation after drying. Concentrations of hypochlorite solutions were determined by iodimetry, and conversions were quantitative since solutions showed no –OH absorption by ir nor extraneous nmr peaks. However, material losses on the small scale involved limited yields to 80–90%. Primary hypochlorite solutions were stable cold in the dark in halocarbon solvent, but secondary hypochlorites and primary hypochlorites in the presence of olefins decomposed slowly and so such solutions were used at once.

Decompositions.—Except for initial experiments carried out under N_2, decompositions were carried out in sealed, degassed tubes,[2] placed in thermostats and irradiated by a 40-W incandescent lamp at a distance of 30 cm for twice the time (*ca.* 60 min) for disappearance of the hypochlorite color. Products were analyzed by glc using internal standards added after reaction. Conversion of δ-chloro alcohols to tetrahydrofurans was accomplished by refluxing reaction mixtures briefly with 1.5 equiv of 5% alcoholic KOH.

Preparative Scale Experiments. 4-Chloro-1-pentanol.—A mixture of 105 ml of 2 *M* 1-pentyl hypochlorite in CCl_4 and 1.01 *M* *cis*-dichloroethylene was photolyzed at 0° and concentrated on a

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TABLE III

PHOTODECOMPOSITION OF ADDITIONAL HYPOCHLORITES

[ROCl]	M	[Olefin]	M	Yield, % Chloro alcohol	Yield, % Tetrahydrofuran	Yield, % Alcohol
1-Pentyl	1.16	*cis*-$C_2H_2Cl_2$	5.8	34[a]		
	1.12	*cis*-$C_2H_2Cl_2$	5.6		50[a]	
4-Phenyl-1-butyl	0.888	*cis*-$C_2H_2Cl_2$	4.44		56[a]	
2-Pentyl	1.15	*trans*-$C_2H_2Cl_2$	2.3		25.7 ± 0.4	43.5 ± 0.3
	0.91		4.55		40.1 ± 1.8	36.6 ± 1.8
	0.536		7.94		49.1	21.6
2-Hexyl	0.885	*cis*-$C_2H_2Cl_2$	4.43		89.0 ± 0.4[b]	6.7 ± 0.5
	0.663		6.63		82.7 ± 2.3[b]	5.3 ± 0.1

[a] Isolated product in preparative-scale experiments. [b] Equimolar mixture of cis and trans isomers.

TABLE IV

CONVERSION OF ALCOHOLS TO TETRAHYDROFURANS

Alcohol (or hypochlorite)	Yield, % ROCl	Yield, % $Pb(OAc)_4$[a]
1-Butyl	60	20
1-Pentyl	75	43
2-Pentyl	49	9.5
2-Hexyl	89	41
4-Phenyl-1-butyl	56	40–49
2-Methyl-2-pentyl	80[b]	10

[a] Reference 8. [b] Reference 2. No radical trap is required in the case of *tert*-hypochlorites.

rotary evaporator. Three vacuum distillations of the residue yielded 34% product, bp 67–68° (4 mm). The purity by glc was >95% and ir and nmr spectra consistent with the structure. The major impurity was 2-methyltetrahydrofuran formed during distillation and accounting for the low yield.

2-Methyltetrahydrofuran.—1-Pentyl hypochlorite (0.530 mol) (2 *M* solution in Freon-113) and 2.65 mol of *trans*-dichloroethylene were photolyzed at 0°. One-half of the reaction mixture was refluxed with 0.53 mol of 2,6-lutidine for 1 hr. Two fractional distillations yielded 11.7 g (51%) of 2-methyltetrahydrofuran, bp 68–70° (648 mm), purity by glc >98%. The other half of the reaction mixture was refluxed for 1 hr with 200 ml of 15% KOH in propylene glycol. Distillation yielded 11.1 g (49%) of 2-methyltetrahydrofuran.

2-Phenyltetrahydrofuran.—A mixture of 30.5 ml of 1.33 *M* 4-phenyl-1-butyl hypochlorite and 0.204 mol of *cis*-dichloroethylene was photolyzed at 0° (3 hr). The product was refluxed overnight with 91 ml of 5% KOH in methanol. Water was added and the mixture was extracted with three portions of ether. Fractional distillation yielded 3.36 g (56%) of 2-phenyltetrahydrofuran, bp 105–107.5° (15 mm), ir and nmr spectra consistent with structure. A higher boiling fraction (1.05 g) contained 59% of the furan by glc, indicating a total yield of 66%.

Registry No.—*n*-Butyl hypochlorite, 5923-22-8; *n*-pentyl hypochlorite, 35042-28-5; 4-chloro-1-pentanol, 35096-45-8; 2-methyltetrahydrofuran, 96-47-9; 2-phenyltetrahydrofuran, 16133-83-8.

Photosensitized Oxidation of Dialkyl Disulfides[1]

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Dialkyl disulfides are photooxidized in the presence of methylene blue sensitizer to the corresponding thiosulfinates. Quenching experiments indicate that singlet oxygen is the oxidant. A mechanism for the reaction, involving an adduct between the disulfide and singlet oxygen as an intermediate, is proposed. The implications of these results for the photodynamic effect are discussed.

By a variety of ways and particularly through the work of Foote and coworkers,[2] it has been amply demonstrated that the Kautsky[3,4] mechanism for photosensitized oxidation is a valid mechanism. According to this mechanism the photooxygenation occurs with excited singlet molecular oxygen as the oxidant. This demonstration has important implications both for organic chemistry and biological chemistry. In biological chemistry, photosensitized oxidation leading to pathological effects in organisms has been known as photodynamic action. Foote[5] and Hastings and Wilson[6] have pointed out that in some cases photodynamic action may also involve singlet oxygen. Indeed, Foote[7] has demonstrated that β-carotene efficiently quenches singlet oxygen and has suggested that the function of carotenoid pigments is to provide protective action against photodynamic damage.

In addition to photosensitization, a number of other methods for producing singlet oxygen have been described. Included are the reaction of sodium hypochlorite and hydrogen peroxide,[8] the use of a radiofrequency discharge in gaseous oxygen,[9,10] the reaction of bromine and hydrogen peroxide,[11] the decomposition of alkaline solutions of peracids,[11] the decomposition of photoperoxides,[12,13] the self-reaction of *sec*-butylperoxy

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radicals,[14] and the base-induced decomposition of peroxyacetylnitrate.[15]

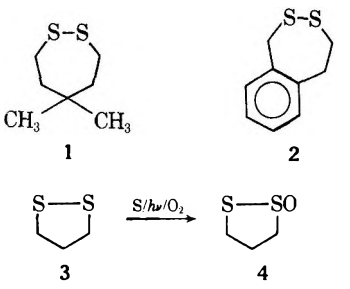
We have shown that certain exothermic reactions of ozone with organic compounds also give singlet oxygen.[16-19] These observations have important consequences for air pollution studies, since ozone continues to be regarded as an important and highly toxic air pollutant. Because many of these reactions occur under very mild conditions and offer a very convenient and efficient source of singlet oxygen, we have sought to use them to study the possible intervention of singlet oxygen in some photodynamic reactions.

One such exothermic reaction is that between ozone and triphenyl phosphite, first studied by Thompson,[20] and shown by us[16-18] to give singlet oxygen. We have recently found[21] that the triphenyl phosphite–ozone adduct reacts with simple dialkyl disulfides to produce thiolsulfinates and sometimes thiolsulfonates. These reactions were studied as models for photodynamic action in biological molecules containing the cystine residue.

Interpretation of these results requires consideration of the singlet oxygen mechanism previously observed[16-18] and a bimolecular mechanism involving the phosphite–ozone adduct and a disulfide molecule. This latter type of mechanism has been suggested for the reaction between the phosphite ozonide and tetramethylethylene[22] and for the corresponding reaction with *cis*- and *trans*-diethoxyethylenes.[23] Also, Koch has shown[24] that certain substrates can induce the decomposition of the phosphite ozonide *via* a bimolecular reaction, although this work cannot distinguish between a direct donation of the oxygen and the intervention of free singlet oxygen in the oxidation step. Thus, whether the ozonide will give singlet oxygen by unimolecular decomposition or perhaps *via* induced decomposition may depend upon substrate concentration in some cases.

To facilitate the interpretation of the results using the phosphite ozonide we have also subjected the disulfides to photosensitized oxidation. The only other reported case of attempted photooxidation of a noncyclic disulfide is that for diphenyl disulfide, which was found to be inert to these reaction conditions.[25] Among cyclic disulfides, **1** and **2** were also found to be inert to photosensitized oxidation[25] while **3** gives the corresponding cyclic thiolsulfinate **4**.[26]

On the other hand, there are a number of reports of



monosulfides being photooxidized to the corresponding sulfoxides.[25,27,28]

Results and Discussion

As indicated in Table I, photosensitized oxidation of the dialkyl disulfides leads to good yields of the corresponding thiolsulfinates. In the case of dimethyl disulfide the thiolsulfinate undergoes a thermal disproportionation reaction to thiolsulfonate and disulfide. Traces of thiolsulfonate were also evident in the diethyl disulfide case. This side reaction appears to be analogous to that observed for aryl thiolsulfinates[29-32] and alkyl thiolsulfinates[33] synthesized by nonoxidative processes. The thiolsulfonates are not further photooxidation products of the thiolsulfinates, since we have shown in a separate experiment that the thiolsulfinate from di-*tert*-butyl disulfide, for example, is not oxidized to thiolsulfonate under the reaction conditions.

The rate of disproportionation observed in the dimethyl case is faster than that observed for an authentic sample of thiolsulfinate synthesized by a nonoxidative procedure. The presence of a small impurity peak in the nmr coupled with the observation that addition of a trace of pyridine decreased the rate to that of the authentic sample suggests that a small amount of an acidic impurity is responsible for the observed differ-

TABLE I

RESULTS OF PHOTOSENSITIZED OXIDATION OF VARIOUS DIALKYL DISULFIDES

		Reaction conditions			Yield,[b] %	
Registry no.	Substrate RSSR R =	Time, min	Temp,[a] °C	Oxygen absorbed per mole of disulfide	RSSR O	RSSR O_2
110-06-5	$(CH_3)_3C$	215	0	0.551	75[c]	0
882-33-7	C_6H_5	53	0	0	0	0
624-92-0	CH_3	135	0	0.56	60	13
	CH_3	60	25	0.4	69	8
110-81-6	C_2H_5	205	0	0.514	48.7[c]	Trace
629-19-6	CH_3CHCH_3	352	17–21[d]	0.454	73	
	$(CH_3)_3C$	271	13–17[d]	0.620	63[c]	
	$(CH_3)_3$[e]	270	15–20[d]	0.04	2.3	0
	$(CH_3)_3C$[f]	270	15–17[d]	0.113	3.1	0

[a] Bath temperature unless otherwise stated. [b] Determined by gpc analysis using an internal standard. [c] Isolated yield. [d] Reaction mixture temperature. [e] In the presence of a 3 molar excess of DABCO. [f] In the presence of an equimolar amount of DABCO.

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ence in disproportionation rates. Distillation of the crude thiolsulfinate leads to no improvement in this situation, presumably because of further decomposition of the unstable thiolsulfinate.

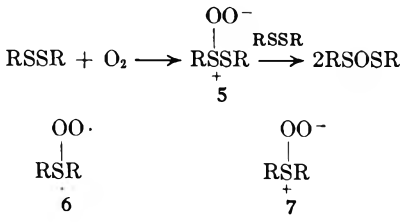
Kice and coworkers[34] have shown that the acid-induced disproportionation of aryl thiolsulfinates is catalyzed by sulfide. The mechanism given for this reaction calls for a rate-determining nucleophilic attack of the sulfide on the protonated thiolsulfinate. Operation of a similar mechanism in the present work, where disulfide acts as the nucleophile and a trace impurity acts as the acid, could explain the observed relative stability of the thiolsulfinate products toward the disproportionation process. Thus methyl methanethiolsulfinate is most troublesome, presumably because the S–S bond is most susceptible toward nucleophilic attack. On the other hand, *tert*-butyl *tert*-butanethiolsulfinate is formed and retained without contamination by the disproportionation product thiolsulfonate because steric factors make it highly resistant to nucleophilic attack.[35]

The products of these reactions therefore are the same as those obtained[21] when the triphenyl phosphite ozonide is used. As reported previously,[25] we have found that diphenyl disulfide is not oxidized under the conditions used.

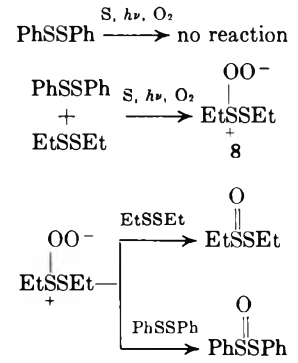
Evidence that the oxidations involve singlet oxygen comes from the observation (Table I) that the oxidation of di-*tert*-butyl disulfide can be essentially prevented, or severely retarded, in the presence of a 3 *M* excess or an equimolar amount, respectively, of the known[36] singlet oxygen quencher, 1,4-diazabicyclo[2.2.2]octane (DABCO).

The oxidation reaction does not involve cleavage of the disulfide bond. When di-*tert*-butyl disulfide and diisopropyl disulfide were cooxidized, no mixed thiolsulfinate (*e.g.*, *tert*-butyl isopropanethiolsulfinate) was formed along with the *tert*-butyl and isopropyl thiolsulfinates.

The reaction presumably proceeds *via* the formation of an intermediate zwitterion **5** from the disulfide and singlet oxygen, which can then react further with another molecule of disulfide to give two molecules of thiolsulfinate. This mechanism is analogous to that invoked to explain the photosensitized oxidation of sulfides. In that case, the intermediate was formulated as **6** by Schenck and Krauch,[37] although the alternative formulation **7** given by Foote, *et al.*,[27,28] is more attractive.



This proposed mechanism is supported by the data given in Table I, which indicates that approximately 0.5 mol of oxygen is absorbed per mole of disulfide. Further experimental support for the presence of **5** comes from experiments similar to those of Foote's[28] in which diphenyl disulfide is cooxidized with diethyl disulfide. In this case both disulfides are oxidized. Since diphenyl disulfide is otherwise inert to the conditions of photosensitized oxidation, it is presumably being oxidized by the zwitterion, **8**, produced from diethyl disulfide.



The observation that dialkyl disulfides are photooxidized to the corresponding thiolsulfinates suggests that photodynamic action in biological substrates containing the cystine residue could occur by a similar mechanism. The reported[38] very slow photooxidation of cystine in the presence of methylene blue may be due to the singlet oxygen quenching effect[39] of the free amino groups. Experiments to test this hypothesis are in progress. We have also found that a number of disulfides related to cystine are oxidized by singlet oxygen.[40]

The product thiolsulfinates are interesting themselves, since a large number of dialkyl thiolsulfinates have high antibiotic activity.[31,41,42] The nmr spectra of the thiolsulfinates and thiolsulfonates have several interesting features which will be discussed in detail elsewhere.

Experimental Section

Materials.—Commercial samples of dialkyl disulfides were purified immediately before use by distillation. Methylene blue and methanol used were Fisher reagent grade.

Apparatus.—The apparatus used was similar to that described in the literature.[43,44] A General Electric DWY 650-W lamp was used without filters. The lamp was operated at 90 V in order to reduce the heat generated.

Nmr Analyses.—Nmr spectra were recorded on a Varian Associates Model T-60 nmr spectrometer. The spectra were recorded in CCl_4 solution using TMS as internal standard unless otherwise indicated. Chemical shift values given are τ values.

Gpc Analyses.—Gpc analyses were carried out on a Hewlett-Packard Model 5750 gas-phase chromatograph using a 6-ft, 10% silicone rubber (UCW-98) on 45–60 mesh Chromosorb W column.

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General Procedure.—The methanolic solution of the disulfide was added to a filtered methanolic solution of methylene blue, and the solution was then photooxidized at the desired temperature until the oxygen uptake either stopped or became very slow. Reaction conditions and substrates used are listed in Table I. Products were analyzed by gpc or tlc. Preparative isolation of products was accomplished using gpc, tlc, and distillation. Examples of use of this general procedure are given below.

Photosensitized Oxidation of Di-*tert*-Butyl Disulfide.—A solution of 3.606 g (20 mmol) of di-*tert*-butyl disulfide in 140 ml of methanol was photooxidized in the presence of 0.05 g of methylene blue as sensitizer at a bath temperature of 0°. Oxygen uptake essentially stopped after 3.5 hr, when 252 ml (11.3 mmol) had been absorbed. Gpc analysis of the reaction mixture showed the presence of unreacted disulfide and *tert*-butyl-*tert*-butanethiolsulfinate. The reaction mixture was concentrated and then distilled[45] to give 2.8 g (75% yield) of the thiosulfinate, bp 45° (0.03 mm) [lit.[41] bp 30° (0.05–0.1 mm)]. The infrared spectrum of the product had absorptions at 3.38, 6.81, 6.88 (doublet), 7.34, 8.56, and 9.28 μ (S=O). The product had n^{21}D 1.5040 (lit.[46] n^{25}D 1.5060). The nmr spectrum showed two singlet absorptions at τ 8.47 and 8.68 which were assigned to the *tert*-butyl groups adjacent to the sulfoxy and ether sulfur groups, respectively. The thiosulfinate could also be isolated by preparative tlc on silica gel F of 1.75-mm thickness.

In a separate experiment di-*tert*-butyl disulfide was photooxidized at −68° with subsequent addition of dimethyl disulfide after the lamp had been turned off and the low temperature maintained. Analysis of this reaction mixture both at low temperature and at room temperature showed that the dimethyl disulfide had not been oxidized to methyl methanethiolsulfinate.

Several experiments were run to determine whether oxygen was evolved upon warmup of the oxidation mixture. Oxidation of 21.4 mmol of di-*tert*-butyl disulfide at −60, −70, and −85° until *ca.* 16 mmol of oxygen had been absorbed was followed by subsequent warmup and oxygen measurement. In all cases no evolved oxygen could be detected.

Photosensitized Oxidation of Diisopropyl Disulfide.—A solution of 3.115 g (20.7 mmol) of diisopropyl disulfide in 150 ml of methanol was photooxidized in the presence of 0.067 g of methylene blue at 17–21°. The reaction had essentially stopped when 210 ml (9.40 mmol) of O_2 had been absorbed. The reaction mixture was concentrated on the rotary evaporator to give an oily residue. Distillation of this residue gave isopropyl isopropanethiolsulfinate, bp ~37° (0.015 mm) [lit.[41] bp 25–30° (0.1 mm)]. The infrared spectrum had absorptions at 3.3, 7.2, 8.0, 8.7 and 8.8 (doublet), 9.2, 9.4, 9.6, 10.35, 11.35, and 12.6 μ. The nmr spectrum had absorptions at τ 8.65 (doublet, 6 H), a pair of overlapping doublets at 8.5 (6 H), and a pair of multiplets at 6.92 (1 H) and 6.45 (1 H). The yield as determined by gpc was 73%. Tlc analysis of a reaction mixture which had been standing for 2 days showed the presence of a small amount of isopropyl isopropanethiolsulfonate. This could be isolated using preparative tlc. It had infrared absorptions at 3.35, 6.8, 7.18, 7.29 (doublet), 7.52, 7.58 (doublet), 7.85, 8.6, 8.85, 9.45, 10.6, 11.35, 14.5, and 14.85 μ. The nmr spectrum consisted of a doublet at τ 8.62 (6 H, J = 7 Hz), a doublet at 8.55 (6 H, J = 7 Hz), and a pair of multiplets at 6.53 (2 H).

Photosensitized Oxidation of Diethyl Disulfide.—A solution of 2.937 g (24.7 mmol) of diethyl disulfide in 150 ml of methanol was photooxidized in the presence of 0.05 g of methylene blue. The bath temperature was 0°. Reaction was essentially complete after 3.5 hr, when 285 ml (12.7 mmol) of oxygen had been absorbed. The reaction mixture was concentrated and distilled and the thiolsulfinate was isolated by preparative tlc. The yield was 48.7%. The product had bp 33° (0.12 mm) [lit.[41] bp 52° (0.2–0.3 mm)] and n^{25}D 1.5203 (lit.[41] n^{25}D 1.524). The infrared spectrum had bands at 3.4, 6.9, 7.3, 7.85, 9.25, 9.75, 10.3, 12.85, and 13.2 μ. The nmr spectrum had two multiplets absorptions at τ 8.63 (3 H) and 8.55 (3 H) and a pair of multiplets centered at 7.0 (4 H).

Gpc and infrared analysis of the crude product showed the presence of the thiosulfonate, but there was not a sufficient quantity present to permit its isolation.

Photosensitized Oxidation of Dimethyl Disulfide.—A solution of 1.759 g (18.7 mmol) of dimethyl disulfide in 130 ml of methanol was photooxidized at room temperature in the presence of 0.1 g of methylene blue. After 1 hr, 162 ml (7.2 mmol) of oxygen had been absorbed and the reaction was essentially complete. The reaction mixture was analyzed by gpc using dodecane as an internal standard. It showed the presence of unreacted disulfide as well as methyl methanethiolsulfinate (69% yield) and methyl methanethiolsulfonate (8% yield). The thiolsulfinate was somewhat unstable to distillation, gpc, and tlc analysis. In some cases thiolsulfinate and thiolsulfonate were obtained by distillation for further analysis. In every case the thiolsulfinate underwent disproportionation to disulfide and thiolsulfonate while standing at room temperature. The thiolsulfinate had bp 28° (0.2 mm), distillate not pure [lit.[29] bp 56–56.5° (1.5 mm)], and $n^{24.5}$D 1.5305 (lit.[29] n^{17}D 1.5615). The thiolsulfonate had bp ~45° (0.001–0.005 mm) [lit.[47] bp 115° (13 mm)] and n^{23}D 1.5104 (lit.[47] n^{25}D 1.5112). The thiolsulfinate had nmr absorptions at τ 7.09 (singlet, 3 H) and 7.40 (singlet, 3 H). The thiolsulfonate had singlet absorptions at τ 7.35 (3 H) and 6.80 (3 H).

A comparison of the rate of disproportionation of the thiolsulfinate obtained with that for a sample of thiolsulfinate synthesized by a nonoxidation procedure indicated a higher rate in the present case. It is felt that this may be due to the presence of a trace impurity indicated by a small peak in the nmr spectrum. Addition of a small amount of pyridine decreased the rate of disproportionation to the rate for the authentic sample, perhaps suggesting that the trace impurity is acidic.

Attempted Oxidation of Diphenyl Disulfide.—A solution of 3.19 g (15 mmol) of diphenyl disulfide in 145 ml of methanol was photolyzed in the presence of 0.06 g of methylene blue at a bath temperature of 0°. After 53 min of photolysis no oxygen had been absorbed.

Joint Photosensitized Oxidation of Di-*tert*-butyl Disulfide and Diisopropyl Disulfide.—A solution of 1.7 g (9.5 mmol) of di-*tert*-butyl disulfide and 0.752 g (5 mmol) of diisopropyl disulfide in 150 ml of methanol was photooxidized in the presence of 0.009 g of methylene blue at a bath temperature of 0°. Oxidation was continued for 50 min, at which time 88 ml (3.4 mmol) of oxygen had been absorbed. Gpc analysis of the reaction mixture showed the presence of unreacted disulfides as well as isopropyl isopropanethiolsulfinate and *tert*-butyl *tert*-butanethiolsulfinate and the isopropyl isopropanethiolsulfonate. No products of exchange reactions (*e.g.*, isopropyl *tert*-butanethiolsulfinate or *tert*-butyl isopropanethiolsulfinate) could be detected.

Photosensitized Oxidation of Di-*tert*-butyl Disulfide in the Presence of 1,4-Diazabicyclo[2.2.2]octane (DABCO).—A solution of 3.63 g (20 mmol) of di-*tert*-butyl disulfide in 100 ml of methanol was photooxidized in the presence of 0.82 g of methylene blue and 9.29 g (82.9 mmol) of DABCO. Gpc analysis of the reaction mixture showed a 2.35% yield of the thiolsulfinate. When the same reaction was repeated with 2.25 g (20 mmol) of DABCO present a 3.13% yield of the thiolsulfinate was obtained.

Attempted Photooxidation of Di-*tert*-butyl Thiolsulfinate.—A methanolic solution of 0.118 g (0.61 mmol) of *tert*-butyl *tert*-butanethiolsulfinate and 0.058 g of methylene blue was photolyzed at a bath temperature of 0°. After 70 min, there had been no oxygen uptake.

Joint Photosensitized Oxidation of Diphenyl Disulfide and Diethyl Disulfide.—A solution of diphenyl disulfide (6.50 g, 30 mmol), diethyl disulfide (0.70 g, 5.7 mmol), and methylene blue (0.059 g) in a mixture of benzene (75 ml) and methanol (125 ml) was photooxidized at room temperature for 165 min. Oxygen was bubbled through the reaction solution at a rate of 250 ml/min. Solvent was removed under reduced pressure and the residue (7.20 g) was analyzed by tlc on silica gel using CH_2Cl_2 as solvent. Ethyl ethanethiolsulfinate was separated and identified as described above. The presence of phenyl benzenethiolsulfinate and phenyl benzenethiolsulfonate was confirmed by comparing tlc R_f values with those of authentic samples prepared by oxidizing diphenyl disulfide with H_2O_2. Samples of phenyl benzenethiolsulfinate and phenyl benzenethiolsulfonate were separated from the reaction mixture by dry column chromatography on silica gel (Woelm, activity III, 3 in. flat diameter, 36 in. long). The products were identified by comparing infrared, nmr, and tlc R_f data with those of the authentic samples.

When the product phenyl benzenethiolsulfinate was subjected to glc analysis, only peaks corresponding to diphenyl disulfide

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and phenyl benzenethiolsulfonate were obtained. This glc disproportionation behavior was confirmed with an authentic sample of phenyl benzenethiolsulfinate.

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The Preparation and Reactions of Novel *O*-Acylhydroxylamines

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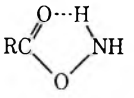
The new compounds *O*-pivaloyl-, *O*-(*p*-nitrobenzoyl)-, and *O*-(*m*-chlorobenzoyl)hydroxylamine as well as the previously prepared *O*-acetyl-, *O*-benzoyl-, and *O*-mesitoylhydroxylamines have been prepared in order to study their behavior with various nucleophiles. Because of the propensity of most *O*-acylhydroxylamines to isomerize to hydroxamic acids, attention was given to the bulky *O*-pivaloyl and *O*-mesitoyl compounds. *O*-Pivaloylhydroxylamine does transfer nitrogen to iodide ion (product is iodine), dibenzylamine (product is *N*,*N*-dibenzylhydrazine), and triphenylphosphine (product is iminotriphenylphosphorane). Nevertheless, olefins fail to react in the presence of *O*-acylhydroxylamines. Preferential isomerization of the *O*-acyl compounds to the corresponding hydroxamic acids occurs even when the highly substituted tetramethylethylene is treated with the bulky *O*-pivaloylhydroxylamine. Although *O*-mesitoylhydroxylamine does not isomerize, it decomposes to mesitoic acid when heated with or without an olefin (*cis*-3-hexene).

In an effort to develop a new and economical method for preparating N-unsubstituted aziridines from olefins, a study has been undertaken of the ability of *O*-acylhydroxylamines[1c] to transfer nitrogen. *O*-Acylhydroxylamines (1) are nitrogenous analogs of organic peracids (2) and, like the latter, have the potential to react with various nucleophilic regents. Nevertheless, there are surprisingly few reports of nucleophilic reactions on *O*-acylhydroxylamines and, indeed, few *O*-acylhydroxylamines have even been prepared and characterized.



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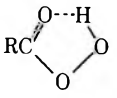

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There is only a meager amount of literature citing the attack of nucleophiles upon *O*-acylhydroxylamines. Treatment with potassium iodide liberates iodine (eq 1).[2] Also documented are the reactions of

$$1 + I^- \xrightarrow{H_2O} RCO_2H + [H_2NI] \xrightarrow{I^-,\ H_2O} NH_3 + I_2 \quad (1)$$

O-mesitoylhydroxylamine [*O*-(2,4,6-trimethylbenzoyl)-hydroxylamine] with secondary amines to give hydrazides,[3] and with sulfonamides to give sulfohydrazides.[4] *O*-acylhydroxylamines are known to rearrange to the thermodynamically more stable *N*-acyl compounds, hydroxamic acids. Since Jencks has found[5] that hydroxylamine often is acylated at the oxygen end of the molecule, this rearrangement must be at least partly responsible for the finding that direct acylation gives only the hydroxamic acid as an isolable entity. In order to minimize the isomerization of *O*-acylhydroxylamines, the carbonyl group must be protected by sufficient bulk in its vicinity. Carpino has shown[3] that such stability is imparted by a mesityl group. In the present work the *tert*-butyl group was relied upon to provide similar stability to the product.

Results and Discussion

If hydroxylamine is acylated initially upon its oxygen, and if the *tert*-butyl group provides the necessary stability to the O-acylated material, then treatment of hydroxylamine with pivaloyl chloride (trimethylacetyl chloride) should constitute a simple, direct procedure for the synthesis and isolation of *O*-pivaloylhydroxylamine. Although the *tert*-butyl group does provide some stability toward isomerization (see below), the reaction of pivaloyl chloride with hydroxylamine gave the *N*-pivaloylhydroxylamine (pivalohydroxamic acid) as the only product. Since the direct synthesis appeared inadequate, indirect methods were necessary.

The two procedures[6,7] that we followed to obtain new *O*-acylhydroxylamines both relied on initial addition of a blocking group upon the nitrogen of hydroxylamine, then O-acylation, and finally removal of the nitrogen block. For this study the known compounds *O*-benzoyl- and *O*-mesitoylhydroxylamine were prepared, as well as the new compounds *O*-pivaloyl-, *O*-(4-nitrobenzoyl)-, and *O*-(3-chlorobenzoyl)hydroxylamine. A variety of new compounds classified as intermediates in the synthetic procedures were also synthesized.[8]

We found that both the new and the reported "bulky" *O*-acylhydroxylamines do in fact suffer some decomposition. Solutions of *O*-pivaloylhydroxylamine in chloroform are stable at room temperature for longer than 1 month, but the neat free base does isomerize to pivalohydroxamic acid within hours at room temperature and over Dry Ice within 1 week. We found that *O*-mesitoylhydroxylamine has a tendency to revert to the carboxylic acid upon heating.

(1) (a) National Research Council–Agricultural Research Service Postdoctoral Research Associate, 1970–1972; (b) Eastern Marketing and Nutrition Research Division, Agricultural Research Service, U. S. Department of Agriculture; (c) for brevity, the term "acyl" is to be taken to include various "aroyl" groups as well.

(2) (a) G. Zinner, *Angew. Chem.*, **72**, 76 (1960); (b) P. A. S. Smith, H. R. Alul, and R. L. Baumgarten, *J. Amer. Chem. Soc.*, **86**, 1139 (1964).

(3) L. A. Carpino, *ibid.*, **82**, 3133 (1960).

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(8) Attempts to carry some of these compounds through to *O*-acylhydroxylamines failed.

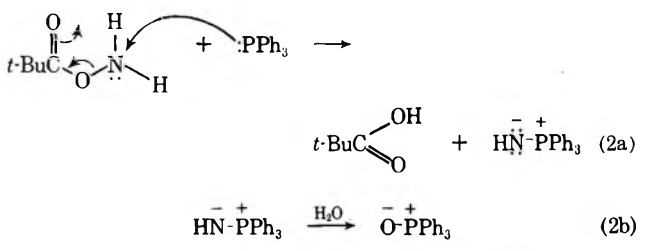
The hydrochloride salts of *O*-acylhydroxylamines are considerably more stable than the free bases. We have ascertained by differential scanning calorimetry that solid *O*-pivaloylhydroxylamine hydrochloride is stable below 127° (and *O*-benzoylhydroxylamine hydrochloride below 73°).

Nitrogen Transfer Reactions.—*O*-Acylhydroxylamines, like their peracid analogs, are expected to show some reactivity as both nucleophiles and electrophiles. As nucleophiles, the amino groups of the *O*-acylhydroxylamines should behave as *hard* bases. *O*-Acylhydroxylamines demonstrate this property both in their ease of salt formation and in their reaction with ketones to form *O*-acyl oximes. Indeed, oxime formation was used to demonstrate proof of structure of *O*-pivaloylhydroxylamine. The product isolated from treatment of the *O*-acylhydroxylamine with cyclohexanone was identical with the compound obtained by treatment of cyclohexanone oxime with pivaloyl chloride. As electrophiles, the electron-deficient amino groups should undergo nucleophilic attack by soft bases. In this process, nitrogen should be transferred to the nucleophile. There is a wide range of reactivity among soft-base nucleophiles; we have chosen for reaction upon *O*-pivaloylhydroxylamine two "potent" nucleophiles (iodide ion and triphenylphosphine), an "average" one (dibenzylamine), and a "reluctant" type (compounds with olefinic bonds).

The *O*-acylhydroxylamines prepared in the current work reacted with iodide, thus confirming the results achieved by previous workers.[2] The reaction with iodide was used to obtain a qualitative (starch–iodide test) as well as quantitative (iodometric) measure of the amounts of *O*-acylhydroxylamines.

Triphenylphosphine, regarded as a potent soft-base nucleophile, has been reported to attack chloramine and also hydroxylamine-*O*-sulfonic acid, two analogs of *O*-acylhydroxylamines. In both cases, the expected product, iminotriphenylphosphorane ($^{+}Ph_3P$–NH^{-}), rapidly hydrolyzed to triphenylphosphine oxide ($^{+}Ph_3P$–O^{-}). Isolation of the intermediate was feasible only when the reaction was carried out in liquid ammonia.[9]

We have found that neat *O*-pivaloylhydroxylamine reacts violently with triphenylphosphine, with tri-*n*-butylphosphine, and with methyl phosphite, but the rate of reaction may be controlled by using carbon tetrachloride as a solvent. A 78% yield of triphenylphosphine oxide was obtained from the moderated reaction (eq 2). In the final mixture, no *O*-acyl- and



(2a)

(2b)

N-acylhydroxylamines were detected, but the presence of pivalic acid was confirmed by silylating the product mixture and subsequently analyzing by glpc. When the reaction was carried out under acidic conditions, the P–N compound was isolated as an acid salt. *O*-Pivaloylhydroxylamine hydrochloride reacted with triphenylphosphine in absolute methanol to give iminotriphenylphosphorane hydrochloride.

We have shown that *O*-pivaloylhydroxylamine can transfer nitrogen to dibenzylamine (eq 3). When

$$(CH_3)_3CCO_2NH_2 + NHBz_2 \longrightarrow (CH_3)_3CCO_2H + H_2NNBz_2 \quad (3)$$

the reaction was carried out on a 1:1 molar mixture without cosolvent, it was complete at 100° within 1 min, no *O*-acylhydroxylamine remained, and no isomerization product was present. *N,N*-Dibenzylhydrazine was isolated as its benzaldehyde hydrazone in 14% yield. Similar results were obtained in reactions run in nitromethane or in chloroform. Nmr analysis of a reaction carried out in deuteriochloroform (molar ratio of *O*-pivaloylhydroxylamine:dibenzylamine 1:5; 78°, 16 hr) suggested a quantitative conversion of amine to hydrazine.

Despite the affinity of the aforementioned nucleophiles for *O*-acylhydroxylamines, no evidence for the direct reaction of olefins with *O*-acylhydroxylamines could be detected. In general, *O*-acylhydroxylamines merely isomerized to the corresponding hydroxamic acids, while the olefins remained intact. Such results were obtained with *O*-(3-chlorobenzoyl)hydroxylamine, *O*-benzoylhydroxylamine, *O*-(4-nitrobenzoyl)-hydroxylamine, and even with the bulky *O*-pivaloylhydroxylamine. The olefins tested included *cis*-3-hexene, *cis*-5-decene, 2,3-dimethyl-2-butene, and 2,3-dimethyl-2-hexene. Occasionally, cosolvents such as benzene or methylene chloride were used.

O-Mesitoylhydroxylamine, unlike the other *O*-acylhydroxylamines, did not isomerize on heating with an olefin (*cis*-3-hexene). Although a good yield of mesitoic acid was obtained, there was no evidence for any nitrogen transfer to the olefin. Determination of the fate of the N fragment awaits further study.

Experimental Section

Nmr spectra were produced on a Jeolco C-60H[10] instrument. Chemical shifts are relative to internal tetramethylsilane. Differential scanning calorimetry experiments utilized a Perkin-Elmer DSC-IB instrument. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Thin layer chromatography utilized Eastman chromagram silica gel sheets with fluorescent indicator. Spots were visualized under uv light and after treatment with iodine vapor. Infrared spectra were obtained on a Perkin-Elmer Model 237B grating infrared spectrophotometer.

Synthesis of *tert*-Butyl *N*-Hydroxycarbamate (3) ($HONHCO_2$-*t*-Bu).—The method of Carpino[6] was used to synthesize **3** from *tert*-butoxycarbonyl azide (Aldrich, used as received) and hydroxylamine, yield 75% from Cellosolve B–methylene chloride, mp 55.5–57° (lit.[6] mp 55–57.5°).

Synthesis of *tert*-Butyl *N*-Acyloxycarbamates (4) (RCO_2-$NHCO_2$-*t*-Bu).—Continuation of Carpino's method[6] gave the following new compounds.

A. *tert*-Butyl *N*-Pivaloyloxycarbamate (4, R = *tert*-Butyl).—Pivaloyl chloride (Eastman) was distilled prior to use, and reacted with **3** to give an 87% yield of product, mp 77–78°, from Cellosolve B. *Anal.* Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.63; H, 8.85; N, 6.20.

B. *tert*-Butyl *N*-(4-Nitrobenzoyloxy)carbamate (4, R = 4-$NO_2C_6H_4$).—4-Nitrobenzoyl chloride (Eastman) was recrystal-

(9) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, pp 217–218.

(10) Reference to a particular manufactured product does not constitute a recommendation by the U. S. Department of Agriculture over similar products not mentioned.

lized prior to use, and reacted with **3** to give a 94% yield of product from Cellosolve B–benzene, mp 93–94°. *Anal.* Calcd for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 5.00; N, 9.92. Found: C, 51.66; H, 6.27; N, 9.57.

C. *tert*-Butyl *N*-(3-Chlorobenzoyloxy)carbamate (4, R = 3-ClC_6H_4).—3-Chlorobenzoyl chloride was prepared from 3-chlorobenzoic acid and oxalyl chloride, according to the method of Bosshard, *et al.*[11] A short-path distillation gave a 71% yield of the product, bp 80–90° (10 Torr) [lit.[12] bp 104–106° (14 Torr)]. Treatment with **4** gave a viscous, yellow oil (crude yield 99%). The oil was used in the synthesis of the O-aroylhydroxylamine without further purification.

D. *tert*-Butyl *N*-benzoyloxycarbamate (4, R = C_6H_5) was obtained in 89% yield recrystallized from hexane, mp 81–83° (lit.[6] mp 82–84°).

E. *tert*-Butyl *N*-mesitoyloxycarbamate (4, R = 2,4,6-$(CH_3)_3C_6H_2$) was obtained in 85% yield from Cellosolve B, mp 75–76° (lit.[3] mp 78–79.5°).

Synthesis of Ethyl *N*-Hydroxyacetimidate (5) [$CH_3C(OEt)$=NOH].—This oxime derivative of ethyl acetate was synthesized in 14% yield from ethyl acetimidate, according to the method of Houben and Schmidt.[13] The product solidified as needles: mp 25–26° after distillation; bp 54.5° (9 Torr); nmr (CCl_4) δ 1.25 (t, 3 H, CH_3 of ethyl), 1.9 (s, 3 H, CH_3C=N), 3.85 (q, 2 H, CH_2 of ethyl), 8.3 (s, 1 H, HON=C).

Synthesis of Ethyl *N*-Acyloxyacetimidates (6) [$CH_3C(OEt)$=NOCOR].—The following compounds were synthesized according to the Zinner procedure.[7]

A. Ethyl *N*-Pivaloyloxyacetimidate (6, R = *tert*-Butyl).—Treatment of **5** with pivaloyl chloride (Eastman, distilled) gave a 79% crude yield of product, 69% distilled yield, bp 38–39° (0.10 Torr), 60.5° (1.0 Torr). The sample was too unstable to result in a suitable element analysis. Nmr (CCl_4) δ 1.2 [s, $(CH_3)_3C$] and 1.3 (t, CH_3 of ethyl), sum of areas 11 H, 1.9 (s, 4 H, CH_3C=N) (impurity at baseline), 4.1 (q, 2 H, CH_2 of ethyl).

B. Ethyl *N*-(2,5-Dichlorobenzoyloxy)acetimidate (6, R = 2,5-$Cl_2C_6H_3$).—**5** was aroylated with 2,5-dichlorobenzoyl chloride (Hooker Chemical Co., Industrial Chemical Division; material used without further work-up): crude yield 63%; mp 58–68° from petroleum ether; recrystallized yield 32% from ether; very large, glassy crystals; mp 69.5–71.0°. *Anal.* Calcd for $C_{11}H_{11}NCl_2O_3$: C, 47.85; H, 4.02; N, 5.07; Cl, 25.68. Found: C, 48.24; H, 4.18; N, 5.04; Cl, 25.58. Nmr ($CDCl_3$) δ 1.3 (t, 3 H, CH_3 of ethyl), 2.1 (s, 3 H, CH_3C=N), 7.3 (m, 2 H, meta and para H's), 7.7 (m, 1 H, ortho H), 4.2 (q, 2 H, CH_2 of ethyl).

C. Ethyl *N*-Trifluoroacetoxyacetimidate (6, R = CF_3).—Trifluoroacetylation of **5** with trifluoroacetic anhydride (Eastman, used as received) and pyridine gave a crude yield (oil with fruity odor) of 93%: distilled yield 70%; bp 41° (10 Torr); nmr (CCl_4) δ 1.3 (t, 3 H, CH_3 of ethyl), 2.05 (s, 3 H, CH_3C=N), 4.15 (q, 2 H, CH_2 of ethyl).

D. Synthesis of Ethyl *N*-Methanesulfonoxyacetimidate [CH_3SO_2ON=$C(CH_3)OC_2H_5$].—This sulfonyl analog of **6** was prepared from **5** and methanesulfonyl chloride (Eastman, used as received) with pyridine in ether: crude yield 35% as an oil; distilled yield 24%; bp 122–127° (10 Torr); nmr (CCl_4) δ 1.3 (t, 3 H, CH_3 of ethyl), 2.0 (s, 3 H, CH_3C=N), 3.0 (s, 3 H, CH_3SO_2), 4.1 (q, 2 H, CH_2 of ethyl).

E. Ethyl *N*-Benzoylacetimidate (6, R = C_6H_5).—Benzoylation of **5** gave a 74% yield from petroleum ether (bp 30–60°) of product, mp 72–74° (lit. mp 77–79°,[5] 74–75°[14]).

Synthesis of *O*-Acylhydroxylamines and Their Hydrochlorides (1 and 1·HCl). A. *O*-Benzoylhydroxylamine hydrochloride (1·HCl, R = C_6H_5) was synthesized *via* the Carpino route[6] [4 (R = C_6H_5) + HCl in CH_3NO_2], yield 78%, mp 117–118° dec (lit.[6] mp 120–122° dec).

B. *O*-Mesitoylhydroxylamine hydrochloride [1·HCl, R = 2,4,6-$(CH_3)_3C_6H_2$] was synthesized *via* Carpino's method[3] from 4 [R = 2,4,6-$(CH_3)_3C_6H_2$], yield 83%, mp 123° dec (lit.[3] mp 125–127° dec).

C. *O*-Mesitoylhydroxylamine [1, R = 2,4,6-$(CH_3)_3C_6H_2$] was obtained as crude oil (78% yield) from extraction with methylene chloride of **1**·HCl in aqueous sodium bicarbonate.

D. *O*-Pivaloylhydroxylamine Hydrochloride (1·HCl, R = *tert*-Butyl).—Treatment of **6** (R = *tert*-butyl) with HCl and 1 equiv of water in ether gave the product as a fluocculent precipitate in 75% yield, mp 122–123° subl and dec), iodine equivalent 81.9 (calcd 76.8). The material was sublimed twice at atmospheric pressure by sealing the material into a covered petri dish and then heating the dish at 35° overnight. The resulting product, adhering to the inside lid as bulky fibers, gave an iodine equivalent of 81.8 (calcd 76.8), mp 118–121° dec. *Anal.* (of twice-sublimed material). Calcd for $C_5H_{11}NO_2$·HCl: C, 39.10; H, 7.87; N, 9.12; Cl, 23.08. Found: C, 39.21; H, 8.09; N, 8.81; Cl, 21.67.

An 80% yield of product also was obtained by treatment of **4** (R = *t*-butyl) with anhydrous HCl in ether.

E. *O*-Pivaloylhydroxylamine (1, R = *tert*-Butyl).—A chilled aqueous solution of *O*-pivaloylhydroxylamine hydrochloride was treated immediately with sodium bicarbonate until effervescence ceased. The contents then were extracted immediately with methylene chloride and the resulting organic phase was separated and dried with anhydrous sodium sulfate. Evaporation of the filtered solution under slight vacuum at room temperature left a slightly brown oil that tested positive for *O*-acylhydroxylamine (starch–iodine test) and negative for the isomeric hydroxamic acid ($FeCl_3$ complexing test), crude yield 98%.

The crude oil was distilled through a short column, bp 27° (1.2 Torr), to yield a colorless oil, $n^{28}D$ 1.4205, overall yield from the hydrochloride 87%, iodine equivalent 67.8 (calcd 58.6).

F. *O*-(4-Nitrobenzoyl)hydroxylamine hydrochloride (1·HCl, R = 4-$NO_2C_6H_4$) was synthesized by treating **4** (R = 4-$NC_2C_6H_4$) with anhydrous HCl in nitromethane, crude yield 90%, mp 218° dec.

G. *O*-(4-Nitrobenzoyl)hydroxylamine (1, R = 4-$NO_2C_6H_4$).—Treatment of the hydrochloride as in C gave a solid: mp 111.5°, 110° from methylene chloride; starch–iodide test (+); $FeCl_3$ test (−).

H. *O*-(3-Chlorobenzoyl)hydroxylamine Hydrochloride (1·HCl, R = 3-ClC_6H_4).—Treatment of **4** (R = 3-ClC_6H_4) with anhydrous HCl in nitromethane gave a fluffy solid product, mp 112–113° dec, starch–iodide test (+), $FeCl_3$ test (−).

I. *O*-(3-Chlorobenzoyl)hydroxylamine (1, R = 3-ClC_6H_4).—Treatment of the hydrochloride with aqueous sodium bicarbonate followed by extraction as in C gave the free base, mp 51–52° dec, starch–iodide test (+), $FeCl_3$ test (−).

Treatment of Hydroxylamine with Pivaloyl Chloride.—To an ice-cold suspension of pivaloyl chloride (3.88 g, 0.0321 mol) in aqueous hydroxylamine hydrochloride (2.23 g, 0.0321 mol in 6 ml of H_2O) was added a sodium bicarbonate (5.39 g, 0.0642 mol) suspension in water (10 ml). CO_2 evolved during vigorous stirring. A large amount of bulky precipitate formed immediately. Filtration and, later, chloroform extraction gave 1.74 g (46%) of crude pivalohydroxamic acid, mp 140–150° (recrystallized mp 163–164°), $FeCl_3$ test (+), starch–iodide test (−). Extraction of the aqueous filtrate with chloroform gave a negligible amount of *O*-acylhydroxylamine, along with the hydroxamic acid. Iodimetric analysis of the aqueous phase showed that 33% of the hydroxylamine remained unreacted.

Cyclohexanone Oxime.—Cyclohexanone oxime was synthesized from cyclohexanone and hydroxylamine hydrochloride in aqueous sodium acetate according to an established procedure,[15] yield 62%, mp 88–89° (lit.[15] mp 90°).

***O*-Pivaloylcyclohexanone Oxime. A.**—To a solution of pyridine (1.80 ml, 0.0224 mol) and cyclohexanone oxime (mp 88–89°, 2.54 g, 0.0224 mol) in ether (10 ml) was added pivaloyl chloride (2.70 g, 0.224 mol). The ether solution, after filtration from pyridinium chloride, removal of volatiles, and recrystallization from Cellosolve B, gave the crystalline product, 3.73 g, 84% yield, mp 54–56°, off-white in color. Snow white material was obtained by dissolving the product in methylene chloride, treating the solution with Norit A, evaporating the filtered solvent, and recrystallizing from Cellosolve B once again, yield 3.00 g (68%), mp 55.5–56.5°. *Anal.* Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.89; H, 9.88; N, 7.03.

B.—Pyridine (65 μl, 0.810 mmol) was added to a suspension of *O*-pivaloylhydroxylamine hydrochloride (124 mg, 0.810 mmol) in ether (10 ml). The formation of a new precipitate, pyridinium chloride, was apparent. To the mixture was added cyclohexanone

(11) H. H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, **42**, 1653 (1959).

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(80 μl, 0.810 mmol). The contents were allowed to stand at room temperature overnight, after which they were washed with water, and the ether layer was dried with anhydrous sodium sulfate, filtered, and evaporated. This left an oily, white solid residue, mp 49–54°, yield 0.09 g (56%). Recrystallization from Cellosolve B gave white crystals, yield (0.01 g (6%), mp 54–55°, mmp 55–56° with material from procedure A. Infrared spectra of both products A and B were identical, as were tlc retention times (benzene, on silica gel).

Reaction of Triphenylphosphine with *O*-Pivaloylhydroxylamine.—A chilled solution of triphenylphosphine (K & K, 0.104 g, 0.397 mmol) in carbon tetrachloride (0.801 g) was prepared. Neat *O*-pivaloylhydroxylamine (0.0299 g, 0.255 mmol) was added, and the resulting solution was allowed to warm to room temperature while being stirred. A white precipitate of triphenylphosphine oxide quickly developed, yield 0.0555 g (78%), mp 156–157° (lit.[16] mp 156°).

Reaction of Triphenylphosphine with *O*-Pivaloylhydroxylamine Hydrochloride.—A solution of *O*-pivaloylhydroxylamine hydrochloride (0.60 g, 3.90 mmol) in absolute methanol (6 ml) was combined with a solution of triphenylphosphine (1.02 g, 3.90 mmol) in absolute methanol (10 ml). Crude iminotriphenylphosphorane hydrochloride was precipitated out of solution upon the addition of ether, yield 0.58 g (48%), mp 218° (lit.[17] mp 230–232°). *Anal.* Calcd for $C_{18}H_{17}ClNP$: Cl, 11.32. Found: Cl, 11.21. A small amount was recrystallized from methanol–ether, mp 233°. *Anal.* Calcd for $C_{18}H_{17}ClNP$: C, 68.90; H, 5.42; Cl, 11.32; N, 4.46; P, 9.89. Found: C, 69.00; H, 5.59; Cl, 11.09; N, 4.43; P, 10.10. Treatment of an aqueous solution of this product with aqueous sodium hydroxide liberates ammonia and triphenylphosphine oxide. Treatment with aqueous silver nitrate produces a white precipitate insoluble in nitric acid.

Conversion of Dibenzylamine to *N,N*-Dibenzylhydrazine. A.—The neat base, *O*-pivaloylhydroxylamine (0.488 g, 4.17 mmol), was added to neat dibenzylamine (Chem. Service, Media, Pa., used as received) (0.801 ml, 4.17 mmol). A slight exotherm was detectable. The contents were heated for 1 min at 100°. The $FeCl_3$ complexing test on the crude product mixture confirmed the absence of pivalohydroxamic acid. To the filtrate was added acetic acid (3 ml) and benzaldehyde (2 ml). After work-up per Carpino,[3] the dibenzylhydrazone of benzaldehyde was isolated, yield 0.18 g (14%), mp 76–78°.

B.—A solution of *O*-pivaloylhydroxylamine in chloroform-*d* was treated with dibenzylamine. The contents were sealed into an nmr tube previously flushed with nitrogen. Immediate nmr analysis showed only starting materials, in a molar ratio (amine: *O*-acylhydroxylamine) of 5:1: δ 1.2 [s, 9 H, $(CH_3)_3C$], 3.73 [s, 20 H, benzylic $(CH_2)_2$ of amine], 7.15 (m, aromatic H of amine). The sealed tube was heated for 16 hr at 78°, after which the following nmr spectrum was observed: δ 1.2 [s, 9 H, $(CH_3)_3C$], 3.67 [s, 4 H, benzylic $(CH_2)_2$ of hydrazine], 3.75 [s, 16 H, benzylic $(CH_2)_2$ of amine], 4.95 (s, NH), 7.15, (m, aromatic H). The contents were treated with benzaldehyde, per Carpino,[3] and the resulting dibenzylhydrazone of benzaldehyde was observed by thin layer chromatography. Prior to the benzaldehyde addition, the product mixture tested negative to *O*-acylhydroxylamine (starch–iodide) and negative to hydroxamic acid ($FeCl_3$).

Registry No.—**1** (R = *t*-Bu), 35657-34-2; **1** (R = *t*-Bu) HCl, 35657-35-3; **1** (R = 4-$NO_2C_6H_4$), 35657-36-4; **1** (R = 4-$NO_2C_6H_4$)HCl, 35657-37-5; **1** (R = 3-Cl-C_6H_4), 35657-38-6; **1** (R = 3-ClC_6H_4) HCl, 35657-39-7; **4** (R = *t*-Bu), 35657-40-0; **4** (R = 4-$NO_2C_6H_4$), 35657-41-1; **5**, 10576-12-2; **6** (R = *t*-Bu), 35657-43-3; **6** (R = 2,5-$Cl_2C_6H_3$), 35657-44-4; **6** (R = CF_3), 35657-45-5; ethyl *N*-methanesulfonoxyacetimidate, 35657-46-6; *O*-pivaloylcylcyclohexanone oxime, 35657-47-7; triphenylphosphine, 603-35-0; iminotriphenylphosphorane hydrochloride, 21612-82-8; benzaldehyde dibenzylhydrazone, 21136-32-3.

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Reduction of Dehydroascorbic Acid Osazone and Related Compounds

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Reduction of dehydro-L-ascorbic acid phenylosazone (**1**) with $LiAlH_4$ resulted in the hydrogenation of the hydrazone residues and cyclization to a bicyclic compound **2**, which was dehydrated during acetylation with boiling Ac_2O to give diacetate **3**, and then partially hydrolyzed to monoacetate **4**. Reduction of the L-threo and D-erythro derivatives of 1-phenyl-3-trihydroxypropyl-4,5-pyrazoledione-4-phenylhydrazone (**5**) with Zn in AcOH afforded the bis(L-*threo*- and -(D-*erythro*-trihydroxypropyl)rubiazonic acid analogs **6**, which could be converted to the starting pyrazoles by treatment with phenylhydrazine, or oxidized with periodate to the formylrubiazonic acid.

Although the properties of reducing sugar osazones have been extensively studied,[1] the seemingly different reactions of dehydroascorbic acid osazones have only recently been investigated.[2–8] The presence of an additional carbonyl group enables dehydroascorbic acid osazones to undergo numerous cyclization reactions which do not occur with reducing sugar osazones, for example, the formation of 1-aryl-3-hydroxyalkyl-4,5-pyrazoledione-4-phenylhydrazones of type **5** by participation of the C-3 hydrazone nitrogen. This reaction is so facile that pyrazoles of this type are formed

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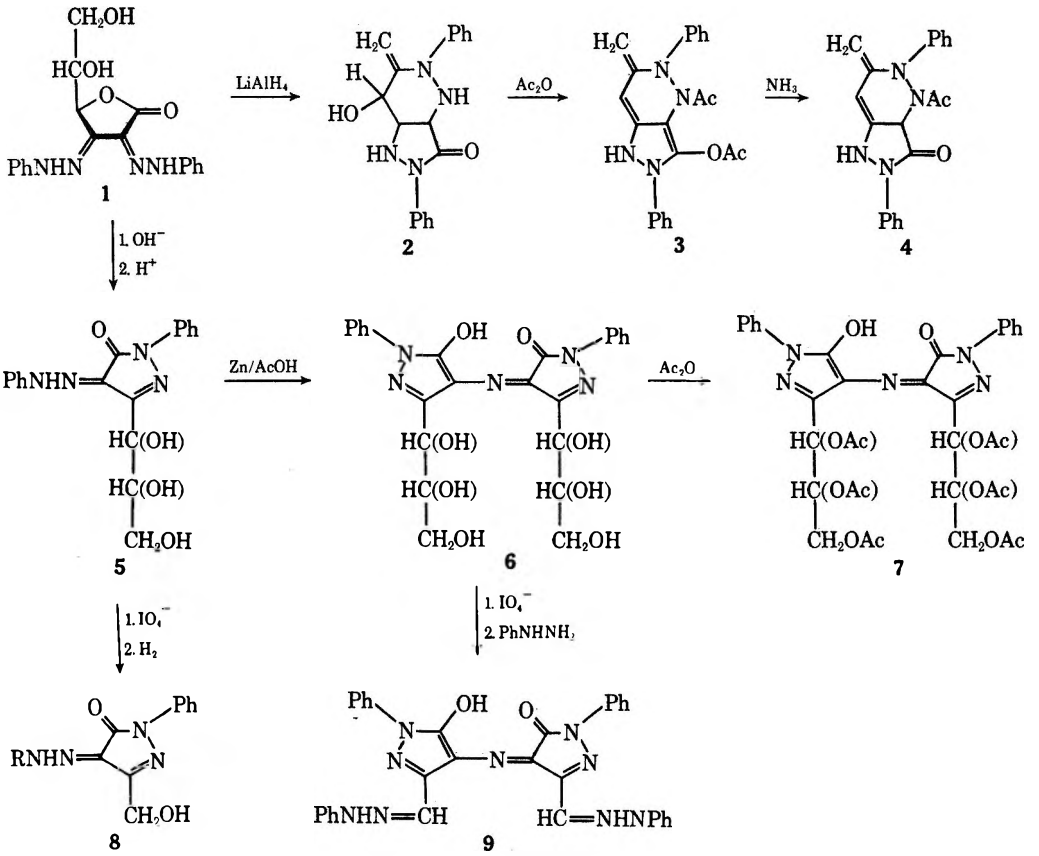


even when they are unwanted, namely, during the preparation of dehydroascorbic acid osazones. Another peculiar reaction takes place during oxidation, and, unlike the sugar osazones, which yield the corresponding osotriazoles, dehydroascorbic acid osazones are oxidized to phenylazo derivatives which can revert back to the starting osazones by mild reduction.[7,8]

The present study deals with the reduction of dehydro-L-ascorbic acid phenylosazone (**1**) and of 1-phenyl-3-trihydroxypropyl-4,5-pyrazoledione-4-phenylhydrazones (**5**) and the elucidation of the structure of the crystalline heterocycles produced.

Reduction of dehydro-L-ascorbic acid phenylosazone with lithium aluminum hydride in dioxane resulted in a reduction of the hydrazone residues instead of the carbonyl group. This was apparent in the ir spectrum of the reduction product, which showed a carbonyl absorption at 1675 cm^{-1} assigned to an amide I band. The replacement of the lactone band of the starting osazone (1720 cm^{-1}) by this amide band suggested that a rearrangement had occurred, possibly with the formation of a pyrazoledione, which absorbs in the same region. Combustion analyses of the reduction product agreed with the formula $C_{18}H_{18}N_4O_2$, denoting that the starting osazone ($C_{18}H_{18}N_4O_4$) might have added two molecules of hydrogen, then lost two water molecules. The mass spectrum of **2** (Figure 1) showed a weak molecular peak at *m/e* 322 followed by another weak M − OH fragment. The base peak at *m/e* 290 resulted from the loss of both the OH and the side chain, possibly *via* the tautomeric α-methylenol, and afforded on further loss of C=O a peak at *m/e* 262. At smaller units appeared fragments corresponding to Ph (*m/e* 77), $PhNH_2$ (*m/e* 93), and PhNC (*m/e* 103), which may be expected from structure **2**. The formation of compound **2** in this reaction is rationalized by assuming that a reduction of the bishydrazone residues to bishydrazines was followed by (a) an attack by the nitrogen of the C-3 hydrazine on the carbonyl group at C-1 to form the pyrazoledione ring, and (b) by another attack from the C-2 hydrazine nitrogen on C-5 to form the pyrazine ring, and (c) finally by dehydration of the C-6 OH to afford compound **2**. Such reactions are by no means uncommon with dehydroascorbic acid bishydrazones. Thus the cyclization of the C-3 hydrazine to a pyrazoledione[5] as mentioned earlier is very easy; similarly, the cyclization of a C-2 hydrazone to a pyrazine and the formation of an olefinic compound by dehydration of the side chain has been previously observed with dehydroascorbic acid mono- and bishydrazones.[6]

Acetylation of compound **2** with boiling acetic anhydride gave a crystalline diacetate **3**, whose combustion analysis indicated that during acetylation a further dehydration had taken place. It seems that under the vigorous conditions used for acetylation the triacetate formed initially eliminated the C-5 OAc group to give diacetate **3**. The infrared spectrum of **3** showed an *O*-acetate band at 1720 cm^{-1} and an *N*-acetyl band at 1680 cm^{-1}. Its nmr spectrum showed the *O*-Ac protons at δ 2.13 and the *N*-acetyl protons at δ 2.62. This was followed at lower field by a signal of two-proton intensity at δ 5.12 due to the methylene group of the side chain. At δ 6.90 appeared a singlet of one-proton intensity assigned to the methyne of the diazine ring; the proton of the phenyl ring appeared at δ 7.55. The mass spectrum of **3** (Figure 1) showed no peaks corresponding to the molecular weight, but

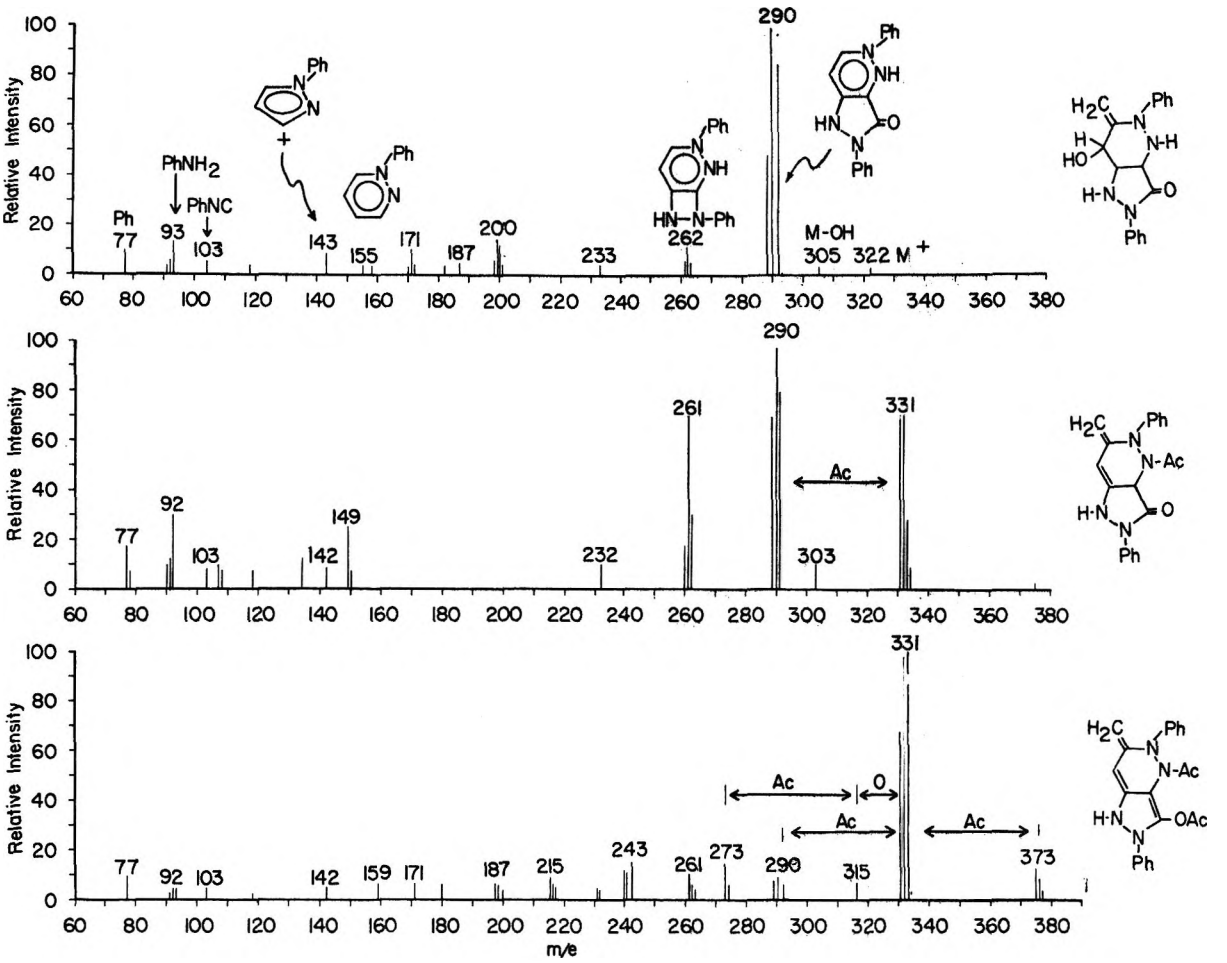
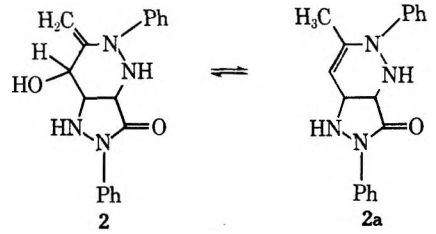


Figure 1.—Mass spectra of compounds 2 (upper), 4 (middle), and 3 (bottom); Ac = 42, McLafferty rearrangement.

showed a small peak at *m/e* 373 probably due to the loss of the side chain. This was followed by the base peak at *m/e* 331, probably formed by the loss of both the side chain and one acetyl group. Alternate loss of acetoxy and/or another acetyl group afforded peaks at *m/e* 290, 315, and 273. The remaining peaks of the spectrum were identical with those of compound 2. Partial deacetylation of compound 3 with ammonia afforded a mono-*N*-acetyl derivative which now showed an amide band at 1690 cm^{-1} and whose mass spectrum (Figure 1) was quite similar to that of the diacetate 3, showing major peaks at *m/e* 331, 290, etc. Its nmr spectrum was also similar to that of compound 3 except that it lacked the *O*-acetyl protons. It revealed that the *N*-acetyl protons at δ 2.58, the methylene proton at δ 4.63, and the methyne proton at δ 6.9 and the phenyl protons appeared between δ 7.3 and 7.6 in approximately the same positions as in compound 3.

In the light of the above, the reduction product of dehydro-L-ascorbic acid osazone was tentatively given structure 2; its acetylation product was assigned



2 2a

structure 3 and its partial deacetylation products structure 4. It should be noted that compounds 2, 3, and 4 may exist in other tautomeric forms, such as that depicted for compound 2. These forms may be significant enough in the solid state to contribute to the mass spectra, but in solution they constitute less than 10% of the equilibrium as evidenced by the nmr data.

Careful reduction of the L-threo- and D-erythro isomers of 1-phenyl-3-(1,2,3-trihydroxypropyl)-4,5-pyrazoledione-4-phenylhydrazone (5) with zinc and acetic acid afforded the substituted L-*threo*- and D-*erythro*-rubiazonic acid 6. This is a one-step modification of Duffin and Kendall's[9] reduction of the hydroxymethyl derivative, 3-hydroxymethyl-1-phenyl-4,5-pyrazoledione-4-phenylhydrazone, with zinc and hydrochloric acid to the 4-amino compound and oxidation of the latter with ferric chloride to the hydroxy rubiazonic acid. The bis-L-*threo*- and -D-*erythro*-trihydroxypropyl derivatives (6) showed the characteristic color reactions[9] of rubiazonic acids, their ir spectra exhibited a characteristic amide band at 1680 cm^{-1}, and their mass spectra (Figure 2) exhibited a hydroxyalkyl fragmentation pattern similar to that of the parent 1-phenyl-3-trihydroxypropyl-4,5-pyrazoledione-4-phenylhydrazone (5) and the hydroxymethyl derivative depicted in Figure 3. Upon acetylation they afforded hexaacetates, which now showed ester bands at 1740 cm^{-1} and amide bands at 1680 cm^{-1}. Their mass

(9) G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, 3969 (1955).

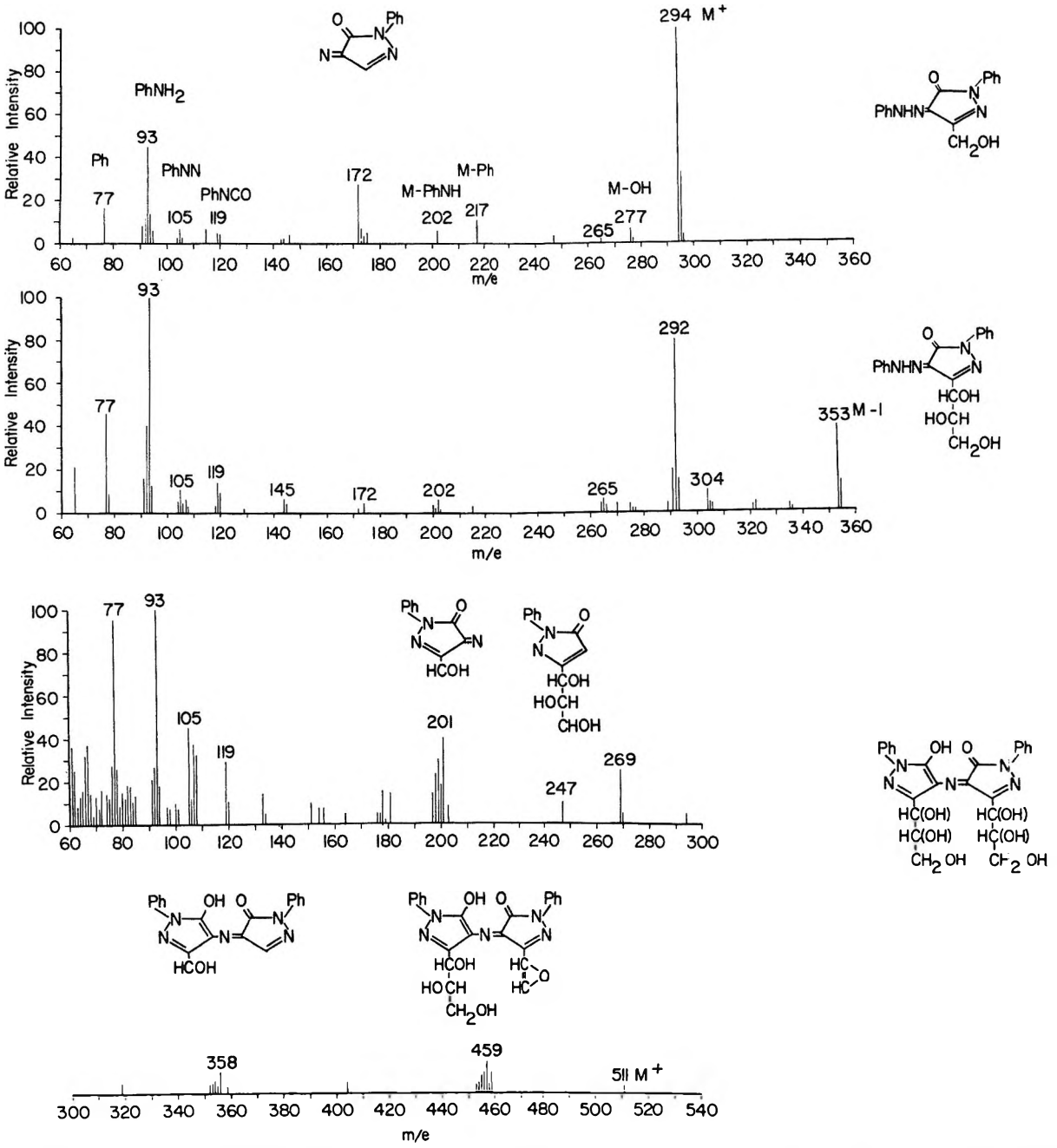


Figure 2.—Mass spectra of 3-hydroxymethyl-1-phenyl-4,5-pyrazoledione-4-phenylhydrazone (upper), 1-phenyl-3-(L-*threo*-trihydoxypropyl)-4,5-pyrazoledione-4-phenylhydrazone (**5**) (middle), and bis(L-*threo*-trihydroxypropyl)rubiazonic acid (**6**) (bottom).

spectra were identical and showed no molecular peaks (*m/e* 763). The heaviest fragment was at *m/e* 732 (M − 2Me), which was followed by a peak at *m/e* 699 corresponding to the loss of CH_2OAc and a series of peaks resulting from the consecutive loss of acetyl (*m/e* 43) and *O*-acetyl (*m/e* 59) groups characteristic of acetoxyalkyl chains. Fragments arising from the disruption of the bond linking the two rings of the dimer appeared at *m/e* 314 and 286. The nmr spectra of the L-threo- and D-erythro acetates **7** were quite similar, differing only slightly in the coupling constants of the side-chain protons. The equivalence of the two side chains of the dimer **7** was apparent in the fact that three distinct *O*-acetyl protons were observed instead of six. Similarly, the methylene protons appeared as two quartets having a geminal coupling of 10 Hz and couplings of 5.2 and 3 Hz for the A and B halves of the ABX system. This was followed by a multiplet at δ 5.80 and a doublet at δ 6.40 (J = 5 Hz) due to the proton α to the heterocyclic ring.

Treatment of dimeric reduction product **6** with phenylhydrazine regenerated the starting pyrazole **5**. This reaction opens the way for the synthesis of substituted 2-phenyl-5-trihydroxypropyl-3,4-pyrazolediones having various 3-aryl or 3-aroyl hydrazones by treatment of the dimer **6** with the desired substituted hydrazines. Furthermore, periodate oxidation of **6** afforded a formyl derivative which was characterized by conversion to the phenylhydrazone (**9**). Finally, periodate oxidation of **5** followed by reduction with sodium borohydride afforded 3-hydroxymethyl-1-phenyl-4,5-pyrazoledione-4-phenylhydrazone (**8**), which was characterized by conversion to the acetate and benzoate.

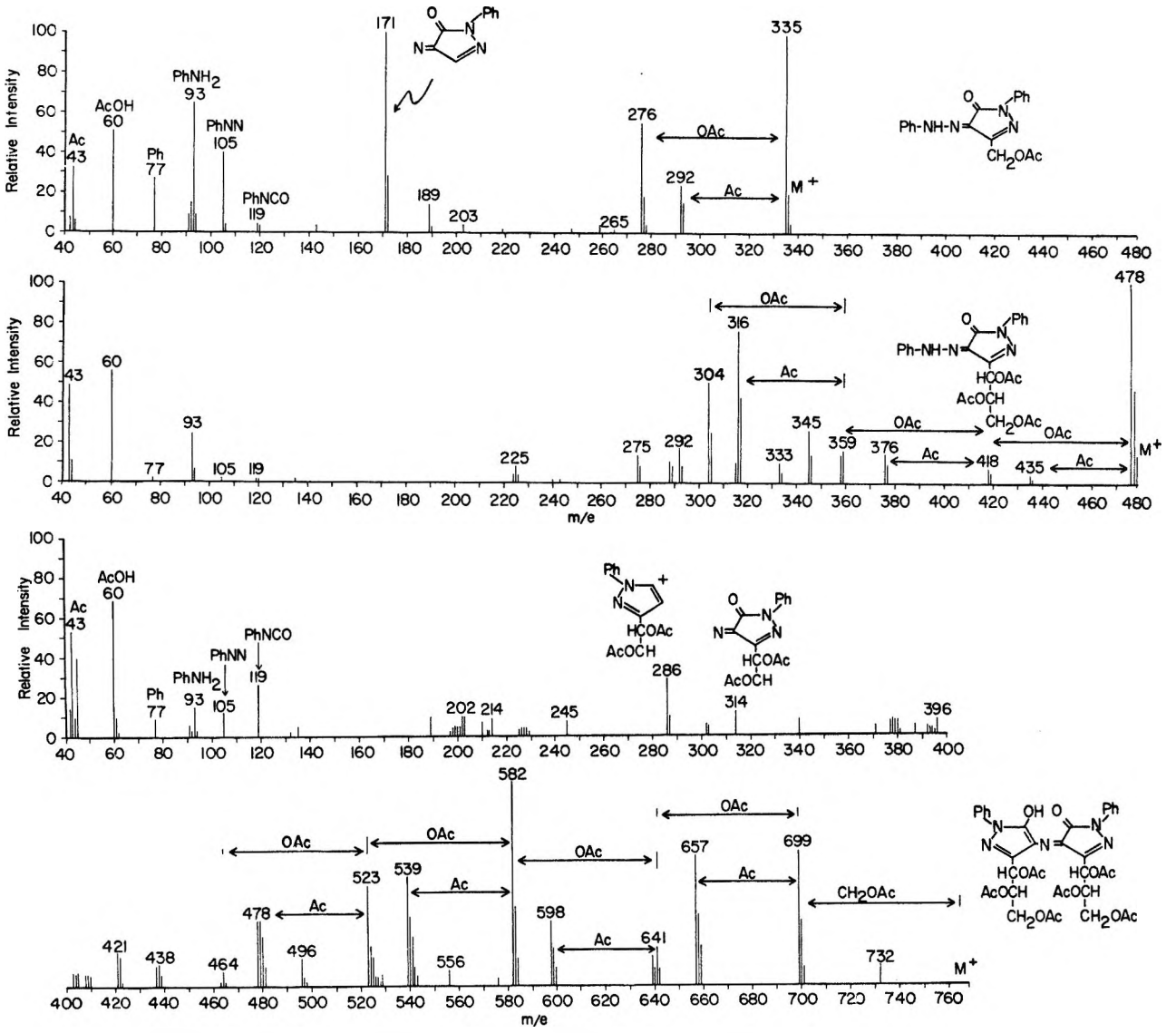


Figure 3.—Mass spectra of 3-acetoxymethyl-1-phenyl-4,5-pyrazoledione-4-phenylhydrazone (upper), 1-phenyl-3-(L-*threo*-triacetoxypropyl)-4,5-pyrazoledione-4-phenylhydrazone (middle), and bis(L-*threo*-triacetoxypropyl)rubiazonic acid (**7**) (bottom); Ac = 43.

Experimental Section

Melting points were measured on a Kofler block and are uncorrected; ir spectra were recorded for potassium bromide discs with a Unicam Sp 200 spectrophotometer; nmr and mass spectra were recorded and measured by Mr. M. P. Gilles, Department of Chemistry and Chemical Engineering, Michigan Technological University, on Varian HA-100 and M-66 instruments, respectively.

Reduction of Dehydro-L-ascorbic Acid Phenylosazone.—To a well-stirred solution of dehydro-L-ascorbic acid phenylosazone [L-*threo*-2,3-hexodiuolosono-1,4-lactone-2,3-bis(phenylhydrazone)][6] (2 g) in dry dioxane (50 ml), a suspension of lithium aluminum hydride (0.8 g) in dry *p*-dioxane was added dropwise during 0.5 hr and in an atmosphere of nitrogen. The reaction mixture was refluxed for 6 hr, and the excess of lithium aluminum hydride was decomposed by adding ethyl acetate (5 ml) followed by dilute sulfuric acid (10 ml). The solution was deionized with an Amberlite mixture of IR-120 and IRA-400, and the filtrate was evaporated under reduced pressure to dryness. Water was then added (250 ml) and the solid that separated was filtered off, washed with water and ethanol, and dried (yield 1 g). Reduction product **2** crystallized from ethanol as pale yellow needles, mp 223–225°, ν_{max}^{KBr} 1675 (CO) and 3400 cm^{-1} (OH). It is soluble in acetone, sparingly soluble in methanol, and insoluble in water.

Anal. Calcd for $C_{18}H_{18}N_4O_2 \cdot 1/2\ H_2O$: C, 65.24; H, 5.78; N, 16.91. Found: C, 64.98; H, 5.39; N, 16.86.

Diacetate 3.—A solution of product **2** (0.1 g) in acetic anhydride (10 ml) was refluxed for 0.5 hr. The mixture was poured onto crushed ice, and the solid that separated was filtered off, washed with water, and dried (yield 0.09 g). The product crystallized from ethanol as colorless needles: mp 198–200°; ν_{max}^{KBr} 1680 (NAc) and 1720 cm^{-1} (OAc); nmr (100 MHz, chloroform-*d*) δ 2.13 (3 protons, OAc), 2.62 (3 protons, NAc), 5.12 (2 protons, methylene), 6.90 (1 proton, methyne), 7.55 (10 protons, 2 phenyls).

Anal. Calcd for $C_{22}H_{20}N_4O_3$: C, 68.02; H, 5.19; N, 14.42. Found: C, 67.95; H, 5.52; N, 14.47.

Monoacetate 4.—The diacetate (0.05 g) was dissolved in ethanol (10 ml) and the mixture was saturated with ammonia at 0°. After 24 hr the solvent was evaporated under vacuum and the product was crystallized from dilute ethanol: mp 105°; ν^{KBr} 1690 cm^{-1}; nmr (100 MHz, chloroform-*d*) δ 2.58 (3 protons, NAc), 4.63 (2 protons, methylene), 4.63 (1 proton, methyne), 6.90 (10 protons, 2 phenyls).

Anal. Calcd for $C_{20}H_{18}N_4O_2$: C, 69.34; H, 5.24; N, 16.17. Found: C, 69.55; H, 5.36; N, 16.32.

Bis-L-*threo*-1,2,3-trihydroxypropyl Derivative (6).—A solution of 1-phenyl-3-(L-*threo*-1,2,3-trihydroxypropyl)-4,5-pyrazoledione-4-phenylhydrazone[5] (**5**) (5 g) in ethanol (200 ml) was treated with zinc dust (5 g) and the mixture was refluxed gently for 15 min while acetic acid (5 ml) was added dropwise. The reaction mixture was filtered off, and the filtrate was deionized with Amberlite mixture 1:1 IR-120 and IRA-400 (20 g). The solution was evaporated to dryness under diminished pressure, whereby a red, crystalline solid was obtained, which was filtered off, washed with ethanol, and dried (yield 3 g). The bis-L-*threo*-1,2,3-trihydroxypropyl derivative (6) crystallized from ethanol as red needles:

mp 219°; ν_{max}^{KBr} 1680 (CO) and 3450 cm^{-1} (OH); λ_{max}^{EtOH} 208, 254, 350, 540 nm (log ϵ 4.02, 4.43, 4.23, 4.00); λ_{min} 224, 308, 410 nm (log ϵ 3.87, 3.41, 3.54). It is soluble in acetone, sparingly soluble in methanol, and insoluble in water.

Anal. Calcd for $C_{24}H_{25}N_5O_8$: C, 56.36; H, 4.92; N, 13.71. Found: C, 56.82; H, 5.03; N, 13.71.

Bis-D-*erythro*-1,2,3-trihydroxypropyl Derivative (6).—When 1-phenyl-3-(D-*erythro*-1,2,3-trihydroxypropyl)-4,5-pyrazoledione-4-phenylhydrazine[3] (5) (1 g) was treated in exactly the same manner as for the threo derivative, it yielded 0.4 g of product, mp 205–207°.

Anal. Calcd for $C_{24}H_{25}N_5O_8$: C, 56.36; H, 4.92; N, 13.69. Found: C, 55.97; H, 5.20; N, 13.30.

Bis-L-*threo*-1,2,3-triacetoxypropyl Derivative (7).—A solution of L-*threo*-trihydroxypropyl derivative (6) (0.3 g) in pyridine (15 ml) was treated with acetic anhydride (5 ml) and left overnight at room temperature. The mixture was poured on crushed ice, and the product that separated was filtered off, washed with water, and dried (yield 0.3 g). The product crystallized from dilute ethanol in red needles: mp 130–132°; ν_{max}^{KBr} 1680 (CO), 1740 cm^{-1} (OAc); λ_{max}^{EtOH} 210, 255, 352, 541 nm (log ϵ 4.19, 4.35, 4.03, 4.04), λ_{min} 225, 310, 410 nm (log ϵ 3.95, 3.29, 3.45); nmr (100 MHz, chloroform-*d*) δ 2.06, 207, 216 (3 protons each, OAc), 432 (1 proton quadruplet, J_{AB} = 10, J_{AX} = 5.2 Hz), 4.54 (1 proton quadruplet, J_{BX} = 3 Hz), 5.80 (1 proton multiplet), 6.40 (1 proton doublet, J = 5 Hz), 725–791 (5 proton multiplet, phenyl).

Anal. Calcd for $C_{36}H_{37}N_5O_{14}$: C, 57.62; H, 4.88; N, 9.17 Found: C, 57.19; H, 4.89; N, 9.14.

Bis(D-*erythro*-1,2,3-triacetoxypropyl)rubiazonic Acid (7).—When the D-erythro-1,2,3-trihydroxy derivative (6) (0.3 g) was acetylated in the same manner as above, it yielded 0.4 g of the acetate, mp 101°.

Anal. Calcd for $C_{36}H_{37}N_5O_{14}$; C, 57.62; H, 4.88; N, 9.17. Found: C, 57.47; H, 5.03; N, 9.31.

Conversion of 6 to the Starting 1-Phenyl-3-(L-*threo*-1,2,3-trihydroxypropyl)-4,5-pyrazoledione-4-phenylhydrazone (5).—A solution of bis-L-*threo*-trihydroxypropyl derivative (6) (0.2 g) in ethanol (50 ml) was treated with phenylhydrazine (2 ml) and acetic acid (3 ml) and the solution was refluxed for 0.5 hr and concentrated to a small volume. Hot water was added to the solution to incipient turbidity, and the product was filtered off, washed with water, and dried (yield 0.1 g). 1-Phenyl-3-(L-*threo*-1,2,3-trihydroxypropyl)-4,5-pyrazoledione crystallized from chloroform–ethanol as orange needles, mp 212–215°, not depressed on admixture with an authentic sample; both samples had identical ir spectra.

1-Phenyl-3-(L-*threo*-1,2,3-trihydroxypropyl)-4,5-pyrazoledione-4-benzoylhydrazone.—Bis-L-*threo*-trihydroxypropyl derivative (6) (0.2 g) in ethanol (100 ml) was treated with benzoylhydrazine (0.3 g) and acetic acid (5 ml), and the solution was refluxed for 0.5 hr and concentrated to a small volume. Water was added to the solution to incipient turbidity, and the product was filtered off, washed with water, and dried (yield 0.2 g). 1-Phenyl-3-(L-*threo*-1,2,3-trihydroxypropyl)-4,5-pyrazoledione-4-benzoylhydrazone crystallized from ethanol as orange needles: mp 218°; ν_{max}^{KBr} 1660 (CO) and 3450 cm^{-1} (OH); λ_{max}^{EtOH} 243, 325 nm (log ϵ 4.79, 4.07), λ_{min} 290 nm (log ϵ 3.90).

Anal. Calcd for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.74; N, 14.62, Found: C, 59.91; H, 4.85; N, 14.64.

1-Phenyl-3-(L-*threo*-1,2,3-triacetoxypropyl)-4,5-pyrazoledione-4-benzoylhydrazone.—A solution of bis-1-phenyl-3-(L-*threo*-1,2,3-trihydroxypropyl)-4,5-pyrazoledione-4-benzoylhydrazone (0.1 g) in dry pyridine (5 ml) was treated with acetic anhydride (5 ml) and left overnight at room temperature. The mixture was poured onto crushed ice, and the product that separated was filtered off, washed with water, and dried (yield 0.1 g). 1-Phenyl-3-(L-*threo*-1,2,3-triacetoxypropyl)-4,5-pyrazoledione-4-benzoylhydrazone crystallized from ethanol as yellow needles: mp 150°; ν_{max}^{KBr} 1660 (CO) and 1710 cm^{-1} (OAc); λ_{max}^{EtOH} 238, 320 nm (log ϵ 4.52, 3.76), λ_{min} 295 nm (log ϵ 3.74).

Anal. Calcd for $C_{25}H_{24}N_4O_8$: C, 59.05; H, 4.75; N, 11.02. Found: C, 58.92; H, 4.64; N, 11.38.

1-Phenyl-3-(D-*erythro*-1,2,3-trihydroxypropyl)-4,5-pyrazoledione-4-benzoylhydrazone.—Bis-D-*erythro*-1,2,3-trihydroxypropyl derivative (0.5 g in 100 ml of ethanol) was treated with benzoylhydrazine (0.3 g) and acetic acid (5 ml), and the solution was refluxed for 0.5 hr and concentrated to a small volume. Hot water was added to the solution to incipient turbidity, and the product that separated was filtered off, washed with water, and dried (yield 0.5 g). 1-Phenyl-3-(D-*erythro*-1,2,3-trihydroxypropyl)-4,5-pyrazoledione-4-benzoylhydrazone crystallized from ethanol as orange needles: mp 205–207°; ν_{max}^{KBr} 1660 (CO) and 3450 cm^{-1} (OH); λ_{max}^{EtOH} 239, 318 nm (log ϵ 4.45, 3.83), λ_{min} 295 nm (log ϵ 3.79).

Anal. Calcd for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.79; N, 14.63. Found: C, 59.34; H, 4.70; N, 14.81.

1-Phenyl-3-(D-*erythro*-1,2,3-triacetoxypropyl)-4,5-pyrazoledione-4-benzoylhydrazone.—A solution of 1-phenyl-3-(D-*erythro*-1,2,3-trihydroxypropyl)-4,5-pyrazoledione-4-benzoylhydrazone (0.1 g) in dry pyridine (10 ml) was treated with acetic anhydride (5 ml) and left overnight at room temperature. The mixture was poured onto crushed ice, and the product was filtered off, washed with water, and dried (yield 0.1 g). 1-Phenyl-3-(D-*erythro*-1,2,3-triacetoxypropyl)-4,5-pyrazoledione-4-benzoylhydrazone crystallized from ethanol as yellow needles: mp 138°; ν_{max}^{KBr} 1660 (CO) and 1740 cm^{-1} (OAc); λ_{max}^{EtOH} 235, 320 nm (log ϵ 4.34, 4.00); λ_{min} 295 nm (log ϵ 3.91).

Anal. Calcd for $C_{25}H_{24}N_4O_8$: C, 59.05; H, 4.76; N, 11.01. Found. C, 58.82; H, 4.68; N, 11.21.

Bis(formyl)rubiazonic Acid Phenylhydrazone (9).—Bis-L-*threo*-1,2,3-trihydroxypropyl derivative (6) (0.1 g) in water (20 ml) was shaken with excess sodium metaperiodate (0.5 g) for 24 hr, and the amorphous formyl derivative was filtered, washed with water, and treated with phenylhydrazine (0.1 g) in ethanol (10 ml) at room temperature. The hydrazone 9 separated and was crystallized from dilute ethanol as dark red needles, mp 178°.

Anal. Calcd for $C_{32}H_{25}N_9O_2$: C, 67.41; H, 4.44; N, 22.21. Found: C, 68.08; H, 4.80; N, 21.81.

3-Hydroxymethyl-1-phenylpyrazoline-4,5-dione-4-phenylhydrazone.—A solution of 1-phenyl-3-formylpyrazoline-4,5-dione-4-phenylhydrazone[5] (0.5 g) in ethyl alcohol (30 ml) was treated with a solution of sodium borohydride (0.5 g) in water (10 ml) in small portions and with continual shaking, and the solution was left overnight at room temperature. The solution was acidified with dilute acetic acid, and the solid that separated was filtered off, washed with water, and dried (yield 0.5 g). 3-Hydroxymethyl-1-phenylpyrazoline-4,5-dione-4-phenylhydrazone (8) crystallized from ethyl alcohol as orange-yellow needles: mp 155°; ν_{max}^{KBr} 1660 (CO) and 3450 cm^{-1} (OH); λ_{max}^{EtOH} 210, 240, 400 nm (log ϵ 4.01, 4.53, 4.65); λ_{min} 218, 300 nm (log ϵ 3.92, 3.87).

Anal. Calcd for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.03. Found: C, 65.28; H, 4.85; N, 19.11.

3-Acetoxymethyl-1-phenyl-4,5-pyrazoledione-4-phenylhydrazone.—A solution of 3-hydroxymethyl-1-phenyl-4,5-pyrazoledione-4-phenylhydrazone (0.1 g) in dry pyridine (5 ml) was treated with acetic anhydride (5 ml) and left overnight at room temperature. The mixture was poured onto crushed ice and the product that separated, on cooling, was filtered off, washed with water, and dried (yield 0.1 g). 3-Acetoxymethyl-1-phenyl-4,5-pyrazoledione-4-phenylhydrazone crystallized from ethanol as yellow-orange needles: mp 131°; ν_{max}^{KBr} 1660 (CO) and 1740 cm^{-1} (Ac); λ_{max}^{EtOH} 209, 240, 400 nm (log ϵ 4.11, 4.44, 4.34); λ_{min} 215, 300 nm (log ϵ 4.11, 3.08).

Anal. Calcd for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.10; H, 4.85; N, 16.95.

3-Benzoyloxymethyl-1-phenyl-4,5-pyrazoledione-4-phenylhydrazone.—A solution of 3-hydroxymethyl-1-phenyl-4,5-pyrazoledione-4-phenylhydrazone (0.1 g) in dry pyridine (10 ml) was treated with benzoyl chloride (0.5 ml) and the mixture was left overnight at room temperature. The mixture was poured onto crushed ice, and the product that separated was filtered off, washed with water, and dried (yield 0.1 g). 3-Benzoyloxymethyl-1-phenyl-4,5-pyrazoledione-4-phenylhydrazone crystallized from ethanol as yellow needles: mp. 151°; ν_{max}^{KBr} 1660 (CO) and 1750 cm^{-1} (OBz); λ_{max}^{EtOH} 208, 240, 400 nm (log ϵ 4.20, 4.44, 4.36); λ_{min} 215, 300 nm (log ϵ 4.11, 3.07).

Anal. Calcd for $C_{23}H_{18}N_4O_3$: C, 69.33; H, 4.55; N, 14.06. Found: C, 69.49; H, 4.69; N, 14.34.

Registry No.—**1**, 3909-11-3; **2**, 35426-80-3; **3**, 35426-81-4; **4**, 35426-82-5; L-**5**, 25314-31-2; D-**5**, 30694-70-3; L-**6**, 35454-88-7; D-**6**, 35426-84-7; L-**7**, 35426-85-8; D-**7**, 35426-86-9; **8**, 35426-87-0; **9**, 35426-88-1; 1-phenyl-3-(L-*threo*-1,2,3-trihydroxypropyl)-4,5-pyrazole-

dione-4-benzoylhydrazone, 35426-89-2; 1-phenyl-3-(L-*threo*-1,2,3-triacetoxypropyl)-4,5-pyrazoledione-4-benzoylhydrazone, 35426-90-5; 1-phenyl-3-(D-*erythro*-1,2,3-triacetoxypropyl)-4,5-pyrazoledione-4-benzoylhydrazone, 35426-91-6; 1-phenyl-3-(D-*erythro*-1,2,3-triacetoxypropyl)-4,5-pyrazoledione-4-benzoylhydrazone, 35426-92-7; 3-acetoxymethyl-1-phenyl-4,5-pyrazoledione-4-phenylhydrazone, 35426-93-8; 3-benzoyloxymethyl-1-phenyl-4,5-pyrazoledione-4-phenylhydrazone, 35426-94-9.

Elucidation of the Mechanism of Reductive Dehalogenation of o-Haloanisole under Aryne-Forming Conditions

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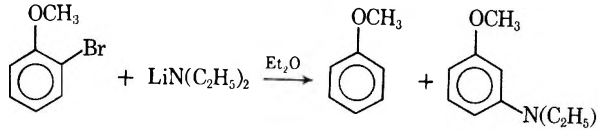
A method for distinguishing between the two proposed reductive dehalogenation mechanisms of haloanisoles is described. At large ratios of di-*n*-propylamine to lithium di-*n*-propylamide, 3-methoxybenzyne is essentially trapped by di-*n*-propylamine, affording the typical aryne addition product, **2**. At this point, reduction occurs solely *via* Mechanism B, direct halogen displacement, the extent of which varies as the haloaromatic is varied along the series I (76%) > F (9%) ~ Br (10%) > Cl (5%). Using low amine:amide values, Mechanism A, reduction of 3-methoxybenzyne by hydride, as well as Mechanism B are operable. In contrast to Wittig's results obtained in the *p*-halotoluene system, no products resulting from Schiff base addition to either aryne or aryl anions were observed.

The reaction of haloaromatic compounds with lithium dialkylamides in ether generally yields typical benzyne addition products, *i.e.*, *N*,*N*-dialkylamino aromatics. However, there are many cases in which certain haloaromatic compounds are also reductively dehalogenated under these conditions.[2] For example, *o*-bromoanisole reacts in the presence of lithium diethylamide to afford *N*,*N*-diethyl-*m*-anisidine (33%) and anisole (10%).[3]



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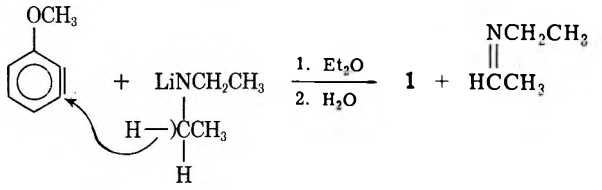
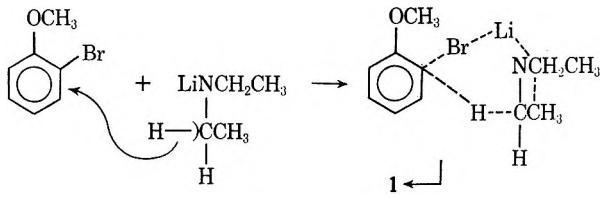
Two mechanisms have been proposed for the formation of anisole (**1**). Mechanism A, shown below, involves a hydride transfer from the α carbon of lithium diethylamide to the meta position of 3-methoxybenzyne.[4] Alternatively, Mechanism B postulates a direct displacement of halogen by a similar hydride transfer.[5]

Mechanism A



Mechanism B



Both mechanisms may be operative in the reductive dehalogenation of *p*-fluoro- and *p*-iodotoluenes.[6] Product analysis indicated that *p*-fluorotoluene was reduced *via* Mechanism A. Conversely, Mechanism B was more likely involved in the formation of toluene from *p*-iodotoluene.

Obviously, deuterium-labeling experiments would provide an unambiguous method for differentiating between these mechanisms. That this study has not been reported is presumedly due to the synthetic and/or analytical difficulties involved in such an investigation.

We report another method for distinguishing between the two mechanisms. 3-Methoxybenzyne is an extremely reactive aryne.[7] Moreover, the reaction of *o*-bromoanisole in various dialkylamine solvents in the presence of undissolved sodamide yielded only the expected aryne addition products, *i.e.*, no anisole formation.[8] Consequently, dialkylamines are not capable of reducing either *o*-bromoanisole or 3-methoxybenzyne. These two facts should allow one to assess the relative amounts of reduction occurring *via* Mechanisms A and B in this system.

Scheme I illustrates the possible paths open to *o*-haloanisoles upon treatment with $LiNR_2$ in the presence of the corresponding secondary amine, R_2NH.

Accordingly, an increase in anisidine production with a concomitant decrease in reduction *via* Mechanism A should be observed as the amount of dialkylamine is increased relative to lithium dialkylamide. Moreover, a limiting value of the anisidine/anisole ratio may be reached even though the amine/amide ratio be further increased. At this point, 3-methoxybenzyne would be converted solely to *m*-anisidine derivatives,

(1) (a) Sponsored in part by Grants N-118 and N-466 of the Robert A. Welch Foundation, Houston, Tex. (b) Robert A. Welch Foundation Predoctoral Fellow.

(2) For a comprehensive review see R. W. Hoffman, "Dehydrobenzene and Cyclohexane," Academic Press, New York, N. Y., 1967.

(3) H. Gilman and R. H. Kyle, *J. Amer. Chem. Soc.*, **74**, 3027 (1952).

(4) G. Wittig, H. J. Schmidt, and H. Renner, *Chem. Ber.*, **95**, 2377 (1962).

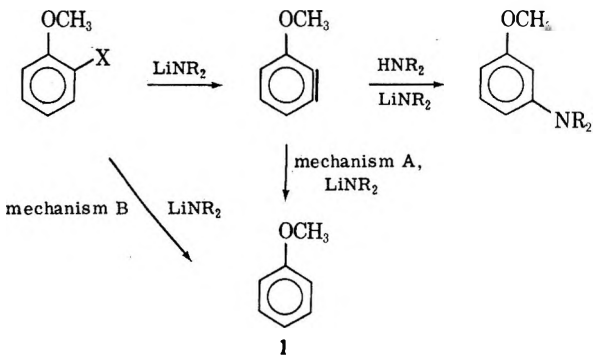
(5) R. A. Benkeser and C. E. DeBoer, *J. Org. Chem.*, **21**, 281 (1956).

(6) G. Wittig, C. N. Rentzen, and M. Rentzen, *Justus Liebigs Ann. Chem.*, **744**, 8 (1971).

(7) E. R. Biehl, E. Nieh, and K. C. Hsu, *J. Org. Chem.*, **34**, 3595 (1969).

(8) E. R. Biehl, S. M. Smith, R. Patrizi, and P. C. Reeves, *ibid.*, **37**, 137 (1972).

SCHEME I



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whereas the formation of anisole would occur exclusively *via* Mechanism B.

Of the several amine/amide systems studied, best combined yields of anisole (1) and *m*-anisidine derivatives were obtained when 1 equiv of the *o*-haloanisoles, 2 equiv of lithium di-*n*-propylamide, and varying equivalents of di-*n*-propylamine were employed; the results are listed in Table I.

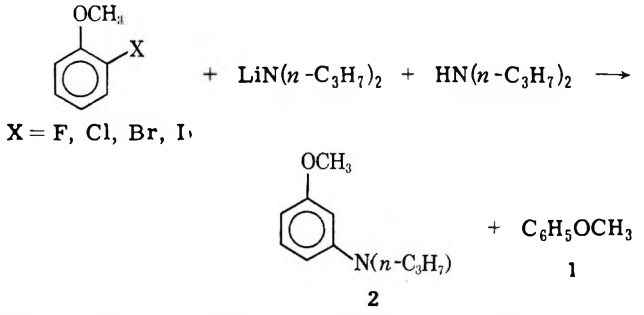


TABLE I

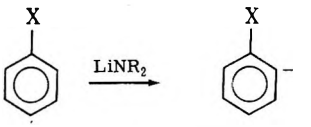
RATIO OF *N*,*N*-DI-*n*-PROPYL-*m*-ANISIDINE/ANISOLE[a] FROM THE REACTION OF *o*-HALOANISOLES WITH VARYING AMINE/AMIDE VALUES

$HN(n\text{-}C_3H_7)_2$[b] / $LiN(n\text{-}C_3H_7)_2$[c,d]	*o*-Iodo-[e]	*o*-Bromo-[f]	*o*-Chloro-[g]	*o*-Fluoro-[b]
0.25	11/87			
0.5	20/76	71/21	78/13	72/23
1.0	20/76	80/17	82/10	79/16
2.0	20/76	86/9	87/7	82/10
2.5			90/6	
3.0		87/9	90/5	84/10

[a] These values are averages of several reactions. [b] Registry no., 142-84-7. [c] Based on 2 equiv of amide to 1 equiv of *o*-haloanisole. [d] Registry no., 4111-53-9. [e] Registry no., 529-28-2. [f] Registry no., 578-57-4. [g] Registry no., 766-51-8. [h] Registry no., 321-28-8.

The data reveal that the ratio of *N*,*N*-di-*n*-propylanisidine (2) to 1 increases with increasing amine/amide values. For example, the reaction of *o*-bromoanisole yields 2 and 1 in the ratios of 71:21, 80:17, and 86:9 as the amine/amide ratio is varied from 0.5 to 1 to 2, respectively. In addition, a limiting 2/1 value is obtained in all cases, indicating that only Mechanism B is operative at this point. That this limiting value depends on the nature of the aromatic halogen atom argues also for reduction *via* Mechanism B, the trend being I (76%) > F (10%) ~ Br (9%) > Cl (5%). The large value for iodine is not unexpected.

Interestingly, *o*-fluoroanisole undergoes reduction *via* Mechanism B to a larger extent (10%) than *o*-chloroanisole (5%). Two factors could be involved. First, the greater electronegativity of fluorine as compared to chlorine would render the carbon atom to which it is bonded more prone toward nucleophilic attack than would chlorine. Second, *o*-fluorophenyl anion (**3a**) produced in the first step of aryne formation would be expected to be more stable than *o*-chlorophenyl anion (**3b**). Consequently, aryne formation



3a, X = F
b, X = Cl

via **3a** may be retarded. An evaluation of the relative importance of these two factors cannot be made at present.

Thus, it is seen that both mechanisms operate at amine/amide ratios below the limiting values in all cases, including *o*-iodoanisole. In further contrast to Wittig's results,[6] no products resulting from Schiff base addition to either aryne or aryl anions were observed. Since different haloaromatics were used, comparisons between the two systems are not possible.

Experimental Section

Glpc analyses were performed on a Beckman GC-5 chromatograph using nitrogen as carrier gas at a flow rate of 60 ml/min, inlet temperature of 150°, detection temperature of 200°, and column temperature of 100°. A 10 ft × 0.125 in. i.d. column packed with 10% SE-30 (silicone rubber) on Chromosorb W, acid-washed, 80–100 mesh was used to analyze anisole. Nmr spectra were obtained using a Perkin-Elmer R-12B nmr spectrophotometer.

Starting Materials.—*o*-Fluoro- and *o*-chloroanisole were purchased from Pierce Chemical Co. and *o*-bromoanisole was obtained from Eastman Kodak Co. These materials were of the highest purity grade available and were distilled and dried before using. *o*-Iodoanisole was synthesized according to the method of Jannasch and Hinterskirch[9] and was distilled until chromatographically pure. Di-*n*-propylamine purchased from Aldrich Co. was dried (CaH_2) for 24 hr, then distilled directly into a thoroughly dried reaction vessel. *n*-Butyllithium was obtained from Alfa Inorganics and used as received.

General Procedure.—All reactions were carried out under a nitrogen atmosphere. To a stirred solution of 50 ml of anhydrous ether and the required equivalents of di-*n*-propylamine was added 0.05 mol of *n*-butyllithium dropwise over a period of 5 min. After the solution was stirred for an additional 10 min, 0.025 mol of the appropriate *o*-haloanisole was added over a period of 5 min. The solution was refluxed with external heating for 15 hr and then quenched by the careful addition of 5 ml of water. The ether solution was washed three times with water (10 ml each), extracted three times with 10% hydrochloric acid (25 ml each) to remove *N*,*N*-di-*n*-propyl-*m*-anisidine (2), dried ($CaCl_2$), and concentrated by careful evaporation of ether to yield anisole. The anisole was quantitatively analyzed by vpc using phenetole as internal standard. The acidic aqueous extract was made basic and was extracted with several portions of ether. The combined ether extracts were dried ($MgSO_4$), concentrated, and then vacuum distilled to yield 2: bp 129–131° (3 mm); nmr (CCl_4) δ 6.9 (m, Ar, 1 H), 6.0 (m, Ar, 3 H), 2.62 (s, OCH_3, 3 H), 3.15 (t, $CH_2CH_2CH_3$, 4 H), 1.55 (sextet, $CHCH_2CH_3$, 4 H), 0.86 ($CH_2CH_2CH_3$, 6 H).

Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.48; H, 10.31; N, 6.98.

Registry No.—2, 35666-61-6.

(9) P. Jannasch and W. Hinterskirch, *Ber.*, **31**, 1710 (1898).

Zwitter Annihilation in the Halogenation of Allylic Alkoxides. II. The 1-Phenyl-2-methyl-2-cyclohexen-1-ol System[1]

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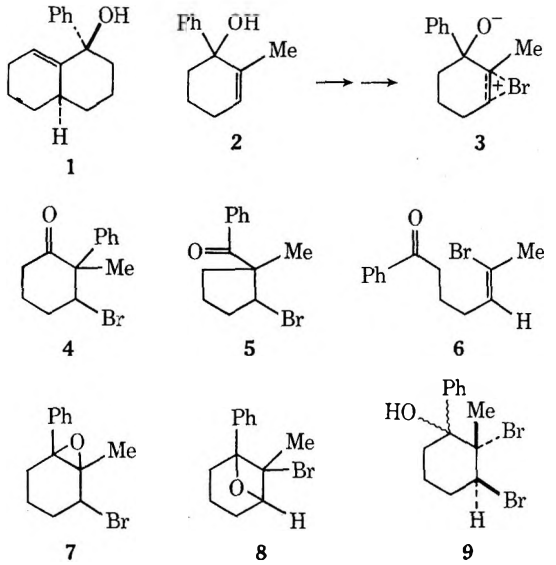
Study of the fate of bromonium alkoxides derived from allylic alcohols has been extended to the title system **2**. The products isolated from bromination of the salt of **2** result from alkyl migration (**5**), epoxide closure (**7t** and **7c**), and bromide attack (**9**) and account for 55% of starting material. Evidence for the stereochemistry of these products is presented and the mechanisms of their formation are discussed. It is argued that **5** and **7t** arise by straightforward zwitter annihilation mechanisms, while **7c** and **9** arise by interrelated routes resulting from the use of $BrMg^+$ as the alkoxide counterion, which also is responsible for the failure to observe phenyl migration.

Our initial investigation of the reactions of bromonium alkoxides derived from allylic alcohols involved the system represented by **1**.[3] We have now extended our study to **2**, which incorporates similar critical elements into a system which is less rigid and which has no predetermined stereochemistry. We hoped thereby to eliminate the influence of these factors in order to discover the reaction's outcome in the more general case. In addition the vinylic methyl group in **2** was expected to provide a readily observable nmr singlet in all of the foreseeable simple products of the reaction (**4**–**9**). These could arise from the bromonium alkoxide **3** by, respectively, bond migration away from the alkoxide carbon (**4**–**6**), direct alkoxide attack on the bromonium ion (**7**, **8**), and attack of external bromide (**9**).

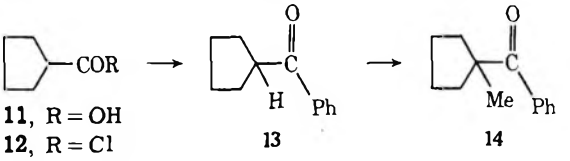


Results

Our allylic alcohol **2** was prepared by addition of phenylmagnesium bromide to 2-methylcyclohexenone, chromatographic separation of the alcohol from ketonic conjugate addition product, and distillation. Regeneration of the bromomagnesium alkoxide with Grignard reagent and bromination, both at 0°, proceeded as previously described[3] to give an isolated product mixture which nmr indicated to contain appreciable quantities of at least four components having unsplit methyl absorptions. The similar reaction of **1** had resulted in isolation of only two products, corresponding in type to **4** and **5**, and arising apparently from attachment of Br^+ on, respectively, the top and bottom sides of **1**. In the present instance no phenyl-migration product (**4**) was detected but the components of the reaction mixture were isolated chromatographically as pure materials whose spectral and other properties are consistent with structures **5**, **7** (two epimers), and **9**. In addition a very small amount of 1-phenyl-1,6-heptanedione (**10**) was isolated. The evidence concerning the structure and stereochemistry of these materials is as follows.

While the analytical data and the position of the infrared carbonyl absorption for compound **5** (6.8% yield) are consistent with either structure **5** or **6**, nmr evidence excludes the latter. Synthetic proof of the carbon skeleton of this material was established by carrying out the sequence in Scheme I, whose product

SCHEME I



(**14**) is identical in all respects with material obtained from catalytic hydrogenolysis of **5**.

Two of the materials isolated from bromination of the bromomagnesium alkoxide of **2** are isomeric with **5** but exhibit neither carbonyl nor hydroxyl absorption (ir). They both exhibit 1-H nmr absorptions in the δ 4.2–4.7 region, possibly consistent with tertiary hydrogens geminal to either bromine (**7**) or oxygen (**8**). However the latter structure also contains a methyl geminal to bromine, requiring a singlet at about δ 1.7.[4] The positions of the methyl singlets (δ 1.21 and 1.13) in the two isolated materials are consistent only with structures having methyl geminal to epoxide oxygen,[4,5] thus excluding an oxetane structure. The low multiplicity of the midfield nmr absorptions clearly indicates that the bromine is in the expected position in both isomers.

The stereochemical assignments for this pair of epimers can be made on the basis of the nmr spectra.

(1) Abstracted in part from the Ph.D. thesis of R. R. M.

(2) National Institutes of Health Predoctoral Fellow, 1970–1971.

(3) H. W. Thompson and R. R. Muccino, *J. Amer. Chem. Soc.*, **94**, 1183 (1972).

(4) (a) "NMR Spectra Catalog," Vol. 1 and 2, N. S. Bhacca, L. F. Johnston, and J. N. Shoolery, Ed., Varian Associates, Palo Alto, Calif., 1962; (b) "Nuclear Magnetic Resonance Spectra," Sadtler Research Laboratories, Philadelphia, Pa., 1970.

(5) P. M. McCurry, Jr., *Tetrahedron Lett.*, 1841 (1971).

In the isomer **7t** the trans arrangement of bromine and epoxide results in deshielding through space of the methinyl proton by the adjacent epoxide and of the methyl protons by bromine. In **7c**, where this reciprocal deshielding is absent, these absorptions are shifted to higher field by 0.18 and 0.08 ppm, respectively. These arrangements would also result in a partial cancellation of dipoles in **7t** *vs.* a reinforcement in **7c**, which is consistent with the more rapid elution of **7t** in column chromatography (Al_2O_3) and vpc.[6] The constants for splitting of the hydrogen geminal to bromine by adjacent methylene have been analyzed in both **7t** and **7c** with respect to the vicinal dihedral CH–CH_2 angles.[7] In each case the result indicated a conformation which models showed to be the one allowing greatest opposition of dipoles.

7t **7c**

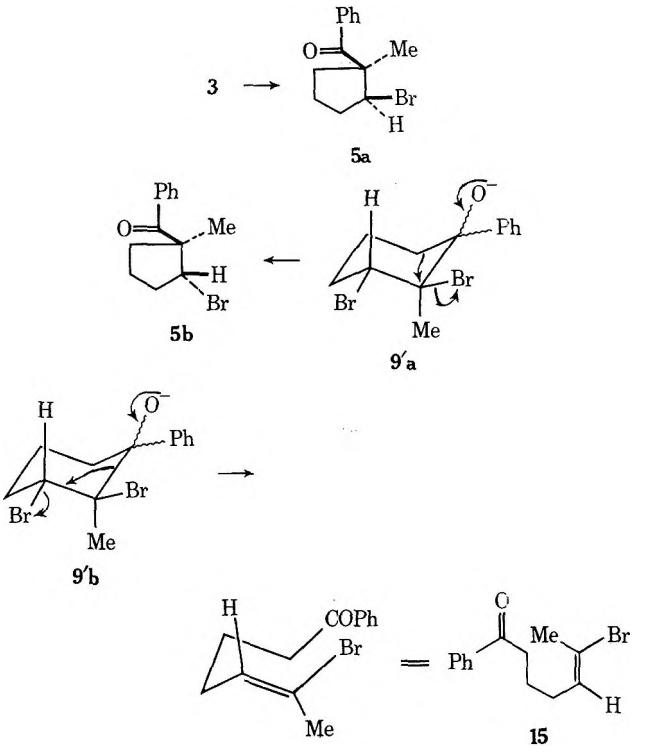
The fourth material isolated from the bromination gave analytical data consistent with addition of two bromine atoms. Its spectral properties indicate that it is an alcohol whose stereochemistry, we have found (see below), arises from trans addition of bromine (**9**).

Discussion

The amount by which the methyl group in **5** is deshielded relative to that in **14** (0.19 ppm) must be attributed to the effect of a vicinal bromine in **5**. While the exact magnitude of this shift should depend on the angular relationship between bromine and methyl, we have not been able to find sufficiently extensive analogies in the literature to allow us to make a firm stereochemical assignment to **5** on this basis. However, the 30% reduction in π–π^* ultraviolet intensity on loss of bromine from **5** seems more easily reconciled with the epimer of **5** having bromine cis to the benzoyl group. This stereochemistry (**5a**) is that to be expected from a zwitter annihilation mechanism. The most obvious source of the alternate isomer **5b** would be rearrangement of the halomagnesium salt of either isomer of **9** which has trans bromines[8] by internal displacement of an equatorial tertiary bromine. Several kinds of evidence suggest that the latter is not the method by which **5** is formed. Halomagnesium salts of vicinal halohydrins normally do not rearrange spontaneously at ice-bath temperature but must be heated to induce rearrangement.[9] Consistent with that, when **9** (obtained in 9.2% yield), which is known to have trans bromines (see below), was reconverted to its bromomagnesium salt and subjected to the original reaction conditions, it was recovered unchanged in 89% yield. Thus **9′** (denoting the anion of **9**) is not a precursor of **5** or of any of the other major products isolated. The possibility remains that **5** arose from the other trans-bromo isomer of **9′**, which we did not find because it was entirely consumed. We have not been able completely to eliminate this possibility. However, if **5** (**5b**) had arisen by this route it would mean that little or no **5a** could have arisen by zwitter annihilation, as only one epimer was detected. We therefore consider **5a** the more probable stereochemistry and zwitter annihilation the likely method of formation.

If **5** did arise from rearrangement of another isomer of **9′** it would presumably mean that that isomer could offer an equatorial tertiary bromine (*cf.* **9′a**, Scheme II),

SCHEME II



while ours could not; hence information about such conformational factors is of some interest. When **9** was converted to its sodium salt at room temperature in dimethoxyethane, rearrangement to compound **15** proceeded in 85% yield. The configuration shown for **15**, which is very clearly supported vis à vis structure **6** by the nmr spectrum,[10] is one which obviously requires two equatorial bromines in **9′** if elimination is to occur by a trans process through a chair form of the molecule. This not only supports our general assumption of trans addition of bromide to **3**,[8] but makes it clear that the sodium alkoxide, at least, has no difficulty attaining a conformation in which both bromines are equatorial.

The failure of **9′** to rearrange to **15** when its counterion is bromomagnesium may be interpreted in several ways. Similar conformations of the alkoxide may be involved for Na^+ and $BrMg^+$, with the difference in

(6) A. 0.125 in. × 6 ft stainless steel column packed with 10% UC-W98 silicone on 80–100 mesh firebrick was used for this analysis.

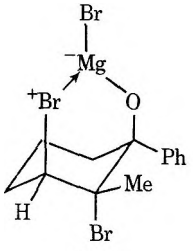
(7) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, pp 116–117.

(8) We have assumed that bromine will be added trans in **9**; see H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 422 ff.

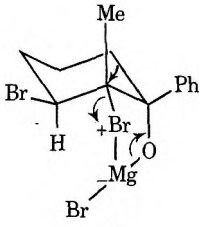
(9) (a) P. D. Bartlett and R. H. Rosenwald, *J. Amer. Chem. Soc.*, **56**, 1990 (1934); (b) M. Tiffeneau and B. Tchoubar, *C. R. Acad. Sci.*, **198**, 941 (1934); (c) M. Tiffeneau and B. Tchoubar, *ibid.*, **207**, 918 (1938); (d) B. Tchoubar, *ibid.*, **208**, 355 (1939); (e) M. Tiffeneau, B. Tchoubar, and S. LeTellier, *ibid.*, **216**, 856 (1943); (f) M. Tiffeneau, B. Tchoubar, and S. LeTellier, *ibid.*, **217**, 588 (1943); (g) T. A. Geissman and R. I. Akawie, *J. Amer. Chem. Soc.*, **73**, 1993 (1951); (h) A. S. Hussey and R. R. Herr, *J. Org. Chem.*, **24**, 843 (1959); (i) A. J. Sisti, *ibid.*, **33**, 453 (1968); (j) A. J. Sisti and A. C. Vitale, *Tetrahedron Lett.*, 2269 (1969).

(10) (a) J. H. Richards and W. F. Beach, *J. Org. Chem.*, **26**, 623 (1961); (b) S. W. Tobey, *ibid.*, **34**, 1281 (1969).

reactivity solely the result of lower negative charge density on oxygen because of the greater covalency of the O–Mg bond.[11,12] This implies that such lack of electron density would probably also prevent rearrangement to **5**, regardless of which isomer of **9** was involved (and that **5** must have arisen therefore from zwitter annihilation). An alternate explanation is that the rearrangement **9′** → **15** does not proceed when the cation is $BrMg^+$ because the secondary bromine to be eliminated cannot occupy an equatorial bond, but can when the cation is Na^+. This requires for the bromomagnesium alkoxide some way of overcoming its 1,3-diaxial crowding interactions which will not operate for the sodium alkoxide, and implies that our isomer is **16a**. A third alternative incorporates both ideas, to the effect that **16a** fails to rearrange through a combination of low electron density on oxygen and lack of facilitating coordination with a bromine in the correct configuration, and that modification of either one of these conditions would suffice to cause rearrangement. Thus the sodium salt of **9′** rearranges to **15** while even the bromomagnesium salt of the other isomer of **9′** (**16b**) should rearrange (to **5b**) because of effective Br coordination. While any of these is a plausible explanation for the difference in behavior of the sodium and bromomagnesium alkoxides, the corollary idea in the last two, that the bromomagnesium salt of opposite alkoxide stereochemistry (**16b**) would rearrange by eliminating bromide, remains speculative.



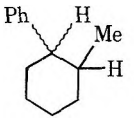
16a



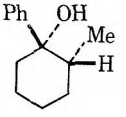
16b

Of the two bromoepoxides isolated, **7t** (21.3% yield) is the one which would be expected to arise in zwitter annihilation by back-side attack of alkoxide on a (trans) bromonium ion. The unexpected stereochemistry of **7c** (18% yield) might arise by several mechanisms. That it does not result from isomerization of the anticipated bromoepoxide was shown by demonstrating the stability of **7t** to the original reaction conditions. Bromoepoxide **7c** might also arise through halohydrin closure in a dibromoalkoxide (**9′**); several lines of evidence operate against this. First, halohydrin salts which involve tertiary (and secondary) halides normally undergo migratory rearrangements rather than epoxide closure[9g,9i,13] (but will not do either at ice-bath temperature[9]). Secondly, because of the requirement for a trans diaxial arrangement in epoxide closure,[14] if **7c** were to arise from **9′**, the required isomer would be that corresponding to **16a**. However there is, as indicated, some reason for believing that this structure represents the isomer of **9** which we have isolated, and yet this material does not produce **7c** on subjection to the original reaction conditions.

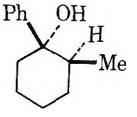
Several attempts were made at proving the epimeric relationship of **7t** and **7c** by conversion to a common debrominated derivative. Subjection of **7c** to catalytic hydrogenolysis (5% Pd/C, H_2, MeOH, $NaHCO_3$) led to rapid debromination. Under minimal conditions (5 min, 1 atm, 25°) loss of halogen proceeded to the extent of 90–95%, the nearly exclusive product being the allylic alcohol **2**. Over longer periods of time additional products appeared, evidently the result of further reduction of **2**. These were separable by vpc[6] and column chromatography and distinguishable by their vpc retention times and their nmr methyl doublets in the region δ 0.5–0.7. Hydrogenation of pure **2** produced the same three materials, which are assigned structures **17**, **18a**, and **18b**. These assignments were based in part on their order of elution from Al_2O_3 columns and vpc[6] (numerical order), the higher degree of crowding about hydroxyl in **18a** allowing more rapid elution. This assignment of stereochemistry to these epimeric alcohols was confirmed by the observations that hydrogenation of **2** produced more **18b** than **18a**, consistent with the often observed haptophilicity of hydroxyl,[15] that **18b** was hydrogenolyzed more rapidly than **18a**, and that **18a** was the preponderant isomer produced by addition of phenylmagnesium bromide to 2-methylcyclohexanone.[16]



17



18a



18b

Under the same minimal hydrogenolysis conditions, loss of bromine from **7t** was only *ca.* 30% complete. Over periods of time long enough to ensure complete loss of bromine, complex mixtures were produced which contained **17**, **18a**, and **18b** as well as two new materials with unsplit nmr methyl absorptions, thought to be isomers of **19**.

Thus the hydrogenolysis of **7c** is appreciably faster than that of **7t**. While a trans process might be thought to be more favorable if loss of bromine from **7** were accompanied by epoxide cleavage,[17] it must be remembered that this reaction may be greatly facilitated by simultaneous transfer of hydrogen to bromine and to oxygen. Since both such transfers would take place from the face of the catalyst, the success of this process for the trans isomer would require a very exact and hence improbable juxtaposition of surfaces. The reaction might be expected therefore to proceed more readily and cleanly in **7c**, as was found to be the case.

Conclusions

Only one of the products (**5**) observed from this bromonium alkoxide reaction is of a type observed in the similar reaction of system **1**. Therefore the fol-

(11) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, pp 97–102.

(12) The evidence concerning rearrangeability of Na *vs.* BrMg salts of halohydrins is not readily interpretable; see, *e.g.*, ref 9h, and P. D. Bartlett and R. V. White, *J. Amer. Chem. Soc.*, **56**, 2785 (1934).

(13) (a) A. J. Sisti, *J. Org. Chem.*, **33**, 3953 (1968); (b) *ibid.*, **35**, 2670 (1970).

(14) J. G. Phillips and V. D. Parker in "Steroid Reactions," C. Djerassi, Ed., Holden-Day, San Francisco, Calif., 1963, Chapter 14.

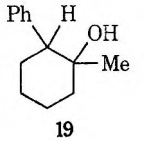
(15) (a) H. W. Thompson, *J. Org. Chem.*, **36**, 2577 (1971); (b) H. W. Thompson and R. E. Naipawer, unpublished results.

(16) J. R. Luderer, J. E. Woodall, and J. L. Pyle, *J. Org. Chem.*, **36**, 2909 (1971).

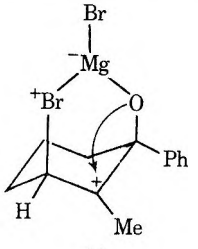
(17) (a) S. Winstein, D. Pressman, and W. G. Young, *J. Amer. Chem. Soc.*, **61**, 1645 (1939); (b) H. O. House and R. S. Ro, *ibid.*, **80**, 182 (1958); (c) C. L. Stevens and J. A. Valicenti, *ibid.*, **87**, 838 (1965).

lowing points require some explanation: (1) the appearance of **7t** and **9**, representing products which are predictable but of types not observed before; (2) the appearance of **7c**, whose stereochemistry is anomalous, at least with respect to simple zwitter annihilation mechanisms; (3) the failure to observe any phenyl-migration product (**4**) of the type isolated from reaction of **1**.

We believe that the following explanation accounts for the observed facts. Formation of a bromonium ion trans to the alkoxide function leads, "normally," to **7t** and possibly to **5** (it should be noted that **5** could arise from either the cis or the trans bromonium alkoxide). Formation of the cis bromonium alkoxide, however, leads to an internally complexed species **20** with most of its positive charge at the tertiary carbon but whose phenyl group is held equatorial by the complexation. The latter effectively prevents the phenyl migration which might be expected from an uncomplexed cis bromonium alkoxide and the former allows closure of the epoxide, which would require trans stereochemistry if a symmetrical bromonium ion were involved.[8] This species is also attacked by bromide ion from below, since the magnesium side of this [3.3.1] ring system would be more hindered by solvation and should bear enough negative charge to repel bromide ion. In **1**[3], however, the entire bromonium ion is rendered immune to involvement with alkoxide oxygen, either in terms of complexation or direct attack, because the C–O bond is approximately in the plane of the olefin (and aimed away from it).



19



20

These explanations imply that direct attack of alkoxide at the bromonium ion is a normal process, not observed in **1** simply because it is atypical stereochemically, and they imply that bromomagnesium as a counterion may, because of Lewis acidity,[18] produce results quite different from those to be found with alkali metal cations.

Experimental Section[19]

1-Phenyl-2-methyl-2-cyclohexen-1-ol (**2**).—A cooled solution of 23.7 g (215 mmol) of 2-methylcyclohex-2-en-1-one[20] in 60 ml of dry ether was treated under N_2 with 100 ml (242 mmol) of ethereal 2.42 *M* phenylmagnesium bromide by dropwise addition. The resulting solution was stirred for 2 hr at room temperature and hydrolyzed with basic saturated aqueous NH_4Cl; this mixture was extracted and the combined organic portions yielded 48.2 g of yellow oil. Chromatography of a 10-g portion of this on 400 g of neutral Al_2O_3 (2% H_2O added) and elution with ether–hexane mixtures allowed the separation of biphenyl, followed by 2-methyl-3-phenylcyclohexanone, isolated as a colorless oil: bp *ca.* 140–145° (5 mm) (675 mg, corresponding to 8%); ir 1710 cm^{-1}; nmr δ 0.95 (3 H d, J = 7 Hz), 1.3–2.6 (7 H complex), 3.15–3.55 (1 H m), 7.0–7.5 (5 H complex).

This ketone (157 mg, 0.828 mmol) was converted to its 2,4-DNP by treatment with 178 mg (0.896 mmol) of 2,4-dinitrophenylhydrazine in 20 ml of refluxing acidic EtOH,[21] providing 306 mg (63%) of the derivative, mp 206–207°. Recrystallization from EtOAc–EtOH gave material melting at 216.5–217°.

Anal. Calcd for $C_{19}H_{20}N_4O_4$: C, 61.95; H, 5.47. Found: C, 62.02; H, 5.73.

Concentration of later chromatographic fractions provided, after distillation at 72–73° (0.03 mm), 4.40 g (representing 52%) of **2**: ir 3615 cm^{-1}; nmr δ 1.48 (3 H d, J = 1.5 Hz), 1.55–2.2 (7 H, complex), 5.65 (1 H, broad), 7.65 (5 H, complex).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.87; H, 8.84.

Bromination of the Magnesium Salt of 2.—Ethereal 1.87 *M* phenylmagnesium bromide (13.8 ml, 25.7 mmol) was slowly added with stirring to a cooled solution of 2.49 g (12.7 mmol) of **2** in 25 ml of dry ether under N_2. The clear solution was stirred for 20 min at room temperature and then recooled and a solution of 1.32 ml (24.2 mmol) of Br_2 in 15 ml of dry CH_2Cl_2 was slowly added with stirring until an orange color persisted. An aqueous solution of $NaHCO_3$ and Na_2SO_3 was added until the color was discharged and the mixture was then washed with aqueous $NaHCO_3$, water, and brine. The dried, concentrated oil, which displayed ir and nmr absorptions corresponding to all the subsequently isolated compounds and a vpc[6] pattern of at least four discernible major peaks, was chromatographed on 150 g of neutral Al_2O_3 (2% H_2O added) and eluted with ether–hexane mixtures.

trans-**3-Bromo-1,2-epoxy-1-phenyl-2-methylcyclohexane** (**7t**).—Concentration of early chromatographic fractions eluted with 1% ether in hexane provided 726 mg (21.3%) of **7t**, mp 47–50°. Sublimation at 60–70° (0.04 mm) and recrystallizations from pentane gave needles melting at 54–54.5°; ir 855 cm^{-1}, no absorption in C=O or OH regions; uv 242 nm (ϵ 124), 247 (138), 252 (172), 262 (200), 264 (143); nmr δ 1.2 (3 H, s), 1.3–2.5 (6 H, complex), 4.55 (1 H, $W_{1/2}$ = 6 Hz), 7.3 (5 H, s).

Anal. Calcd for $C_{13}H_{15}OBr$: C, 58.44; H, 5.66. Found: C, 58.28; H, 5.57.

cis-**3-Bromo-1,2-epoxy-1-phenyl-2-methylcyclohexane** (**7c**).—Concentration of later 1% ether fractions gave 613 mg (18.0%) of **7c**, mp 68–71°. Sublimation at 70–80° (0.04 mm) and recrystallizations from pentane provided needles melting at 73–73.5°; ir 855 cm^{-1}, no absorption in C=O or OH regions; uv 246 nm (ϵ 212), 253 (206), 259 (224), 265 (155); nmr δ 1.12 (3 H, s), 1.4–2.4 (6 H, complex), 4.4 (1 H, t, J = 7 Hz), 7.3 (5 H, s).

Anal. Calcd for $C_{13}H_{15}OBr$: C, 58.44; H, 5.66. Found: C, 58.72; H, 5.92.

1-Benzoyl-1-methyl-2-bromocyclopentane (**5**).—Concentration of chromatographic fractions eluted with 10% ether in hexane afforded 230 mg (6.8%) of **5**, mp 39–43°. Sublimation at 50–60° (0.03 mm) and recrystallizations from pentane yielded material melting at 50–50.5°; ir 1680 cm^{-1}; uv 242 nm (ϵ 10,000), 278 (804); nmr δ 1.6 (3 H, s), 1.8–2.6 (6 H, complex), 5.0 (1 H, t, J = 6 Hz), 7.3–7.65 (3 H, complex), 7.83 (2 H, q, J = 2, 7 Hz).

Anal. Calcd for $C_{13}H_{15}OBr$: C, 58.44; H, 5.66. Found: C, 58.50; H, 5.66.

1-Phenyl-1,6-heptanedione (**10**).—Concentration of fractions eluted with 1:1 ether–hexane yielded 35 mg (1.4%) of dione melting at 39–42.5° (lit.[22] mp 43°), identified by its spectra: ir 1725, 1695 cm^{-1}; nmr δ 1.4–1.95 (4 H, complex), 2.05 (3 H, s), 2.4 (2 H, t, J = 7 Hz), 2.9 (2 H, t, J = 7 Hz), 7.1–7.6 (3 H, complex), 7.9 (2 H, q, J = 2, 7.5 Hz).

2,3-Dibromo-1-phenyl-2-methylcyclohexanol (**9**).—Concentration of chromatographic fractions eluted with ether furnished 409

(18) (a) G. A. Olah in "Friedel-Crafts and Related Reactions," Vol. I, G. A. Olah, Ed., Interscience, New York, N. Y., 1963, pp 220–221; (b) H. O. House, *J. Amer. Chem. Soc.*, **77**, 3070, 5083 (1955).

(19) Melting points were determined with a Mel-Temp apparatus and are uncorrected. Infrared spectra were taken using a Beckman IR-10 spectrometer, with CCl_4 as solvent. Ultraviolet spectra were determined in 95% EtOH solution with a Cary Model 14 spectrophotometer; nmr spectra were taken with a Varian A-60 spectrometer (CH_2Cl_2 and/or TMS internal standard) and using CCl_4 or $CDCl_3$ as solvent. Mass spectra were determined with a Perkin-Elmer Model 270 mass spectrometer through the kindness of Dr. R. E. Naipawer and Givaudan Corp. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(20) E. W. Warnhoff, D. G. Martin, and W. S. Johnson, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 162.

(21) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, N. Y., 1964, pp 249–255, 289–290.

(22) F. Sondheimer and D. Rosenthal, *J. Amer. Chem. Soc.*, **80**, 3995 (1958).

mg (9.2%) of **9**, mp 89–97°. Sublimation at 90–95° (0.03 mm) and recrystallizations from pentane gave material melting at 101–102°; ir 3610, 3555 cm^{-1}; uv 253 nm (ε 199), 258 (278), 262 (278), 264 (247), 268 (208); nmr δ 1.95 (3 H, s), 2.1–2.5 (6 H, complex), 3.12 (1 H, broad s), 4.9–5.3 (1 H, m), 7.15–7.6 (5 H, complex).

Anal. Calcd for $C_{13}H_{16}OBr_2$: C, 44.86; H, 4.63. Found: C, 44.76; H, 4.54.

1-Benzoyl-1-methylcyclopentane (14) by Hydrogenolysis of 5.—A solution of 300 mg (1.12 mmol) of **5** in 8 ml of MeOH was injected into a stirred suspension of 150 mg of 5% Pd/C catalyst and 75 mg of $NaHCO_3$ in 8 ml of MeOH which had been presaturated with H_2. Analysis of material isolated after 30 min indicated substantial carbonyl reduction, which, from other analyses, appeared to occur faster than C–Br hydrogenolysis. Reoxidation with Jones reagent[23] afforded, after isolation, 143 mg (67.5%) of **14**, identical with subsequently described synthetic material.

Benzoylcyclopentane (13).—Cyclopentanecarboxylic acid (4.8 ml, 44 mmol) was cooled with an ice bath and treated with 3.8 ml (53 mmol) of $SOCl_2$ by dropwise addition over 15 min.[24] The solution was refluxed for 45 min and, after removal of excess $SOCl_2$, distilled at 98–100° (102 mm) to give 4.0 g (30 mmol, 69%) of **12**, which was then slowly added in 36 ml of dry benzene to a stirred suspension of 4.1 g (31 mmol) of anhydrous $AlCl_3$ in 73 ml of dry benzene.[25] The solution of bright yellow complex was refluxed for 1 hr and decomposed with cold dilute aqueous HCl. Separation and extraction of the organic solution with aqueous base provided, on concentration, a residue which was distilled at 88–90° (*ca.* 0.25 mm) to give 4.8 g (92%) of **13** [lit.[25] bp 156–160° (15 mm)]: ir 1690 cm^{-1}; nmr δ 1.3–1.9 (8 H, complex), 3.55 (1 H, quintet, J = 7 Hz), 7.3 (3 H, complex), 7.9 (2 H, q, J = 2, 7 Hz).

1-Benzoyl-1-methylcyclopentane (14).—A solution of DMSO anion was prepared from 40 ml of dry DMSO and 1.0 g (41 mmol) of NaH.[26] Benzoylcyclopentane (3.5 g, 21 mmol) in 5 ml of dry DMSO was converted to its anion by titration with this solution under N_2 until the small amount of Ph_3CH present as indicator with the ketone gave a red color. After another 20 min of stirring, 6.2 ml (100 mmol) of MeI was added and the colorless solution was diluted with pentane, washed with water, dried, and concentrated. The residue was chromatographed on 150 g of neutral Al_2O_3 (2% H_2O added) and pure fractions (tlc) were combined and distilled at 83–84° (*ca.* 0.25 mm) to give 2.8 g (74%) of **14** as a colorless oil: ir 1680 cm^{-1}; uv 240 nm (ε 6980), 277 (695); nmr δ 1.4 (3 H, s), 1.5–1.8 (6 H, complex), 2.3–2.5 (2 H, m), 7.6 (3 H, complex), 7.9 (2 H, q, J = 2, 7 Hz), no absorption at 3.0–4.0 (*cf.* **13**).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.98; H, 8.63.

Synthetic **14** and hydrogenolysis product **14** had identical ir and nmr spectra, identical vpc retention times,[6] and only negligible differences in their mass spectra. Parent ion (m/e 188) intensity, expressed as percentage of total intensity for all ions with $m/e \geq 50$, was 1.44% for synthetic **14** and 1.49% for hydrogenolysis product **14**.

Stability of 9 to Reaction Conditions.—A solution of 150 mg (0.43 mmol) of dibromo alcohol **9** in 4.5 ml of dry ether was injected with stirring into 0.50 ml (1.0 mmol) of cold ethereal 2.0 *M* phenylmagnesium bromide under N_2. A solution of 0.27 ml (0.50 mmol) of Br_2 in 0.3 ml of dry CH_2Cl_2 was slowly added and the resultant solution was stirred for 1 hr at ice-bath temperature. Work-up as described and chromatography gave 134 mg (89.3%) of unchanged **9**, mp 97–99°.

Reaction of 9 with Sodium Hydride.—Dry dimethoxyethane (5 ml) was injected into a flask containing 210 mg (0.605 mmol) of dibromo alcohol **9** and 0.75 mmol of NaH (from 32 mg of 56% oil dispersion, washed with pentane) under N_2. Gas was evolved and the resulting gray suspension was stirred for 1 hr. Removal of solvent under vacuum and extraction of the residue with pentane gave material which was chromatographed and sublimed at *ca.* 60° (0.03 mm) to yield 141 mg (85.2%) of compound, mp 47–48°. Recrystallizations from pentane afforded pure **15**: mp 48–49° ir 1690, 1652 cm^{-1}; uv 235 nm (ε 12,700), 268 (984); nmr δ 1.5–2.1 (4 H, complex), 2.18 (3 H, s), 2.90 (2, H, t, J = 7 Hz), 5.83 (1 H, t, J = 6 Hz), 7.3–7.55 (3 H, complex), 7.9 (2 H, q, J = 2, 7 Hz).

Anal. Calcd for $C_{13}H_{15}OBr$: C, 58.44. H, 5.66. Found: C, 58.47; H, 5.73.

Stability of 7t to Reaction Conditions.—Ethereal 2.17 *M* phenylmagnesium bromide (0.03 ml, 0.075 mmol) was added to a cold solution of 10 mg (0.038 mmol) of bromoepoxide **7t** in 0.25 ml of dry ether under N_2. The mixture was stirred at ice-bath temperature for 30 min and 0.032 ml (0.075 mmol) of Br_2 in 0.04 ml of dry CH_2Cl_2 was added. After an additional 1 hr of stirring at ice-bath temperature, the mixture was worked up as described and analyzed by vpc[6] under conditions that were capable of separating and allowing identification of **5**, **7t**, **7c**, and **9**. Only unchanged **7t** was detected.

Catalytic Hydrogenolysis of 7c.—A solution of 100 mg (0.37 mmol) of bromoepoxide **7c** in 2 ml of MeOH was injected into a suspension of 50 mg (0.60 mmol) of $NaHCO_3$ and 50 mg of 5% Pd/C catalyst in 2 ml of MeOH which had been presaturated with H_2. The mixture was stirred vigorously for 5 min under 1 atm of H_2 at room temperature, then rapidly filtered. Analysis by nmr and vpc[6] of the isolated organic product indicated about 90% of **2** and about 5% each of **17** and of remaining **7c**.

When bromoepoxide **7c** was similarly treated under more drastic conditions, with its own weight of catalyst for 15 min, and the product was analyzed by nmr and vpc,[6] the components present and their amounts were similar to those found in the subsequently described hydrogenation of **2**.

Catalytic Hydrogenation of 2.—A solution of 300 mg (1.60 mmol) of allylic alcohol **2** in 5 ml of MeOH was injected into a slurry of 150 mg of 5% Pd/C catalyst in 10 ml of MeOH which had been presaturated with H_2, and stirred under 1 atm of H_2 at room temperature for 110 min Filtration and concentration gave material shown by nmr to be essentially free of starting material. Analysis by vpc[6] at 180° showed three components, with retention times of 3.0 (**17**, *ca.* 50%), 4.5 (**18a**, *ca.* 25%), and 5.1 min (**18b**, *ca.* 25%). Subsequent experiments indicated that **18b** was actually formed more rapidly than **18a** but was also hydrogenolyzed more rapidly to **17**. The above mixture was chromatographed on 12 g of neutral Al_2O_3 (2% H_2O added) as follows.

Elution with hexane gave 129 mg (46.5%) of **17** as an oil whose vpc retention time at 180° was 3.0 min; ir no OH absorption; nmr δ 0.66 (3 H, d, J = 7 Hz), 1.1–2.3 (9 H, complex), 2.75 (1 H, m), 7.1 (5 H, s).

Early fractions eluted with 25% ether in hexane provided 26 mg (14%) of **18a** as an oil whose vpc retention time at 180° was 4.5 min; ir 3620 cm^{-1}; nmr δ 0.56 (3 H, d, J = 6 Hz), 1.1–2.3 (10 H, complex), 7.0–7.8 (5 H, complex). This material was identical with a sample prepared as described below by addition of phenylmagnesium bromide to 2-methylcyclohexanone.

Later fractions eluted with 25% ether in hexane afforded 32 mg (17%) of **18b** as an oil whose vpc retention time at 180° was 5.1 min; ir 3620 cm^{-1}; nmr δ 0.62 (3 H, d, J = 7 Hz), 1.0–2.3 (10 H, complex), 7.0–7.45 (5 H, complex.)

2-Methyl-1-phenylcyclohexanol (18a).[16]—Ethereal 2.0 *M* phenylmagnesium bromide (27 ml, 54 mmol) was added dropwise to a stirred solution of 5.0 g (45 mmol) of 2-methylcyclohexanone in 15 ml of anhydrous ether at ice-bath temperature. The solution was stirred for 1 hr at room temperature and hydrolyzed with basic saturated aqueous NH_4Cl. Fractional distillation of the isolated organic material at 95–96° (*ca.* 0.20 mm) gave 8.5 g (61%) of colorless liquid. One of the distillation fractions, shown by vpc[6] to consist of **18a** with less than 5% of **18b** present, gave ir and nmr spectra identical with those of **18a** produced by hydrogenation of **2**.

Catalytic Hydrogenolysis of 7t.—Hydrogenolytic treatment of **7t** for 5 min under the milder conditions described for **7c** gave material which nmr and vpc analysis indicated to consist of *ca.* 70% **7t** and 30% **17**. Under the more drastic treatment described for **7c**, **7t** yielded material whose nmr spectrum indicated complete loss of **7t**, with conversion principally to **17**, accompanied by smaller amounts of **18a** and **18b** and two materials believed to be epimers of **19** (singlets at δ 0.91 and 1.07).

Registry No.—**2**, 35639-05-5; **5**, 35639-06-6; **7c**, 35639-07-7; **7t**, 35639-08-8; **9**, 35639-09-9; **14**, 17206-

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(25) L. H. Groves and G. A. Swan, *J. Chem. Soc.*, 871 (1951).

(26) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 3782 (1962).

29-0; **15**, 35639-11-3; 2-methyl-3-phenylcyclohexanone, 18018-02-5; 2-methyl-3-phenylcyclohexanone (DNP), 18018-03-6.

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Decarboxylation of Halogenated 2-Oxetanones

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Halogenated 2-oxetanones are less susceptible to decarboxylation than other 2-oxetanones. A trichloromethyl substituent in the 4 position of the 2-oxetanone ring severely inhibits decarboxylation. The decarboxylation of 2-oxetanones derived from the cycloaddition of halogenated ketenes and chloral over an electrically heated wire produces halogenated allenes. This method provides a useful synthesis for trichloromethylallenes.

It is well known that 2-oxetanones are quite susceptible to thermal decarboxylations to yield olefinic compounds.[1,2] However, the effect of substituents such as a halogen on the rate of thermal decarboxylations is relatively unknown. In our investigations concerning the cycloaddition of halogenated ketenes and carbonyl compounds to produce 2-oxetanones we have prepared a number of halogenated 2-oxetanones. It was of interest to study the decarboxylation of these compounds and determine the effect of halogen and other electronegative substituents on the thermal stability of the 2-oxetanones. Consequently, the purpose of this paper is to relate the results of our study on the decarboxylation of halogenated 2-oxetanones. A preliminary report describing a novel method for the preparation of some trichloromethylallenes has appeared.[3]

Preparation of Halogenated 2-Oxetanones.—We have recently reported the cycloaddition of dichloroketene with several simple ketones to produce 3,3-dichloro-2-oxetanones.[4] The generation of dichloroketene by the triethylamine dehydrochlorination of dichloroacetyl chloride in the presence of activated carbonyl compounds also yields 2-oxetanones.[5] This method has been applied to the cycloaddition of bromochloroketene with certain aldehydes to produce 3-bromo-3-chloro-2-oxetanones.

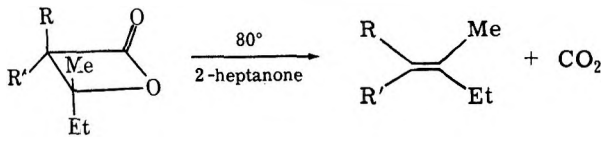
The 3,3-dichloro-2-oxetanones may be selectively reduced with tri-*n*-butyltin hydride to the corresponding monochloro-2-oxetanones. The reduction may also be effected to produce the nonhalogenated-2-oxetanones.

Alkylchloroketenes also undergo *in situ* cycloadditions but only with activated carbonyl compounds such as chloral to yield the expected 2-oxetanones. We have also previously described the cycloaddition of chloroketene with chloral at room temperature to yield both *cis*- and *trans*-2-oxetanones.[6] We have since found that conducting this reaction at −78° and allowing warming to room temperature produces only the trans isomer.

Decarboxylations.—The effect of halogen in the 3 position upon the rate of decarboxylation was easily determined by comparing the rates of decarboxylation of the compounds in Table I. The relative rates represent the time required for 50% decarboxylation. The decarboxylation was measured by observing the disappearance of the carbonyl band in the infrared using the carbonyl band of the solvent, 2-heptanone, as an internal standard.

TABLE I

EFFECT OF CHLORO SUBSTITUENT IN 3 POSITION ON RATE OF DECARBOXYLATION



Compd	R	R'	Relative rate
I	H	H	>100
II	H	Cl	6
III	Cl	Cl	1

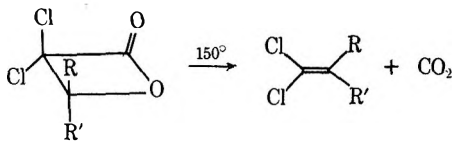
(1) H. E. Zaugg, *Org. React.*, **8**, 305 (1954).
(2) Y. Etiene and N. Fiacher, "Heterocyclic Compounds," Vol. XIX, Part 2, A. Weissberger Ed., Interscience, New York, N. Y., 1964 pp 729–880.
(3) W. T. Brady and A. D. Patel, *J. Chem. Soc. D*, 1642 (1971).
(4) W. T. Brady and A. D. Patel, *J. Heterocycl. Chem.*, **8**, 739 (1971).
(5) D. Borrmann and R. Wegler, *Chem. Ber.*, **102**, 64 (1969).
(6) W. T. Brady and L. Smith, *J. Org. Chem.*, **36**, 1637 (1971).

A further comparison of the effect of chloro substituents in the 3 position was observed when 3,3-dichloro-4-ethyl-4-methyl-2-oxetanone, III, did not decarboxylate in water up to 50° whereas isovalerolactone (4,4-dimethyl-2-oxetanone) readily decarboxylated at room temperature.[7]

Similarly, the effect of a chloromethyl substituent in the 4 position on the rate of decarboxylation can be seen in Table II. The relative rates represent the time

TABLE II

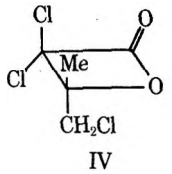
EFFECT OF CHLOROMETHYL SUBSTITUENT IN 4 POSITION ON RATE OF DECARBOXYLATION



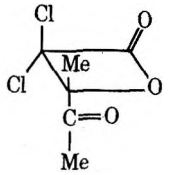
Compd	R	R'	Relative rate
III	Me	Et	116
IV	Me	CH_2Cl	17
V	CH_2Cl	CH_2Cl	1

required for completion of 50% of the reaction. The rate of decarboxylation was measured by observing the disappearance of 2-oxetanones and appearance of olefin by vpc.

The rate of decarboxylation of the 2-oxetanones derived from dichloroketene and chloroacetone and dimethylglyoxal, IV and VI, was compared at 170° and the rates were approximately the same. Presumably, the attainment of a conjugated system in VI upon de-

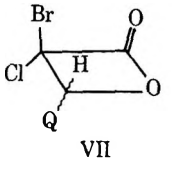


IV

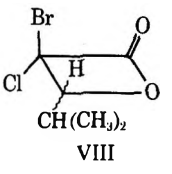


VI

carboxylation serves as a driving force for the decarboxylation. This ease of decarboxylation was also observed when the 2-oxetanones obtained from bromochloroketene and benzaldehyde and isobutyraldehyde, VII and VIII, were prepared. Compound VII could



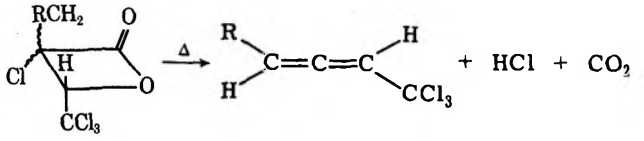
VII



VIII

not be distilled under reduced pressure as decarboxylation occurred at ~100° to yield the corresponding styrene derivative, while VIII could be isolated and did not appreciably decarboxylate prior to ~160°.[8]

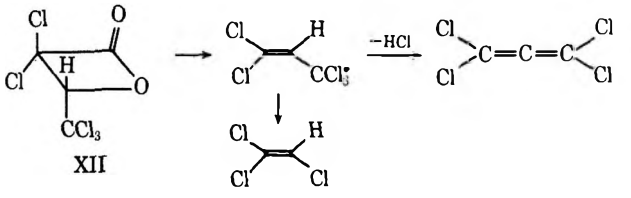
The decarboxylation of the 2-oxetanones derived from methylchloroketene and chloral and *p*-chlorobenzaldehyde and *sym*-dichlorotetrafluoroacetone did not take place up to 250°. However, decarboxylation of the cycloadducts of alkylchloroketene and chloral did take place over an electrically heated wire but this elimination was accompained by a dehydrochlorination to yield trichloromethylallenes in 40–60% yields. No



IX, R = H
X, R = Me
XI, R = Et

evidence of the olefin was found in any system. A consideration of the order of the two elimination steps suggests that the dehydrochlorination preceded the decarboxylation.

The 2-oxetanone obtained from dichloroketene and chloral, XII, was likewise very resistant to decarboxylation. However, refluxing XII over an electrically heated wire produced a mixture of products including the expected olefin, 1,1,1,3,3-pentaehloropropene, the allene, the allene dimer, and trichloroethylene. The perchloroallene was observed in a Dry Ice–acetone trap at −78° as evidenced by a band in the infrared at 1962

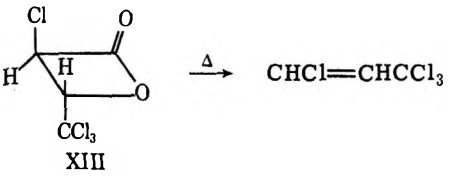


XII

cm^{-1};[9] this band disappeared upon warming to room temperature but the allene dimer was isolated.[10]

The olefin, 1,1,1,3,3-pentachloropropene, dehydrochlorinates under the reaction conditions to yield perchloroallene which dimerizes upon warming to room temperature.

The cycloadduct obtained from chloroketene and chloral, XIII, was also quite resistant to decarboxylation. However, decarboxylation did occur as above but the corresponding olefin, 1,1,1,3-tetrachloroethene, was produced in 80% yield. A trace of allene (trichloroallene) was observed in the cold trap at −78° as evidenced by a band in the infrared at 1962 cm^{-1}.[11]



XIII

However, this was a much weaker band than in the previous system. This decarboxylation was conducted on the *trans*-2-oxetanone and an equal mixture of the two isomeric olefins was obtained.

(7) T. L. Gresham, J. E. Jansen, F. W. Shaver, and W. L. Beears, *J. Amer. Chem. Soc.*, **76**, 486 (1954).

(8) Both isomers of VII and VIII were produced in the cycloaddition reaction in approximately equal amounts and decarboxylation yielded both isomers of the olefin.

(9) A. Roedig, F. Bischoff, B. Heinrich, and G. Markl, *Justus Liebigs Ann. Chem.*, **670**, 8 (1963).

(10) A. Roedig and P. Bernemann, *ibid.*, **600**, 1 (1956).

(11) A. Roedig and N. Detzer, *Angew. Chem., Int. Ed. Engl.*, **7**, 471 (1968).

Conclusions

It is very apparent from our studies that any electronegative substituent on the 2-oxetanone ring decreases the rate of decarboxylation. However, if conjugation results from decarboxylation, this seems to serve as a driving force for the elimination and decarboxylation occurs more readily than expected. The presence of a trichloromethyl substituent on the 4 position of the 2-oxetanone ring severely inhibits decarboxylation. This is perhaps an indication of the mechanism of the elimination reaction and suggests some charge separation whereby the 4 carbon assumes some positive character. Decarboxylation of the alkylchloroketene chloral adducts over an electrically heated wire provides a useful synthesis for these exotic trichloromethylallenes.

Experimental Section

Nuclear magnetic resonance (nmr) spectra were recorded on a Jeolco Minimar 60-Mcps or Jeolco NMR PS 100-Mcps spectrometer. An F & M Scientific Model 700 gas chromatograph with columns of 10% SE-30 on Chromosorb W (DMSC) 60–80 mesh was used for analytical purposes.

Ether and hexane were distilled from sodium immediately prior to use as solvents. The acid halides were commercially available or prepared from the corresponding acid and thionyl chloride except for bromochloroacetyl chloride which was prepared by the general procedure of Crompton and Vanderstichele.[12]

The preparation of the 2-oxetanones derived from dichloroketene and methylethyl ketone, chloroacetone and *sym*-dichloroacetone, as well as the adduct from methylchloroketene and chloral have been described by us.[4] The 2-oxetanone from dichloroketene and chloral has been reported by Borrmann and Wegler.[5]

3-Chloro-4-ethyl-4-methyl-2-oxetanone (II).—A solution of 0.05 mol of freshly distilled tri-*n*-butyltin hydride in hexane was slowly added to a stirred solution of 0.05 mol of III in hexane. The reaction solution was kept cool by cold water. After it stirred for 2 hr, the hexane was evaporated under reduced pressure and the residue distilled at 40–43° (1.5 mm) in quantitative yield. Both cis and trans isomers were obtained in approximately equal amounts: ir 1865 cm^{-1} (C=O); nmr (CCl_4) δ 1.0 (t, 3 H), 1.5 (2 s of cis and trans isomers, 3 H), 1.80 (m, 2 H), and 4.92 (s, 1 H).

Anal. Calcd for $C_6H_9ClO_2$: C, 48.48; H, 6.66. Found: C, 48.36; H, 6.53.

4-Ethyl-4-methyl-2-oxetanone (I).—A solution of 0.05 mol of tri-*n*-butyltin hydride in hexane was added to a solution of 0.025 mol of III and 0.1 g of azobisisobutyronitrile in hexane. The reaction solution was cooled by cold water. After it stirred for 2 hr, the solvent was removed under reduced pressure and I distilled at 60–65° (10 mm) [lit.[13] 60° (10 mm)].[13]

3,3-Dichloro-4-acetyl-4-methyl-2-oxetanone (VI).—A solution of 1.5 mol of triethylamine in 300 ml of hexane containing 1.5 mol of dimethylglyoxal was stirred while a solution of 1 mol of dichloroacetyl chloride in hexane was added at room temperature. After completion of the addition, the reaction mixture was stirred 4 hr and then filtered. The solvent was removed under reduced pressure and VI distilled at 85° (3 mm) (40% yield): ir 1870 cm^{-1} (C=O); nmr (CCl_4) δ 1.85 (s, 3 H) and 2.4 (s, 3 H).

Anal. Calcd for $C_6H_6Cl_2O_3$: C, 36.58; H, 3.08. Found: C, 36.33; H, 2.92.

3-Bromo-3-chloro-4-phenyl-2-oxetanone (VII).—The same procedure was employed as described above for VI except bromochloroacetyl chloride was added to a solution containing benzaldehyde. Prior to vacuum distillation the residue revealed a band in the ir at 1870 cm^{-1}. The nmr spectrum of this residue after complete removal of the solvent revealed a singlet at δ 5.66 and a singlet at 6.0 in equal amounts for the methinyl hydrogens in both isomers. Distillation resulted in decarboxylation and β-bromo-β-chlorostyrene was obtained in 35% overall yield at 80° at 0.5 mm: ir 1600 cm^{-1}; nmr (CCl_4) δ 6.95 and 7.05 (2 s of cis and trans isomers, 1 H) and 7.25 (m, 5 H).

Anal. Calcd for C_8H_6BrCl: C, 44.14; H, 2.75. Found: C, 44.18; H, 2.61.

3-Bromo-3-chloro-4-isopropyl-2-oxetanone (VIII).—The same procedure was employed as described above for cycloaddition with benzaldehyde. Vacuum distillation afforded a 20% yield of two isomers in equal amounts at 60° (0.5 mm): ir 1872 cm^{-1} (C=O); nmr (CCl_4) δ 1.15 (d, 6 H), 1.93 (*m*, 1 H), and 4.26 and 4.40 (2 d for cis and trans isomers, 1 H).

Anal. Calcd for $C_6H_8BrClO_2$: C, 31.63; H, 3.43. Found: C, 31.23; H, 3.41.

3-Chloro-3-ethyl-4-trichloromethyl-2-oxetanone (X).—The same procedure was employed as described for IX.[4] This 2-oxetanone was obtained at 72–75° (0.5 mm) in 50% yield: ir 1875 cm^{-1} (C=O); nmr (CCl_4) δ 1.23 (t, 3 H), 2.5 (m, 2 H), and 4.82 and 5.18 (2 s, 1 H).

Anal. Calcd for $C_6H_6Cl_4O_2$: C, 28.57; H, 2.38. Found: C, 28.52; H, 2.33.

3-Chloro-3-*n*-propyl-4-trichloromethyl-2-oxetanone (XI).—The same procedure was employed as described for IX.[4] This 2-oxetanone was obtained at 72–78° (0.5 mm) in 45% yield: ir 1875 cm^{-1} (C=O); nmr (CCl_4) δ 1.0 (m, 3 H), 1.7 (m, 4 H), and 4.82 and 5.18 (2 s, 1 H).

Anal. Calcd for $C_7H_8Cl_4O_2$: C, 31.57; H, 3.00. Found: C, 31.61; H, 3.05.

***trans*-3-Chloro-4-trichloromethyl-2-oxetanone (XIII).**—The *in situ* cycloaddition of chloroketene and chloral at room temperature produces both cis and trans isomers as we have previously described.[6] The following procedure produces only the trans isomer as evidenced by the nmr coupling constant (J = 3 cps) of the methinyl protons.

A solution of 1 mol of triethylamine in 200 ml of hexane was cooled to −78° and then 1 mol of chloroacetyl chloride added dropwise. After the addition was complete, the reaction mixture was stirred at this temperature for 15–20 min and then 1.5 mol of chloral was added. After the mixture warmed to room temperature, the salt was removed by filtration, the filtrate concentrated, and the residue vacuum distilled to yield only *trans*-3-chloro-4-trichloromethyl-2-oxetanone.

Decarboxylation of I, II and III.—Three solutions of 1.5 g of 2-heptanone containing 1.5 g each of I, II, and III were decarboxylated at 80° in an oil bath. The rate of decarboxylation was determined by observing the disappearance of the 2-oxetanone carbonyl band in the ir at 5.4 mM. The carbonyl band of 2-heptanone at 5.85 mM was used as an internal standard. The relative rates were 1:6:>100 for III, II, and I, respectively.

Decarboxylation of III, IV, and V.—A 3-g portion of each of the 2-oxetanones, III, IV, and V, was thermally decarboxylated at 150° in an oil bath. The rate of decarboxylation was determined by vpc analysis by observing the disappearance of 2-oxetanone and appearance of the olefin. The relative rates were found to be 1:17:116 for V, IV, and III, respectively.

Decarboxylation of IX. Trichloromethylallene.—A 24-g (0.1 mol) portion of IX was pyrolyzed in a ketene generator at 1.5–2 mm as the 2-oxetanone was slowly refluxed over the electrically heated red hot filament. After about 2 hr, trichloromethylallene was isolated from a Dry Ice–acetone trap in the system. Distillation afforded 9.4 g (60%) of the allene at 80–82°: ir 1601 (vs) and 1965 cm^{-1} (w); nmr (CCl_4) δ 5.36 (d, 2 H) and 6.03 (s, 1 H).

Anal. Calcd for $C_4H_3Cl_3$: C, 30.47; H, 1.94; mol wt, 156. Found: C, 30.32; H, 1.91; mol wt, 156 (by mass spectrometry).

Decarboxylation of X. 1,1,1-Trichloro-2,3-pentadiene.—The pyrolysis was effected as described above for IX and the allene was obtained in a 50% yield. Purification was accomplished by preparative vpc: ir 1600 cm^{-1}; nmr (CCl_4) δ 1.75 (d, 3 H), 6.12 (q, 1 H), and 6.32 (s, 1 H).

Anal. Calcd for $C_5H_5Cl_3$: C, 34.98; H, 2.90; mol wt, 170. Found: C, 35.16; H, 2.79; mol wt, 170 (by mass spectrometry).

Decarboxylation of XI. 1,1,1-Trichloro-2,3-hexadiene.—The same procedure was employed as described above for IX and the allene was obtained in 40% yield and purified by preparative vpc: ir 1600 cm^{-1}; nmr (CCl_4) δ 1.0 (t, 3 H), 2.13 (m, 2 H), 6.08 (t, 1 H), and 6.22 (s, 1 H).

Anal. Calcd for $C_6H_7Cl_3$: C, 38.81; H, 3.77; mol wt, 184. Found: C, 38.66; H, 3.65; mol wt, 184 (by mass spectrometry).

Decarboxylation of XII.—A 26-g (0.1 mol) portion of XII was pyrolyzed under the same conditions as described above. The products of the pyrolysis were collected in a Dry Ice–acetone trap at −78°. There was a strong band in the ir at 1962 cm^{-1} at low temperature which disappeared upon warming to room tempera-

(12) H. Crompton and P. Vanderstichele, *J. Chem. Soc.*, **117**, 691 (1920).
(13) H. J. Hagemeyer, *Ind. Eng. Chem.*, **41**, 765 (1949).

ture. Distillation afforded 7.5 g (35%) of 1,1,1,3,3-pentachloropropene, 1.7 g (13%) of trichloroethylene, and 1.8 g (11%) of perchloroallene dimer which crystallized from the residue of the distillation, mp 90–91° (lit.[9] 90–91°). The ir spectrum was identical with that reported in the literature.[9]

Pyrolysis of 5 g of 1,1,1,3,3-pentachloropropene under identical conditions at 25-mm pressure produced products in the Dry Ice–acetone trap which gave a band in the ir at 1962 cm^{-1} at low temperature.

Decarboxylation of XIII.—A 20-g (0.09 mol) portion of XIII was pyrolyzed in a ketene generator under reduced pressure as described above. A 13-g (80%) portion of 1,1,1,3-tetrachloropropene was isolated from the Dry Ice trap. This olefin was approximately an equal amount of cis and trans isomers as evidenced by the nmr coupling constants for the vinyl protons.[14]

(14) R. Fields, R. N. Haszeldine, and D. Peter, *J. Chem. Soc. C*, 165 (1969).

Registry No.—I, 4288-03-3; *cis*-II, 35589-64-1; *trans*-II, 35621-77-3; III, 34624-15-2; IV, 34499-08-6; V, 34499-11-1; VI, 35621-81-9; *cis*-VII, 35621-82-0; *trans*-VII, 35621-83-1; *cis*-VIII, 35621-84-2; *trans*-VIII, 35621-85-3; *cis*-X, 35621-86-4; *trans*-X, 35621-87-5; *cis*-XI, 35621-88-6; *trans*-XI, 35621-89-7; *trans*-XIII, 28186-54-1; *cis*-β-bromo-β-chlorostyrene, 35621-91-1; *trans*-β-bromo-β-chlorostyrene, 35621-92-2; trichloromethylallene, 34819-62-0; 1,1,1-trichloro-2,3-pentadiene, 34819-63-1; 1,1,1-trichloro-2,3-hexadiene, 34819-64-2.

Acknowledgments.—The authors would like to express their appreciation to the Robert A. Welch Foundation and the North Texas State University Faculty Research Fund for their generous support of this work.

A Novel Variant of the Favorskii Reaction[1]

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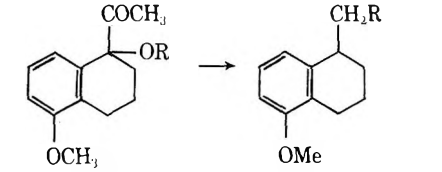
Received May 2, 1972

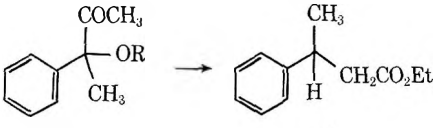
The first examples of α-hydroxy ketones undergoing the Favorskii reaction are presented. The alcohols 1-acetyl-1-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene (**1a**) and 3-phenyl-3-hydroxy-2-butanone (**2a**) undergo the rearrangement with NaH in diethyl carbonate to give the esters ethyl 5-methoxy-1,2,3,4-tetrahydronaphthalene-1-acetate (**3a**) and ethyl 3-phenylbutyrate (**4**), respectively. Possible mechanisms are discussed, and a cyclopropanone intermediate has been verified by the use of the ^{18}O-labeled ketone (**2a**).

Apart from α-halo ketones,[2] there is only one reported instance[3] of an effective α leaving group (2,3-epoxy ketones) generating the necessary intermediate, under the right experimental conditions, to yield the "Favorskii" type of products. We now wish to report a demonstration that the α-hydroxy ketones **1a** and **2a** can undergo the Favorskii rearrangement under suitable conditions.



1a, R = H
b, R = Ac

3a, R = COOEt
b, R = COOH
c, R = CH_2OH



2a, R = H
b, R = CH_3

4

The α-hydroxy ketone **1a** was prepared by the mercury-catalyzed hydration of 1-ethynyl-1-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene, which in turn was obtained from 5-methoxy-1-tetralone and acetylenemonomagnesium bromide.[4] Treatment of **1a** with NaH in diethyl carbonate at 100° under N_2 gave (instead of the desired Claisen condensation) the ester **3a** in nearly quantitative yield. The structure **3a** was confirmed by hydrolysis to the corresponding acid **3b**, and also by its reduction to the alcohol **3c** (3,5-dinitrobenzoate). Under the same conditions, the analogous open-chain alcohol **2a** was converted to **4** and identified by comparison (tlc and ir) with an authentic sample.

It is generally believed that the Favorskii reaction of an α-halo ketone with an α′ hydrogen atom occurs *via* a symmetrical (cyclopropanone)[5] intermediate, whereas α-halo ketones devoid of an α′ hydrogen follow a semibenzilic mechanism.[6]

The cyclopropanone mechanism is feasible in the present instance and could operate if the tertiary alcohol **2a** were converted into a carbonate leaving group. This could occur (Scheme I) by base-catalyzed transesterification with diethyl carbonate to form a mixed carbonate ester, with loss of ethoxide ion. Proton abstraction from the α-methyl group and internal attack with displacement of carbonate ion would then give the cyclopropanone **5**. Attack by ethoxide ion and collapse of the intermediate **6** by cleavage of bond a to afford the rearranged ester **4** correlates well with the expected[7] greater stability of the benzylic carbanion **8** over the primary carbanion **9** formed by fission of bond b. No trace of the isomeric ester **7** was found.

The semibenzilic mechanism, proceeding *via* an intermediate dianion, which was originally proposed[6] only for α-halo ketones without an α′ hydrogen, has in fact been shown[8] to occur also in α-halo ketones with an

(1) Acknowledgment is made to the U. S. Public Health Service (Grant No. MH-04582) for financial support.

(2) A. S. Kende, *Org. React.*, **11**, 261 (1960).

(3) H. O. House and W. F. Gilmore, *J. Amer. Chem. Soc.*, **83**, 3972 (1961).

(4) L. Skattebøl, *Tetrahedron*, **21**, 1357 (1965).

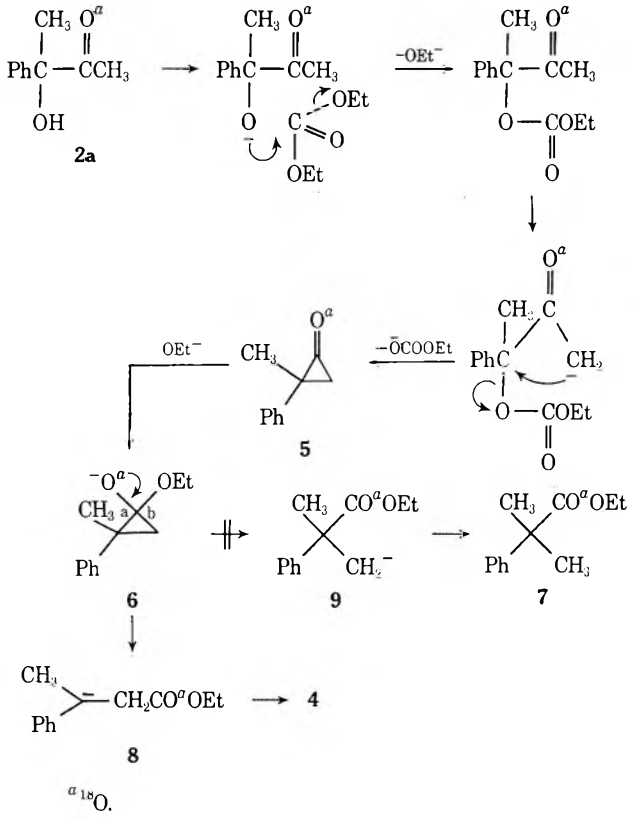
(5) R. B. Loftfield, *J. Amer. Chem. Soc.*, **72**, 632 (1950); **73**, 4707 (1951).

(6) B. Tchoubar and O. Sackur, *C. R. Acad. Sci.*, **208**, 1020 (1939).

(7) (a) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965. (b) N. J. Turro, *Accounts Chem. Res.*, **2**, 25 (1969).

(8) E. W. Warnhoff, C. M. Wong, and W. T. Tai, *J. Amer. Chem. Soc.*, **90**, 515 (1968).

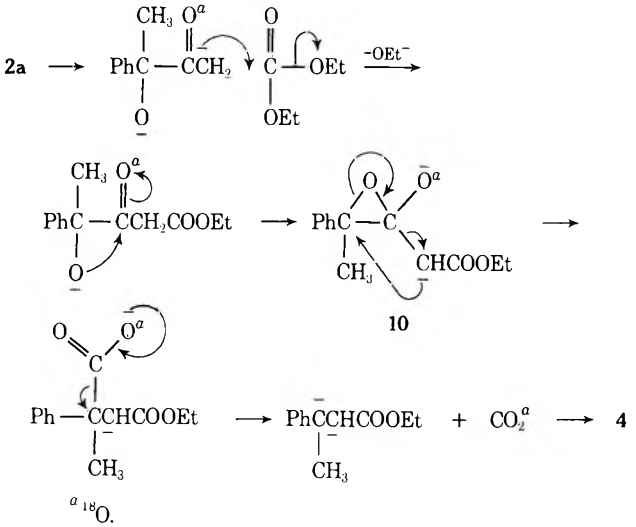
SCHEME I



α' hydrogen atom but is here excluded by reason of the product structure, and the ketene mechanism of Richard[9] is inapplicable in our instances since the tertiary carbon atom bearing the leaving group is incapable of forming the intermediate carbene.

However, an additional possibility exists of the reaction taking place *via* an epoxide mechanism, involving a Claisen condensation with formation of the

SCHEME II



epoxide dianion[10] intermediate **10**, which rearranges with loss of carbon dioxide to give **4** (Scheme II).

(9) G. Richard, *C. R. Acad. Sci.*, **197**, 1432 (1933).

(10) T. M. Harris, S. Boatman, and C. R. Hauser, *J. Amer. Chem. Soc.*, **85**, 3273 (1963).

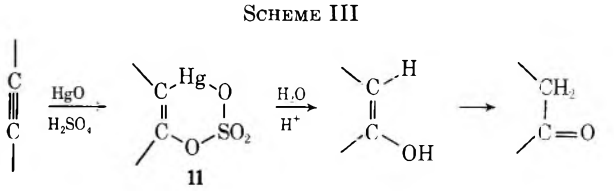
Since the epoxide mechanism cannot be excluded on the basis of product structure, and since both the cyclopropanone and the semibenzilic pathways have recently been shown[8,11] to be applicable, under different experimental conditions, to the *same* compound, it was necessary to distinguish between the two possible mechanisms in the present instance. Such a distinction can be made by the use of **2a** labeled with ^{18}O in the keto group. Mechanism I would result in retention of the isotope in **4** while mechanism II involves loss of isotope as $C^{18}O_2$.

The labeled **2a** was prepared by the hydration of 3-phenyl-3-hydroxy-1-butyne with 10 atom % $H_2{}^{18}O$ and was accompanied by a by-product identified as the corresponding methyl ether **2b**. Although the parent peak in the electron-impact mass spectrum of a tertiary alcohol is either absent or extremely weak,[12] it was possible to use chemical ionization mass spectrometry[13] to determine the amount and location of label in the starting alcohol **2a** and also in the by-product **2b**.[14]

From the differences in the ratios of the $PH^+/(PH^+ + 2)$ peaks between labeled and unlabeled **2a** and **2b**, an incorporation of 8.8 ± 0.4% ^{18}O was calculated. The use of collision-stabilized dimer and trimer peaks permitted an independent check on isotope content. Utilizing the labeled compound **2a**, the isotope peaks of the parent ion minus H_2O indicated that the ^{18}O was still completely present, whereas the isotope peaks of the parent ion minus CH_3CHO indicated total loss of unnatural ^{18}O, clearly showing that the label was all in the carbonyl oxygen.

The observed isotope content of 8.8% ^{18}O in **2a** also casts some additional light on the mechanism of hydration of alkynes.[15] The original 10 atom % ^{18}O will be diluted to 9.65% by the $H_2{}^{16}O$ formed from the reaction of the H_2SO_4 and HgO (see Experimental Section), and this in turn will be diluted to a maximum of ~8.7% by the $H_2{}^{16}O$ generated during the formation of the ether by-product **2b**, if we assume that the rates of formation of **2a** and **2b** are approximately equal.[16] From Scheme III, which shows the generally accepted sequence of

SCHEME III



events in hydrations of this type,[15] it can be seen that hydrolysis of intermediate **11** may occur *a priori* either with S–O or C–O bond cleavage. That the hydrolysis does indeed occur with C–O bond cleavage, as in the case of an alkyl sulfate,[17] is shown by the ^{18}O incorporation results. Attack of $H_2{}^{18}O$ at sulfur followed by S–O cleavage would cause additional ^{16}O incorporation into

(11) J. M. Conia and J. L. Ripoll, *Bull. Soc. Chim. Fr.*, 773 (1963).

(12) R. Silverstein and G. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1968, p 16.

(13) F. Field, *Accounts Chem. Res.*, **1**, 42 (1968).

(14) Our thanks go to Dr. H. M. Fales and to Mr. W. Garland for these measurements, which were carried out at 25° on an MS-9 mass spectrometer.

(15) S. Matsoyan, G. Chukhadzhyan, and S. Vartanyan, *J. Gen. Chem. USSR*, **30**, 1223 (1960).

(16) Monitoring of the reaction *via* tlc showed that some **2b** was formed before all of the alkyne had reacted. Mass spectrometric analysis indicated that within experimental error both **2a** and **2b** had the same ^{18}O incorporation as would be expected if they were formed simultaneously.

(17) E. Bunel, *Chem. Rev.*, **70**, 323 (1970).

2a with dilution of the label to ~7.7% by scrambling all the oxygens of the sulfate with the $H_2{}^{18}O$. Under similar conditions no oxygen exchange between H_2SO_4 and $H_2{}^{18}O$ has been observed.[18] The experimentally found isotope content (8.8% ^{18}O) in both **2a** and **2b** is thus in agreement with a mechanism involving C–O bond cleavage of the intermediate **11**. Experiments using the ^{18}O labeled **2a** showed that the product **4** retained 91 ± 4% of its isotope label, supporting mechanism I.[19]

Experimental Section

1-Acetyl-1-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene (**1a**).—A solution of 0.50 g (2.6 mmol) of 1-ethynyl-1-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene in ethanol was heated to reflux with mercury *p*-toluenesulfonamide[20] (1.0 g) for 18 hr. Hydrogen sulfide gas was bubbled through the cooled solution to decompose the complex, and filtration, evaporation, and recrystallization (hexane) afforded 500 mg (90%) of white crystals: mp 54–54.5°; ir (Nujol) 3400 (OH), 1710 (C=O), 1590 cm^{-1} (OMe); nmr (CCl_4) δ 6.8 (3 H, m, aromatics), 4.1 (1 H, broad s, replaceable OH proton), 3.7 (3 H, s, OCH_3), 3.0–1.5 (6 H, m, methylenes), 1.9 (3 H, s, CH_3CO); mass spectrum peak at *m/e* 220 (M^+), exact mass 220.10989, $C_{13}H_{16}O_3$ requires 220.10994.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.91; H, 7.27. Found: C, 70.77; H,7.33.

This material was also prepared by hydrolysis of **1b** with KOH in ethanol.

1-Acetyl-1-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene 1-Acetate (**1b**).—A mixture of 20 g (0.104 mol) of 1-ethynyl-1-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene and 40 g of mercuric acetate was stirred at room temperature for 24 hr in 900 ml of ethyl acetate. Hydrogen sulfide gas was bubbled through the mixture to decompose the complex and filtration followed by evaporation afforded 17.0 g (61%) of the keto acetate **1b**. Distillation at 130° (0.01 mm) afforded a colorless liquid: ir (neat) 1745 and 1720 (C=O), 1570 cm^{-1} (OCH_3); nmr (CCl_4) δ 7.0 (3 H, m, aromatics), 3.8 (3 H, s, OCH_3), 2.9–1.7 (6 H, m, methylenes), 2.6 and 2.3 (3 H each, s, methyl protons).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.7; H, 6.87. Found: C, 68.89; H, 7.06.

3-Phenyl-3-hydroxy-2-butanone-^{18}O (**2a**).—A mixture of 0.25 g (2.5 mmol) of concentrated H_2SO_4 and 0.5 g of 10 atom % $H_2{}^{18}O$ was poured into 12.5 ml of dry methanol in a 100-ml, three-necked, round-bottom flask and heated to 55° at which time 0.30 g of red HgO was added. A solution of 7.0 g (0.048 mol) of 3-phenyl-3-hydroxy-1-butyne in 12.5 ml of dry methanol containing 0.75 g of 10 atom % $H_2{}^{18}O$ was introduced into the mixture during 1 hr. When half of the alkyne had been added, a further 0.25 g of HgO was introduced.[21] After the addition was complete, the solution was then stirred for 30 min at 55°, cooled, and poured into 200 ml of a NaCl–H_2O solution. Work-up gave 8.0 g of crude liquid. Spinning-band distillation at 60–62° (0.017 mm) gave the pure keto alcohol, 6.0 g (76%), lit.[15] bp 89–91° (2.5 mm). The nmr and ir spectra were in accord with the desired structure.

A lower boiling fraction, 1.5 g (18%) from the distillation, bp 50–52° (0.017 mm), was identified on the basis of its nmr, ir, and mass spectra as 3-phenyl-3-methoxy-2-butanone (**2b**), lit.[22] bp 92° (8 mm).

Ethyl 5-Methoxy-1,2,3,4-tetrahydronaphthalene-1-acetate (**3a**).—1-Acetyl-1-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene (**1a**) (1.1 g, 5 mmol) in diethyl carbonate (3 ml) was added over 3 hr to sodium hydride (1.2 g free from oil) in diethyl carbonate (3 ml) at 100° under N_2. The reaction mixture was stirred for a further 30 min and then cooled and diluted with HOAc (0.5 ml), H_2O (5 ml), and ether (50 ml). The ethereal layer was washed with water, dried ($MgSO_4$), filtered, and evaporated to give an oil (1.2 g, 100%). Distillation at 120° (0.01 mm) gave a colorless liquid: ir (neat) 1745 (ester C=O), 1595 cm^{-1} (OCH_3); nmr (CCl_4) δ 6.8 (3 H, m, aromatics), 4.1 (2 H, q, CH_3CH_2), 3.7 (3 H, s, OCH_3), 3.25 (1 H, broad m, benzylic H), 2.55 and 1.75 (4 H each, m, methylenes), 1.2 (3 H, t, CH_3CH_2).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.58; H, 8.0. Found: C, 72.55; H, 8.19.

The ester was converted to 5-methoxy-1,2,3,4-tetrahydronaphthalene-1-acetic acid (**3b**) in 93% yield by hydrolysis with aqueous sodium hydroxide, mp 145.5–147°, lit.[23] mp 146–147°.

The ester was reduced with $LiAlH_4$ in ether to give 2-(5-methoxy-1,2,3,4-tetrahydronaphthyl)ethyl alcohol (**3c**), the 3,5-dinitrobenzoate of which had mp 105–106°, lit.[23] mp 107–108°.

Ethyl 3-Phenylbutyrate-^{18}O (**4**).—This material was prepared in 29% yield from **2a** under conditions similar to the preparation of **3a**. Its identity was confirmed by nmr and ir comparison with an authentic sample.

The labeled **4** had 8.0% more ^{18}O than a similarly prepared sample of unlabeled **4** as measured by $M^+/(M^+ + 2)$ ratios in their mass spectra. Taking into consideration the amount of ^{18}O in the starting alcohol **2a**, this means the amount of label retained in **4** is in the range of 91 ± 4%.

Registry No.—**1a**, 35031-30-2; **1b**, 35031-31-3; **2a**, 3155-01-9; **3a**, 35026-46-1.

(18) J. Halperin and H. Taube, *J. Amer. Chem. Soc.*, **74**, 375 (1952).

(19) Further support comes from the observation that the acetate **1b** is converted to **3a** with sodium ethoxide in dry benzene (60% yield), conditions under which mechanism II is inoperative.

(20) M. Goldberg, R. Aeschbacher, and E. Hardegger, *Helv. Chim. Acta*, **26**, 680 (1943).

(21) The reaction of the H_2SO_4 and HgO (2.5 mmol of each) produces 2.5 mmol of $H_2{}^{18}O$ which dilutes the $H_2{}^{18}O$ to 9.65 atom % ^{18}O.

(22) D. J. Cram and D. R. Wilson, *J. Amer. Chem. Soc.*, **85**, 1245 (1963).

(23) J. Lockett and W. Short, *J. Chem. Soc.*, 787 (1939).

Notes

Ring-D-Bridged Steroid Analogs. X.[1] Synthesis and Nuclear Magnetic Resonance Spectral Properties of 3β-Acetoxy-14α,17α-ethano-5,15-pregnadien-20-one, 3β-Acetoxy-14α,17α-ethano-5-pregnen-20-one, and 3β-Acetoxy-16,16′-cyclo-14α,17α-ethano-5-pregnen-20-one

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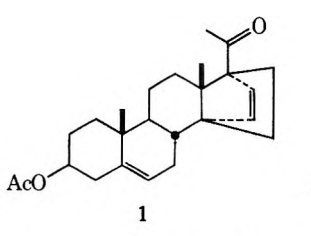
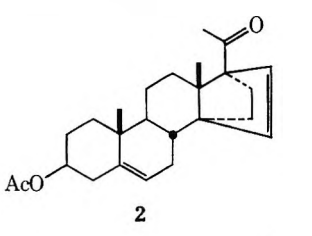
Received May 12, 1972

In a study of the nmr spectra of ring-D-bridged steroid analogs, we noted that the 13β-methyl hydrogens of various substituted 14α,17α,etheno-15-pregnen-20-ones are deshielded by approximately 0.3 ppm relative to those of the corresponding compounds in which the 15,16 double bond or both double bonds are saturated. It seemed of interest to determine empirically whether this deshielding could be caused by the 15,16 double bond of such a bridged steroid or whether it was caused by other factors present in the doubly unsaturated steroids.

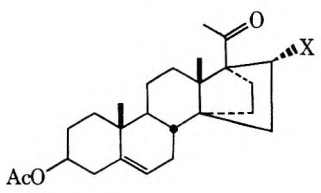
In the course of other studies, we had synthesized 3β-acetoxy-14α,17α-etheno-5-pregnen-20-one (**1**).[2] Selective catalytic hydrogenation of **1** afforded 3β-acetoxy-14α,17α-ethano-5-pregnen-20-one.



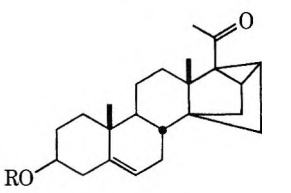
1



2



3, X = I
4, X = CO_2H
5, X = NHC(=O)OMe
6, X = N(N=O)C(=O)OMe



7, R = Ac
8, R = H

As previously reported,[3] treatment of the iodide **3** with potassium hydroxide in refluxing ethanol led only to the hydrolysis of the acetate moiety. In a further attempt to obtain 3β-acetoxy-14α,17α-ethano-5,15-pregnadien-20-one (**2**), we also treated **3** with KO-*t*-Bu in *tert*-butyl alcohol, but we again failed to effect dehydrohalogenation.

3β-Acetoxy-14α,17α-ethano-20-oxo-5-pregnene-16α-carboxylic acid (**4**) was transformed, by a modification of the Curtius rearrangement,[3,4] into the urethane **5**. Dinitrogen tetroxide was used to convert the urethane into the *N*-nitroso derivative **6**.[5] The latter compound was not isolated because it decomposed during work-up to give a difficultly separable mixture of the desired olefin **2** and of an isomeric substance. The latter compound had ir and nmr spectra and melting point virtually identical with those previously observed for a by-product isolated on Hunsdiecker degradation of **4**. A satisfactory analysis had not been obtained for the by-product of the Hunsdiecker reaction, but it had been hydrolyzed to afford a substance analyzing as $C_{23}H_{36}O_3$. In view of its origin[6] and of its properties,[7] we assigned the nortricyclene structure **7** to the by-product isolated from the *N*-nitrosourethane decomposition. A reinvestigation of the $C_{23}H_{36}O_3$ substance showed that it was a monohydrate, since, on reacetylation, it gave **7**, identical in all respects with that formed in the *N*-nitrosourethane formation.

Tables published by Jackman[9] for estimating the long-range shielding effect of a double bond allow one to estimate that a double bond in the α bridge of our system should result in deshielding of the C-18 protons by 0.02–0.13 ppm while a double bond in the β bridge should result in their being shielded by approximately 0.05 ppm. In contrast, calculations by ApSimon's method[10] indicate that a double bond in either bridge should result in deshielding, but that a double bond in the α bridge causes the greater effect (shifts of approximately 0.05 and 0.01 ppm for the α and β bridges, respectively).

The nmr spectra of 3β-acetoxy-14α,17α-ethano-5-pregnen-20-one, 3β-acetoxy-14α,17α-etheno-5-pregnen-20-one (**1**), and 3β-acetoxy-14α,17α-ethano-5,15-pregnadien-20-one (**2**) in $CDCl_3$ had peaks corresponding to the C-18 hydrogens at δ 0.90, 0.90, and 0.89, respectively. While these results are in slightly better accord with the predictions based on Jackman's models than with those based on ApSimon's, the differences

(1) For part IX see A. J. Solo, J. N. Kapoor, S. Eng, and J. O. Gardner, *Steroids*, **18**, 251 (1971).

(2) A. J. Solo and B. Singh, *J. Med. Chem.*, **9**, 957 (1966).

(3) A. J. Solo, B. Singh, E. Shefter, and A. Cooper, *Steroids*, **11**, 637 (1968).

(4) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).

(5) (a) W. M. Jones and D. L. Muck, *J. Amer. Chem. Soc.*, **88**, 3798 (1966); (b) E. H. White, *ibid.*, **77**, 6008 (1955).

(6) (a) E. H. White, *ibid.*, **77**, 6011, 6014 (1955); (b) R. Huisgen and H. Reimlenger, *Justus Liebigs Ann. Chem.*, **599**, 183 (1956); (c) R. H. Shapiro, J. H. Duncan, and J. C. Clopton, *J. Amer. Chem. Soc.*, **89**, 1442 (1967), and references cited therein; (d) C. J. Collins and B. M. Benjamin, *ibid.*, **92**, 3182 (1970).

(7) Note especially the abnormal chemical shift of the C-21 hydrogens of **7** and **8**. We attribute this shift to long-range shielding by the cyclopropyl group.[8]

(8) L. M. Jackman and S. Sternhill, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, pp 98–101, and references cited therein.

(9) Reference 8, pp 83–88, and references cited therein.

(10) J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders, and W. B. Whalley, *Tetrahedron*, **23**, 2357 (1967).

are too small to permit a clear decision between the methods, especially in view of the unknown effect of such substituents as the acetyl group in the steroids.[11] However, these findings do clearly indicate that the anomalous deshielding of the C-18 hydrogens of substituted 14α,17α-etheno-15-pregnen-20-ones cannot be attributed solely to the presence of the 15,16 double bond.[12]

Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. The ir spectra were determined on a Beckman IR-8 spectrophotometer. Nmr spectra were run in $CDCl_3$ on a Varian A-60 spectrometer and are reported in parts per million downfield from a TMS standard.

3β-Acetoxy-14α,17α-ethano-5-pregnen-20-one.—A solution of 120 mg of **1** in 110 ml of ethanol and 5 ml of H_2O was hydrogenated over 30 mg of 10% Pd/C at an initial pressure of 3.16 kg/cm² for 16 hr. Standard work-up afforded 3β-acetoxy-14α,17α-ethano-5-pregnen-20-one in a yield of 68 mg as colorless needles (from ethanol): mp 140–141°; ν^{Nujol} 1739, 1701, 1239 cm⁻¹. The nmr spectrum had peaks at δ 0.90 (s, C-18 H's), 1.04 (s, C-19 H's), 2.02 [s, OC(=O)CH_3], 2.10 (s, C-21 H's), and 5.40 (m, C-6 vinyl H).

Anal. Calcd for $C_{25}H_{26}O_3$: C, 78.08; H, 9.44. Found: C, 78.12; H, 9.50.

3β-Acetoxy-16α-carbomethoxyamido-14α,17α-ethano-5-pregnen-20-one (**5**).—A solution of 1.00 g of **4** in 75 ml of acetone was cooled in an ice bath, and a solution of 0.41 g of triethylamine in 25 ml of acetone was added to it dropwise, with stirring. The resulting solution was stirred for 0.5 hr, and then 0.43 g of ethyl chloroformate in 25 ml of acetone was added dropwise. Stirring was then continued for 1.5 hr. A solution of 0.34 g of NaN_3 in 1 ml of water was then poured into the cold solution. The resulting mixture was stirred for 3 hr and was then concentrated under vacuum. The residue was partitioned between ether and water. The organic layer was dried, filtered, and concentrated. The residue was dissolved in 65 ml of benzene and heated under reflux for 1 hr. After 15 ml of absolute methanol had been added to the hot solution, reflux was continued overnight. The resulting solution was concentrated. The residue crystallized from ethanol to afford **5** in a yield of 0.89 g (66%), as colorless prisms: mp 225–226°; ν^{CHCl_3} 3468, 1720, 1512, 1250–1210, and 1030 cm⁻¹. The nmr spectrum had singlets at δ 1.05 (C-18 and 19 H's), 2.04 [OC(=O)CH_3], 2.18 (C-21 H's), 3.67 (OCH_3), and a multiplet at 5.38 (C-6 H).

Anal. Calcd for $C_{27}H_{29}NO_5$: C, 70.87; H, 8.59; N, 3.06. Found: C, 70.98; H, 8.48; N, 2.97.

3β-Acetoxy-14α,17α-ethano-5,15-pregnadien-20-one (**2**).—A mixture of 475 mg of **5** and 107 mg of NaOAc in 10 ml of ether was stirred and cooled in a Dry Ice–acetone bath while approximately 0.2 ml of N_2O_4 (purified by passage through P_2O_5) was added. Stirring was continued for 1 hr in the cold and then for 10 min at 0°. The inorganic salt was removed by filtration. The filtrate was extracted with 5% aqueous $NaHCO_3$ and then was washed with water. The neutral solution was dried ($MgSO_4$), filtered, and concentrated. The residue, on tlc, appeared to consist of starting material and of two faster moving spots of very similar R_f. The mixture was purified by thick layer chromatography on silica gel. The plates were developed three times with 15% ethyl acetate–85% hexane, and the fast-moving zone was rechromatographed under similar conditions. The fastest moving band gave **2** in a yield of 23 mg, as fine colorless needles from MeOH: mp 120–121°; ν^{CHCl_3} 1725, 1691, 1252, and 1025 cm⁻¹. The nmr spectrum had singlets at δ 0.89 (C-18 H's), 1.04 (C-19 H's), 2.03 [OC(=O)CH_3], and 2.17 (C-21 H's) and peaks corresponding to vinyl hydrogens at δ 5.45 (C-6 H, m), 6.02 (C-15 H, d, J = 6 Hz), and 6.18 (C-16 H, d, J = 6 Hz).

Anal. Calcd for $C_{25}H_{34}O_3$: C, 78.49; H, 8.96. Found: C, 78.68; H, 9.06.

3β-Acetoxy-14α,17α-ethano-16,16′-cyclo-5-pregnen-20-one (**7**). **A.**—Extraction of the second fastest moving band on the tlc of the reaction mixture, which gave **2**, afforded **7**, in a yield of 50 mg, as colorless prisms from MeOH: mp 190–190.5°; ν^{CHCl_3} 1723, 1666, 1253, and 1025 cm⁻¹. The nmr spectrum had singlets at δ 1.01 (C-18 H's), 1.04 (C-19 H's), 1.90 (C-21 H's shielded by cyclopropane), and 2.03 [OC(=O)(CH_3)], and a multiplet corresponding to the C-6 vinyl hydrogen at δ 5.38.

Anal. Calcd for $C_{25}H_{34}O_3$: C, 78.49; H, 8.96. Found: C, 78.51; H, 9.12.

B.—During the work-up of the mixture resulting from Hunsdiecker reaction of **4**, the crude product was chromatographed over alumina and benzene eluted **3**. Further development of the column with 1:1 benzene–ethyl acetate resulted in the elution of a fraction which crystallized from ethanol to give 143 mg (31%) of impure **7** as white crystals, mp 189.5–190.5°.

Anal. Calcd for $C_{25}H_{34}O_3$: C, 78.49; H, 8.96; mol wt, 382.5. Found: C, 76.45, 76.64, 77.38; H, 8.92, 8.80, 8.74; mol wt, 390.

C.—Acetylation of **8**, by the usual method, afforded **7** which crystallized from ethanol as colorless needles identical in melting points, mixture melting point, ir, and nmr with **7** prepared as in A.

3β-Hydroxy-14α,17α-ethano-16,16′-cyclo-5-pregnen-20-one (**8**). —A mixture of 158 mg of **7** (prepared as in B), 300 mg of KOH, 25 ml of MeOH, and 3 ml of H_2O was stirred at room temperature for 48 hr and then under reflux for 6 hr. The mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was partitioned between ether and H_2O. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue crystallized from MeOH to afford **8** as tiny colorless rods, in a yield of 125 mg: mp 183–185°; ν^{Nujol} 3600, 1662 cm⁻¹. The nmr spectrum had singlets at δ 0.98 (C-18 H's), 1.03 (C-19 H's), and 1.87 (C-21 H's shielded by cyclopropane) and a multiplet at δ 5.39 (C-6 H).

Anal. Calcd for $C_{23}H_{32}O_2 \cdot H_2O$: C, 77.05; H, 9.56. Found: C, 77.20; H, 9.61.

Later, 44 mg of **8** was purified by tlc on silica gel. The plate was developed with 20% EtOAc in benzene. The sample isolated (34 mg) was dissolved in ethanol containing 5% benzene and evaporated to dryness under vacuum. This process was then repeated six times. The residue was dried for 3 days at 100° over P_2O_5.

Anal. Calcd for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 79.35; H, 9.53.

Registry No.—**1**, 19605-66-4; **2**, 35639-00-0; **5**, 35639-01-1; **7**, 35639-02-2; **8**, 35639-03-3.

Acknowledgment.—This work was supported, in part, by research grants AM-006900 from the National Institute of Arthritis and Metabolic Diseases and by general research grant 5 S01 FR-05454 from the U. S. Public Health Service.

(11) N. Bhacca and D. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 29.

(12) The methyl hydrogens of 7-methylbicyclo[2.2.1]heptene have been reported to appear in the nmr spectrum (CCl_4) at δ 0.70 for the cis compound and at δ 0.79 (CCl_4) for the trans.[13]

(13) Reference 8, p 84.

A Facile Synthesis of (±)-*ar*-Artemisene *via* Olefin Metalation

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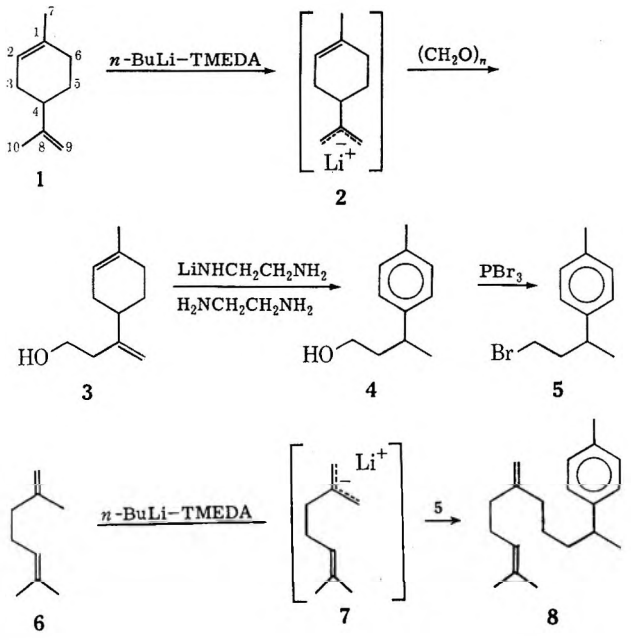
Received May 2, 1972

The monocyclic diterpene hydrocarbon *ar*-artemisene (**8**) was isolated from wormwood oil by Šorm and coworkers in 1951.[1] Its racemate was later synthesized

(1) F. Šorm, M. Suchý, F. Vonášek, J. Plíva, and V. Herout, *Collect. Czech. Chem. Commun.*, **16**, 268 (1951); *Chem. Listy*, **45**, 135 (1951).

by Vig, *et al.*,[2] by three different routes. Although these syntheses are unambiguous and serve to confirm the structure of **8**, they require a large number of steps from readily available materials. This communication reports a simple four-step synthesis of (±)-*ar*-artemisene starting with the hydrocarbons limonene (**1**) and geraniolene (**6**) (Chart I). Two of the steps make use

CHART I



of the olefin metalation process that we have described in detail in the case of limonene.[3]

We have shown that limonene, on reaction with the 1:1 complex of *n*-butyllithium and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), undergoes selective metalation at C-10 to afford the 2-substituted allyllithium species **2**.[3] Treatment of this intermediate with various reagents provides a general synthesis of 10-substituted limonene derivatives, and the products are obtained in high purity after simple distillation. We have now found that geraniolene can be converted in a similar manner to products derived from the intermediate **7**. However, the reaction mixtures from metalation–derivatization of geraniolene usually contain a complex mixture of minor components that must be separated from the major product by preparative glpc.[4]

In the present study, paraformaldehyde was added to a solution of **2** to provide the alcohol **3** in 57% yield.[5] Treatment of **3** with *N*-lithioethylenediamine in refluxing ethylenediamine[7] resulted in smooth conversion to the aromatic alcohol **4** in 72% yield. The bromide **5** was obtained from **4** by a known procedure[8] using phosphorus tribromide. Geraniolene was metalated with *n*-butyllithium–TMEDA under conditions similar to those used for limonene. Addition of the bromide **5** to the solution containing **7** afforded a mixture in which **8** was the major component. The (±)-*ar*-artemisene was purified by preparative glpc and was identified by its spectral properties and by comparison of its ir spectrum with that reported[1,2] for the natural product.

Experimental Section

Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 grating spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian Associates Model HA-100 spectrometer. Chemical shifts are reported in parts per million on the τ scale, with tetramethylsilane as internal standard; coupling constants are in hertz. Nmr data are recorded in the following order: chemical shift, multiplicity (where s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant, interpretation. Samples were run in 1.5-mm-o.d. glass capillary tubes according to the micro-nmr technique developed in these laboratories.[9] Mass spectra were determined on an Atlas CH-4 spectrometer. Gas chromatographic separations were carried out on a Varian Aerograph Model 202-2B instrument equipped with the following columns: column A, 10 ft × 0.25 in. stainless steel packed with 20% SE-30 on 60/80 mesh AW-DMCS Chromosorb W; column B, 10 ft × 0.25 in. stainless steel packed with 20% FFAP on 60/80 mesh AW-DMCS Chromosorb W; column C, 20 ft × 0.375 in. stainless steel packed with 20% Carbowax 20 M on 45/60 mesh AW-DMCS Chromosorb W. Helium was used as the carrier gas, and was operated at a flow rate of 60 ml/min on columns A and B and 150 ml/min on column C. All reactions were run under a static atmosphere of dry argon using an apparatus of the type described by Johnson and Schneider.[10] The procedure for isolation of products following solvent extraction consisted of drying the organic solution over anhydrous sodium sulfate and removal of solvent at reduced pressure on a rotary evaporator. Molecular distillations were carried out in a vertical bulb-to-bulb apparatus. Microanalysis was performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Materials.—*d*-Limonene was obtained from Matheson Coleman and Bell. Geraniolene was prepared in 95% yield by pyrolytic distillation of geranic acid (Fritzsche Bros.) according to the procedure of Bateman, *et al.*[11] *n*-Butyllithium in hexane was supplied by Foote Mineral Co. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) and ethylenediamine were both obtained from Matheson Coleman and Bell and were dried immediately prior to use by distillation from calcium hydride.

3-(4-Methyl-3-cyclohexen-1-yl)-3-buten-1-ol (3).—To a stirred solution of 50.0 ml (0.075 mol) of 1.5 *M* *n*-butyllithium in hexane was added dropwise 11.3 ml (8.8 g, 0.076 mol) of dry TMEDA, followed by 25.0 ml (21.0 g, 0.154 mol) of *d*-limonene. The resulting mixture was stirred for 1 hr and allowed to stand overnight at room temperature. Stirring was resumed, and 3.0 g (0.10 mol) of paraformaldehyde was added in small portions over a period of 30 min. The solution temperature was maintained below 30° during the addition and for a period of 3.5 hr after the addition was complete. Water (50 ml) was added, the layers were separated, and the aqueous solution was extracted with three portions of ether. The combined organic solutions were washed successively with 5% sodium chloride, 1 *M* hydrochloric acid, and 5% sodium chloride solutions, and were dried and evaporated.

(2) (a) O. P. Vig, K. L. Matta, A. Singh, and I. Raj, *J. Indian Chem. Soc.*, **42**, 773 (1965); (b) O. P. Vig, R. Anand, B. Ram, and B. Vig, *Indian J. Chem.*, **5**, 538 (1967); (c) O. P. Vig, J. M. Sehgal, M. M. Mahajan, and S. D. Sharma, *J. Indian Chem. Soc.*, **46**, 887 (1969).

(3) R. J. Crawford, W. F. Erman, and C. D. Broaddus, *J. Amer. Chem. Soc.*, **94**, 4298 (1972).

(4) Although minor products have not been identified, many of them probably arise from competing reactions in the metalation step (*e.g.*, metalation at the trisubstituted double bond or double bond migration followed by reactions of conjugated dienes). Side reactions are virtually insignificant in the metalation of **1**.

(5) This alcohol can also be obtained in comparable yield by acid-catalyzed addition of formaldehyde to limonene.[6] The metalation route offers the advantage that the product is obtained in higher purity.

(6) (a) A. T. Blomquist and R. J. Himics, *J. Org. Chem.*, **33**, 1156 (1968); (b) R. J. Himics, Ph.D. Thesis, Cornell University, Ithaca, N. Y., 1967.

(7) (a) B. N. Joshi, R. Seshadri, K. K. Chakravarti, and S. C. Bhattacharyya, *Tetrahedron*, **20**, 2911 (1964); (b) B. S. Tyagi, B. B. Ghatge, and S. C. Bhattacharyya, *ibid.*, **19**, 1189 (1963); (c) B. S. Tyagi, B. B. Ghatge, and S. C. Bhattacharyya, *J. Org. Chem.*, **27**, 1430 (1962); (d) L. Reggel, S. Friedman, and I. Wender, *ibid.*, **23**, 1136 (1958).

(8) V. K. Honwad and A. S. Rao, *Tetrahedron*, **21**, 2593 (1965).

(9) L. V. Haynes and C. D. Sazavsky, *Appl. Spectrosc.*, **24**, 452 (1970).

(10) W. S. Johnson and W. P. Schneider, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 132.

(11) L. Bateman, J. I. Cunneen, and E. S. Waight, *J. Chem. Soc.*, 1714 (1952).

Distillation of the residue afforded 12.5 g of recovered limonene and 5.89 g (57% based on limonene consumed) of **3** as a colorless oil, bp 72–84° (0.1–0.15 mm) [lit.[6] bp 80–83° (0.2–0.3 mm)], glpc purity 94% (column B, 225°); the ir and nmr spectra were identical with the published spectra of **3**.[6]

3-*p*-Tolyl-1-butanol (4).—To 30 ml of vigorously stirred, anhydrous ethylenediamine at 100–110° was added 0.417 g (0.06 g-atom) of lithium wire in small pieces over a period of 30 min. When the blue color of the solution had disappeared, the mixture was heated to reflux, and a solution of 1.0 g (0.006 mol) of **3** in 5 ml of ethylenediamine was added. The solution was refluxed for 45 min, and then was cooled in ice while 70 ml of water was added. The resulting mixture was extracted with three portions of ether, and the combined extracts were washed with 5% sodium chloride solution, dried, and evaporated to afford 0.90 g of oil. Molecular distillation [bath temperature >60° (0.1 mm)] of this material afforded 0.71 g (72%) of **4** as a colorless oil: glpc purity 94% (column A, 200°); the ir spectrum was in close agreement with published ir data for **4**;[12] nmr ($CDCl_3$) τ 3.02 (s, 4 H, *p*-$CH_3C_6H_4$–), 6.60 (t, 2 H, J = 7 Hz, –CH_2OH), 7.12 (s, 1 H, –OH), 7.25 (m, 1 H, $C_7H_7CHCH_3$–), 7.78 (s, 3 H, *p*-$CH_3C_6H_4$–), 8.27 (q, 2 H, J = 7 Hz, –CH_2CH_2OH), and 8.81 (d, 3 H, J = 7 Hz, $C_7H_7CHCH_3$–).

1-Bromo-3-*p*-tolylbutane (5).—To 0.38 ml (4.0 mmol) of freshly distilled phosphorus tribromide cooled to 0° was added a solution of 0.66 g (4.0 mmol) of **5** in 2 ml of anhydrous petroleum ether. The mixture was stirred at room temperature for 18 hr, and then was poured into 10 ml of cold water. The resulting mixture was extracted with four portions of ether, and the combined extracts were washed twice with water and then dried and evaporated to afford 0.80 g of oil. Molecular distillation [bath temperature >80° (0.07 mm)] of this material afforded 0.38 g (42%) of **5** as a pale yellow oil: glpc purity 92% (column A, 200°); the ir spectrum was in close agreement with published ir data for **5**;[8] nmr ($CDCl_3$) τ 3.00 (s, 4 H, *p*-$CH_3C_6H_4$–), 6.86 (m, 2 H, –CH_2Br), 7.16 (m, 1 H, $C_7H_7CHCH_3$–), 7.77 (s, 3 H, *p*-$CH_3C_6H_4$–), 8.00 (m, 2 H, –CH_2CH_2Br), and 8.80 (d, 3 H, J = 7 Hz, $C_7H_7CHCH_3$–).

(±)-*ar*-Artemisene (2-Methyl-6-methylene-10-*p*-tolyl-2-undecene) (8).—To a stirred solution of 5.0 ml (7.5 mmol) of 1.5 *M* *n*-butyllithium in hexane was added 0.87 g (7.5 mmol) of dry TMEDA followed by 1.86 g (15.0 mmol) of geraniolene (**6**). The resulting mixture was stirred for 3 hr at room temperature, after which a 2.3-ml aliquot was removed, placed in a separate flask, and cooled below 0°. To this aliquot was added dropwise 0.354 g (1.56 mmol) of **5**. The reaction mixture was allowed to warm to room temperature over a period of 45 min, diluted with water, and extracted with three portions of ether. The combined extracts were washed successively with 5% sodium chloride, 1 *M* hydrochloric acid, 5% sodium chloride, 2% sodium bicarbonate, and 5% sodium chloride solutions, and were dried and evaporated. Molecular distillation of the residue afforded 0.245 g (58%) of colorless oil. Glpc analysis of this material (column C, 240°) showed a mixture in which the component with longest retention time (65 min) was a single major constituent representing *ca.* 50% of the total. This substance was purified by preparative glpc (column C, 240°) followed by molecular distillation to afford (±)-*ar*-artemisene as a colorless oil: bp (bath) 110° (0.03 mm) [lit.[2b] bp 110° (4–5 mm)]; glpc purity 100% (column B, 240°); ir (film) 3075 (>C=CH_2), 3050 and 3020 (–C_6H_4–), 3010 (>C=CH–), 1649 (>C=CH_2), 1519 (–C_6H_4–), 1456, 1380, 1311 (w), 1110, 1044 (w), 1026, 990 (w), 894 (>C=CH_2), 822 (*p*-C_6H_4–), and 730 cm^{-1} (this spectrum agrees closely with published ir data for **8**[1,2]); nmr ($CDCl_3$) τ 3.00 (s, 4 H, *p*-$CH_3C_6H_4$–), 4.94 [m, 1 H, –CH=$C(CH_3)_2$], 5.36 (broadened s, 2 H, >C=CH_2), 7.39 (m, 1 H, $C_7H_7CHCH_3$–), 7.75 (s, 3 H, *p*-$CH_3C_6H_4$–), 7.9–8.2 (m, 6 H, allylic –CH_2–), 8.3–8.8 [m, 10 H, including 8.34 and 8.43 (two broadened s, –CH=$C(CH_3)_2$)], and 8.80 (d, 3 H, J = 7 Hz, $C_7H_7CHCH_3$–); mass spectrum (70 eV) *m/e* (rel intensity) 270 (7), 255 (1), 227 (13), 201 (1), 199 (2), 185 (6), 171 (4), 159 (12), 157 (7), 145 (26), 132 (65), 131 (21), 119 (100), 109 (35), 105 (25), 91 (19), 69 (74), 55 (12).

Anal. Calcd for $C_{20}H_{30}$: C, 88.82; H, 11.18. Found: C, 89.01; H, 11.20.

Registry No.—**8**, 19907-39-2.

Acknowledgment.—The technical assistance of Mr. F. W. Vonderahe is gratefully acknowledged.

(12) V. K. Honwad and A. S. Rao, *Tetrahedron*, **20**, 2921 (1964).

The Diels–Alder Dimerization of 2-Pyrone

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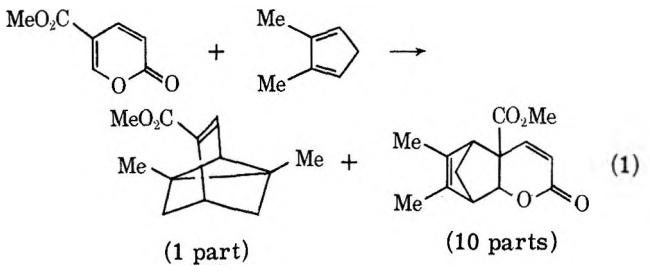
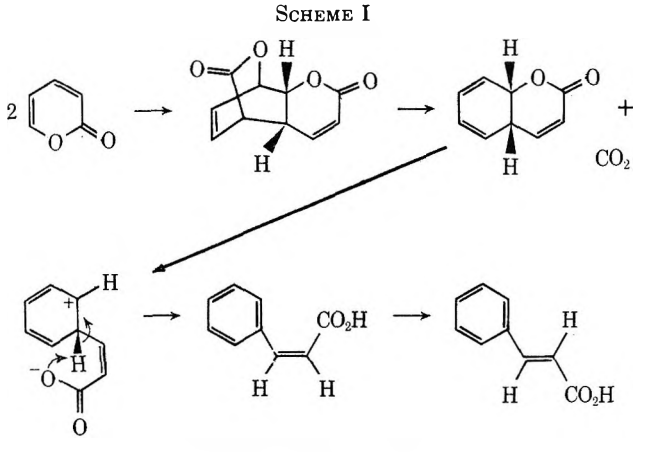
The recent report by Imagawa, *et al.*,[1] concerning reactions in which a 2-pyrone (methyl coumalate) functions as a dienophile (rather than as a diene) in a Diels–Alder reaction (eq 1) prompts us to relate an observation made during the course of our studies of the Diels–Alder reactions between 2-pyrone and group IVB element substituted acetylenes.[2,3] Although the reaction of 2-pyrone proceeded well with acetylenes such as $Me_3SiC{\equiv}CSiMe_3$,[3] $Me_3GeC{\equiv}CGeMe_3$,[3] and $Me_3SnC{\equiv}CSnMe_3$,[2] the expected adduct, 1,2-di-*tert*-butylbenzene, could not be obtained on attempted reaction with di-*tert*-butylacetylene, even after solutions of the reactants in bromobenzene had been heated in a sealed tube at 210° for 5 days. However, a white solid, subsequently identified as *trans*-cinnamic acid by mixture melting point and comparison of its ir and nmr spectra with those of an authentic sample, was isolated from such a reaction mixture in low yield. The formation of this unexpected product was explained[4] in terms of a Diels–Alder reaction of 2-pyrone with itself, the dienophilic C=C bond being the 5,6 double bond as in the examples of the Japanese workers (Scheme I).



SCHEME I



The strenuous reaction conditions would serve to explain the degradative process outlined. Such Diels–

(1) T. Imagawa, N. Sueda and M. Kawanisi, *J. Chem. Soc., Chem. Comm.*, 388 (1972).
(2) A. B. Evnin and D. Seyferth, *J. Amer. Chem. Soc.*, **89**, 952 (1967).
(3) D. Seyferth and D. L. White, *J. Organometal. Chem.*, **34**, 119 (1972).
(4) D. L. White, Ph.D. Thesis, Massachusetts Institute of Technology, 1970.

Alder dimerization of 2-pyrone appears not to have been observed by the previous workers who have studied its chemistry.

In a previous study[2] it had been noted that the reaction of 2-pyrone with $Me_3SnC{\equiv}CSnMe_3$ (and, by implication, with the silicon and germanium analogs) was an example of a Diels–Alder reaction with "inverse electron demand," in which the greater electron density in the dienophile favors the reaction. On this basis, di-*tert*-butylacetylene would be expected to react with 2-pyrone and the failure of this reaction to occur even under forcing conditions can be ascribed primarily, if not solely, to unfavorable steric factors. Support for this idea was given by the observation that diethylacetylene reacts with 2-pyrone to give 1,2-diethylbenzene in ~12% yield (5 days at 180°). The electron density of the triple bond in di-*tert*-butylacetylene would be expected to be greater than that in the triple bond of diethylacetylene, but the steric hindrance associated with the two *tert*-butyl groups would be substantially greater than that due to two ethyl groups. In the absence of a reactive substrate, 2-pyrone then reacts in part with itself as outlined above.

Experimental Section

Attempted Reaction of 2-Pyrone with Di-*tert*-butylacetylene.—Di-*tert*-butylacetylene,[5] 2.5 g (18 mmol), in 20 g of dry bromobenzene and 1.8 g (19 mmol) of 2-pyrone[6] were placed in a 2.5 × 18 cm heavy-walled Pyrex bomb tube. The contents were cooled to −78° and the tube was evacuated to 0.1 mm and sealed. It then was heated to 200 ± 10° for 24 hr. The contents of the tube were cooled to −78°, the tube was opened, and the reaction mixture was charged into a distillation flask. The low boiling components were removed by trap to trap distillation at 0.05 mm (pot temperature to 95°). The residue was short path distilled *in vacuo* to yield 0.2 g of clear, colorless distillate, bp 65–70° (3 mm). Glc analysis of the distillate indicated that only unreacted starting materials were present. Small crystals were observed in the neck of the distillation apparatus. These, plus the pot residue, were sublimed at 100° (0.05 mm), yielding 0.1 g of an off-white solid whose ir spectrum indicated the presence of 2-pyrone ($\nu_{C=O}$ 1745 cm^{-1}) and an α,β-unsaturated carboxylic acid [major bands at 2710 (m), 2600 (m), 2530 (m), 1690 (s), and 1630 (s) cm^{-1}]. Recrystallization of this solid from water gave a white solid, mp 132–133°, whose ir and nmr spectra were identical with those of an authentic sample of *trans*-cinnamic acid. A mixture melting point with authentic material was undepressed, 132–133°.

Reaction of 2-Pyrone with Diethylacetylene (3-Hexyne).—A similar procedure was used in the sealed tube reaction of 0.994 g (12.1 mmol) of 3-hexyne (Farchan Chemicals) and 1.064 g (11.0 mmol) of 2-pyrone in the presence of 0.1 g of hydroquinone in 3 ml of dry benzene for 5 days at 180 ± 10°. After the lower boiling materials had been removed by trap to trap distillation at 1 mm (pot temperature to 95°), the residue was short path distilled to give 0.17 g (12% yield) of 1,2-diethylbenzene, bp 60° (10 mm), contaminated with minor amounts of starting materials and solvent. Purification by glc (F & M 700, 6-ft 20% Carbowax 20M on Chromosorb P, at 150°) gave material whose glc and spectral properties were identical with those of an authentic sample (Aldrich Chemical Co.).

Registry No.—2-Pyrone, 504-31-4; di-*tert*-butylacetylene, 17530-24-4; diethylacetylene, 928-49-4.

Acknowledgments.—The authors are grateful to the National Science Foundation (Grant GP 31429X) for generous support of this work and to the IBM Corp. for the award of a fellowship to D. L. W.

(5) G. F. Hennion and T. F. Bannigan, *J. Amer. Chem. Soc.*, **68**, 1202 (1946).

(6) H. E. Zimmerman, G. L. Grunwald and R. M. Paufler, *Org. Syn.*, **46**, 101 (1966).

Sulfonation of Catechin

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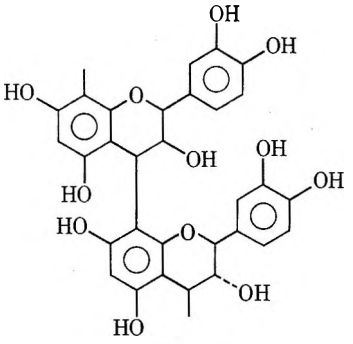
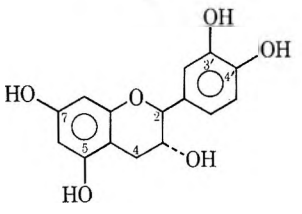
Polyflavanoids of western hemlock bark (*Tsuga heterophylla*) have the structure I, composed of catechin-like units derived from leucocyanidin.[1-3] Extraction of bark with aqueous sodium sulfite–bisulfite yields sulfonated polyflavanoid extracts that have widespread commercial utility.[3] In order to clarify the chemical structure of these materials and to supplement earlier studies,[2,4] a reaction simulating bark extraction conditions was carried out on the flavan catechin (II). No such study has been made on flavans bearing phenolic hydroxyl groups.



I



II

Thin layer chromatographic analysis of material obtained after reaction of catechin with an aqueous solution of sodium sulfite and bisulfite (pH 5.9) for 0.5 hr at 170° showed very little catechin remaining; a spot with low R_f predominated. The acidity of the material and the ease with which it decomposed indicated that sulfonation had occurred. The technique of Gellerstedt and Gierer[5] was used to prepare acetylated methyl sulfonates of the reaction products; a mixture of several components was obtained. Application of an additional acetylation step made one of the products heavily predominant (tlc). Spectral

(1) H. L. Hergert, Abstracts of Papers, 155th National Meeting of the American Chemical Society, San Francisco, Calif., March 31–April 5, 1968, p 21D.

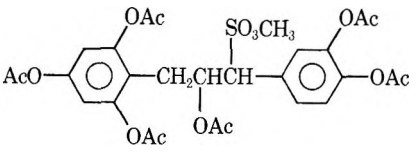
(2) K. D. Sears and R. L. Casebier, *Phytochemistry*, **4**, 359 (1965).

(3) H. L. Hergert, Abstracts of Papers, 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 28–April 2, 1971, Cell. 66.

(4) K. D. Sears and R. L. Casebier, *Chem. Commun.*, 1437 (1968).

(5) G. Gellerstedt and J. Gierer, *Sv. Papperstidn.*, **15**, 117 (1971).

data for this material, purified by tlc, shows it to have structure III.



III

The nmr spectrum and acetyl analysis shows the presence of six acetyl groups. The two protons in the phloroglucinol ring appear as a singlet, as theory would predict, at τ 3.15. The hydrogen on the carbon bearing the sulfonate group is seen as a one-proton doublet at τ 5.23 with the methyl sulfonate absorption being observed as a singlet at τ 6.20. A small amount of the stereoisomeric epimer which differs in configuration about the carbon bearing the methyl sulfonate group is present; a small singlet (τ 6.35, $-SO_2OCH_3$) and doublet (τ 5.33, $-CHSO_2OCH_3$) for the epimer were observed in the nmr spectrum. The ir spectrum shows strong alkyl sulfonate absorption for III at 1370 and 1180 cm^{-1}. An elemental analysis corroborated the molecular formula as $C_{28}H_{30}O_{15}S$. An attempt to obtain a parent peak by mass spectrum failed; the highest mass observed was at *m/e* 596, corresponding to M − 42 (loss of ketene).

On the basis of these results, it is clear that catechin undergoes ready attack by the sulfonate group at C-2 in the pyran ring. Facile introduction of a sulfonic acid group at this position is reasonable, since it is a benzylic carbon involved in ether formation that is activated to attack by a *p*-hydroxyl group; the corresponding position in lignin molecules was also shown to be readily reactive to acidic sulfonation in recent model compound studies.[5-7] Sulfonation at this position is clearly inhibited by methylation of the *p*-hydroxyl group; reaction of a flavan bearing a 4′-methoxyl group with calcium bisulfite at pH 1.5 and 130° resulted in substitution of a sulfonic acid group at C-2 only after 48 hr.[8]

Experimental Section

Nmr spectra were obtained with a Varian T-60 spectrometer and the ir spectra on a Beckman IR-20 spectrophotometer. Analyses were performed by Alfred Bernhardt Microanalytical Laboratories, Elbach über Engelskirchen, West Germany. Decationizations were carried out with Ionac C-242 resin (H^+ form). Evaporations were *in vacuo* (25 mm).

Reaction of D-Catechin (II) with Aqueous Sodium Sulfite–Bisulfite.—D-Catechin (1.000 g), a mixture of sodium metabisulfite (0.130 g) and sodium sulfite (0.060 g), and water (8 ml) were placed in a small stainless steel vessel that was sealed and heated for 0.5 hr at 170°. After cooling, the solution was diluted with water (75 ml) and decationized.

Processing by the General Method of Gellerstedt and Gierer.[5]—The cation-free solution was adjusted to 50 ml by evaporation and neutralized with aqueous barium hydroxide to pH 8.0. After removal of a small amount of precipitate by centrifuging, the solution was decationized. The solution was neutralized with triethylamine to pH 8.0 and evaporated to dryness. The solids were dissolved in pyridine–acetic anhydride (10 ml of each). After 24 hr, the solution was poured into ice water (150 ml) and stirred for 2 hr. This mixture was evaporated at 40–45°, and the residue was dissolved in water and decationized. The solution was neutralized to pH 8.5 with silver acetate and freeze dried, yield 1.30 g.

The sample was placed in a solution of acetonitrile (125 ml) and methyl iodide (25 ml). The mixture was gently refluxed, with stirring, for 20 hr, during which time more methyl iodide (2 × 10 ml) was added. Solids were removed by centrifuging and the filtrate was evaporated to give 0.90 g. Tlc analysis (silica gel G) using 200:47:15:1 (v/v) benzene:ethanol:water:acetic acid (upper layer) (solvent A) or 5:4:1 (v/v) toluene:ethyl acetate:formic acid (solvent B) with I_2 visualization showed a mixture of four to five components.

Preparation and Isolation of 1-Methylsulfonate-(3,4-diacetoxyphenyl)-2-acetoxy-3-(1,3,5-triacetoxyphenyl)propane (III).—The product (0.90 g) of the preceding sequence was placed in benzene (200 ml). Sodium acetate (1.5 g) and acetic anhydride (2 ml) were added. The suspension was refluxed overnight with stirring; the condenser was fitted with a drying tube. After cooling, the mixture was poured into water (v/v) and stirred for 0.5 hr. The benzene layer was removed using a separatory funnel. Two additional extractions were carried but with benzene. Drying ($MgSO_4$) and evaporation gave 0.254 g of III. Tlc showed only one major spot upon development with solvents A and B and I_2 visualization. Purification by preparative tlc using solvents A and B gave purified III as an amorphous, white solid. The material was stored under N_2 to prevent decomposition: nmr ($CDCl_3$) τ 2.72 (m, 3), 3.15 (s, 2), 4.42 (m, 1), 5.23 (d, 1, J = 7 Hz), 6.20 (s, 3), 7.12 (m, 2), 7.73 (m, 15), 8.08 (m, 3) (nmr spectra were also obtained in CD_3CN and CD_3COCD_3); ir ($CHCl_3$) 1770 (s), 1370 (s), and 1189 cm^{-1} (s). An attempt to crystallize purified III (CH_2Cl_2 and C_6H_{14}) gave an amorphous white solid that melted at 68°. *Anal.* Calcd for $C_{28}H_{30}O_{15}S$: C, 52.66; H, 4.74; S, 5.02. Found: C, 52.55; H, 4.87; S, 4.89. Calculated acetyl analysis for six acetyl groups: 40.4%. Found: 37.7%.

Registry No.—II, 154-23-4; III, 35639-04-4.

(6) G. Gellerstedt and J. Gierer, *Acta Chem. Scand.*, **22**, 2029 (1968).
(7) G. Gellerstedt and J. Gierer, *ibid.*, **22**, 2510 (1968).
(8) H. Richtzenhain and B. Alfredsson, *Ber.*, **89**, 378 (1956).

α,β-Ethylenic Sulfones from Sulfonomethylphosphonate Carbanions and Aldehydes and Ketones

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For our current investigation into the reactions of organocopper reagents with α,β-unsaturated sulfur compounds, we required an efficient method for converting aldehydes and ketones to vinylic sulfones. α,β-Ethylenic sulfones have been prepared in various ways.[2] Oxidation of ethylenic sulfides to sulfones can be accomplished with hydrogen peroxide in acetic acid, but the yields of unsaturated sulfone are generally low.[3] The most direct procedure is reaction of a carbonyl substrate with the anion of a sulfonomethylphosphonate ester (**1a**, **1b**). This Horner–Wittig reaction using sodium hydride or sodium methoxide at room temperature to generate the phosphonate anion

(1) NSF Trainee, 1970–present.
(2) I. C. Popoff, J. L. Dever, and G. R. Leader, *J. Org. Chem.*, **34**, 1128 (1969), and references cited therein.
(3) (a) V. Baliah and S. Shanmuganathan, *J. Indian Chem. Soc.*, **35**, 31 (1958). (b) G. Wittig and M. Schlosser, *Chem. Ber.*, **94**, 1373 (1961). (c) In our hands, hydrogen peroxide–acetic acid oxidation of methyl cyclohexylidenemethyl sulfide (prepared from cyclohexanone) and *trans*-methyl styryl sulfide (prepared from benzaldehyde) to the corresponding vinylic sulfones proceeded in 33 and 40% overall yields (from cyclohexanone and benzaldehyde, respectively).

TABLE I

CONVERSION OF CARBONYL SUBSTRATES TO α,β-ETHYLENIC SULFONES USING SULFONOMETHYLPHOSPHONATE CARBANIONS (EQ 1)

Product	R_1	R_2	R_3	Mp or bp, °C (mm)	Yield, %	Nmr: C=CHSO₂	Nmr: R_2
I	C_6H_5	H	CH_3	78–79[a]	87[b]	7.01 (d, 16)	7.75[c] (d,[d] 16[e])
II	$CH_3(CH_2)_5$	H	CH_3	105–106 (0.15)	97[b]	6.40 (d, 15)	6.90 (d of t, 15, 6)
III	$CH_3(CH_2)_4$	CH_3	CH_3	80–81 (0.05)	86[b]	See Experimental Section	
IV	Cyclohexanone		CH_3	94–95 (0.1)	97[b]	6.13 (s)	
V	C_6H_5	H	p-ClC_6H_4	78–78.5	90[f]	6.95 (d, 16)	
VI	$CH_3(CH_2)_5$	H	p-ClC_6H_4	158–160 (0.05)	80[g]	6.50 (d, 15)	7.13 (d of t, 15, 6.5)
VII	Cyclohexanone		p-ClC_6H_4	71–72.5	72[h]	6.20 (s)	

[a] Lit.[4] mp 80°. [b] Yield of crude product. [c] Chemical shift (δ) relative to TMS. [d] Multiplicity: s (singlet), d (doublet), t (triplet). [e] Coupling constant in cps. [f] Yield after recrystallization (ethanol). [g] Yield after distillation. [h] Yield after column chromatography (Florisil/benzene).

has thus far been limited to preparation of arylidene sulfones.[2,4] We report here a modification of this procedure; when *n*-butyllithium is used to generate the phosphonate anion in tetrahydrofuran at −78°, this anion reacts not only with aryl aldehydes to form arylidene sulfones but also with aliphatic aldehydes *and ketones* to give alkylidene sulfones in high yield (eq 1).[4a]

$$(EtO)_2POCH_2SO_2R_3 \xrightarrow[2.\ R_1R_2C{=}O]{1.\ n\text{-BuLi/THF/}-78^\circ} R_1R_2C{=}CHSO_2R_3 \quad (1)$$

1a, $R_3 = CH_3$
b, $R_3 = p$-ClC_6H_4

The results are summarized in Table I.[5]

In agreement with previous reports,[2,4] the *trans*-vinyl sulfone is the exclusive product in reactions with aldehydes, as indicated by the high nmr coupling constants of the vinyl protons (see Table I); in the reaction with 2-heptanone, two products are formed in 2:1 ratio, but no stereochemical assignment could be made (see Experimental Section for nmr of sulfone III).

Experimental Section

Nmr spectra were recorded on a Varian A-60 nmr spectrometer in CCl_4 (liquid products) or $CDCl_3$ (solid products), with chemical shifts reported in parts per million (δ), relative to internal TMS. Infrared spectra were recorded on a Perkin-Elmer 337 spectrophotometer as neat films or in $CHCl_3$ solution (solid products). Melting points are uncorrected.

Starting Materials.—Diethyl methylthiomethylphosphonate, prepared by the method of Green,[6] was oxidized with $KMnO_4$ in neutral solution, as described by Shahak and Almog,[4] to yield diethyl methylsulfonomethylphosphonate (1a), which was recrystallized from benzene (71% yield, mp 96°).

Chloromethyl *p*-chlorophenyl sulfide, which was prepared according to Fancher,[7] was refluxed with triethyl phosphite (1:1.7 molar ratio) for 6 hr and distilled [bp 144–147° (0.05 mm), 82% yield]. Oxidation with $KMnO_4$ in acidic solution[4] followed by recrystallization from benzene–octane (1:1) gave diethyl (*p*-chlorophenylsulfono)methylphosphonate (80% yield, mp 68–70°).

The ketones and aldehydes were freshly distilled. Tetrahydrofuran was dried by distillation over $LiAlH_4$. *n*-Butyllithium (1.32 *M* in pentane, Foote Mineral Co.) was used without purification.

General Procedure for the Formation of Vinyl Sulfones.—To a stirred solution of 2.415 g (10.0 mmol) of diethyl methylsulfonomethylphosphonate (1a) or 3.267 g (10.0 mmol) of diethyl (*p*-chlorophenylsulfono)methylphosphonate (1b) in 50 ml of dry THF under N_2 and at −78° was added 7.5 ml (10.0 mmol) of 1.32 *M* *n*-butyllithium in pentane. The resulting solution was stirred at −78° for 15 min to 3 hr, at which time 10.0 mmol of the aldehyde or ketone was added in 10 ml of THF. The clear, colorless solution was stirred at −78° for 1 hr, then allowed to warm to 25°, and stirring was continued at that temperature overnight, or at 35–50° for 3–4 hr.

The resulting pale yellow solution was poured into 50 ml of saturated aqueous NH_4Cl and extracted with three 25-ml portions of ether. The combined extract was successively washed with 50-ml portions of H_2O, saturated $NaHCO_3$, and brine, and each aqueous phase was back-extracted with a 10-ml portion of ether. The combined ether extracts were dried over $MgSO_4$, and the solvents were removed on a rotary evaporator, yielding the crude product, which was generally pure by nmr.

Following are three examples of this general procedure, *i.e.*, the preparation of vinyl sulfones III, IV, and VII.

Methyl 2-Methyl-1-heptenyl Sulfone (III).—The solution of diethyl methylsulfonomethylphosphonate anion was stirred at −78° for 1 hr before addition of 2-heptanone. Work-up involved stirring at 40° for 3 hr. The crude product III (1.628 g, 86% from 2-heptanone) was analyzed by vpc on a 5-ft 3% SE-30 column (Varaport 30), with temperature programming from 110 to 150°, which indicated 2% 2-heptanone and two product peaks in a ratio of 1.75:1. Preparative gas chromatography on a 20-ft 20% SE-30 (Chromosorb W) column at 245° allowed separation of the isomers. The major product had nmr δ 0.90 [distorted t, 3 H, $CH_3(CH_2)_3$], 1.3–1.4 (multiplet, 6 H, CH_2 protons), 1.92 (d, 3 H, J = 1 Hz, allylic CH_3), 2.2–2.4 (multiplet, 2 H, allylic CH_2), 2.90 (s, 3 H, SO_2CH_3), 5.23 (broad s, 1 H, vinyl proton); ir 1130 and 1160 $(SO)_2$ and strong bands at 1320, 965, and 915 cm^{-1}. The minor product had nmr δ 0.90 [distorted t, 3 H, $CH_3(CH_2)_3$], 1.35 (broad multiplet, 6 H, CH_2 protons), 2.15 (d superimposed on multiplet, 5 H, J = 1.3 Hz, allylic CH_3 on allylic CH_2), 2.87 (s, 3 H, SO_2CH_3), 6.17 (broad s, 1 H, vinyl proton). The ir was identical with that of the major product, but lacked absorption at 915 cm^{-1}. The analytical sample was prepared by distillation of the crude product and thus contained both isomers.

Anal. Calcd for $C_9H_{18}SO_2$: C, 56.80; H, 9.53; S, 16.85. Found: C, 56.57; H, 9.70; S, 16.87.

Methyl Cyclohexylidenemethyl Sulfone (IV).—The solution of diethyl methylsulfonomethylphosphonate anion was stirred at −78° for 30 min before addition of cyclohexanone. Work-up involved stirring overnight at 25°. The crude product IV (1.638 g, 97%) was analyzed by vpc on a 5-ft 3% SE-30 column (Varaport 30) at 150°, which showed about 0.5% impurity: nmr δ 1.67 (broad s, 6 H, cyclohexyl protons β and γ to double bond), 2.2 (broad multiplet, 2 H, cyclohexyl protons α to double bond), 2.7–2.8 (broad multiplet, 2 H, cyclohexyl protons α to double bond), 2.90 (s, 3 H, SO_2CH_3), and 6.13 (s, 1 H, vinyl proton); ir 1030 and 1190 cm^{-1} (SO_2). The product was distilled [bp 94–95° (0.1 mm)] for microanalysis.

Anal. Calcd for $C_8H_{14}SO_2$: C, 55.14; H, 8.10; S, 18.36. Found: C, 55.00; H, 7.97; S, 18.34.

(4) I. Shahak and J. Almog, *Synthesis*, 170 (1969); 145 (1970).

(4a) NOTE ADDED IN PROOF.—The diethyl (*p*-chlorophenylsulfono)-methylphosphonate anion does not react well with *n*-alkyl ketones.

(5) All new compounds gave satisfactory microanalyses.

(6) M. Green, *J. Chem. Soc.*, 1324 (1963).

(7) German Patent 1,112,735 (1958); L. W. Fancher (Stauffer Chemical Co.); *Chem. Abstr.*, **56**, 11499 (1962).

p-Chlorophenyl Cyclohexylidenemethyl Sulfone (VII).—The solution of diethyl (*p*-chlorophenylsulfono)methylphosphonate anion was stirred at −78° for 2 hr before addition of cyclohexanone. Work-up involved stirring at 50° for 4 hr. The crude product (2.865 g of yellow oil) was purified by column chromatography over 100 g of Florisil with benzene eluent, to give 1.953 g (72% of VII, mp 70–71.5°) upon evaporation. Recrystallization from ethanol gave 1.782 g of white needles: mp 71–72.5°; nmr δ 1.6 (broad s, 6 H, cyclohexyl protons β and γ to double bond), 2.2 (broad s, 2 H, cyclohexyl protons α to double bond), 2.79 (broad s, 2 H, cyclohexyl protons α to double bond), 6.20 (s, 1 H, vinyl proton), 7.55 (d, 2 H, J = 9 Hz, aromatic protons), and 7.92 (d, 2 H, J = 9 Hz, aromatic protons); ir 2925, 2845 (CH), 1620, 1580 (C=C), 1140, 1083 cm^{-1} (SO_2).

Anal. Calcd for $C_{13}H_{15}SO_2Cl$: C, 57.66; H, 5.58; S, 11.84; Cl, 13.09. Found: C, 57.79; H, 5.67; S, 11.98; Cl, 12.92.

Registry No.—II, 35324-47-1; III, 35378-30-4; IV, 35378-31-5; V, 7854-83-7; VI, 35324-49-3; VII, 35324-50-6.

Synthesis of Sulfonyl Fluorides by Use of a Fluoride Ion Exchange Resin

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We wish to report an extremely rapid and efficient method for the synthesis of small quantities of sulfonyl fluorides from the corresponding sulfonyl chlorides by ion exchange chromatography. The technique is characterized by high yields (82–94%, starting with 1 g of aromatic sulfonyl chloride) and pure products which are easily isolated by evaporation of the solvent and need no recrystallization.

Experimental Section

General.—Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were measured on a Perkin-Elmer Model 700 spectrophotometer. Solvents were evaporated on a Buchler flash evaporator. Elemental analyses were determined by Galbraith Laboratories, Knoxville, Tenn.

Starting Materials.—2,4-Dinitrobenzenesulfonyl chloride, *p*-chlorobenzenesulfonyl chloride, *p*-bromobenzenesulfonyl chloride, and *p*-fluorosulfonylbenzenesulfonyl chloride were purchased from Aldrich Chemical Co. *p*-Nitrobenzenesulfonyl chloride and *m*-nitrobenzenesulfonyl chloride were purchased from Matheson Coleman and Bell. *p*-Toluenesulfonyl chloride was obtained from Eastman Organic Chemicals, and methanesulfonyl chloride was a product of the J. T. Baker Co. For the purposes of comparison, authentic samples of *p*-nitrobenzenesulfonyl fluoride, *m*-nitrobenzenesulfonyl fluoride, *p*-chlorobenzenesulfonyl fluoride, and *p*-bromobenzenesulfonyl fluoride were synthesized by the method of Davies and Dick.[2]

Preparation of the Fluoride Anion Exchange Resin.—The strongly basic quaternary amine anion exchange resin, AG1-X10 (200–400 mesh), was purchased from Bio-Rad Laboratories in the chloride form. Oven-dried resin (80 ml, 40 g) was suspended in water and transferred to a burette. The resin was eluted with 5.0 M aqueous potassium fluoride, at a rate of 150 ml per hour, until a spot test of the eluate with aqueous $AgNO_3$ indicated the absence of chloride. Approximately 3 l. of 5.0 M KF solution was needed to elute the chloride from the resin.[3] The fluoride form resin was washed with three 100-ml portions of distilled water, dried in an oven at 115° for 2 hr, and stored in a desiccator. This preparation yielded 38.7 g of dried resin.

Synthesis of Sulfonyl Fluorides.—The oven-dried fluoride form resin (5 ml) was transferred to a 10-ml B-D disposable syringe and washed with 20 ml of acetonitrile. The appropriate sulfonyl chloride (1.000 g) was dissolved in 10 ml of acetonitrile and passed through the resin at a rate of approximately 1 ml/min.[4] The resin was then washed with two 5-ml portions of acetonitrile, and the combined eluent and washings were evaporated to near dryness on a rotary evaporator. On cooling in an ice bath for several minutes, the solid products crystallized. For the synthesis of methanesulfonyl fluoride (**8**), the quantities were increased by a factor of 3, and the final product was purified by microdistillation.

Results and Discussion

The results of the synthesis of eight different sulfonyl fluorides from the corresponding sulfonyl chlorides by the ion exchange method are indicated in Table I.

TABLE I
SYNTHESIS OF SULFONYL FLUORIDES BY USE OF A FLUORIDE ION EXCHANGE RESIN[a]

Compd	No.	Mp (bp), °C	Lit. mp (bp), °C	Yield, %
4-Bromobenzenesulfonyl fluoride	1	64–65	65–66[b]	92
4-Chlorobenzenesulfonyl fluoride	2	47–48	47–48[c]	82
p-Toluenesulfonyl fluoride	3	39–41	41–42[c]	86
3-Nitrobenzenesulfonyl fluoride	4	45–46	46–47[b]	86
4-Nitrobenzenesulfonyl fluoride	5	76–77	75–78[b]	89
2,4-Dinitrobenzenesulfonyl fluoride	6	97.5–98.5	*d*	91
1,4-Benzenedisulfonyl fluoride	7	155–156	*e*	94
Methanesulfonyl fluoride	8	(120–122)	(124)[f]	71

[a] Acetonitrile used as solvent. [b] See M. E. Aberlin and C. A. Bunton, *J. Org. Chem.*, **35**, 1825 (1970). [c] See ref 2. [d] Not reported in literature. Recrystallized from absolute ethanol. *Anal.* Calcd for $C_6H_3FN_2O_6S$: C, 28.45; H, 1.44. Found: C, 28.56; H, 1.50. [e] Not reported in literature. Recrystallized from ethanol–water. *Anal.* Calcd for $C_6H_4F_2O_4S_2$: C, 29.75; H, 1.66. Found: C, 29.55; H, 1.54. [f] See W. Davies and J. H. Dick, *J. Chem. Soc.*, 483 (1932).

These results were obtained using acetonitrile as solvent. They indicate high purity, as determined by the comparison of melting points to literature values for reported compounds, and by comparison of infrared spectra to those of the authentic materials for compounds **1**–**4**.

Infrared spectra were a useful tool in determining the extent of conversion of the sulfonyl chlorides to sulfonyl fluorides. The strong asymmetric and symmetric sulfur–oxygen stretching frequencies of aromatic sulfonyl chlorides occur at 1385–1340 and 1185–1160 cm^{-1}, respectively.[5] On conversion to the sulfonyl

(1) (a) Taken in part from the Senior Independent Study Thesis of D. L. MacDonell, The College of Wooster, 1972. (b) NSF undergraduate research participant, summer, 1971.

(2) W. Davies and J. H. Dick, *J. Chem. Soc.*, 2104 (1931).

(3) Subsequent regeneration steps required approximately 2 l. of 5.0 M aqueous KF.

(4) When the sulfonyl chloride was dissolved in 50 ml of acetonitrile and passed through the resin, a low yield of impure product was obtained.

(5) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Boston, Mass., 1966, p 181.

fluorides, these stretching frequencies are shifted to 1420–1395 and 1235–1200 cm^{-1}. In addition a very strong peak, due to the vibrational stretching of the sulfur–fluorine bond, appears at 800–750 cm^{-1}.[6]

Several encouraging aspects of this work include the high yields obtainable with small quantities of starting material (Table I), and the applicability of this technique to the synthesis of aliphatic sulfonyl fluorides. This type of compound is more difficult to synthesize than analogous aromatic sulfonyl fluorides. It is reported by Davies and Dick to require longer reaction times at higher temperatures, and produces lower yields of product.[7] When methanesulfonyl chloride was passed through the fluoride resin in this work, under the identical conditions used for aromatic analogs, methanesulfonyl fluoride (**8**) was produced in 71% yield.

The choice of solvents for the described technique was fairly critical. Since at least some of the reacting species were ionic, the dielectric constant of the solvent was a determining factor. An added consideration was that the solvent should not undergo reaction with the starting material or product. Acetonitrile was the obvious choice, and proved to give excellent results. Methanol was also tried, but infrared analysis of the products obtained using methanol as solvent and eluent indicated that only a portion of the starting material had been converted to the sulfonyl fluoride, while the major portion of the product was undoubtedly the methyl sulfonate.

Strongly basic quaternary amine type anion exchange resins have a low affinity for fluoride ion.[8] In fact, fluoride has the lowest affinity for Bio-Rad AG1 resins of some 16 monovalent anions reported in the commercial literature of this compound.[9] Sulfonyl fluorides are also much less reactive than the corresponding sulfonyl chlorides.[2,10] Thus, when fluoride exchanges with the chloride in the sulfonyl chlorides, the chloride generated binds tightly to the resin and the resulting more stable sulfonyl fluoride is easily isolated in the eluent from the resin. Another advantage of using the resin technique is that any sulfonic acids resulting from hydrolysis of the sulfonyl halides would have a very strong affinity for the resin,[8] and would thus be separated from the sulfonyl fluoride.

The large amount of fluoride necessary to convert a small amount of the resin from the chloride to the fluoride form bear out the observations of Gregor, *et al.*[8] This large amount of fluoride is rather prohibitive if one were to attempt to use this technique to synthesize sulfonyl fluorides in large quantities. Still, we feel that it is a very valuable method where small quantities or difficult-to-obtain starting materials are involved.

We are pursuing the use of the fluoride ion exchange resin described here in the synthesis of other fluorine-containing compounds.

Registry No.—2,4-Dinitrobenzenesulfonyl fluoride, 35426-71-2; 1,4-benzenedisulfonyl fluoride, 35426-72-3.

(6) C. J. Pouchert, "The Aldrich Library of Infrared Spectra," Aldrich Chemical Co., Inc., 1970, p 839.
(7) W. Davies and J. H. Dick, *J. Chem. Soc.*, 483 (1932).
(8) H. P. Gregor, J. Belle, and R. A. Marcus, *J. Amer. Chem. Soc.*, **77**, 2713 (1955).
(9) Price List W, Bio-Rad Laboratories, June 1971, p 12.
(10) C. G. Swain and C. B. Scott, *J. Amer. Chem. Soc.*, **75**, 246 (1953).

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The Stepwise Removal of the *S*-*p*-Nitrobenzyl Protecting Group

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In the course of our work on 4-thio-substituted β-lactams[1] the need for a sulfhydryl protecting group which can be removed without destroying the β-lactam ring arose. It was initially considered that the *p*-nitrobenzyl group, proposed by Berse and coworkers[2] as a sulfur protecting group, can fulfill this requisite. According to these authors the *p*-nitrobenzyl group is removable from *S*-*p*-nitrobenzyl-L-cysteine by catalytic hydrogenation in the presence of palladium/charcoal. A similar reductive cleavage was postulated by Baker and Kozma[3] who reported that catalytic hydrogenation of 2- and 8-*p*-nitrobenzylthiohypoxanthine afforded the respective 2- and 8-mercaptohypoxanthine and *p*-toluidine; unfortunately no quantitative figures were given. Although it could have been expected that a protective group having this quality would be widely used in peptide syntheses, the removal of the *S*-*p*-nitrobenzyl group from peptide derivatives has not yet been described.[4] This protecting group was applied by Katsoyannis[5] for the protection of cysteine in the synthesis of some peptides related to insulin, but no experiments describing its removal were reported. Ondetti and Bodanszky[6] reported that *N*-benzyloxycarbonyl-*S*-*p*-nitrobenzyl-L-cysteinylglycine was catalytically hydrogenated to *N*-benzyloxycarbonyl-*S*-*p*-aminobenzyl-L-cysteinylglycine, and *S*-*p*-nitrobenzyl-L-cysteine was reduced to *S*-*p*-aminobenzyl-L-cysteine (only R_f values are given for the last compound). Similarly Hiskey and Tucker[7] observed the absorption of the required amount of hydrogen for the catalytic hydrogenation of ethyl *N*-benzyloxycarbonyl-*S*-*p*-nitrobenzylcysteinate but could not isolate any thiol. The stepwise removal of the sulfur protecting group from *S*-*p*-nitrobenzyl-L-cysteine which is described in the present paper might offer an explanation for the discrepancy between the reported[2,6,7] results.

Hydrogenation of *S*-*p*-nitrobenzyl-L-cysteine in the presence of 10% palladium/charcoal, under the condi-

(1) M. D. Bachi and O. Goldberg, *J. Chem. Soc., Chem. Commun.*, 319 (1972).
(2) C. Berse, R. Boucher, and L. Piche, *J. Org. Chem.*, **22**, 805 (1957).
(3) B. R. Baker, and J. Kozma, *J. Med. Chem.*, **10**, 682 (1967).
(4) For examples and references to the use of sulfhydryl protecting groups in peptide synthesis, see E. Schröder and K. Lübke (transl. E. Gross) in "The Peptides," Academic Press, New York and London, Vol. 1, 1965; M. Bodanszky and M. A. Ondetti, "Peptides Synthesis," Interscience, New York, N. Y., 1966; J. H. Jones in "Amino Acids, Peptides, and Proteins," Vol. I, The Chemical Society Specialist Periodical Reports, London, 1969, Chapter 3, and Vol. II, 1970, Chapter 3.
(5) P. Katsoyannis, *J. Amer. Chem. Soc.*, **83**, 4053 (1961).
(6) M. A. Ondetti and M. Bodanszky, *Chem. Ind. (London)*, 697 (1962).
(7) R. G. Hiskey, and W. P. Tucker, *J. Amer. Chem. Soc.*, **84**, 4789 (1962).

tions reported by Berse and coworkers,[2] afforded in our hands *S*-*p*-aminobenzyl-L-cysteine. The reduction involved the absorption of 3 equiv of hydrogen and the hydrogenated mixture gave a negative nitroprusside test for sulfhydryl. Berse and coworkers[2] who claimed that hydrogenation of *p*-nitrobenzyl-L-cysteine afforded cysteine have used the Hopkins reagent (10% $HgSO_4$ in 5% aqueous H_2SO_4)[8] for its isolation as a mercury mercaptide. The mercaptide was finally converted to L-cystine by treatment with hydrogen sulfide followed by aerial oxidation. Pursuing exactly the same procedure we have obtained L-cystine from *S*-*p*-aminobenzyl-L-cysteine.

It is therefore concluded that the benzylic C–S bond in *S*-*p*-nitrobenzyl-L-cysteine did not undergo hydrogenolysis during the catalytic hydrogenation, while the benzylic C–S bond in the resulting *S*-*p*-aminobenzyl-L-cysteine was readily cleaved by mercury salts. Comparative experiments showed that *S*-benzyl- and *S*-*p*-nitrobenzyl-L-cysteine are unaffected by the Hopkins reagent under similar conditions.

Experimental Section

Melting points were determined with a Büchi apparatus under controlled conditions: heating the oil rapidly to a temperature ~20° lower than the melting point and then raising the temperature 5°/min until decomposition occurred. Nmr spectra were recorded with a Varian A-60 spectrometer.

***S*-*p*-Nitrobenzyl-L-cysteine.**—L-Cysteine hydrochloride monohydrate (17.5 g, 0.10 mol) was added, under a nitrogen atmosphere, at 0–3°, to 1 *N* NaOH (300 ml). To this was added with vigorous stirring, during 30 min, a solution of *p*-nitrobenzyl chloride (17.2 g, 0.10 mol) in freshly distilled peroxide-free dioxane (150 ml). After being stirred for additional 30 min at 0–3°, and 30 min at room temperature, the mixture was washed with ether and then acidified (pH 4–5) with concentrated hydrochloric acid (~10 ml). Concentration to 300 ml *in vacuo* (10 mm), followed by cooling (to 5°), afforded a precipitate which was filtered and washed successively with water (100 ml), ethanol (100 ml), and ether (100 ml). The crude product (23.3 g), mp 192–195°, was recrystallized from water to give 17.5 g (68%) of light yellow crystals, mp 202° dec (lit. mp 172.5–174°,[7] mp 233–234° for hydrate[2]). Two more recrystallizations from water followed by drying during 20 hr at 50° (1 mm) over P_2O_5 afforded an analytical sample: mp 197° dec; $[\alpha]^{20}D$ −4.0° (*c* 1.0, 1 *N* HCl); nmr (D_2O + CF_3CO_2D)[9] δ 2.84 (d, 2, *J* = 6 Hz, $CHCH_2S$), 3.63 (s, 2, SCH_2Ar), 4.11 (t, 1, *J* = 6 Hz, CH), 7.23 (d, 2, *J* = 9 Hz, Ar), 7.77 (d, 2, *J* = 9 Hz, Ar).

Anal. Calcd for $C_{10}H_{12}N_2O_4S$: C, 46.9; H, 4.7; N, 10.9; S, 12.5. Found: C, 47.0; H, 4.8; N, 10.7; S, 12.6.

The ethyl ester hydrochloride had mp 172–173° (lit. mp 172–173°,[2] mp 161–163°[7]).

***S*-*p*-Aminobenzyl-L-cysteine Monohydrochloride.**—A solution of *S*-*p*-nitrobenzyl-L-cysteine (1.37 g, 5.3 mmol) in ethanol (100 ml) and 1 *N* hydrochloric acid (50 ml) was hydrogenated at room temperature and at atmospheric pressure over 10% palladium/charcoal (345 mg). After the absorption of 3 equiv of hydrogen (7–8 hr) the catalyst was removed by filtration. The filtrate, which gave a negative nitroprusside test for sulfhydryl, was evaporated *in vacuo*. The oily residue was dissolved in ethanol–water (19:1 v/v 25 ml) and the solution was brought to pH 4–5 by addition of pyridine (~0.8 ml). Crystallization of the product started immediately. After this was kept for 24 hr at 5°, the yellow crystalline precipitate was filtered and washed with ethanol (10 ml) and then with ether (10 ml). The crude product (1.17 g), mp 207–208° dec, was recrystallized from ethanol–water (50 ml, 9:1 v/v) to give 0.95 g (68%) of the title compound: mp 215–216° dec; $[\alpha]^{20}D$ −5.5° (c 1.0, 1 *N* HCl); nmr (D_2O) δ 2.94 (d, 2, *J* = 6 Hz, $CHCH_2S$), 3.80 (s, 2, SCH_2Ar), 3.90 (t, 1, *J* = 6 Hz, CH), 7.25–7.65 (m, 4, Ar).

Anal. Calcd for $C_{10}H_{15}ClN_2O_2S$: C, 45.7; H, 5.7; N, 10.7; S, 12.2. Found: C, 45.6; H, 5.9; N, 10.4; S, 12.1.

Action of Mercury Salts on *S*-*p*-Aminobenzyl-L-cysteine.—To a stirred solution of *S*-*p*-aminobenzyl-L-cysteine (1.13 g, 4.3 mmol) in ethanol (100 ml) and 1 N hydrochloric acid (50 ml) Hopkins reagent (10% $HgSO_4$ in 5% aqueous H_2SO_4,[8] 75 ml) was added. Precipitation of a mercury mercaptide started within a few minutes. The mixture was stirred for additional 20 hr, filtered, and washed successively with water (20 ml), ethanol (20 ml), and ether (20 ml). The solid (1.86 g), mp >250°, was suspended in water (50 ml) and then saturated with H_2S. After 15 min the precipitated mercury sulfide was filtered off and excess of H_2S was removed *in vacuo*. The mixture was made alkaline by addition of 3 *N* NaOH (~4 ml), and air was bubbled through during 2.5 hr. Crystallization began on adjusting the pH to ~4 by addition of 3 *N* hydrochloric acid. The mixture was kept overnight at 5° and then filtered and washed successively with water (10 ml) and acetone (10 ml) to give crude cystine (0.41 g) mp 245–248° dec. This was dissolved in 1 *N* NaOH (3.4 ml) and then precipitated by addition of 1 *N* hydrochloric acid (3.4 ml). The solid was filtered and washed successively with water (10 ml), ethanol (10 ml), and ether (10 ml) to give 0.39 g (76%) of cystine, mp 248–250° dec (lit.[2] mp 255–260°), $[\alpha]^{25}D$ −212° (*c* 1.04, 1 *N* HCl) {lit.[2] $[\alpha]^{25}D$ −225° (c 1.04, 1 *N* HCl)}.

Registry No.—*S*-*p*-Nitrobenzyl-L-cysteine, 6341-94-2; *S*-*p*-aminobenzyl-L-cysteine monohydrochloride, 35340-27-3.

Acknowledgment.—The authors thank Professor W. Taub for discussions and encouragement.

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(9) A few drops of CF_3CO_2D were added to assist the solution of the sample in D_2O.

Enol Esters. XV.[1] Synthesis of Highly Hindered Esters *via* Isopropenyl Ester Intermediates

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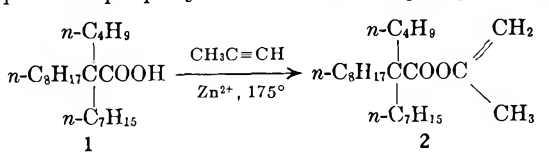
In recent years we have demonstrated the powerful acylation properties of isopropenyl esters, compounds capable of acylating even weakly nucleophilic secondary amides and imides.[3] We presently report the application of isopropenyl esters to the facile acylation of highly hindered alcohols. Our test compound, 2-butyl-2-heptyldecanoic acid[4] (1), was totally inert to esterification with ethanolic hydrogen chloride under reflux for periods up to 70 hr[5] but the isopropenyl ester of compound 1 rapidly acylated hindered as well as normal alcohols in a few minutes under our usual operating conditions.[3] Conversion of compound 1 to its isopropenyl ester 2 was obtained by our standard method[6] in accordance with the reaction shown by eq 1. Isopropenyl ester 2 efficiently acylated the fol-



1 2 (1)

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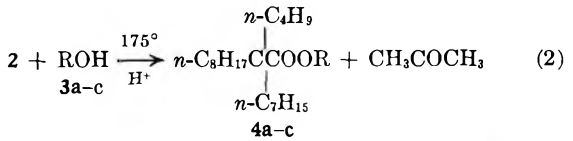
lowing representative alcohols—*n*-octadecanol (**3a**), 2-methyl-2-propanol (**3b**), and 2-butyl-2-heptyldecanol (**3c**) (obtained by sodium in alcohol reduction of **2**)—to the corresponding esters **4a**, **4b**, and **4c** in good



$$2 + \underset{\textbf{3a-c}}{ROH} \xrightarrow[H^+]{175^\circ} n\text{-}C_8H_{17}\overset{\displaystyle n\text{-}C_4H_9}{\overset{|}{C}}\overset{\displaystyle n\text{-}C_7H_{15}}{\overset{|}{C}}OOR + CH_3COCH_3 \qquad (2)$$

4a-c

a, R = *n*-$C_{18}H_{37}$; **b**, R = *t*-C_4H_9; **c**, R = *n*-$C_8H_{17}\overset{\displaystyle n\text{-}C_4H_9}{\overset{|}{C}}\overset{\displaystyle n\text{-}C_7H_{15}}{\overset{|}{C}}H_2$

yields. The acylations when carried out neat at 175° with a trace of acid catalyst were complete in 5–10 min.

The mechanism of the acylation is uncertain, but it is evident that a ketene intermediate cannot be involved with trialkylacetic acid derivatives. Our previous work with isopropenyl stearate indicated the formation of hexadecylketene as the probable intermediate in the acylation reaction.[7] Apparently, there is more than one pathway available in isopropenyl ester acylations.

Experimental Section

The carboxylic acid starting material was of higher purity than 99% as estimated by glc. Products described below were of a similar order of purity as assayed by the same method.

Isopropenyl 2-Butyl-2-heptyldecanoate (**2**).—The carboxylic acid **1** (9.5 g, 0.029 mol) and ZnO (61 mg) were heated in an autoclave[6] with propyne under N_2 (auxiliary pressure 400 psi) for 70 hr. Zinc salts were removed by chromatography on Florisil and the liquid ester **2** (9.5 g, 90%) was eluted with pentane: ir (CS_2) 1740 (C=O), 1670 (C=C), 838 (C=CH_2) cm^{-1}; nmr (CCl_4) δ 4.58 (s, 1, C=CH), 4.53 (s, 1, C=CH), 1.90 (s, 3, C=CCH_3), 1.75–0.70 (m, 41); mass spectrum, *m/e* (rel intensity) 309 (1.24), 281 (92.8), 85 (58), 57 (100).

Anal. Calcd for $C_{24}H_{46}O_2$: C, 78.62; H, 12.65. Found: C, 78.81; H, 12.75.

Octadecyl 2-Butyl-2-heptyldecanoate (**4a**).—A mixture of enol ester **2** (406 mg, 1.11 mmol) and *n*-octadecanol (300 mg, 1.11 mmol) was melted, treated with *p*-toluenesulfonic acid (5 mg), and heated for 6 min at 180° (Woods metal bath). The ir of the crude product was similar to the ir of the analytical sample. Purification for removal of catalyst was effected by dissolving in pentane and filtering through a small plug of Florisil in a microcolumn to give the ester **4a** (591 mg, 92%): ir (CS_2) 1727 cm^{-1} (C=O); nmr δ 4.00 (t, 2, OCH_2) 1.70–0.70 (m, 76); mass spectrum, *m/e* (rel intensity) 57 (100, butyl), 99 (17.5, heptyl), 113 (12, octyl), 253 (0.9, octadecyl), 269 (1.33, octadecyloxy), 281 (48, trialkylmethyl), 309 (1.19, trialky acetyl). The gaseous product of the reaction was acetone al confirmed by conversion to the 2,4-dinitrophenylhydrazone derivative, mp 125° (lit.[8] mp 126°). Prolonged hydrolysis of **4a** with aqueous alcoholic potassium hydroxide under vigorous conditions gave a single acid identical with the starting acid **1** in glc retention time (single peak) and ir. The ester **4a** is a liquid.

Anal. Calcd for $C_{39}H_{78}O_2$: C, 80.89; H, 13.58. Found: C, 80.93; H, 13.74.

tert-**Butyl 2-Butyl-2-heptyldecanoate** (**4b**).—The enol ester **2** (200 mg, 0.55 mmol) and *p*-toluenesulfonic acid (2 mg) were heated to 200° (Woods metal bath) and an excess of dry 2-methyl-2-propanol was added as rapidly as possible through a reflux condenser (caution); this was followed by a 3-min reaction time. (The procedural modification was necessary owing to the low boiling point of the alcohol.) The product was contaminated with a little anhydride[9] removable by a pass in pentane solution through a microcolumn of mildly alkaline alumina (Florisil was unsuitable since the anhydride impurity eluted easily and with the same R_f value as the ester). The *tert*-butyl ester **4b** (156 mg, 75%) gave ir (CS_2) 1721 cm^{-1} (C=O); nmr (CCl_4) δ 1.42 [s, 9, $C(CH_3)_3$], 1.40–0.70 (m, 41); mass spectrum (*m/e*, rel intensity), 281 (31), 57 (100).

Anal. Calcd for $C_{25}H_{50}O_2$: C, 78.47; H, 13.17. Found: C, 78.52; H, 13.15.

2-Butyl-2-heptyldecanol (**3c**).—A sample of the enol ester **2** (700 mg, 1.9 mmol) was dissolved in dry ethanol and treated with an excess of sodium metal until the rate of metal dissolution became very sluggish. Dilution with water, extraction of the organic material with ether, drying ($MgSO_4$), and solvent removal gave the carbinol **3c**. To prepare the analytically pure material, small amounts of impurities[10] were removed by chromatography on Florisil. The product (475 mg, 85%) was eluted with CH_2Cl_2: ir (CS_2) 3620 (OH), 1193 cm^{-1} (CO); nmr (CCl_4) δ 3.25 (s, 2, CH_2OH) 1.62 (s, 1, OH) 1.50–0.70 (m, 41); mass spectrum (*m/e*, rel intensity) 281 (100).

Anal. Calcd for $C_{21}H_{44}O$: C, 80.69; H, 14.19. Found: C, 81.02; H, 14.02.

2′-Butyl-2′-heptyldecyl 2-Butyl-2-heptyldecanoate (**4c**).—The alcohol **3c** (105 mg, 0.34 mmol) and the enol ester **2** (123 mg, 0.34 mmol) were heated to 195° for 6 min in the presence of *p*-toluenesulfonic acid (2 mg). Gas evolution (acetone vapor) was immediate. The product was freed of catalyst by passing its pentane solution through a Florisil column to yield ester **4c** (199 mg, 95%): ir (CS_2) 1720 (C=O), 1190 cm^{-1} (CO); nmr ($CDCl_3$) δ 3.76 (s, 2, OCH_2) 1.70–0.70 (m, 82); mass spectrum (*m/e*, rel intensity) 57 (100, butyl), 99 (39, heptyl), 113 (0.4, octyl), 281 (100, trialkylmethyl), 295 (9.7, RCH_2).

Anal. Calcd for $C_{42}H_{84}O_2$: C, 81.22; H, 13.63. Found: C, 81.28; H, 13.66.

Registry No.—**2**, 35341-91-4; **3c**, 35341-92-5; **4a**, 35341-93-6; **4b**, 35341-94-7; **4c**, 35341-95-8.

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(7) Such indications in the case of isopropenyl stearate include (a) isolation of tetrameric hexadecylketene as the sole product when no acylatable substrate was provided [see E. Rothman, *J. Amer. Oil Chem. Soc.*, **45**, 189 (1968)], (b) loss of half the deuterium label when the isopropenyl ester of α-deuteriostearic acid was used as the acylation agent (unpublished data), and (c) formation of stearic *anhydride* or *tert*-butyl stearate *from addition of water* or 2-methyl-2-propanol, respectively, to an isopropenyl stearate–acid catalyst mixture which had been heated to 200° and cooled to room temperature prior to addition of reagent (unpublished data).

(8) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, Ed., "Systematic Identification of Organic Compounds," 4th ed, Wiley, New York, N. Y., 1962, p 221.

(9) The anhydride of acid **1** [ir (CS_2) 1803, 1737 cm^{-1}] may arise *via* the following sequence: dehydration of 2-methyl-2-propanol liberating water, hydrolysis of **2** to acid **1**, and reaction of **1** with **2**.

(10) The impurities were essentially traces of acid **1**, its ethyl ester, and a nonpolar fraction, apparently the ether corresponding to alcohol **3c**.

A Facile Reduction of Unsaturated Compounds Containing Nitrogen[1]

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Catalytic hydrogenation reactions involving compounds containing nitrogen have been reported to give a variety of products depending on reaction condi-

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tions. Maxted,[2] in a series of papers, has described the poisoning of platinum catalysts by free amines. Rylander,[3] in summarizing the catalytic reductions of nitriles, lists primary, secondary, and tertiary amines, imines, hydrocarbons, aldehydes, amides, and alcohols among the products, the major product depending on the catalyst, substrate and reaction conditions. Hartung and Simonoff[4] have summarized the hydrogenolyses of some benzylamines, employing platinum, palladium, and nickel catalysts. Southard[5] has employed the catalytic hydrogenolysis of a urethane group as a major step in a general peptide synthesis.

We have found that nickel boride exhibits a high proficiency for catalyzing the addition of hydrogen to unsaturated compounds containing nitrogen. First reported over twenty years ago,[6] the catalyst has been found to cause no rearrangements of unsaturated hydrocarbons during catalytic hydrogenation reactions.[7] The catalyst is also highly selective for the reduction of unsaturated compounds containing oxygen,[8] causing neither hydrogenation nor hydrogenolysis of oxygen functions.

A representative selection of the nitrogen-containing unsaturated compounds studied by us appear in Table I. The reaction products of the compounds listed were isolated and identified by spectral comparisons.

TABLE I
TIMES OF HYDROGENATION OVER NICKEL BORIDE

Compd	Time,[a] min
Allylamine	10
Diallylamine	25[b]
Acrylamide	8
Methacrylamide	15
3-Butenenitrile	30
2-Butenenitrile	30[c]
Cinnamonitrile	16 hr[c]

[a] Time required for the uptake of 1 equiv of hydrogen, 100 mmol of substrate, 5 mmol of catalyst, 50 ml of solvent. [b] Time required for the uptake of 2 equiv of hydrogen. [c] 20 mmol of catalyst.

The amines and amides gave quantitative yields of single compounds from reduction of the carbon–carbon π bonds. No products resulting from hydrogenation or hydrogenolysis of the functional groups were detected by gas chromatography. Also, no further uptake of hydrogen was observed following the uptake of the calculated amount for the carbon–carbon π bonds.

However, the carbon–nitrogen π bonds of the nitriles could be reduced, yielding primary amines. While not unique, nickel boride does exhibit a high selectivity for the carbon–carbon π bond. For example, butyronitrile, formed quantitatively in 30 min from either 2- or 3-butenenitrile, gives a 56% yield of butylamine in 6 days with 5 mmol of catalyst or 2 days with 20 mmol of catalyst. No products from the coupling reactions listed by Rylander[3] were detected in the reaction mixture.

From the short reaction times, it is apparent that the poisoning by amines of palladium catalysts reported by Maxted[2] does not extend to the nickel of nickel boride.

The catalyst is exceedingly simple to prepare. The reaction of nickel(II) salts (dissolved in water or suspended in ethanol) and sodium borohydride yields the black precipitate of interest. It may be used directly or stored for future use.

The physical appearance of the catalyst changes with the preparation medium, but this change does not appear to affect the selectivity of the catalyst. It does, however, effect the times of reduction. The granular material from water solvent exhibits longer hydrogenation times than the colloidial material from alcohol.

These findings, coupled with the earlier results on oxygen-containing compounds,[8] indicate the potential applications of nickel boride in the synthesis of complex organic molecules. Work on further applications of nickel boride on compounds containing π-bonded nitrogen, halogen, and small rings is currently underway.

Experimental Section

Chemicals.—All chemicals were used directly from the bottles with no further purification. Nitriles were Eastman practical grade. Other chemicals were reagent grade.

Catalyst Preparation.—For a single hydrogenation, 5 mmol of powdered nickel(II) salt, 50 ml of liquid, and a short magnetic spinbar are placed in a Parr hydrogenation flask. Stirring is begun and the flask flushed with hydrogen. Addition of 5 mmol of sodium borohydride (5 ml of 1.0 *M* solution in water or alcohol or 185 mg of solid) to the flask produces the catalyst.

Nickel salts used are acetate, chloride, nitrate, and sulfate. Liquids include water as a solvent and absolute and 95% ethanol as suspension media.

For a bulk preparation, the above procedure is followed using larger amounts of nickel(II) salts and sodium borohydride. The catalyst can be isolated by either filtering or centrifuging, depending on particle size. The isolated catalyst can be stored indefinitely under nitrogen, either dry or under alcohol.

Hydrogenation Procedure.—To the catalyst and preparatory solution in a Parr hydrogenation flask is added the compound to be hydrogenated, neat if liquid or dissolved in a minimum amount of solvent if solid. If the preprepared catalyst is used, the compound to be hydrogenated is added to ~50 mg of the catalyst in 50 ml of the solvent. The flask is then attached to the hydrogenator and shaken until the theoretical pressure drop for hydrogen is observed. Initial pressure was 30 psi and temperature was ambient with no external cooling in all experiments.

The contents of the hydrogenation flask were centrifuged to separate the catalyst, the decantate being analyzed by gas chromatography. All reaction products were isolated and identified by comparisons of infrared spectra with authentic samples. Yields of the amines and nitriles were determined by gas chromatographic methods employing external standards. The yields of the amides were estimated from the melting points of the reaction products following evaporation of the hydrogenation solvent.

Acknowledgments.—We are grateful to the National Science Foundation (Grant No. GY-7101 and GU-3531) and Eastern New Mexico University for support of this work.

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The Sodium Borohydride Reduction of 2,2,2-Triphenylethylmercuric Chloride

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The mechanism of the borohydride reduction of organomercurials is a subject of considerable current interest.[2-5] The formation of radical intermediates in these reductions has been inferred from labeling experiments, observations of loss of stereochemistry, and structural rearrangements; however, a clear distinction between radical-cage and radical-chain processes has not been possible.[4] While investigating the chemistry of 2,2,2-triphenylethyl organometallic derivatives, it was found that alcohols rather than hydrocarbons are the major products from the sodium borohydride reduction of 2,2,2-triphenylethylmercuric chloride (**1**).

The sodium borohydride reduction of **1** in basic aqueous tetrahydrofuran for 1 hr according to the procedure of Brown and Geoghegan[6] (*i.e.*, open to the atmosphere) produced only a 6% yield of the corresponding hydrocarbon 1,1,1-triphenylethane, although elemental mercury was approximately quantitatively deposited (90–100%). The principal product (70%) was found to be the rearranged alcohol, 1,1,2-triphenylethanol. It was considered that this unusual product could have resulted from solvolysis of the mercurial[7] or from oxygen trapping of intermediate radicals. A control experiment involving stirring the mercurial **1** without sodium borohydride in basic aqueous tetrahydrofuran open to the air for 7.5 hr did not produce any detectable amounts of mercury or alcohol products. This experiment also indicates that oxygen-induced decomposition of the mercurial is not competitive with the reduction reaction. The role of oxygen in the course of these reactions was investigated by carrying out the reductions on a vacuum line after careful degassing. The reaction products using degassed solutions are 1,1,1-triphenylethane (8%) and 1,1,2-triphenylethane (92%) in addition to elemental mercury (99%). It is significant that under these conditions no alcoholic products are observed although predominant rearrangement still occurs. If molecular oxygen is introduced into the reaction flask after the degassing cycles, the reaction products are 1,1,1-triphenylethane (13%), 1,1,2-triphenylethane (3%), 1,1,2-triphenylethanol (58%), and 2,2,2-triphenylethanol (19%).

The observation of rearranged products from all the sodium borohydride reductions of **1** is consistent with the free-radical pathways proposed for this reaction.[8] The production of alcohols in the presence of oxygen is also consistent with the formation of intermediate radicals since oxygen is known to be an efficient radical scavenger.[9,10] It is tempting to conclude that the sodium borohydride reduction of organomercurials proceeds *via* a noncage process since the rate of rearrangement of the 2,2,2-triphenylethyl radical (5×10^7 sec^{-1} at 100°)[11,12] would be expected to be several orders of magnitude slower than diffusion-controlled rates at room temperature.[13] However, since the alcoholic products from the sodium borohydride reduction of **1** are rather anomalous, it is not certain that these conclusions are applicable to other systems.

In contrast to the sodium borohydride reduction, the reduction of **1** with either lithium aluminum hydride or sodium bis(2-methoxyethoxy)aluminum hydride in tetrahydrofuran under an argon atmosphere produced only the unrearranged hydrocarbon, 1,1,1-triphenylethane, in 92%–98% yields. Similarly, reduction of **1** with sodium amalgam in aqueous methanol under argon produced only 1,1,1-triphenylethane in 99% yield. Neither rearranged hydrocarbon nor oxidation products could be detected by vpc analyses of these reaction mixtures. Therefore, these reagents would seem to be preferrable to sodium borohydride for reduction of organomercurials since intermediate radicals apparently are not involved.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nmr spectra were obtained on dilute solutions using a Varian Model A-60 spectrometer and TMS as an internal standard. The ir spectra were obtained using a Perkin-Elmer Model 337 grating spectrophotometer. Vpc measurements were conducted with a Varian-Aerograph Model 90-P using the internal standard method for quantitative analyses. Hydrocarbon products were separated using a 13-ft, 5% Apiezon L on Chromosorb W column at 200°; the alcohols were analyzed using a 4-ft, 3% Carbowax 20M on Chromosorb G column at 210°. Combustion analyses were performed by Alfred Bernhardt Mikroanalytische Laboratorium, 5251 Elbach über Engelskirchen, West Germany. The yields of elemental mercury were determined by direct weighing of samples after careful washing with water, acetone, and diethyl ether followed by drying.

2,2,2-Triphenylethylmercuric Chloride (1).—A solution of 2,2,2-triphenylethyllithium was prepared from chloro-2,2,2-triphenylethane and lithium ribbon in freshly distilled tetrahydrofuran at −70° according to the procedure of Grovenstein and Williams.[14] The lithium reagent was quenched at −70° with mercuric chloride in diethyl ether to afford after recrystallization from ethanol–benzene a 42% yield of **1** as colorless crystals: mp 196.5–197.5°; nmr (CS_2) δ 7.17 (s, 15), 3.0 (s, 2).

Anal. Calcd for $C_{20}H_{17}HgCl$: C, 48.68; H, 3.47. Found: C, 48.76; H, 3.48.

Reduction of 1 with Sodium Borohydride.—The reduction of **1** with sodium borohydride was carried out employing the procedure of Brown and Geoghehan.[6] The products were recovered

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

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by extraction with diethyl ether followed by drying of the solution over $MgSO_4$.

In general, product identification was based on nmr analysis of the crude reaction mixtures and vpc retention times by comparison with known compounds. 1,1,2-Triphenylethanol, mp 88–89°, mmp 88–89° (lit.[15] mp 88–89°), was also identified as the major product from the reductions in the presence of air by column chromatography of the crude reaction mixture on silica gel using hexane as eluent, followed by recrystallization from hexane and comparison of its ir and nmr spectra with those of an authentic sample.

The following procedure was followed for reactions carried out on a high vacuum line. The mercurial 1 and the basic aqueous sodium borohydride solutions were mixed in a flask followed by six freeze–evacuate–thaw cycles to remove dissolved oxygen and other gases. A degassed flask of tetrahydrofuran over lithium aluminum hydride was then opened to the manifold and the desired amount of tetrahydrofuran was flash distilled into the reaction flask. The evacuated flask was then isolated from the vacuum system and stirred for the desired period. Normal work-up procedure followed.

It is noteworthy that, contrary to previous reports regarding reductions in aqueous solution,[16] significant gas evolution was observed in all sodium borohydride reductions carried out in aqueous tetrahydrofuran. This indicates that diborane may be produced since it would be rapidly hydrolyzed with evolution of hydrogen under the reaction conditions.[17]

Reduction of 1 with Lithium Aluminum Hydride and Sodium Bis(2-methoxyethoxy)aluminum Hydride.—The reductions of the organomercurial 1 with lithium aluminum hydride and sodium bis(2-methoxyethoxy)aluminum hydride were carried out in freshly distilled tetrahydrofuran under an argon atmosphere. After stirring for several hours the reaction mixtures were quenched with 10% H_2SO_4, extracted with diethyl ether, dried over $MgSO_4$, and analyzed by vpc and nmr.

Reduction of the Organomercurial with Sodium Amalgam.—The reduction of 2,2,2-triphenylethylmercuric chloride with 1.5% sodium amalgam was carried out according to the procedure of Sokolov, Rodina, and Reutov.[18] The products were recovered by extraction with diethyl ether followed by drying with $MgSO_4$.

Registry No.—1, 35341-90-3; sodium borohydride, 16940-66-2.

(15) C. Hell and F. Wiegandt, *Chem. Ber.*, **37**, 1429 (1904).
(16) F. G. Bordwell and M. L. Douglass, *J. Amer. Chem. Soc.*, **88**, 993 (1966).
(17) A. Stock and K. Friederici, *Chem. Ber.*, **46**, 1959 (1913).
(18) V. I. Sokolov, N. B. Rodina, and O. A. Reutov, *J. Organometal. Chem.*, **17**, 477 (1969).

Hydrogenolysis of Aromatic Halides with Thiophenol

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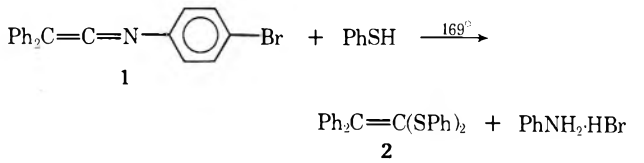
The hydrogenolysis of aromatic halides has received attention both as a mechanistic curiosity[2] and as a synthetic tool.[3] Reagents employed for halide hydrogenolyses include Friedel–Crafts catalysts,[2] triphenylphosphine,[4] triphenyltin hydride,[3] and standard reducing agents such as Raney nickel with base, hydrogen iodide, and catalytic systems. Of these reagents, only the triphenyltin hydride system offers much synthetic utility. We wish to report an additional system for effecting hydrogenolysis of aromatic halides.

In an investigation of the reaction of ketenimines with thiols, we observed that treatment of diphenylketene-*N*-(*p*-bromophenyl)imine (1) with excess thiophenol at 169° resulted in the production of diphenylketene diphenylmercaptal (2) and aniline hydrobromide in 84% yields, respectively.[5] To test the utility of the unexpected debromination observed, a series of model aromatic halides was treated with thiophenol.



1 2

The *o*- and *p*-bromoanilines and *p*-iodoaniline were found to undergo hydrogenolysis readily in refluxing thiophenol to produce aniline hydrobromine and aniline hydriodide in 78%, 88%, and quantitative yields, respectively. Only a 15.8% yield was obtained with *p*-chloroaniline, and no aniline hydrohalide was obtained from the treatment of *p*-fluoro- or *m*-bromoaniline with thiophenol. Hydrogenolysis of iodine also occurs with *p*-iodonitrobenzene (44.3%) and, in fact, with iodobenzene (9.0%). However, *p*-bromonitrobenzene did not undergo this reaction.

The results indicate that the ease of halogen removal is I > Br > Cl > F, and that haloanilines undergo hydrogenolysis of the halide more easily than halonitrobenzenes, which undergo hydrogenolysis of the halide more easily than halobenzenes. Although no mechanistic study has been undertaken on the reaction, the observation that radical initiators do not effect the reaction at a lower temperature leads one to lean toward an ionic mechanism such as has been demonstrated for the triphenylphosphine hydrogenolysis of aromatic halides.[4] The greater facility of hydrogenolysis of the iodide on *p*-iodonitrobenzene compared to iodobenzene would indicate the advantage of having an electron-withdrawing substituent in the para position and would suggest that the anilines may well be protonated prior to hydrogenolysis of the halide.

The excellent yields obtained for the hydrogenolysis of haloanilines with thiophenol and the reported utility of the triphenyltin hydride hydrogenolysis of other aromatic halides offer good synthetic procedures for the hydrogenolysis of bromo- and iodo-substituted compounds. In essence, thiophenol can be used effectively on aniline compounds for which the use of the tin hydride system is limited.

Experimental Section

Hydrogenolysis of Haloanilines.—The following procedure for the hydrogenolysis of *p*-bromoaniline with thiophenol typifies the method used for all haloanilines. A solution of 5.0 g (0.028 mol) of *p*-bromoaniline in 20 ml of freshly distilled thiophenol was heated to reflux for 3 hr. During reflux, aniline hydrobromide precipitated. The reaction mixture was cooled and the solid was collected to yield 4.4 g (88%) of aniline hydrobromide which was identical (ir and mixture melting point) with an authentic sample.

(1) (a) NDEA Predoctoral Fellow. (b) Taken in part from the Ph.D. Dissertation of J. R. W., Mississippi State University, Aug 1970.
(2) G. R. Pettit and D. M. Piatak, *J. Org. Chem.*, **25**, 721 (1960).
(3) D. H. Lorenz, P. Shapiro, A. Stern, and E. I. Becker, *ibid.*, **28**, 2332 (1963); G. F. Karabatsos, R. L. Shone, and S. E. Scheppele, *Tetrahedron Lett.*, 2113 (1964).
(4) H. Hoffmann and D. Michael, *Ber.*, **95**, 528 (1962).
(5) M. W. Barker and J. R. West, Abstracts, 21st Southeastern Regional Meeting of the American Chemical Society, Richmond, Va., 1969, Paper 204.

Under similar conditions *p*-iodoaniline yielded a quantitative amount of aniline hydroiodide in 1 hr, *o*-bromoaniline produced a 78.4% yield of aniline hydrobromide in 6 hr, and *p*-chloroaniline produced a 15.8% yield of aniline hydrochloride in 96 hr. Neither *p*-fluoro- nor *m*-bromoaniline showed evidence of hydrogenolysis with thiophenol.

Hydrogenolysis of *p*-Iodonitrobenzene.—A mixture of 6.1 g (0.024 mol) of *p*-iodonitrobenzene, 10 ml of thiophenol, and 10 ml of aniline was heated to reflux for 17 hr. Aniline hydriodide (2.4 g, 44.3%) was isolated from the reaction mixture by aqueous extraction. Under similar conditions, *p*-bromonitrobenzene gave no evidence for hydrogenolysis.

A similar reaction without ainiline was studied to see if nitrobenzene could be isolated from the hydrogenolysis of *p*-iodonitrobenzene. A solution of 10 g (0.04 mol) of *p*-iodonitrobenzene and 60 ml of thiophenol was refluxed for 7 hr. The precipitate formed was collected, washed with ether, and dissolved in water. The solution was made alkaline with NaOH and extracted with ether. Removal of the solvent left 1 g (27% yield) of aniline identified by retention time on a 6-ft 3% SE-30 column at 100° in a Hewlett-Packard Model 402 gas chromatograph. Apparently an oxidation–reduction reaction occurs between thiophenol and the nitro group. No nitrobenzene was observed in the gc. Treatment of nitrobenzene with thiophenol under similar conditions gave little aniline; thus the reduction observed must be intimately associated with the hydrogenolysis reaction.

Hydrogenolysis of Iodobenzene.—A solution of 10.0 g (0.05 mol) of iodobenzene, 10 ml of thiophenol, and 10 ml of aniline was heated to reflux for 7 days. Aniline hydriodide (1.0 g, 9.0% yield) was isolated from the reaction mixture by collection of the solid. From a similar reaction, a gc of the filtrate on a 6-ft 3% SE-30 column at 65° in a Hewlett-Packard Model 402 gas chromatograph showed the presence of a small amount of benzene identified by retention time of an authentic sample.

Attempted Radical Initiation.—No reaction between thiophenol and *p*-bromoaniline was observed at 100° with or without the addition of AIBN.

Registry No.—Thiophenol, 108-98-5; *p*-bromoaniline, 106-40-1; *p*-iodoaniline, 540-37-4; *o*-bromoaniline, 615-36-1; *p*-chloroaniline, 106-47-8; *p*-iodonitrobenzene 636-98-6; iodobenzene, 591-50-4.

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The Addition of *tert*-Butyl Hypochlorite to Isocyanates[1]

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Addition of *tert*-butyl hypochlorite (2) to an isocyanate (1) gives an unisolated *N*-chlorocarbamate (3). Previously known adducts required insertion of the azomethine linkage of an isocyanate into the single bond between (1) hydrogen and each of many elements; (2) oxygen and certain elements, *e.g.*, titanium, tin, and carbon (the reactive ether linkage in orthoformates, formaldehyde acetals, and epoxides); (3) silicon and nitrogen; (4) boron and sulfur; and (5) phosphorus and chlorine.[2] The present work is terminal and grew out of a continuing study of the relationship between an *N*-acylimine and the isomeric isocyanate, $R_2C{=}NC(=O)Z$ and $R_2C(Z)N{=}C{=}O$.

Under mild conditions the hypochlorite 2 combined with cyclohexyl, benzhydryl, and phenyl isocyanates (**1a–c**). An assumed initial formation of an undetected *N*-chlorocarbamate (**3**) provided an explanation for each product formation. From **3a** hydrolysis during work-up produced *N*-cyclohexylcarbamate (**4a**) and dehydrochlorination to a small extent gave the *N*-*tert*-butoxycarbonylimine (**5a**) of cyclohexanone, detected by hydrolysis into *tert*-butyl carbamate and a product (**6**) in low yield which appears to be a hydrogen chloride adduct.[3]

At 70° an adduct obtained from the neat mixture of 2 and benzhydryl isocyanate (**1b**) underwent dehydrochlorination, affording the *N*-*tert*-butoxycarbonylimine (**5b**) of benzophenone in 87% yield. Identification of benzophenone and *tert*-butyl carbamate, obtained upon hydrolysis, confirmed the structure of the imine. In contrast with the thermolysis of the *N*-benzoylimine of benzophenone at 110–115° into benzophenone[4] (and presumably benzonitrile) the ester **5b** was thermally stable under 170°. At 180° it fragmented to give the imine of benzophenone in 57% yield, but the ketone itself was not detected. Presumably carbon dioxide and isobutylene were also formed.

An apparent rearrangement of the *N*-chloro-*N*-phenylcarbamate (**3c**), obtained from 2 and **1c**, gave both *o*- and *p*-chlorophenylcarbamates (**7** and **8**), with the latter in slight predominance.[5] Each was identified by saponification and decarboxylation into the corresponding chloroaniline.

$$\underset{1}{RNCO} + \underset{2}{(CH_3)_3COCl} \longrightarrow \underset{3}{RN(Cl)CO_2C(CH_3)_3}$$

a, R = $(CH_2)_5CH$; b, R = $(C_6H_5)_2CH$; c, R = C_6H_5

$$\underset{4}{R'_2CHNHCO_2C(CH_3)_3} \xleftarrow{H_2O} \underset{3}{R'_2CHN(Cl)CO_2C(CH_3)_3} \xrightarrow{-HCl} \underset{5}{R'_2C{=}NCO_2C(CH_3)_3}$$

a, $R'_2 = (CH_2)_5$; b, R′ = C_6H_5

$$\mathbf{5a} \xrightarrow{HCl} \underset{6}{R_2'C(Cl)NHCO_2C(CH_3)_3}$$

$$\mathbf{3c} \longrightarrow \textit{o}\text{-}\mathbf{7} \text{ and } \textit{p}\text{-}ClC_6H_4NHCO_2C(CH_3)_3 \quad (\mathbf{8})$$

$$\mathbf{5b} \xrightarrow{180^\circ} (C_6H_5)_2C{=}NH + [(CH_3)_2C{=}CH_2 + CO_2]$$

Experimental Section

***tert*-Butyl *N*-Cyclohexylcarbamate (4a).**—A mixture of 5.5 g (44.0 mmol) of cyclohexylisocyanate and 5.1 g (47.0 mmol) of *tert*-butyl hypochlorite in 30 ml of petroleum ether (bp 30–60°) was stirred at room temperature for 15 hr in a 50-ml three-necked round-bottom flask equipped with a stream of dry nitrogen, a stirrer, and a condenser with a drying tube. Unreacted isocyanate, detected by ir absorption at 2250 cm^{-1}, disappeared

(1) Financial support was received from NASA Grant No. NGR 14-012-004.

(2) S. Ozaki, private communication.

(3) A referee suggests an alternative transformation which does not require the assumption that water is available during chromatography: **3** + HCl (anhydrous) → **4** + Cl_2.

(4) R. Ahmed and W. Lwowski, *Tetrahedron Lett.*, 3611 (1969).

(5) Migration of chlorine in *N*-chloroacetanilide gives *o*- (32.5%) and *p*-chloroacetanilide (67.5%) as reported by J. Kennedy, P. Orton and A. E. Bradfield, *J. Chem. Soc.*, 986 (1927). The evidence indicates an intermolecular process: J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill, New York, N. Y., 1968, p 431.

after 15 ml of absolute ethanol was added with thorough stirring. Solvents were removed and the residue was separated from a column of silica gel (15 × 0.5 in.). The carbamate 4a was eluted with 900 ml of a 1:1 mixture of *n*-hexane and benzene; after removal of solvent, sublimation at 40° (0.4 mm) gave 3.16 g (39.2%) of a colorless powder, mp 78–79.5° dec, identical by melting point and ir comparison with an authentic sample prepared from cyclohexyl isocyanate and *tert*-butyl alcohol, ir ($CHCl_3$) 3470 (NH), 1705 (CO), and 1510 cm^{-1} (secondary amide). Next the chlorocyclohexylcarbamate 6 was eluted with 300 ml of a 1:2 mixture of *n*-hexane and benzene; after removal of solvent, sublimation at 80° (0.4 mm) gave 112 mg (1.2%) of a colorless powder: mp 124–125.5°; ir ($CHCl_3$) 3450 (NH), 1705 (CO), and 1495 cm^{-1} (secondary amide). *Anal.* Calcd for $C_{11}H_{20}NO_2Cl$: C, 56.52; H, 8.62; N, 5.99; Cl, 15.16. Found: C, 56.31; H, 8.71; N, 5.82; Cl, 15.47.

A third component was eluted with 300 ml of chloroform; after removal of solvent, sublimation at 40° (0.4 mm) gave 0.11 g (2.1%) of *tert*-butyl carbamate as colorless needles, mp 106–108°. Finally 600 ml of 95% ethanol removed cyclohexylamine hydrochloride; after removal of solvent, sublimation at 120° (0.4 mm) gave 1.26 g (21.1%) of a colorless powder, mp 204° dec. Both *tert*-butyl carbamate and cyclohexylamine hydrochloride were identical with authentic samples.

In a similar reaction between benzhydryl isocyanate and *tert*-butyl hypochlorite (in a molar excess) without a solvent at 70°, the ester **5b** was isolated by sublimation at 85° (0.4 mm) in 87% yield: ir ($CHCl_3$) 1725 (CO) and 1625 cm^{-1} (C=N); nmr ($CDCl_3$) δ 7.5 (s, 10, C_6H_5), 1.3 [s, 9, $(CH_3)_3C$]; mass spectrum (70 eV) *m/e* 281 (M^+). *Anal.* Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.97; mol wt, 281.36. Found: C, 76.58; H, 6.83; N, 4.94. Hydrolysis gave *tert*-butyl carbamate and benzophenone, identified by comparison with authentic data. Decomposition resulted from heating in a sealed melting point tube at 180° for 2 hr. Dissolving the combined residues from six tubes containing a total of 56 mg of 5b in petroleum ether which was then saturated with a stream of anhydrous hydrogen chloride gave 25 mg (57%) of the hydrochloride of the imine of benzophenone, sublimation point 250°,[6] ir absorption identical with an authentic spectrum.

From phenyl isocyanate and *tert*-butyl hypochlorite in equimolar portions in petroleum ether at room temperature *o*- (7) and *p*-chlorophenylcarbamate (8) were obtained by elution from silica gel with hexane. The ortho isomer separated first, 1.7 g (17.7%) after distillation at 120–122° (0.4 mm). Redistillation gave a yellow liquid with constant $n^{25}D$ 1.5231; ir ($CHCl_3$) 3420, 1725, and 1510 cm^{-1}; nmr ($CDCl_3$) δ 8.37–8.22 (br, 1, NH), 7.32 (m, 4, C_6H_4), 1.52 [s, 9, $(CH_3)_3C$]; mass spectrum (70 eV) *m/e* 227 (M^+). *Anal.* Calcd for $C_{11}H_{14}NO_2Cl$: C, 58.02; H, 6.19; N, 6.15; Cl, 15.57; mol wt, 227.69. Found: C, 57.82; H, 6.16; N, 6.12; Cl, 15.55.

The para isomer 8 sublimed at 80° (0.4 mm) and gave 2.27 g (23.5%) of a colorless powder, mp 95–99°, which recrystallized from *n*-heptane as needles: mp 102–104°; ir ($CHCl_3$) 3420, 1725, and 1510 cm^{-1}; nmr ($CDCl_3$) δ 7.28 (m, 4, C_6H_4), 6.7 (br, 1, NH), 1.5 (s, 9, $(CH_3)_3C$]; mass spectrum (70 eV) *m/e* 227 (M^+). Chloroform eluted *N,N'*-diphenylurea identified by comparison with authentic data.

Registry No.—**2**, 507-40-4; **4a**, 3712-40-1; **5b**, 35426-67-6; **6**, 35426-68-7; **7**, 35426-69-8; **8**, 18437-66-6.

(6) R. Appel and A. Hauss, *Chem. Ber.*, **93**, 405 (1960).

Anomalous Properties of Halogen Substituents

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The electron-attracting tendencies of halogen substituents in aliphatic compounds are well established, on the basis of such familiar evidence as the increase in the acidity of carboxylic acids[1] and many other organic compounds[2,3] upon substitution by halogens. A quantitative measure of this "inductive effect" is the substituent constant σ_I.[4,5] The values of σ_I for the halogens are given in Table I; as anticipated, they show the same trend as the electronegativities of these elements.

TABLE I
HALOGEN ELECTRONEGATIVITIES AND SUBSTITUENT CONSTANTS

Halogen	Electronegativity[a]	σ_I[b,c]	σ_R[b,c]
F	4.0	+0.51	−0.34
Cl	3.0	+0.47	−0.20
Br	2.8	+0.45	−0.16
I	2.5	+0.39	−0.12

[a] L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960. [b] P. R. Wells, S. Ehrenson, and R. W. Taft, in "Progress in Physical Organic Chemistry," Vol. 6, A. Streitwieser and R. W. Taft, Ed., Interscience, New York, N. Y., 1968. [c] The more positive the value of σ_I, the greater is the electron-attracting tendency; the more negative the value of σ_R, the greater is the electron-donating tendency.

These electron-attracting powers are presumably also operative when the halogens are substituents on aromatic rings; indeed, the halobenzenes are less reactive toward electrophilic attack than is benzene.[6] However, substituents which simply withdraw electrons from the ring are found to be meta directing,[7] whereas the halogens are ortho and para directing.[6,7] This is generally interpreted as indicating a concomitant donation, or feedback, of electrons to the ring by the halogen substituent,[7,8] and is usually described as a "resonance effect." Surprisingly, this supposed electron-donating tendency increases in the order I < Br < Cl < F; the greatest feedback seems to occur when the substituent is fluorine, the most electronegative element. For instance, fluorine deactivates a benzene ring less than does chlorine,[6] and in fact, using partial rate factors, some electrophilic substitutions are found to occur more rapidly at the para position in fluorobenzene than at any single position in benzene. Relatively stable protonated fluorobenzenes have even been observed.[9] The extent of this "resonance effect" is measured by another substituent constant, σ_R (Table I).[10]

The trend in the supposed electron-donating powers, as indicated by the σ_R values, and especially the be-

(1) See, for example, R. T. Morrison and R. N. Boyd, "Organic Chemistry," 2nd ed, Allyn and Bacon, Boston, Mass., 1966.
(2) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962.
(3) B. L. Dyatkin, E. P. Mochalina, and I. L. Knunyants, *Tetrahedron*, **21**, 2991 (1965).
(4) R. W. Taft in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956.
(5) R. W. Taft, *J. Phys. Chem.*, **64**, 1805 (1960); R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davis, *J. Amer. Chem. Soc.*, **85**, 709 (1963).
(6) L. M. Stock and H. C. Brown in "Advances in Physical Organic Chemistry," Vol. 1, V. Gold, Ed., Academic Press, New York, N. Y., 1963.
(7) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969.
(8) W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, New York, N. Y., 1969. This book gives an excellent review of many of the points discussed in this paper.
(9) G. A. Olah and T. E. Kiovsky, *J. Amer. Chem. Soc.*, **89**, 5692 (1967).
(10) R. W. Taft and I. C. Lewis, *ibid.*, **81**, 5343 (1959); R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *ibid.*, **85**, 3146 (1963).

TABLE II

VALUES OF OVERLAP AND REPULSION INTEGRALS

Halogen, X	C–X bond length,[a] Å	Overlap values: Slater-type orbitals	Overlap values: Cusachs–Corrington orbitals	$R_{\pi C-\pi X}$	$R_{\pi C-\sigma X}$	$R_{\sigma C-\pi X}$	$R_{\sigma C-\sigma X}$
F	1.328	0.146	0.217	0.353	0.373	0.422	0.457
Cl	1.70	0.166	0.230	0.279	0.315	0.309	0.361
Br	1.85	0.152	0.225	0.256	0.296	0.279	0.334
I	2.05	0.138	0.207	0.231	0.275	0.246	0.304

[a] These are the average C–X bond lengths for halogens substituted on aromatic rings, as given in "Tables of Interatomic Distances and Configuration in Molecules and Ions," Supplement, L. E. Sutton, Ed., Special Publication No. 18, The Chemical Society, London, 1965.

havior of fluorine, are commonly explained in terms of overlap considerations.[8,11–13] It is argued that the extent of electron back-donation depends upon the degree of overlap between the filled outer $p\pi$ orbitals of the halogen and the $2p_\pi$ orbitals of the aromatic ring carbon to which it is bonded. This overlap, it is claimed, should decrease in the order F > Cl > Br > I, due to the increasing carbon–halogen bond length and the increasing disparity between the sizes of the carbon and the halogen $p\pi$ orbitals. Since the C–F bond is by far the shortest of the four (Table II), and since the p_π orbitals of fluorine are supposedly the most similar to those of carbon, the overlap, and hence the feedback of electrons, should be greatest in the case of fluorine.

In order to test this interpretation, we have evaluated the relevant overlap integrals, $\int(2p_{\pi C})(np_{\pi X})d\tau$, where n = 2, 3, 4, 5 and X = F, Cl, Br, I. Using Slater-type atomic orbitals with the optimized exponents of Clementi and Raimondi,[14] and taking the C–X bond lengths to be the average values for the respective halogens substituted on aromatic rings (Table II), the overlap values listed in column 3 of Table II were obtained.[15]

The results certainly do not support the overlap and back-donation theory. Not only are all four overlap values remarkably similar, but the C–F value, which the theory predicts to be very much the largest, is in fact *smaller* than both the C–Cl and the C–Br values! There is clearly no correlation between degree of overlap and σ_R.

To confirm these results, the overlap integrals were determined for another set of atomic orbitals, the Cusachs–Corrington "overlap-matched" orbitals, which are designed to reproduce as well as possible the overlaps of extended-basis-set self-consistent-field atomic orbitals.[16] The values obtained (Table II, column 4) are slightly different from the previous ones, as is to be expected when using a different set of atomic orbitals, but the same trend is observed. The key C–F overlap is again completely at variance with the theory. It is evident, therefore, that some factor other than overlap and back-donation is responsible for the observed trend in the halogen σ_R values.

It has been suggested that this factor is a repulsive interaction between the outer p_π electrons of the halogen and the $2p\pi$ electrons of the aromatic ring, especially those associated with the carbon on which the halogen is substituted.[17–19] This repulsion has the effect of pushing the aromatic π electrons away from the substituted position and into the ring, and will lead to some buildup of π charge at the ortho and para positions.[17,20]

If these repulsive interactions are indeed of such key importance, then there should be a correlation between the coulomb integrals

$$R_{\pi C-\pi X} = \int 2p_{\pi C}(1)2p_{\pi C}(1)\frac{1}{r_{12}}np_{\pi X}(2)np_{\pi X}(2)d\tau_1 d\tau_2$$

and the substituent constants σ_R. The indicated integral is equal to the coulombic energy of repulsion between an electron in a $2p_\pi$ orbital of carbon and one in an np_π orbital of atom X. These integrals were evaluated, using the Slater-type atomic orbitals mentioned earlier, and their values are in column 5 of Table II.[21] The results show the desired trend: $R_{\pi C-\pi F} \gg R_{\pi C-\pi Cl} > R_{\pi C-\pi Br} > R_{\pi C-\pi I}$. The relationship of these integral values to the substituent constants σ_R is examined more precisely in Figure 1, and the correlation is found to be excellent. A nearly exact linear relationship exists between the repulsion integrals, $R_{\pi C-\pi X}$, and the corresponding σ_R values. This is strong support for the resulsion theory.

While the experimentally observed effects which the present discussion has sought to explain probably involve primarily π electron interactions, a similar line of reasoning can help to elucidate certain rather puzzling

(11) J. N. Murrell, S. F. A. Kettle, and J. M. Tedder, "Valence Theory," Wiley, New York, N. Y., 1965.

(12) R. D. Chambers and R. H. Mobbs in "Advances in Fluroine Chemistry," Vol. 4, M. Stacey, J. C. Tatlow, and A. G. Sharpe, Ed., Butterworths, London, 1965.

(13) J. B. Hendrickson, D. J. Cram, and G. S. Hammond, "Organic Chemistry," 3rd ed, McGraw-Hill, New York, N. Y., 1970.

(14) J. C. Slater, *Phys. Rev.*, **36**, 57 (1930); E. Clementi and D. L. Raimondi, *J. Chem. Phys.*, **38**, 2686 (1963).

(15) E. A. Boudreaux, L. C. Cusachs, and L. D. Dureau, "Numerical Tables of Two-Center Overlap Integrals," W. A. Benjamin, New York, N. Y., 1970.

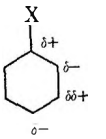
(16) L. C. Cusachs, and J. H. Corrington in "Sigma Molecular Orbital Theory," O. Sinanoglu and K. B. Wiberg, Ed., Yale University Press, 1970.

(17) D. T. Clark, J. N. Murrell, and J. M. Tedder, *J. Chem. Soc.*, 1250 (1963).

(18) J. N. Murrell, "The Theory of the Electronic Spectra of Organic Molecules," Wiley, New York, N. Y., 1963.

(19) An interesting quantitative treatment of halogen substituent effects, which also emphasizes the importance of repulsive interactions, has been given by D. P. Craig and G. Doggett, *Mol. Phys.*, **8**, 485 (1964).

(20) This point is discussed in ref 17, and also by A. R. Katritzky and R. D. Topsom, *J. Chem. Educ.*, **48**, 427 (1971). Both invoke the structure



(21) The integrals were computed by the Electronic Structure Software Center, Department of Physics, University of Utah, through the courtesy of Professor Frank E. Harris.

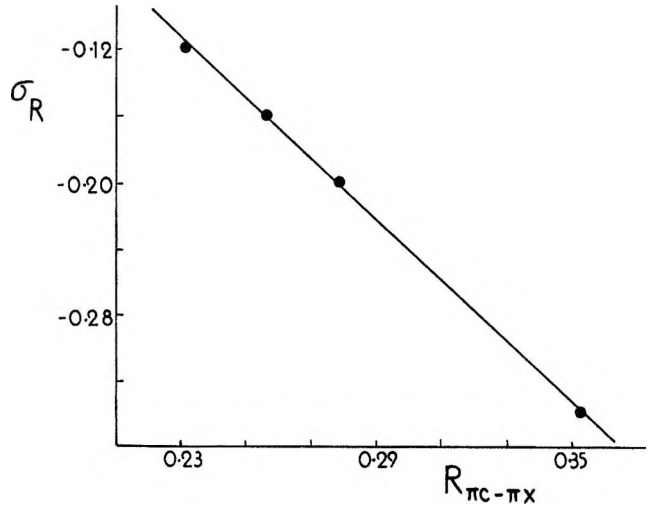


Figure 1.—Relationship between the halogen substituent constants σ_R and the repulsion integrals $R_{\pi C-\pi X}$, where X = F, Cl, Br, I. The repulsion integrals are given in atomic units (1 au = 627.2 kcal/mol).

features of some nonaromatic systems. It has already been shown that several anomalous properties of fluorine, both as a free atom and also in various inorganic and aliphatic compounds, can be explained in terms of the exceptionally strong repulsive force exerted by the fluorine atom's electrons upon any approaching electron.[22] Another interesting anomaly is the fact that the localization of the negative charge in the trihaloacetate and the trihalomethide anions appears to increase as the halogen changes from bromine to fluorine.[23,24] The least delocalization occurs with fluorine, despite its being the most electronegative. Again, this can be interpreted as the result of a very strong repulsive interaction between the fluorine electrons and the negative charge, an interaction which diminishes markedly in going on to chlorine and bromine. In columns 6–8 of Table II are presented the values of three more types of coulomb repulsion integrals: $R_{\pi C-\pi X}$, $R_{\sigma C-\pi X}$, and $R_{\sigma C-\sigma X}$.[21] These integrals represent the other possible combinations of p_π and p_σ orbitals on the carbon and the halogen atoms; they are defined analogously to $R_{\pi C-\pi X}$. In each case, the same trend is observed as before: $R_{C-F} \gg R_{C-Cl} > R_{C-Br}, > R_{C-I}$. Thus, whether any given situation of interest involves primarily one of these types of interaction or, as is more likely, two or more of them simultaneously, it is evident that a consideration of electronic repulsion interactions will help to explain many of the seemingly anomalous properties of the halogens, and of fluorine in particular.

Registry No.—F, 16984-48-8; Cl, 16887-00-6; Br, 24959-67-9; I, 20461-54-5.

Acknowledgments.—The authors wish to thank Dr. Ieva Ruks Politzer for suggesting this study, and for very helpful discussions. They also greatly appreciate the assistance of Dr. Milan Randic, Professor Frank E. Harris, and Dr. David Klint in the evaluation of the repulsion integrals.

(22) P. Politzer, *J. Amer. Chem. Soc.*, **91**, 6235 (1969).
(23) J. Hine and N. W. Burske, *ibid.*, **78**, 3337 (1956).
(24) K. R. Brower, B. Gay, and T. L. Konkol, *ibid.*, **88**, 1681 (1966).

Synthesis and Reactivity of 2,2′-Bis(phenylethynyl)diphenylacetylene

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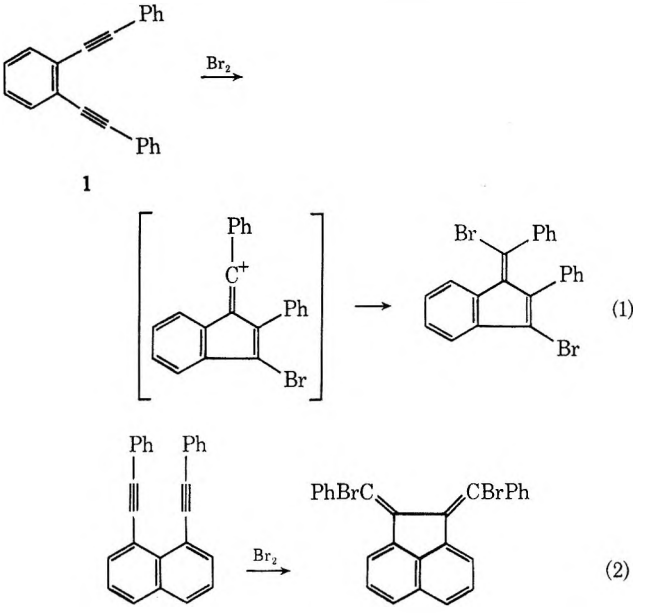
Interaction between spatially proximal acetylenic groups on chemical reaction has been demonstrated.[1-6] This occurs even if there is little angle strain to be relieved on addition of reagents (eq 1[1] and 2[5]). Evidence for the concerted nature of acetylene–acetylene interaction following attack of electrophilic reagents on **1** has been presented.[1] The type of ring system produced by addition of reagents to oligoacetylenes of this type must be at least partially dependent on the geometrical disposition of the triple bonds relative to one another. On consideration of the above results we have been prompted to synthesize the title triyne **2** to see whether it is attacked by electrophilic reagents in a manner analogous to **1**. This is observed (Scheme I).



Results

The reaction of **2** with controlled amounts of bromine affords, in addition to starting material, a mixture of di- and tetrabromides. Chromatography of the hexane-soluble portion of the reaction product afforded an oily dibromide that is assigned the gross structure **3**

(1) H. W. Whitlock, Jr., P. E. Sandvick, L. E. Overman, and P. B. Reichardt, *J. Org. Chem.*, **34**, 879 (1969); H. W. Whitlock, Jr., and P. E. Sandvick, *J. Amer. Chem. Soc.*, **88**, 4525 (1966).
(2) E. Muller, J. Heiss, and M. Sauerbier, *Justus Liebigs Ann. Chem.*, **723**, 61 (1969); E. Muller, M. Sauerbier, and G. Zountsas, *Tetrahedron Lett.*, 3003 (1969); E. Muller, J. Heiss, M. Sauerbier, D. Streichfuss, H. Geisel, and R. Thomas, *ibid.*, 1195 (1968); E. Muller, H. G. Fritz, K. Munk, H. Straub, and H. Geisel, *ibid.*, 5167 (1969).
(3) E. H. White and A. A. F. Sieber, *ibid.*, 2713 (1967).
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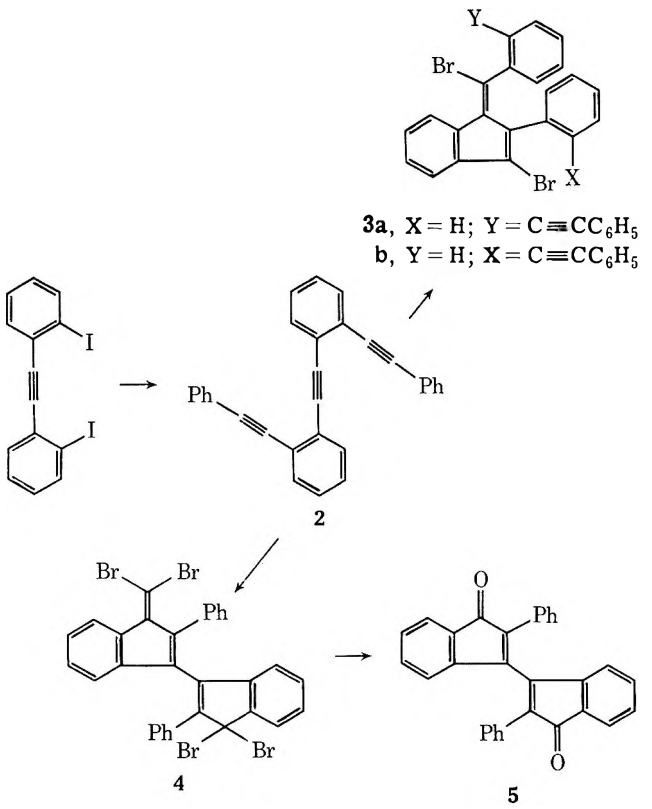
(5) B. Bossenbroek, D. C. Sanders, H. M. Curry and H. Shechter, *J. Amer. Chem. Soc.*, **91**, 371 (1969).
(6) R. H. Mitchell and F. Sondheimer, *Tetrahedron*, **24**, 1397 (1968).

SCHEME I

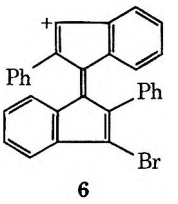


on the basis of its ir and uv spectra, both characteristic of the benzofulvene chromophore. Our inability to isolate crystalline material from the oil is consistent with the presence of *cis–trans* and structural isomers (**3a** *vs.* **3b**) of **3** arising from the site of attack of bromine on **2**. The major product from bromination of **2** was a broad-melting crystalline dibromide–tetrabromide mixture. To determine the number of rings formed, this mixture was reduced with a large excess of sodium in ethanol. A low voltage mass spectrum of the product obtained indicated that hydrocarbons $C_{30}H_{24}$ and $C_{30}H_{30}$ were present in approximately equal amounts. Assuming that the aromatic rings would not be reduced under these conditions[7] the latter hydrocarbon must be derived from acyclic bromides in which *no* acetylene–acetylene bridging occurred during bromine addition. This is in marked contrast to the behavior of **1** in which bridging accompanies electrophilic attack. The $C_{30}H_{24}$ product, possessing three double-bond equivalents other than those associated with the aromatic rings, is thought to contain a double bond on the basis of the uv spectrum [$E^{1\%}_{1\,cm}$ (Et_2O) 0.2 at 273 mμ] of the hydrocarbon mixture. A hydrocarbon with two rings and one double bond may arise from tetrabromide **4** (see below) or its dibromide precursor.

Reaction of **2** with a large excess of bromine afforded, in addition to the above di- and tetrabromide mixture, a crystalline and apparently homogeneous tetrabromide **4**. The isolation of 3,3′-bi(2-phenylindenone) (**5**) from the silver acetate mediated acetolysis of **4** provides confirmation of the assigned structure. Biindenone **5** was synthesized from reaction of 2-phenyl-3-bromoindenone with copper powder[8] in hot dimethylformamide.

(7) D. P. Wyman, *J. Org. Chem.*, **27**, 3712 (1962).
(8) P. K. Gore and G. K. Hughes, *J. Chem. Soc.*, 1615 (1959).

Our results are interpretable in terms of a domino-like folding of the triple bonds in **2** similar to the behavior of **1** on electrophilic attack, at least in the initial stages of the reaction. It seems unlikely that the carbon skeleton of **4** arises in a single cyclization process as this would involve vinyl cations, *e.g.*, **6**, incapable of resonance stabilization.[9–12] Instead we feel that



6

4 arises as a product of secondary attack of bromine on one of the **3** species. The apparent reluctance of **2** to react with bromine relative to the reactivity of its bromination products may reflect the presence of an additional electronegative phenylethynyl substituent in **2**.

Experimental Section[13]

2,2′-Diiododiphenylacetylene.—To a stirred solution of 4.95 g (0.015 mol) of dibromodiphenylacetylene[14] in 50 ml of ether under nitrogen at 0° was added dropwise 21 ml (0.046 mol) of a 2.2 *M* solution of *n*-butyllithium in hexane. A stirred ethereal solution containing 14 g (0.055 mol) of iodine was then added and the dark brown solution was stirred for 30 min at 25°. After addition of 75 ml of 10% sodium bisulfite solution, the reaction mixture was worked up to afford 6.2 g of brown solid. Crystallization gave 4.4 g (69% yield) of 2,2′-diiodophenylacetylene as colorless needles: mp 106–106.5° (ethanol); λ^{EtOH}_{max} 315 mμ (ε 16,400), 305 (13,900), 294 (20,900), 238 (25,000), 229 (26,000), with shoulders at 286 and 278 mμ; δ ($CDCl_3$, 100 MHz), 7.86 (1 H, d, J = 8 Hz), 7.59 (1 H, d, J = 7.5 Hz), 7.31 (1 H, t, J = 7.5 Hz), 7.00 (1 H, t, J = 7.5 Hz). Further splitting was observed.

Anal. Calcd for $C_{14}H_8I_2$: C, 39.10; H, 1.88. Found: C, 39.14; H, 1.91.

2,2′-Bis(phenylethynyl)diphenylacetylene (**2**).—A mixture of 174 mg (0.4 mmol) of 2,2′-diiododiphenylacetylene and 155 mg (0.94 mmol) of cuprous phenylacetylide[15] in 21 ml of pyridine was refluxed with stirring under nitrogen for 9 hr. The cooled reaction mixture was concentrated, diluted with water, and worked up. The product, 0.4 g, was chromatographed on Florisil to afford 93 mg (61% yield) of **2** as colorless needles: mp 108–109° (ethanol); $\lambda^{CHCl_3}_{max}$ 4.5 μ; λ^{EtOH}_{max} 313 mμ (ε 22,900), 292 (33,600), 265 (68,000), 250 (41,800), with shoulders at 340 and 275 mμ; δ ($CDCl_3$) 7.7–7.35 (8 H, m), 7.35–7.05 (10 H, m); R_f 0.25.

Anal. Calcd for $C_{30}H_{18}$: C, 95.21; H, 4.79. Found: C, 95.23; H, 4.74.

Reaction of 2 with 1.1 Equiv of Bromine.—To a solution of 0.5 g (1.32 mmol) of **2** in 12 ml of chloroform at 0° was added, over 5 min, 0.23 g (1.45 mmol) of bromine in 25 ml of chloroform. After the mixture was stirred for 1 hr, 50 ml of 5% sodium thiosulfate solution was added. The aqueous layer was separated and extracted three times with chloroform. The combined extracts were washed with thiosulfate solution and water, dried over anhydrous sodium sulfate, and concentrated to a yellow gum. Trituration with hexane afforded 0.3 g of a yellow hexane-insoluble solid (mixture A). Repeated recrystallization of mixture A afforded yellow needles: mp 170–195° (benzene–hexane); λ^{MeOH}_{max} 370 mμ (sh, 1900), 320 (sh, 13,300), 307 (32,500),

(9) Z. Rappoport and Y. Apeloig, *J. Amer. Chem. Soc.*, **91**, 6734 (1969).
(10) D. S. Noyce and M. D. Schiavelli, *ibid.*, **90**, 1020 (1968).
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(14) H. W. Whitlock and J. K. Reed, *J. Org. Chem.*, **34**, 874 (1969).
(15) C. E. Castro, E. J. Gaughan and D. C. Owsley, *ibid.*, **31**, 4071 (1966).

295 (32,400), 282 (33,500), 273 (32,400); λ_{max}^{KBr} 7.55 μ; R_f 0.08, 0.13, 0.21, 0.32.

Anal. Calcd for 61:39 $C_{30}H_{18}Br_2$–$C_{30}H_{18}Br_4$: C, 60.86; H, 3.07; Br, 35.97. Found: C, 60.53; H, 3.20; Br, 35.95.

The mass spectrum of mixture A (190° probe temperature) exhibited prominent peaks at 536, 538, 540 ($C_{30}H_{18}Br_2$, P), 456, 458 (P − HBr), 378 (P − 2Br), and 376 (P − 2HBr).

Preparative tlc of mixture A (11 mg) on silica gel afforded 4 mg of orange needles: mp 309–316°; λ_{max}^{KBr} 5.97 μ; λ_{max}^{MeOH} 430 μ (4400), 335 (15,500), 321 (15,600), 305 (21,500), 267 (51,000); *m/e* 410.

Anal. Calcd for $C_{30}H_{18}O_2$: C, 87.78; H, 4.42. Found: C, 87.81; H, 4.41.

Chromatography of the hexane-soluble fraction afforded a yellow oil in 23% yield that was a mixture of two components: R_f 0.32, 0.38; $\lambda_{max}^{Et_2O}$ 327 mμ (sh, ϵ 11,500), 275 (43,400), 244 (35,800); $\lambda_{max}^{CHCl_3}$ 4.5, 7.41 μ; *m/e* 536, 538, 540 ($C_{30}H_{18}Br_2$, P), 457, 459 (P − Br), 378 (base, P − Br_2).

Anal. Calcd for $C_{30}H_{18}Br_2$: C, 66.94; H, 3.37; Br, 29.69. Found: C, 66.52; H, 3.58; Br, 29.84.

Triyne **2** was also isolated in 19% yield.

Reduction of Mixture A.—Sodium, 13 g, was added in small portions to a suspension of 0.3 g (0.56 mmol) of mixture A in 80 ml of refluxing ethanol. After addition of the sodium was complete, the reaction mixture was heated to reflux for 3 hr, diluted with water, and worked up to afford 239 mg of a dark green gum, $\lambda_{max}^{Et_2O}$ 273 mμ ($E_{1\,cm}^{1\%}$ 0.36). Chromatography of this on silica gel afforded 130 mg (61% yield) of a pale oil, $\lambda_{max}^{Et_2O}$ 273 mμ ($E_{1\,cm}^{1\%}$ 0.2). Low voltage mass spectrometry indicated the following composition: mass 384 ($C_{30}H_{24}$), 35%; 386 ($C_{30}H_{26}$), 8%; 388 ($C_{30}H_{28}$), 15%; 390 ($C_{30}H_{30}$), 32%.

Reaction of 2 with Excess Bromine.—Addition of 2.0 g (12.0 mmol) of bromine in 18 ml of chloroform to a stirred solution of 500 mg (1.32 mmol) of **2** in 10 ml of chloroform at 0° gave, after 5-min stirring and work-up, 1.0 mg of a yellow gum. Trituration of the gum with ether afforded 0.66 g of an ether-insoluble yellow solid. Three recrystallizations of this from benzene–hexane afforded 171 mg (19% yield) of a tetrabromide (**4**) as yellow needles: dec pt 200°; λ_{max}^{MeOH} 340–355 mμ (ϵ 5600), 261 (31,400); R_f 0.32.

Anal. Calcd for $C_{30}H_{18}Br_4$: C, 51.61; H, 2.60; Br, 45.79. Found: C, 51.54; H, 2.56; Br, 45.82.

Recrystallization of the combined mother liquors from the above recrystallization afforded 400 mg of yellow needles: mp 170–185° dec; λ_{max}^{MeOH} 307 mμ (ϵ 23,200), 274 (30,600), 370 (sh, 2200), 320 (sh, 12,600), 294 (sh, 24,800), 282 (sh, 28,200); R_f 0.1, 0.22, 0.28, 0.33.

Anal. Calcd for 60:40 $C_{30}H_{18}Br_2$–$C_{30}H_{18}Br_4$: C, 60.81; H, 3.06; Br, 36.13. Found: C, 60.35; H, 3.17; Br, 36.45.

Hydrolysis of Tetrabromide 4.—A mixture of 64 mg (0.092 mmol) of **4** and 79 mg (0.47 mmol) of silver acetate in 8 ml of acetic acid was heated under reflux for 4 hr. Water (8 ml) was added and refluxing was continued for 7 hr. The reaction mixture was filtered and the filtrate was worked up to afford 48 mg of red needles: mp 220–230° dec (benzene–hexane); λ_{max}^{MeOH} 446–466 mμ (ϵ 3400), 261 (51,700); $\lambda_{max}^{CHCl_3}$ 5.87 μ; *m/e* 410.

Anal. Calcd for $C_{30}H_{18}O_2$: C, 87.78; H, 4.42. Found: C, 87.48; H, 4.34.

3-Bromo-2-phenylindenone.—This compound was prepared by heating under reflux a mixture containing 2.2 g (0.01 mol) of 2-phenyl-1,3-indandione in chloroform and 4.3 g (0.016 mol) of phosphorus tribromide. After work-up, the crude product was chromatographed on silica gel and crystallized from hexane to give 3-bromo-2-phenylindenone, mp 73–75° (lit.[16] mp 73–74°), as orange needles in 45% yield.

3,3′-Bi(2-phenyl-1-indenone) (5).—A mixture of 197 mg (0.7 mmol) of 3-bromo-2-phenylindenone and 1 g of copper powder[8] in 6 ml of dry dimethylformamide was refluxed under nitrogen for 1 hr. An additional 1 g of copper was added and heating was continued for 3 hr. After addition of 150 ml of water, the mixture was filtered and the filtrate was worked up to afford 157 mg of a red oil. Chromatography of this on silica gel gave 19 mg (13% yield) of red solid, crystallization of which from benzene–hexane afforded 4 mg of **5**: mp 215–232° dec; λ_{max}^{MeOH} 450–465 mμ (ϵ 3400), 261 (52,200); $\lambda_{max}^{CHCl_3}$ 5.87 μ; *m/e* 410.13178 [$C_{30}H_{18}O_2$ (P) requires 410.1307], 381.12863 [$C_{29}H_{17}O$ (P − HCO) requires 381.1279], 333.09107 [$C_{24}H_{13}O_2$ (P − C_6H_5) requires 333.0916], 273.09408 [$C_{22}H_{12}$ (P − 2CO − C_6H_5) requires 267.09390]. Comparison (ir, mass spectrum) of **5** with the diketone obtained by hydrolysis of tetrabromide **4** showed them to be identical.

(16) E. Bergmann and W. Schreiber, *Chem. Ber.*, **66**, 44 (1933).

Registry No.—**2**, 35324-43-7; **4**, 35324-44-8; **5**, 35324-45-9; 2,2′-diiododiphenylacetylene, 35324-46-0.

Alkene Isomerization. An Improved One-Step Synthesis of *trans*-Cyclooctene[1]

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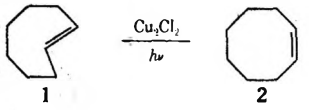
Received May 8, 1972

Ever since the pioneering work of Cope,[3] the unusual chemical properties of *trans*-cyclooctene (**1**) have attracted the attention of numerous chemists. In spite of the interest in this useful molecule, the published syntheses require a number of steps and/or proceed in low yield.[4] We would like to report a new procedure by which *trans*-cyclooctene (**1**) may be obtained in gram quanitities *via* one efficient light-induced step from its readily available isomer, *cis*-cyclooctene (**2**).



The isomerization of **2** was achieved by the irradiation of a stirred solution of Cu_2Cl_2 in a 2.6-fold excess of *cis*-cyclooctene at 2537 Å for 24 hr. Unisomerized **2** was removed *in vacuo* and the Cu(I) salts were successively extracted with aqueous ammonia and cyanide. Separation of **1** from **2** was accomplished by taking advantage of the former's solubility in aqueous silver nitrate.[4a] Liberation of the alkene from its silver complex afforded **1** in 19% yield (based on Cu_2Cl_2) in over 99% purity.

This photosensitized isomerization probably succeeds because the greater stability of the *trans*-cyclooctene–Cu_2Cl_2 complex shifts the equilibrium in favor of isomerization. Although other workers have employed Cu_2Cl_2 in the isomerization of alkenes which form stable complexes,[5] our work has demonstrated that prior synthesis and isolation of the Cu(I)–olefin complex is unnecessary. Thus, in addition to its convenience, our procedure allows isomerization of alkenes

(1) Support of this work by the National Science Foundation (Grant GP-17642) is gratefully acknowledged.

(2) Author to whom inquiries should be directed.

(3) A. C. Cope, R. A. Pike, and C. F. Spencer, *J. Amer. Chem. Soc.*, **75**, 3212 (1953).

(4) (a) A. C. Cope and R. D. Bach, *Org. Syn.*, **49**, 39 (1969); (b) G. Wittig and R. Polster, *Justus Liebigs Ann. Chem.*, **612**, 102 (1957); (c) E. J. Corey, F. A. Carey, and R. A. E. Winter, *J. Amer. Chem. Soc.*, **87**, 934 (1965); (d) J. S. Swenton, *J. Org. Chem.*, **34**, 3217 (1969); (e) E. Vedejs and P. L. Fuchs, *J. Amer. Chem. Soc.*, **93**, 4070 (1971).

(5) G. M. Whitesides, G. L. Goe, and A. C. Cope, *J. Amer. Chem. Soc.*, **91**, 2608 (1969).

which do not form readily isolable complexes[6] in good yield.[7] Even alkenes which form relatively stable complexes may be isomerized *via* our procedure with clearly superior results. For example, 1,5-*cis*,*cis*-cyclooctadiene (**3**) can be converted to 1,5-*cis*,*trans*-cyclooctadiene (**4**) in 30–40% yields. It is interesting to note, however, that Cu_2Br_2 was much less effective than Cu_2Cl_2.

Although the precise role of the Cu(I) salts cannot be specified at this time, we have made several pertinent observations. Irradiation of **1** in pentane in the presence of Cu_2Cl_2 gave an 80:20 mixture of **2** and **1**, respectively. As a result we conclude that the isomerization is reversible and that **1** and **2** and their respective complexes are in equilibrium under conditions of irradiation. It is known that Cu_2Br_2–olefin complexes have an absorption maximum at approximately 245 nm.[8] Irradiation of **2** under our conditions but in the absence of Cu_2Cl_2 failed to produce detectable **1**.[9] Irradiation in the presence of Cu_2Cl_2 at 2537 Å with a low-pressure lamp was far more effective than irradiation with an intense unfiltered broad spectrum medium-pressure lamp. We believe, therefore, that the complex itself is the probable primary absorbing species.

Our results suggest that, in principle, photosensitized cis–trans isomerization should be practical in any case where the respective complexes are on significantly different stability. A wide range of metals and ligands should be investigated in order to extend the generality of these isomerizations.

Experimental Section

Irradiations at 2537 Å were done in a Southern New England Ultraviolet Co. (Middletown, Conn.) "Rayonet" Model RS preparative photochemical reactor. Irradiation at longer wavelengths was carried out using a Hanovia 550-W medium pressure quartz mercury arc lamp equipped with a water-cooled Pyrex immersion well (Ace Glass Co., Vineland, N. J.). Infrared spectra were obtained with a Perkin-Elmer (Norwalk, Conn.) Model 137 Infracord. Analytical gas chromatographs were obtained on a Varian Associates (Palo Alto, Calif.) Aerograph Hy-Fi Model 600-D analytical gas chromatograph using 6 ft × 0.125 in. columns. Peak areas were measured by disc integration.

trans-**Cyclooctene** (**1**).—A 60-ml quartz irradiation tube was charged with 25 ml of *cis*-cyclooctene (**2**), (0.18 mol) and 7.0 g of freshly prepared[10] cuprous chloride (0.07 mol). The tube was fitted with a condenser and mercury bubbler and the entire apparatus was flushed with nitrogen. With all the cuprous chloride had dissolved in the olefin, the magnetically stirred mixture was irradiated at 2537 Å for 24 hr. The solution was then evaporated at 1.0 mm to a thick oil. To this oil was added concentrated ammonia and pentane, and it was shaken, decolorized with sodium cyanide, and separated. The aqueous layer was then extracted twice with pentane, and all pentane solutions were combined, dried over $MgSO_4$, and concentrated by distillation to *ca.* 50 ml. The solution was then extracted with 20% aqueous $AgNO_3$ and the aqueous layer was washed once with pentane. Treatment of the aqueous layer with concentrated ammonia followed by three pentane extractions yielded *trans*-cyclooctene in 99% purity (gc, Carbowax 20M). The extracts were dried over $MgSO_4$, concentrated by distillation using a wire gauze column, and finally evaporated at 0°, yield 1.4 g (19% based on Cu_2Cl_2 used) of *trans*-cyclooctene. The infrared spectrum of this material was identical with that of authentic *trans*-cyclooctene. Degassing the reaction mixture failed to change the yield.

Irradiation of *trans*-**Cyclooctene** (**1**) **with Cuprous Chloride.**—To the 60-ml quartz tube arranged as before were added 1.0 g (9.0 mmol) of *trans*-cyclooctene, 2.0 g (0.021 mol) of freshly prepared cuprous chloride, and 10 ml of pentane. The apparatus was flushed with nitrogen and irradiated, with vigorous magnetic stirring, at 2537 Å for 33 hr. Work-up consisted of adding the entire mixture to concentrated ammonia, decolorizing with sodium cyanide, and extracting three times with pentane. Analysis of the pentane extracts by gas chromatography (Carbowax 20M) showed that 80% of the material had been converted back to *cis*-cyclooctene (**2**). Distillation of the pentane extracts, using a wire gauze column, to *ca.* 25 ml, drying over $MgSO_4$, evaporation at 0° to an oil, and distillation of the oil at 55–60° (29 mm) gave 0.95 g (95%) of a mixture of the two cyclooctene isomers. Only traces of any other material were found by gc analysis.

Irradiation of *cis*-**Cyclooctene** (**2**) **without Cuprous Chloride.**—A 60-ml quartz tube equipped with magnetic stirring was charged with 25 ml (20 g, 0.18 mol) of *cis*-cyclooctene. The apparatus was flushed with nitrogen and irradiated at 2537 Å for 24 hr. Analysis by gas chromatography (Carbowax 20M) of the irradiated solution showed no evidence of isomerization. Repeating the experiment with 8 g (10 ml, 0.09 mol) of *cis*-cyclooctene dissolved in 40 ml of pentane again gave no evidence of isomerization.

cis,*trans*-**1,5-Cyclooctadiene** (**4**).—This compound can be prepared from the di-μ-chlorobis(*cis*,*cis*-1,5-cyclooctadiene)dicopper(I) complex using published procedures (13% yield).[5] A more convenient preparation consisted of adding 5.0 g (0.046 mol) of commercial *cis*,*cis*-1,5-cyclooctadiene (**3**) followed by 200 ml of reagent grade pentane, 5.0 g (0.05 mol) of commercial cuprous chloride, and 300 ml more of pentane to a 1.5-l. quartz irradiation vessel fitted with a condenser leading to a mercury bubbler. The entire apparatus was flushed with dry nitrogen and the vigorously stirred suspension was irradiated at 2537 Å for 24 hr. The solid material was then filtered off and stored in the dark under N_2 at room temperature. Approximately 45 g of this material (the result of five runs) was worked up by shaking it with pentane and concentrated ammonia until all the solid had dissolved. To the mixture was then added ice and sufficient sodium cyanide to decolorize the solution. The solution was then shaken again and separated. The aqueous layer was then extracted twice more with pentane, and the pentane solutions were combined and dried over $MgSO_4$. Analysis of this solution by gas chromatography (SE-30) showed approximately equal amounts of *cis*,*cis*-1,5-cyclooctadiene and *cis*,*trans*-1,5-cyclooctadiene along with a small amount (*ca.* 1%) of *trans*,*trans*-1,5-cyclooctadiene. The solution was then concentrated by distillation, using a wire gauze column, to *ca.* 200 ml. To this solution was added an equal amount of water containing sufficient $AgNO_3$ (usually 10–13 g was required) to eliminate the product peak from a gas chromatogram of the pentane solution. The aqueous layer was then washed once with pentane and to it was added excess concentrated ammonia in order to liberate the olefin. The mixture was extracted three times with pentane, and the pentane solutions were combined, dried over $MgSO_4$, and concentrated to about 100 ml by distillation of the pentane through a wire gauze column. Analysis of this solution by gas chromatography showed 99% pure *cis*,*trans*-1,5-cyclooctadiene (**4**) and integration data gave a yield of 8–10 g (30–40%).

Irradiation of *cis*,*cis*-**1,5-Cyclooctadiene** (**3**) **with Cuprous Bromide.**—A mixture of 7.25 g (0.05 mol) of cuprous bromide, 200 ml of pentane, 5 g (0.046 mol) of *cis*,*cis*-1,5-cyclooctadiene, and 300 ml more of pentane was placed in a 1.5-l. quartz irradiation vessel. The apparatus was arranged and flushed with nitrogen as before. Using vigorous magnetic stirring, the mixture was irradiated at 2537 Å for 26.0 hr. The reaction mixture was filtered to give 7.4 g of irradiated solid. Working up the solid in the usual way with ammonia and sodium cyanide followed by gc analysis (SE-30) showed that 40% of the complexed material had been converted to *cis*,*trans*-1,5-cyclooctadiene (**4**), the remainder being starting material. The actual yield, however, of *cis*,*trans*-cyclooctadiene was 0.045 g (0.9%) from gc data.

Registry No.—*trans*-Cyclooctene, 931-89-5.

(6) H. L. Haight, J. R. Doyle, N. C. Baenziger, and G. F. R. Richards, *Inorg. Chem.*, **2**, 1301 (1963).

(7) J. A. Deyrup, M. Betkouski, W. Szabo, M. Mathew, and G. Palenik, *J. Amer. Chem. Soc.*, **94**, 2147 (1972).

(8) D. J. Trecker, R. S. Foote, J. P. Henry, and J. F. McKeon, *ibid.*, **88**, 3021 (1966).

(9) The work of Swenton suggests that the photoequilibrium between **1** and **2** can give detectable amounts of **1**.[4]

(10) W. L. Jolly, "Synthetic Inorganic Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1960, pp 142–143. Commercial curpous chloride is also satisfactory.

The Lack of an α Effect for Proton Abstraction from Carbon Acids

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Interest in the α effect remains unabated after 10 years of investigation and speculation.[3] The question of whether there is a kinetic α effect associated with proton abstraction by a nucleophile has not been satisfactorily answered. Methoxylamine and diethyl ketoxime exhibit large positive deviations from the Brønsted plot for general base catalysis of the hydrolysis of ethyl trifluorothiolacetate.[4] However, this deviation has been established to be due to a change in mechanism from general base catalysis of hydrolysis to nucleophilic attack for methoxylamine and diethyl ketoxime.[5] The α effect in general base catalyzed aminolysis is well known,[3,6] but finds ready explanation in the fact that the ester is undergoing simultaneous nucleophilic attack. Oximate anions have been shown to be considerably better catalysts than expected in reactions such as the dehydration of acetaldehyde hydrate[7] and the hydration of *s*-dichloroacetone;[8] however, explanations not involving the α effect have been suggested for these cases.[9,10] In particular, the solvents used for the reaction (91% acetone–water and 95% dioxane–water, respectively) were not those in which the pK_a's were obtained (water). The only quantitative approach to the question of the appearance of an α effect in proton abstraction from carbon is found in a study of the general base (amine) catalyzed ionization of nitroethane. The Brønsted β value for this reaction was found to be 0.5 and no α effect was observed with hydrazines. It was concluded from this study that general base proton removal from a carbon acid was not subject to the α effect. However, the factors leading to the kinetic α effect for hydrazine and peroxy anions are now known to differ,[11] and peroxy anion was not investigated with nitroethane. In addition, it has recently been shown, in the reaction of hydrazine with 17 substrates of assorted type, that a positive linear relationship exists between the magnitude of the α effect and the position of the transition state as determined by the Brønsted β value.[12] It would appear that our previous study with nitroethane is inconclusive because β_{max} values for nitroalkane ionization exceed 1.0, making β difficult to interpret[13] in terms of the position of the transition state along the reaction coordinant.

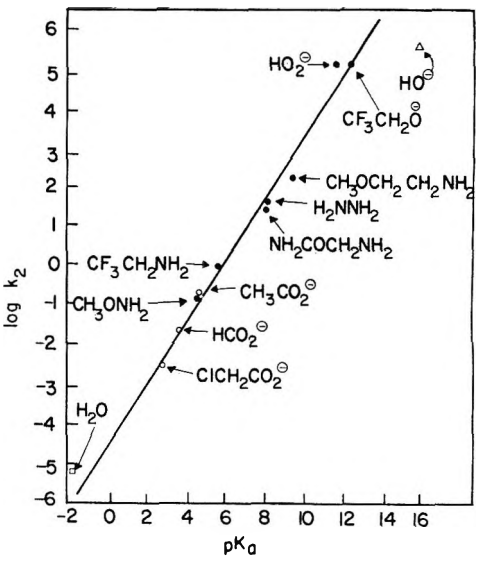

Figure 1.—Brønsted plot for the general base catalyzed detritiation of *tert*-butylmalononitrile-*1-t*. The points for water, hydroxide, and carboxylate ions are from ref 9.

Hibbert, Long, and Walters[14] have shown that the detritiation of *tert*-butylmalononitrile-*1-t* is a general base catalyzed reaction whose slow step is triton transfer from the cyanocarbon acid. They report a β value of *ca.* 0.9 derived from points for three carboxyl ions and a very small tritium kinetic isotope effect suggesting the transition state to be productlike. In addition, from their finding of an almost diffusion-controlled rate of reprotonation of the anion they suggest that in cyanocarbon acid anions far less delocalization of electrons occurs than in the case of the nitroalkanes.[15]

Having noted a positive correlation between the magnitude of the α effect and the Brønsted β[12] it occurred to us that proton (triton) abstraction from *tert*-butylmalononitrile with its β of *ca.* 0.9 would be an ideal reaction to provide a conclusive answer as to whether the α effect is operative when a carbon acid is the substrate. We have, therefore, studied the rates of detritiation of *tert*-butylmalononitrile-*1-t* in suitable α-effector and non-α-effector buffers employing the experimental procedure of Long, *et al.*[14,16] The second-order rate constants for triton abstraction (Table I) are plotted *vs.* the pK_a of the conjugate acid of the nucleophile in the Brønsted fashion in Figure 1. Included in Figure 1 are the experimental results reported from Long's laboratory.[14] The straight line of Figure 1 (slope 0.8) is the least squares line through all points regardless of base type except those for water and hydroxide ion. It is clear from Figure 1 that no significant α effect is present with methoxylamine, hydrazine, or peroxide anion. The values of $k_{hydrazine}/k_{gl}$, $k_{HO_2^-}/k_{CF_3CH_2O^-}$, and $k_{HO_2^-}/k_{HO^-}$, often used as criteria of the α effect, are 1.53, 1.02, and 0.61, respec-

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(2) To whom inquiries should be addressed.

(3) For a tabulation and discussion of the various mechanistic suggestions to account for the α effect, see T. C. Bruice, A. Donzel, R. W. Huffman, and R. A. Butler, *J. Amer. Chem. Soc.*, **89**, 2106 (1967).

(4) L. R. Fedor and T. C. Bruice, *ibid.*, **87**, 4138 (1965).

(5) J. E. Dixon and T. C. Bruice, unpublished work.

(6) T. C. Bruice, A. F. Hegarty, S. M. Felton, A. Donzel, and N. G. Kundu, *J. Amer. Chem. Soc.*, **92**, 1370 (1970).

(7) R. P. Bell, *J. Phys. Chem.*, **55**, 885 (1951).

(8) R. P. Bell and M. B. Jensen, *Proc. Roy. Soc., Ser. A*, **261**, 38 (1961).

(9) M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 2327 (1967).

(10) See also R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 155.

(11) J. E. Dixon and T. C. Bruice, *J. Amer. Chem. Soc.*, **93**, 3248 (1971).

(12) J. E. Dixon and T. C. Bruice, *ibid.*, **94**, 2052 (1972).

(13) F. G. Bordwell, W. J. Boyle, Jr., J. A. Hautala, and K. C. Yee, *ibid.*, **91**, 4002 (1969); R. A. Marcus, *ibid.*, **91**, 7224 (1969); A. J. Kresge, *ibid.*, **92**, 3210 (1970); F. G. Bordwell, Jr., J. Boyle, Jr., and K. C. Yee, *ibid.*, **92**, 5926 (1970); F. G. Bordwell and W. J. Boyle, Jr., *ibid.*, **93**, 512 (1971).

(14) F. Hibbert, F. A. Long, and E. A. Walters, *ibid.*, **93**, 2829 (1971).

(15) See also B. Holmquist and T. C. Bruice, *ibid.*, **91**, 3003 (1969).

(16) E. A. Halevi and F. A. Long, *ibid.*, **83**, 2309 (1961).

TABLE I
SECOND-ORDER RATE CONSTANTS FOR TRITON ABSTRACTION FROM *tert*-BUTYLMALONONITRILE-*1-t*

Base	pK_a	k_2, sec^{-1} M^{-1}
H_2O[a]	−1.74	5.89×10^{-6}
$ClCH_2CO_2^-$[a]	2.85	3.25×10^{-3}
HCO_2^-[a]	3.75	2.52×10^{-2}
$CH_3CO_2^-$[a]	4.76	2.31×10^{-1}
OH^-[a]	15.75	2.48×10^{5}
Glycinamide	8.10	30.4
Hydrazine	8.16	46.6
2-Methoxyethylamine	9.43	184
Trifluoroethylamine	5.71	1.03
Methoxylamine	4.69	0.176
Trifluoroethanol	12.37	1.49×10^{5}
Hydrogen peroxide	11.6	1.53×10^{5}

[a] F. Hibbert, F. A. Long, and E. A. Walters, *J. Amer. Chem. Soc.*, **93**, 2829 (1971).

tively, which supports the conclusion of a lack of an α effect. In contrast, from the relationship of β and the value of the α effect alluded to previously,[12] the ratio of $k_{hydrazine}/k_{gl}$ would be anticipated as *ca.* 40. Of the various rationales which have been put forth to explain the α effect, that of repulsive interaction of adjacent electron pairs[17] appears most useful in explaining the relationship of the α effect to the Brønsted β constant as well as the finding of no α effect for proton abstraction. Thus, the more productlike the transition state the less available are the bonding electrons and the greater is the relief of repulsion. The lack of an α effect for proton abstraction from a carbon acid may be ascribed to the anticipated lessened perturbing influence of a proton upon the electron structure of a base.[18]

Registry No.—Glycinamide, 598-41-4; hydrazine, 302-01-2; 2-methoxyethylamine, 109-85-3; trifluoroethylamine, 753-90-2; methoxylamine, 67-62-9; trifluoroethanol, 75-89-8; hydrogen peroxide, 7722-84-1; *tert*-butyl malononitrile-*1-t*, 33407-05-5.

Acknowledgment.—This work was supported by a grant from the National Institutes of Health.

(17) K. M. Ibne-Rasa and J. O. Edwards, *J. Amer. Chem. Soc.*, **84**, 763 (1962). This suggestion is very similar to that suggested by Ingold: C. K. Ingold, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, J. F. Norris Award Address.

(18) J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962).

Stereochemistry of Iminoxy Radicals Derived from Some Benzohydroximoyl Chlorides

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The formation of iminoxy σ radicals by oxidation of oximes in organic solvents using ceric ion[1] or lead tetracetate[2,3] is well established. The electron resonance spectra of these radicals are strongly dependent on their geometrical structure,[2,3] since the transmission of spin density through space by direct overlap or through the framework of the molecule is greatly affected by the relative orientation of the σ orbital containing the unpaired electron and of the interacting nuclei. For instance, in the anti radical from benzaldoxime, a definite coupling constant of 1.4 G with the ortho protons of the aromatic ring is observed, whereas in the syn isomer there is no interaction with any of the phenyl protons;[3] moreover, the splitting due to the hydrogen of the iminoxy group is considerably different in the two configurations, *viz.* 27 G in the syn and 6.5 G in the anti form.[3] Consequently, the marked stereochemical dependence of the hyperfine splitting (hfs) constants of the coupled nuclei in the iminoxy radicals gives a means of obtaining information concerning their molecular geometry.

We wish to report the results of an esr study on iminoxy radicals derived from benzohydroximoyl chlorides (**1**–**8**). The aim of this investigation was to assign the molecular geometry of these radicals from hfs parameters. The configuration on the C=N bond and the conformation on the N–O bond of hydroximoyl chlorides have been recently investigated through the analysis of dipole moment data.[4] Even though the results were less reliable than in studies of other oximino compounds[5] and imidoyl chlorides,[6] they favor the *E* ap (anti, trans) form. This assignment differs from that given by Lumbroso and coworkers, who preferred the *Z* ap (syn, trans) form.[7]

E ap *Z* ap

The radicals have been generated at room temperature by oxidation of the hydroximoyl chlorides with lead tetracetate in deoxygenated solutions of benzene or methylene chloride. Several compounds were examined, but in some cases the decay of the radical produced was so rapid that the esr spectrum could not be recorded. The compounds giving detectable concentrations of the radical for a sufficiently long time and their hyperfine splitting constants are listed in Table I. In each case the esr spectrum of the observed radical shows the presence of only one of the two geometric isomeric forms either in benzene or methylene chloride. This behavior differs from that of other oximino compounds, such as aldoximes and ketoximes, which usually give a mixture of syn and anti radicals in methylene chloride or other polar solvents.[1-3] The nature of the atom X in the CX=NOH group seems to be very important in determining the stability of the isomeric

(1) J. R. Thomas, *J. Amer. Chem. Soc.*, **86**, 1446 (1964); W. H. Fox and W. A. Waters, *J. Chem. Soc.*, 4628 (1965).

(2) M. Bethoux, H. Lemaire, and A. Rassat, *Bull. Soc. Chim. Fr.*, 1985 (1964).

(3) R. O. C. Norman and B. C. Gilbert, *J. Phys. Chem.*, **71**, 14 (1967); B. C. Gilbert and R. O. C. Norman, *J. Chem. Soc. B*, 86 (1966); 123 (1968).

(4) A. Battaglia, A. Dondoni, and O. Exner, *J. Chem. Soc., Perkin Trans. 2*, in press.

(5) O. Exner, *Collect. Czech. Chem. Commun.*, **30**, 652 (1965); D. Šnobl and O. Exner, *ibid.*, **34**, 3325 (1969); O. Exner, M. H. Bern, and F. Willis, *Can. J. Chem.*, **46**, 1873 (1968).

(6) A. Dondoni and O. Exner, *J. Chem. Soc., Perkin Trans. 2*, in press.

(7) J. Barassin, J. Armand, and H. Lumbroso, *Bull. Soc. Chim. Fr.*, 3409 (1969).

TABLE I
HFS CONSTANTS (GAUSS) OF IMINOXY RADICALS DERIVED FROM BENZOHYDROXIMOYL CHLORIDES
ArC(Cl)=NOH

Ar	a_N	a_{Cl}	a_X[a]	Solvent[b]
2,4,6-Trimethyl-3,5-dichlorophenyl (1)	30.9	1.71[c] 1.43[d]		B
	30.5	1.73[c] 1.44[d]		M
2,4-Dichlorophenyl (2)	32.0	1.89[e]	1.89[e] (1 Cl)	B
	32.2	1.76	2.15 (1 Cl)	M
2,6-Dichlorophenyl (3)	30.5	1.57		B
2-Bromophenyl (4)	31.9	1.70	9.80 (1 Br)	B
4-Nitrophenyl (5)	30.0	1.30	0.70 (2 H)	B
2-Nitrophenyl (6)	30.0	1.33		B
3-Nitrophenyl (7)	30.0	Unresolved hyperfine structure		B
4-Chlorophenyl (8)	30.4	Unresolved hyperfine structure		B

[a] Hfs constants of the nuclei X of the phenyl ring are indicated in parentheses. [b] B = benzene; M = methylene chloride. [c] Splitting due to ^{35}Cl. [d] Splitting due to ^{37}Cl. [e] Average values for the two coupled chlorine atoms.

radicals produced in the course of the oxidation; for instance, in the present case the chlorine atom greatly stabilizes one of the two configurations. By examining the hfs constants it was possible to decide in which form the observed radical was present.

The spectra[8] were characterized by splittings due to nitrogen (a_N *ca.* 30 G) typical of σ-type iminoxy radicals,[1-3] and to chlorine. When the unpaired electron was not coupled with other nuclei, it was possible to resolve the lines due to isotopes ^{35}Cl and ^{37}Cl, which have different magnetogyric ratios. The splittings from nitrogen and chlorine are not very useful in assigning the preferred configuration of the radicals, since a_N is almost independent of the molecular geometry and the values due to chlorine in the syn and anti isomers are not known. However, considering the relative values of a_H on the two isomeric radicals derived from benzaldoxime,[3] a large chlorine coupling constant would be expected for the syn configuration; the observed splitting of only 1.7 G may indicate that the anti isomer is the more stable.

The analysis of other hfs parameters supports this conclusion. The spectra of the radicals derived from **5** show the presence of coupling with the ortho aromatic protons, and those derived from **2** and **4** show ortho halogen splittings, the one resulting from bromine being very large. Also the lack of resolution in the spectra of the radicals derived from **7** and **8** may indicate that the unpaired electron is coupled with other nuclei, besides the chlorine, namely with the ortho aromatic protons. All these couplings should be absent in the syn isomers, since direct orbital overlap between the cited nuclei and the orbital containing the unpaired electron is prevented by the greater distance. No interaction has been detected with ortho nuclei on the phenyl ring placed in the opposite side with respect to the iminoxy oxygen.[3] All these results confirm the anti isomer as the more stable geometrical form of these radicals.

The data obtained also allow some conclusions to be advanced on the conformation of the phenyl ring with respect to the Cl–C=N plane. A similar problem has been discussed for radicals derived from ortho-substituted acetophenone oximes.[3] As mentioned above, the radicals from **2** and **4** show definite ortho halogen splittings (a_{Cl} = 2.1 G, a_{Br} = 9.8 G), whereas the coupling with the ortho aromatic proton is absent. Similarly, in the radical from 2-nitro derivative **6**, the splitting from the ortho proton was not observed. This indicates that the preferred arrangement of the phenyl ring is that which places the ortho substituent on the same side of the iminoxy oxygen, because of the steric overcrowding between the substituent and the aliphatic chlorine atom. However, full coplanarity of the phenyl ring with the Cl–C=N fragment seems unlikely for steric reasons, while a less crowded arrangement is that keeping the phenyl ring distorted at some angle from the Cl–C=N plane. This conclusion is supported by the greater values of ortho halogen hfs constants reported in iminoxy radicals where the coplanarity is granted by the rigid skeleton of the molecule.[3]

When radicals were generated from the ortho-disubstituted benzohydroximoyl chlorides **1** and **3**, the splittings from methyl protons or chlorine were not observed. In these cases the steric overcrowding appears to have held the phenyl ring in an arrangement almost perpendicular to the Cl–C=N plane, thus preventing any interaction between the ortho substituents and the unpaired electron.

The anti configuration of iminoxy radicals derived from benzohydroximoyl chlorides (**1**–**8**) has been established from their esr spectra. This constitutes evidence for the same configurational assignment for the radical as for its precursor,[4] since, considering that only *one* isomer has been observed for both radical and precursor, it seems unlikely that the stability of syn and anti forms is completely reversed in the two cases.

Experimental Section

A Varian Model V-4502 spectrometer was used to obtain the esr spectra. Solutions of the reactants were deoxygenated by bubbling nitrogen through them before mixing. The spectra were recorded at room temperature under nitrogen.

Hydroximoyl chloride (**1**) was prepared by the literature method;[9] compounds **2** and **4**–**8** were obtained as described.[4] **2,6-Dichlorobenzohydroximoyl chloride** (**3**) was prepared by slow addition of dry hydrochloric acid to an ice-cooled solution of the corresponding nitrile oxide[10] (1 g) in 75 ml of methylene dichloride. The reaction was completed within 1 hr. The solvent was removed *in vacuo* and the oily residue was treated with petroleum ether (bp 30–60°) to yield **3**, which after recrystallization from benzene–petroleum ether had mp 93–94°. Ir and nmr spectra were similar to those of the other compounds.

Anal. Calcd for $C_7H_4Cl_3NO$: C, 37.45; H, 1.79; Cl, 47.38; N, 6.24. Found: C, 37.49; H, 1.80; Cl, 47.24; N, 6.18.

(8) The esr spectra of the radicals derived from compounds **1** (in methylene chloride) and **2** (in benzene) will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D. C. 20036, by referring to code number JOC-72-3564. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(9) P. Beltrame, C. Veglio, and M. Simonetta, *J. Chem. Soc. B*, 867 (1967).

(10) C. Grundmann and J. M. Dean, *J. Org. Chem.*, **30**, 2809 (1965).

Attempts to prepare this compound by chlorination of the corresponding oxime with chlorine or nitrosyl chloride were unsuccessful.

Registry No.—*anti*-**1**, 35623-67-7; *anti*-**2**, 35623-68-8; *anti*-**3**, 35623-69-9; *anti*-**4**, 35623-70-2; *anti*-**5**, 35623-71-3; *anti*-**6**, 35623-72-4; *anti*-**7**, 35623-73-5; *anti*-**8**, 35623-74-6.

A Reexamination of the Reactions of 1,2-Diaminonaphthalene with Ethyl Acetoacetate and Crotonic Acid[1-3]

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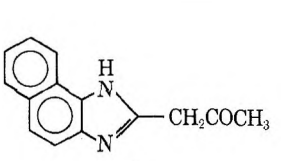
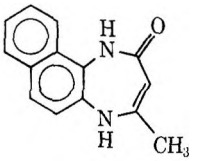
The direct condensation of 1,2-diaminonaphthalene with ethyl acetoacetate in boiling xylene has been reported[4] to give a mixture of the two isomeric products, 2-acetonylnaphthimidazole (1) and the dihydrodiazepinone 2. Structure 2, rather than the alternate cyclization possibility **3**, was assigned because, upon reduction, the product gave material isomeric with that obtained from the reaction of the naphthalenediamine with crotonic acid.[4] However, the structure of the crotonic acid product was not established with certainty and, therefore, structure 2 has remained open to question.[5] Furthermore, there is now reason in the literature[6,7] to suspect that 1 is an erroneous assignment. A recent reinvestigation in our laboratory of the reactions of 1,2-diaminonaphthalene with ethyl acetoacetate and crotonic acid has revealed that all of the previous structural assignments for the reaction products are indeed incorrect.



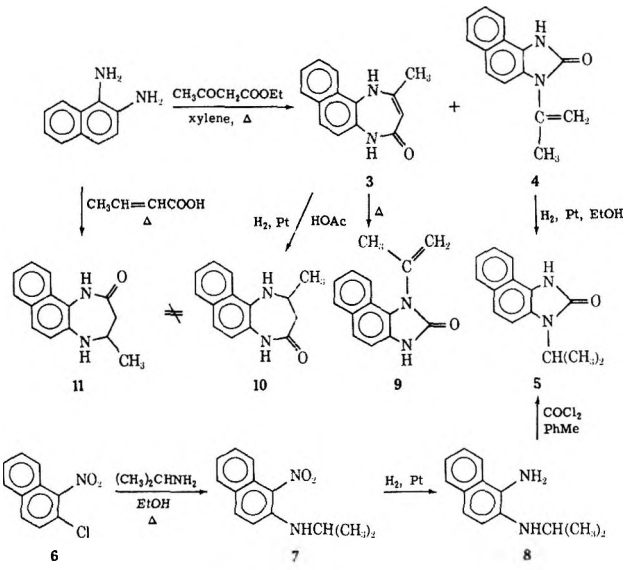
1



2

The structures of the various products involved in this study are shown in Scheme I. The lower melting product from the reaction of the diamine with ethyl acetoacetate, previously thought to be **1**, was found to be an isopropenylimidazolone on the basis of its ir spectrum (λ_{max}^{KCl} 5.85 μ) and nmr spectrum ($CDCl_3$) (methyl signal at δ 2.48 and two vinyl proton quartets at 5.53 and 5.65 ppm). Assignment of structure **4** to this material followed from the observation that, upon reduction, it afforded a product identical with a sample of 1,2-dihydro-3-isopropyl-3*H*-naphth[1,2-*d*]imidazol-2-one (**5**) prepared by unambiguous synthesis (**6** → **7** → **8** → **5**). The isomeric product from the condensation reaction (reported[4] mp 228°) had mp 228° when first isolated but this was raised to 246° upon purification. The nmr spectrum in various solvents showed, in addition to the aromatic ring protons, a methyl singlet, a methylene singlet, and a broad downfield NH signal, a pattern similar to that of other acetoacetic ester diazepinone products.[7-11]

SCHEME I



Often, but not always, the reaction of an *o*-diamine with a β-keto ester in boiling hydrocarbon solvent gives rise to a mixture of a diazepinone and an isomeric alkenylimidazolone.[6-8,10-14] The imidazolone product is now known to arise in these reactions *via* thermal rearrangement of the diazepinone.[7] Based upon previous experience,[7,8,10,11] the presence of **4** in the naphthalenediamine–ethyl acetoacetate reaction mixture suggested that the diazepine product was **2**. However, all attempts to convert the diazepinone into **4** either by fusion[7] or under conditions of base catalysis[6,9] were unsuccessful. Thermal rearrangement of the diazepinone, under stronger conditions than normally required for this reaction, afforded instead an isomeric isopropenylimidazolone, mp 222°, the nmr spectrum ($CDCl_3$) of which showed the methyl quartet 0.18 ppm upfield from that of **4** and the two vinyl quartets at δ 5.43 and 5.60 ppm. This information identified the rearranged material as **9** and, since C–N bonds are not disrupted during the ring contraction process,[7] the

(1) This investigation was supported in part by Research Grant C6516 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) This is part 4 of the series, "Application of a Thermal Rearrangement Reaction to Questions of Structure of Condensed Dihydrodiazepinones." For part 3, see M. Israel, L. C. Jones, and M. M. Joullié, *J. Heterocycl. Chem.*, **8**, 1015 (1971).

(3) A brief account of part of this work has appeared: M. Israel, L. C. Jones, and E. C. Zoll, Abstracts of Papers, Third International Congress of Heterocyclic Chemistry, Sendai, Japan, Aug 1971, p 550.

(4) W. Ried and W. Höhne, *Chem. Ber.*, **87**, 1801 (1954).

(5) The lack of certainty of Ried and Höhne's structure assignments has been noted by J. A. Moore in "Heterocyclic Compounds," Vol. 9, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1967, pp 319 and 327.

(6) J. Davoll, *J. Chem. Soc.*, 308 (1960).

(7) M. Israel, L. C. Jones, and E. J. Modest, *Tetrahedron Lett.*, 4811 (1968).

(8) M. Israel, L. C. Jones, and E. J. Modest, *J. Heterocycl. Chem.*, **4**, 659 (1967).

(9) M. Israel, S. K. Tinter, D. H. Trites, and E. J. Modest, *ibid.*, **7**, 1029 (1970).

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(11) Unpublished results from these laboratories.

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diazepinone product must be **3**.[15] The nmr spectrum of **9**, as compared to that of **4**, can be accounted for by anisotropic shielding of the alkenyl protons by the bay proton on the naphthalene nucleus.

Careful examination of the reaction mixture and subsequent mother liquors from crystallizations failed to reveal the presence of any **2**. Interruption of the boiling xylene reaction in the hope of isolating **2** or other intermediates was unsuccessful. Condensation reactions carried out at lower temperatures also failed to give **2**; a similar product distribution of **3** and **4** was obtained in boiling toluene as solvent and in boiling benzene essentially no reaction occurred. We believe that the formation of **3** and **4** in this reaction can best be explained by considering that both diazepinone products **2** and **3** were initially formed. **3**, which was found to be resistant to thermal rearrangement, was not further affected by the reaction conditions. However, **2**, because of an apparently very low energy barrier for ring contraction, must have been converted immediately and quantitatively into **4**. Attempts to prepare **2** by an independent route in order to study its rearrangement unfortunately failed to give the desired product.

Catalytic reduction of **3** in acetic acid[4] afforded the tetrahydrodiazepinone **10**, mp 209°. This material was similar to but not identical with the tetrahydrodiazepinone, mp 229–230°, prepared by fusion of 1,2-diaminonaphthalene with crotonic acid, according to the procedure of Ried and Höhne.[4] The crotonic acid product is, therefore, correctly identified as **11**, and not **10** as previously suggested.[4]

Experimental Section[16]

1,5-Dihydro-2-methyl-4*H*-naphth[1,2-*b*][1,4]diazepin-4-one (3).—Prepared according to the procedure of Ried and Höhne,[4] this material was previously described as **2**. It formed white crystals from xylene: mp 246°; nmr (C_5D_5N) δ 2.43 (3 H, s), 3.28 (2 H, s), and 7.42–7.70 ppm (6 H, multiple aromatic peaks); uv $\lambda_{max}^{ethanol}$ 243 nm (ε 55,700), 294 (7100), 308 (6900), 323 (4500), and 337 (4800). The presence of **2** in the reaction mixture could not be observed by spectral or tlc studies.

1,2-Dihydro-3-isopropenyl-3*H*-naphth[1,2-*d*]imidazol-2-one (4).—The ether-soluble product from the reaction of 1,2-diaminonaphthalene and ethyl acetoacetate by the Ried and Höhne procedure,[4] this material was erroneously reported to be **1**. It formed white crystals from cyclohexane: mp 198°; nmr ($CDCl_3$) (time averaged)[17] δ 2.48 (3 H, fine splitting), 5.53 (1 H, q, J = 6 Hz), and 5.65 ppm (1 H, q, J = 6 Hz); ir λ_{max}^{KCl} 5.85 μ.

2-Isopropylamino-1-nitronaphthalene (7).—2-Chloro-1-nitronaphthalene (**6**) was prepared from 2-amino-1-nitronaphthalene essentially according to the procedure of Hodgson and Leigh;[18] in place of steam distillation, the product was purified by crystallization from ligroin (bp 95–110°). A solution of 3.2 g of **6** and 32 g of isopropylamine in 70 ml of absolute ethanol was heated at 100° for 6 hr in a stainless steel bomb. The red reaction solution was taken to dryness and the residue was washed with water to remove isopropylamine hydrochloride. The water-insoluble product was crystallized once from benzene–petroleum ether (bp 60–90°) and once from cyclohexane to give 3.5 g (100%) of **7**, mp 104–105°.

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.83; H, 6.08; N, 12.17. Found: C, 67.82; H, 5.81; N, 11.89.

1-Amino-2-isopropylaminonaphthalene (8).—A solution of **7** (350 mg) in 50 ml of absolute ethanol was shaken under hydrogen in the presence of 200 mg of 5% palladium on charcoal on a Parr apparatus for 30 min. The catalyst was separated and the filtrate was evaporated to dryness. The residue was crystallized from ligroin to give white crystals of **8**, yield 130 mg (42%), mp 102–103°.

Anal. Calcd for $C_{13}H_{16}N_2$: C, 78.00; H, 7.99; N, 13.99. Found: C, 78.28; H, 7.97; N, 14.02.

1,2-Dihydro-3-isopropyl-3*H*-naphth[1,2-*d*]imidazol-2-one (5). Method A. Cyclization of 8.—Phosgene was passed into 30 ml of xylene for 30 min at room temperature and to this solution was added, in small portions with stirring, 300 mg of **8**. Phosgene was again bubbled into the solution (15 min), following which the reaction mixture was warmed at 60° for 5 hr. After overnight standing, the clear, pale yellow solution was evaporated to dryness under reduced pressure and the residue was crystallized several times from cyclohexane to give 330 mg (97%) of white crystals: mp 200–201°; ir λ_{max}^{KCl} 5.90 μ; uv $\lambda_{max}^{ethanol}$ 246 nm (ε 67,300), 293 (3800), 305 (3500), and 340 (4000); nmr ($CDCl_3$) δ 1.66 (6 H, d, J = 7 Hz), 4.98 (1 H, m, J = 28 Hz), and 7.27–8.23 ppm (6 H, multiple aromatic peaks).

Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.30; H, 6.25; N, 12.38. Found: C, 74.45; H, 6.33; N, 12.28.

Method B. Reduction of 4.—A solution of 125 mg of **4** in 40 ml of absolute ethanol was shaken overnight under hydrogen in the presence of 60 mg of platinum oxide. The catalyst was separated and the ethanolic filtrate was evaporated to give a brown oil, which was dissolved in hot cyclohexane. After treatment with charcoal, the solution was reduced to 10 ml and the white precipitate was collected and crystallized twice from cyclohexane to give material identical in all respects with that obtained by method A.

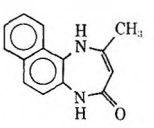
2,3-Dihydro-1-isopropenyl-1*H*-naphth[1,2-*d*]imidazol-2-one (9).—A 100-mg sample of **3** in a small test tube was heated at 250° for 3 hr in the absence of solvent. Upon cooling, the solidified mass was treated with warm (60°) benzene and the insoluble material (mostly unchanged **3**) was separated. Addition of petroleum ether to the benzene solution gave an off-white precipitate. This material was crystallized several times from benzene–petroleum ether to give 32 mg (32%) of **9** as small white crystals: mp 222°; ir λ_{max}^{KCl} 5.88 μ; nmr ($CDCl_3$) δ 2.30 (3 H, fine splitting), 5.43 (1 H, q, J = 6 Hz), and 5.60 ppm (1 H, q, J = 6 Hz).

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.40; N, 12.49. Found: C, 75.17; H, 5.47; N, 12.62.

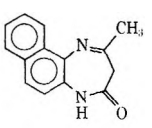
Registry No.—**3**, 35624-19-2; **4**, 35624-20-5; **5**, 35624-21-6; **7**, 35624-22-7; **8**, 35624-23-8; **9**, 35624-24-9; **11**, 35624-25-0; 1,2-diaminonaphthalene, 938-25-0; ethyl acetoacetate, 141-97-9; crotonic acid, 3724-65-0.

Acknowledgment.—We thank Mrs. Lynne C. Jones and Mrs. Marilyn A. Whitesell for technical assistance at different times during this work.

(15) Solutions of **3** in chloroform, pyridine, and dimethyl sulfoxide are bright yellow and the nmr spectrum is consistent with structure **3b**. However, the diazepinone, a white solid, probably exists in the solid state in the form of the leuco tautomer **3a**.[7-9]



3a



3b

(16) Analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(17) The time-averaged spectrum was obtained by means of a Japan Electron Optics Laboratory Co. Model JRA-1 Spectrum Accumulator interfaced with a Varian Associates Model A-60 spectrometer.

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Trifluoromethanesulfonyl Azide. Its Reaction with Alkyl Amines to Form Alkyl Azides

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p-Toluenesulfonyl azide is a widely used reagent for the transfer of the diazo group to active methylene

compounds.[1] The use of certain other sulfonyl azides for this purpose has been investigated by Hendrickson and Wolf,[2] who found that in some reactions product purification could be facilitated by the use of carboxybenzenesulfonyl azide. Chlorosulfonylbenzenesulfonyl azide was expected to be more reactive than toluenesulfonyl azide but was generally found to give lower yields.

In our study of sulfonyl leaving groups,[3] it occurred to us that the very great electron-withdrawing ability of the trifluoromethanesulfonyl (triflyl) group[4] might confer sufficient reactivity on triflyl azide that it could be used without basic promotion to diazotize active methylene compounds and with basic promotion to diazotize less active compounds. Triflyl azide was quickly produced by the reaction of triflic anhydride with aqueous sodium azide at 0° and separated into a water-insoluble, lower layer. After experiencing one explosion, we carried out subsequent preparations of the azide, without further trouble, in the presence of a solvent. The strong characteristic infrared spectrum of triflyl azide persisted even after 24 hr standing in methylene chloride, *N*,*N*-dimethylformamide, tetrahydrofuran, dimethyl sulfoxide, dioxane, acetonitrile, methanol, or acetone, indicating only slow, if any, reaction with these solvents. The characteristic infrared spectrum also persisted for at least several hours in the presence of potassium *tert*-butoxide, hydroxide, or fluoride, sodium methoxide or 2,6-lutidine indicating that it was only slowly destroyed by these bases. Despite these observations of reasonable stability, product yields using the new reagent (see below) were found to be significantly lower if the azide was prepared before use rather than in the presence of coreactant.

Although infrared spectral changes seemed to indicate that triflyl azide gave products of diazo transfer with 5,5-dimethylcyclohexa-1,3-dione, 1-benzoylacetone, and even cyclohexanone (all with or without a catalytic amount of 2,6-lutidine), none of the reaction conditions tried permitted the isolation of the desired products in reasonable yields.

Toluenesulfonyl and the less reactive azides do not react directly with primary amines but do form alkyl azides when treated with the Grignard[5] or lithium[6] salts of the amines. The utility of the new reagent is demonstrated in its ability to transfer the diazo group directly to the primary amine function to form the corresponding alkyl azide.

Alkyl azides are usually prepared by the displacement of halide, sulfate, or tertiary amine leaving groups by the azide ion.[7] Rearrangements and steric hindrance limit the scope of these reactions for tertiary azides, which can sometimes be produced by the solvolysis of the appropriate derivative in the presence of azide salts. Recently, the synthesis of secondary and tertiary alkyl azides has been achieved through mercuration of olefins in a solution containing azide salts;[8] however, this method is only effective for terminal and strained cyclic olefins. β-Haloalkyl and vinyl azides can be prepared from olefins and halo azides.[9] As outlined in the Experimental Section, the triflyl azide method has been successful for the preparation of *n*-hexyl azide and 2,4,4-trimethyl-2-pentyl azide in isolated yields of about 70%. *tert*-Butyl azide has also been prepared but an isolated yield was not determined. Reactions of *n*-hexyl amine in the absence of 2,6-lutidine generally give yields of 50% or lower and less pure products.

The fact that 2,2,4-trimethyl-2-pentyl trifluoromethanesulfonamide does not react with aqueous sodium azide under reaction conditions indicates further that the alkyl azide must be formed by diazo transfer from triflyl azide. Although the point remains to be established experimentally, it appears likely that triflyl azide would convert the amine to the azide with retention of configuration and should, therefore, be useful in the correlation of configurations of amines and azides. We are continuing to explore the apparent reaction of benzamide with triflyl azide in the presence of lutidine. Amides and magnesium salts of amides are apparently unreactive with other sulfonyl azides.

Experimental Section

Triflyl Azide.—To a magnetically stirred solution of 8 g of NaN_3 in 20 ml of H_2O over 25 ml of CH_2Cl_2 at 0° was added 7 g (0.025 mol) of trifluoromethanesulfonyl anhydride.[10] The low temperature and stirring were maintained for 2 hr, and trifluoromethanesulfonyl azide (triflyl azide) was found in the organic layer and in the first two extractions of the water layer with 10-ml portions of the solvent: ir 4.65, 7.1, 8–9 μ (three peaks); ^{19}F nmr 183 Hz at 94.6 MHz (capillary standard trifluoroacetic acid).

Caution.—The resulting sulfonyl azide conveniently separates from the water solution if no organic layer is present, but we experienced an explosion in one preparation of it without organic solvent.

n-Hexyl Azide.—A sample of 0.5 ml (0.84 g) of freshly distilled trifluoromethanesulfonic anhydride was slowly added to 2 ml of 6.25 *N* aqueous NaN_3 over 0.375 g of *n*-hexyl amine and 0.162 g of 2,6-lutidine in 5 ml of CH_2Cl_2. The mixture was stirred and kept at 0° for 2 hr. The organic layer was extracted twice with concentrated aqueous KOH solution to remove the sulfonamide, with 0.5 *N* HCl until the extract was acidic to litmus, then with H_2O until it was neutral. Evaporating the solvent left 0.251 g (66.3%) of *n*-hexyl azide: bp 81–83° (60 mm) [lit.[11] bp 83° (63 mm)]; ir 4.80 μ (N_3); uv (C_2H_5OH) λ_{max} 287 nm (ε 20) [lit.[12] 287 nm (ε 21)]; nmr (CCl_4) δ 0.94, 1.0, 1.38 (broad), 2.5, 3.25 (modified triplet).

Preparations in which the product azide was contaminated with excess amine were purified by chromatography through deactivated alumina or silica gel, or by vacuum distillation.

2,4,4-Trimethyl-2-pentyl Azide.—Similarly, 0.5 ml (0.84 g) of trifluoromethanesulfonyl anhydride was slowly added to 2 ml of a 6.25 *N* aqueous solution of NaN_3 over 5 ml of CH_2Cl_2 containing 0.496 g of 2,4,4-trimethyl-2-pentylamine and the mixture was stirred for 2 hr at 0°. The reaction mixture was treated as described above for *n*-hexyl azide and yielded 0.359 g (77.7%) of 2,4,4-trimethyl-2-pentyl azide: bp 40° (3.5 mm); ir 4.75

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(5) W. Fischer and J. P. Anselme, *J. Amer. Chem. Soc.*, **89**, 5284 (1967); P. A. S. Smith, C. O. Rowe, and L. B. Bruner, *J. Org. Chem.*, **34**, 3430 (1969).
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(8) C. H. Heathcock, *Angew. Chem., Int. Ed. Engl.*, **8**, 134 (1969).
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(12) E. Lieber, *et al.*, *J. Sci. Ind. Res.*, **16B**, 95 (1957).

μ (N_3); uv (C_2H_5OH) λ_{max} 289–290 nm (ϵ 18); nmr δ 1.03 (9), 1.30 (6), 1.49 (2).

Registry No.—Triflyl azide, 3855-45-6; *n*-hexyl azide, 6926-45-0; 2,4,4-trimethyl-2-pentyl azide, 35426-97-2.

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A Convenient Synthesis of Homocubane-4-carboxylic Acid

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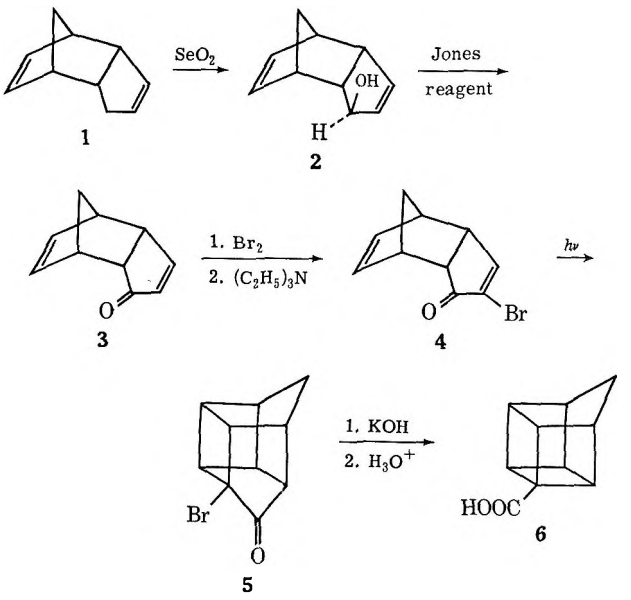
Received May 12, 1972

In connection with studies concerning mechanistic aspects of the Ag^+-catalyzed rearrangement of cubyl systems,[2] a number of various 4-substituted homocubanes (pentacyclo[4.3.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]nonanes) were required.[3] Since all of the desired compounds could be derived readily from that member of the series at the highest oxidation level, attention was given to the preparation of suitable quantities of homocubane-4-carboxylic acid (**6**). The original route to this compound reported in 1968 by Dunn, DiPasquo, and Hoover[4] began with relatively expensive 2-cyclopentenone and afforded **6** in less than 10% yield. We describe now a procedure which comprises only five readily executable steps, utilizes inexpensive dicyclopentadiene (**1**) as starting material, and results in at least 27% overall conversion to **6**.

Selenium dioxide oxidation of freshly distilled **1** according to the procedure of Woodward and Katz[5] led to the formation of allylic alcohol **2** in 63% yield. Efficient oxidation (75% yield) of this compound was achieved by treatment with Jones reagent.[6] Further studies indicated that **3** could be selectively brominated α to the carbonyl group by direct addition of



elemental bromine in carbon tetrachloride solution and subsequently dehydrobrominated with triethylamine. The halogenated ketone obtained in this manner (75% yield) was identical with an authentic sample of **4** prepared in unequivocal fashion.[4] Photocyclization of **4** and Favorskii-type ring contraction of **5**[4] complete the sequence.

Experimental Section

endo-**3a,4,7,7a-Tetrahydro-4,7-methanoinden-1-one** (**3**).—A solution of 40 g (0.27 mol) of **2**[5] in 500 ml of acetone was cooled in an ice bath and titrated with a total of 170 ml of Jones reagent (*ca.* 0.2 *M*) prepared according to the method of Meinwald, *et al.*[7] The reaction mixture was added to 1 l. of brine and extracted with ether. The combined organic extracts were washed with water and dried. Evaporation of the solvent left an oily residue which solidified on standing. Recrystallization of the white solid from pentane gave 30 g (75%) of crystalline ketone, mp 80° (lit.[6] mp 80°).

endo-**2-Bromo-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one** (**4**).—A solution of bromine (20.1 g, 0.126 mol) in 200 ml of carbon tetrachloride was added rapidly to a vigorously stirred solution of ketone **3** (18.3 g, 0.126 mol) in 500 ml of the same solvent. This was quickly followed by the addition of triethylamine (25 g, 0.25 mol) in 100 ml of carbon tetrachloride. The reaction mixture was warmed on a steam bath for 30 min and then stirred for a final 1.5 hr. The precipitate was separated by filtration and the filtrate was washed with water. The aqueous washings were extracted with ether and the combined organic layers were dried and evaporated. Short-path distillation of the residue afforded 21.5 g (75%) of **4** as a pale yellow oil, bp 95–100° (0.1 mm), which crystallized subsequently, mp 55–57° (lit.[4] mp 56–57°). The nmr spectrum of this material conformed to the reported spectrum of **4**.

Registry No.—**3**, 5530-96-1; **4**, 10481-35-3; **6**, 15844-05-0.

(1) Postdoctoral Fellow of the National Institutes of Health, 1972.

(2) L. A. Paquette, R. S. Beckley, and T. McCreadie, *Tetrahedron Lett.*, 775 (1971); L. A. Paquette and J. C. Stowell, *J. Amer. Chem. Soc.*, **93**, 2459 (1971); **92**, 4295 (1970); L. A. Paquette, *ibid.*, **92**, 5765 (1970).

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Communications

See Editorial, *J. Org. Chem.*, **37**, No. 19, 4A (1972).

A General Conversion of Phenols to Anilines[1]

Summary: Phenols are converted to aryl diethyl phosphates which, upon treatment with KNH_2 and potassium metal in liquid ammonia, afford anilines in good yield.

Sir: Methods for the synthetic transformation of phenols to the corresponding anilines, that is, for replacement of the hydroxy group by an amino group in the same position, are few and mostly arduous and/or restricted to narrow classes of phenols. When we recently read of a general method for effecting that transformation,[2] we realized that reactions we had investigated[3,4] should, when properly combined, be adaptable for the purpose of preparative aminodehydroxylation. Accordingly we did a few experiments, now reported, which demonstrate the practicability and suggest the generality of the method.

Operationally, the method involves two steps. First (eq 1), the phenol is converted to the corresponding

$$ArOH + NaOH + (C_2H_5O)_2POCl \longrightarrow ArOPO(OC_2H_5)_2 \quad (1)$$

aryl diethyl phosphate ester through reaction with NaOH and $(C_2H_5O)_2POCl$,[5] an inexpensive chemical. Ester yields are typically 80–90%. Second (eq 2), the

$$ArOPO(OC_2H_5)_2 + KNH_2 + K \longrightarrow ArNH_2 \quad (2)$$

aryl diethyl phosphate reacts with KNH_2 and potassium metal in liquid ammonia, forming the aniline. In the three cases we have examined, yields in the second step are 56–78%.

The aminodephosphation reaction (eq 2) is believed to occur by the SRN1 mechanism,[6] as shown in eq 3–6.

$$ArOPO(OC_2H_5)_2 + e_{solv}^- \longrightarrow [ArOPO(OC_2H_5)_2]\cdot^- \quad (3)$$

$$[ArOPO(OC_2H_5)_2]\cdot^- \longrightarrow Ar\cdot + (C_2H_5O)_2PO_2^- \quad (4)$$

$$Ar\cdot + NH_2^- \longrightarrow [ArNH_2]\cdot^- \quad (5)$$

$$[ArNH_2]\cdot^- + ArOPO(OC_2H_5)_2 \longrightarrow ArNH_2 + [ArOPO(OC_2H_5)_2]\cdot^- \quad (6)$$

The phosphate ester accepts an (solvated) electron (eq 3), and the resulting radical anion ruptures to form aryl radical and diethyl phosphate ion (eq 4). The aryl radical combines with amide ion to form the radical anion of an aniline (eq 5), which finally transfers an electron to another phosphate ester molecule (eq 6) or otherwise gets rid of it. Finally, the aniline is converted to an anilide ion in the strongly basic medium.

We have applied this method to phenol, 2,6-dimethylphenol, and 2-methoxy-4-methylphenol. Yields are summarized in Table I.

Among others, this method has the advantage that the two operational steps can be performed quickly at low temperatures. The method is convenient, and it should be feasible for use with thermally labile molecules. It has the disadvantage that some substituents are destroyed or lost on exposure to solvated electrons or to KNH_2. For example, it is unlikely to be serviceable with nitro- or halogen-substituted phenols. Alkyl, alkoxy, aryloxy, and aryl substituents survive, and probably also carbonyl groups of enolizable ketones.

TABLE I
SYNTHESES ACCORDING TO EQ 1 AND 2

Phenol	Yield of $ArOP(O)(OC_2H_5)_2$, %	Yield of $ArNH_2$,[a] %
Unsubstituted	87	73[b]
2,6-Dimethyl	72	78[c]
2-Methoxy-4-methyl	98	56[c]

[a] Yield from phosphate ester. [b] Yield by glpc. [c] Yield by isolation and weighing.

The method of Scherrer and Beatty[2] involves conversion of the phenol to a 4-aryloxy-2-phenylquinazoline, heating the latter at ~300° to effect O → N aryl migration, and finally alkaline hydrolysis to release the aniline. The last two steps involve long periods of heating, the last in an alkaline environment. Their method is applicable to chloro- and nitro-substituted phenols, but clearly not to thermally labile or alkali-sensitive structures. The two methods are to some extent complementary, but the present method is likely to be chosen when both are feasible.

Aryl Diethyl Phosphates.—Our preparations, by the method of Bliznyuk, *et al.*,[6] and properties of the esters obtained are described elsewhere.[7] Alternatively, these esters may be synthesized by a method due to Kenner and Williams.[8]

Anilines.—In a representative preparation, 0.32 mol of KNH_2 was formed in 320 ml of liquid ammonia by the iron-catalyzed reaction of potassium metal with the solvent. To the stirred solution, at −78°, were added a total of 0.078 g-atom of potassium metal and 0.114 mol of 2,6-dimethylphenyl diethyl phosphate. About a third of the potassium was initially added, then the ester dropwise from a dropping funnel until the blue color was discharged, then another third of the potassium, etc. After addition of the ester was complete, the solution was blue. The mixture was acidified by addition of excess NH_4Cl, 150 ml of diethyl ether was added, and the ammonia was allowed to evaporate. Water was added to the residue, and the ether layer was washed with 10% aqueous NaOH and then with 20% aqueous H_2SO_4. The acidic extract was basified and extracted with ether. The ether extract was dried and evaporated, affording 10.7 g (78%) of 2,6-dimethylaniline, of purity >96% by glpc and structure confirmed by ir, nmr, and mass spectra.

(1) Research supported in part by the National Science Foundation.
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(9) Grateful recipient of a fellowship from the Consejo Nacional de Investigaciones Cientificas y Técnicas, Argentina.

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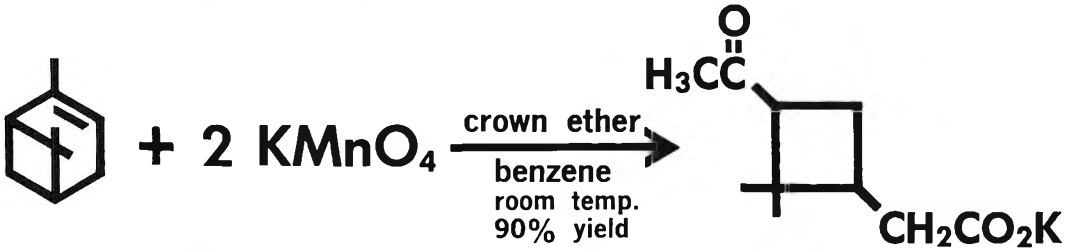

In addition, the strongly alkaline solution obtained by dissolving an equimolar mixture of potassium hydroxide and dicyclohexyl-18-crown-6 in methanol and replacing as much as possible of the methanol with benzene or toluene, readily saponifies even the highly hindered esters of 2,4,6-trimethylbenzoic acid.[3] This solution is also a powerful anionic catalyst, capable of inducing the polymerization of anhydrous formaldehyde and the trimerization of aromatic isocyanates.

Clearly the solubilizing power of crown ethers enables novel applications in catalysis, enhancement of chemical reactivity, separation and recovery of salts, electrochemistry and analytical chemistry.[1]

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